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# Fungal evolution: cellular, genomic and metabolic complexity

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## ABSTRACT

The question of how phenotypic and genomic complexity are inter-related and how they are shaped through evolution is a central question in biology that historically has been approached from the perspective of animals and plants. In recent years, however, fungi have emerged as a promising alternative system to address such questions. Key to their ecological success, fungi present a broad and diverse range of phenotypic traits. Fungal cells can adopt many different shapes, often within a single species, providing them with great adaptive potential. Fungal cellular organizations span from unicellular forms to complex, macroscopic multicellularity, with multiple transitions to higher or lower levels of cellular complexity occurring throughout the evolutionary history of fungi. Similarly, fungal genomes are very diverse in their architecture. Deep changes in genome organization can occur very quickly, and these phenomena are known to mediate rapid adaptations to environmental changes. Finally, the biochemical complexity of fungi is huge, particularly with regard to their secondary metabolites, chemical products that mediate many aspects of fungal biology, including ecological interactions. Herein, we explore how the interplay of these cellular, genomic and metabolic traits mediates the emergence of complex phenotypes, and how this complexity is shaped throughout the evolutionary history of Fungi.

*Key words*: fungi, complexity, multicellularity, secondary metabolism, genome evolution

## CONTENTS



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## I. INTRODUCTION

Although less often considered than animals or plants, the ecological success of Fungi is equally impressive, and comprises a broad diversity of lineages and life styles that populate every corner of our planet (Naranjo-Ortiz & Gabaldón, 2019a,*b*), with most estimates predicting millions of extant fungal species (Hawksworth, 2001; Blackwell, 2011; Aime & Brearley, 2012; Hawksworth & Lücking, 2017). At the heart of this success lies a series of interwoven cellular and biochemical traits, which are ultimately determined by the genome. The question of how phenotypic complexity is related to genomic complexity, and how these change during evolution, historically has been approached from the perspective of animals and plants. However, in recent years fungi have increasingly been the focus of research aiming to understand the origin and evolution of genomic and morphological complexity. Fungi originated from a flagellated ancestor, but most current diversity encompasses non-flagellated cells that often grow in a form of simple multicellularity called the mycelium, a true cellular network that sometimes extends over large areas. From this mycelial growth, many fungal organisms can switch to a unicellular growth form (e.g. yeast), often depending on the environmental conditions or on the stage of their life cycle. In several lineages throughout the fungal tree of life, mycelial growth has been abandoned, often completely but sometimes only to be recovered later. Some other lineages have taken multicellularity one step further, originating complex fruiting bodies whose macroscopic morphologies compete in intricacy and beauty with those of plants and animals. Complex multicellularity implies coordination of different cell types to form tissues and the existence of a tightly regulated developmental program. To achieve such levels of complexity, fungi have developed specific structural and regulatory systems that are still not fully understood. From a biochemical perspective, fungi present a truly vast diversity, with levels of complexity that are comparable or surpass those of other eukaryotic clades. Fungal organisms are osmotrophs and their cells are generally in contact with the surrounding environment. The relationship of a fungus with its immediate environment is defined by an array of secreted proteins and metabolites. The origin and diversification of these secreted metabolites is of great practical interest, given the often powerful effects they have on other organisms. Furthermore, production of these metabolites is tightly regulated and localized within the mycelial network, which saves resources, protects the fungus from damage from highly toxic intermediate metabolites and opens up a wide array of phenotypes in their interactions with other organisms.

This cellular and biochemical diversity is ultimately reflected in the highly dynamic nature of fungal genomes. Fungi are ideal subjects for genomic studies, since they tend to have highly compact genomes [theyrarely reach genome sizes of giga base pairs (Gbp)], are usually haploid, and can often be grown in axenic conditions. Consequently, the number of fully sequenced fungal genomes is now in the order of thousands. Hence, in combination with decades of studies in genetics, biochemistry and cell biology, fungal genomics is revolutionizing our understanding of this group (Scazzocchio, 2014). The study of the genetic repertoire of a growing diversity of fungi is unveiling a metabolic landscape far wider and intriguing than we could have imagined two decades ago. In addition, evolutionary genomic analyses are not only helping us to identify the components in the mycelial and multicellular fungal machinery, but also are uncovering what processes may drive the evolution of fungal genomes. In this respect, fungi have recently challenged evolutionary paradigms adopted from the study of animals and plants. For instance, non-vertical evolutionary processes such as horizontal gene transfer or hybridization seem to be far more common in fungi than previously anticipated, and prokaryotic paradigms such as that of pangenomes seem also to be applicable to fungi. In this review, we discuss recent advances in our understanding of the evolution of phenotypic and genomic complexity within the fungal kingdom, focusing on the cellular and biochemical traits that have driven the success of fungi in the biosphere. In so doing we emphasize, when known, the genomic features that underlie those traits as well as their evolution.

## II. CELLULAR COMPLEXITY

The last fungal common ancestor was likely a flagellated, unicellular organism with a saprotrophic or parasitoid lifestyle (James, Porter & Martin, 2014; Karpov *et al.*, 2014a; Powell & Letcher, 2014; Naranjo-Ortiz & Gabaldón, 2019b). However, very early in the evolution of fungi, a shift towards more complex forms of cellular organization occurred. This shift made possible the conquest of non-aquatic environments, leading to loss of the flagellum in several lineages and explosive radiation (Liu, Hodson & Hall, 2006; Berbee, James & Strullu-Derrien, 2017; Naranjo-Ortiz & Gabaldón, 2019b). Even though many fungal lineages have independently

returned to a (non-flagellated) unicellular lifestyle, most extant fungi exist (at least for a sizeable fraction of their life cycle) as networks of filamentous cells able to grow indefinitely and in intricate patterns (Fig. 1). These networks are populated by an array of nuclei that may or may not be genetically identical. Non-identical nuclei within a population are subjected to ecological pressures that have the potential to affect the phenotype of the whole network (Pontecorvo, 1956; James *et al.*, 2008). The sheer physical size of fungal networks allows the simultaneous exploitation of several nutrient sources, a huge advantage for an otherwise sessile microbe. These properties allow filamentous fungi effectively to influence a far greater volume than would be suggested by simple measures of their biomass; they can thus be seen as true territorial microbes (Simonin *et al.*, 2012; Fricker *et al.*, 2017). In addition, many fungi are able to form tissues out of their filamentous cells, which generally act as support structures for the dissemination of propagative spores (Kües, Khonsuntia & Subba, 2018). The origin of this complex multicellularity presents many similarities with that of plants and animals, and many unique characteristics that we are only now starting to unravel (Niklas, 2014; Nagy, Kovács & Krizsán, 2018). In this section we discuss the evolutionary transition from a unicellular to mycelial form, the implications that a hyphal lifestyle has for fungal biology, and current knowledge regarding the development of complex multicellularity in the different lineages where this trait is found.

## (1) Unicellular fungi

Members of several fungal lineages have a mostly unicellular organization, a trait that can be both ancestral and derived within a group. Zoosporic lineages tend to exist as swimming individual cells with a saprotrophic or predatory–parasitic lifestyle. The swimming cell typically attaches to a substrate or host and produces feeding structures that range from amoeboid phagocytic protrusions in the Aphelidea (Gromov, 2000; Karpov *et al.*, 2014b; Letcher *et al.*, 2017) to polycentric rhizoids in many members of the Chytridiomycota (Powell & Letcher, 2014). Information regarding these groups is scarce, at least at the cellular, biochemical, ecological and phylogenetic levels. Environmental studies indicate that the described diversity in these lineages represents only a small fraction of the real diversity of the group (Lara, Moreira & López-García, 2010; Jones *et al.*, 2011; Rojas-Jimenez *et al.*, 2017; Tedersoo *et al.*, 2017; Karpov *et al.*, 2018). Several genomic studies have been conducted in these groups, but the lack of a solid phylogeny makes it difficult to obtain an accurate global picture. Despite their morphological simplicity, zoosporic lineages seem to have genome sizes and gene numbers comparable to or larger than filamentous fungi (Fig. 2). This seems to be valid for the Blastocladiomycota and Monoblepharidomycetes (Chytridiomycota), and for several species of Chytridiomycetes. The genomes of highly specialized anaerobes in the Neocallimastigomycotina are even larger, having genomes ranging from approximately 40 Mbp and 11000 genes (in *Piromyces sp*. E2) to almost 200 Mbp and 20200 genes (in *Neocallimastix californiae*). This genome size is rather high for fungi, and comparable to mushroom-forming Agaricomycotina (Fig. 2). Many other members of the zoosporic lineages, however, have small genomes and gene content. Several members of the Chytridiomycetes fall into this category. The Opisthosporidia (Aphelidea, Rozellidea and Microsporidia) (Karpov *et al.*, 2014a) are highly specialized parasites and show a high degree of genomic compaction. It is difficult to specify whether these differences in genome sizes within the zoosporic lineages result from reductions or expansions relative to their last common ancestor, as the only sequenced non-fungal member of Holomycota, *Fonticula alba*, has a genome size similar to that of zoosporic fungi with small genomes. These observations suggest that there is little correlation in Fungi between cellular complexity and genomic characteristics such as haploid genome size or the number of protein-coding genes. Some small-genome chytrids appear to be parasites, which might suggest that adaptation to a parasitic lifestyle has driven genome reduction relative to a saprotrophic ancestor with a larger genome.

In many fungal lineages, a unicellular lifestyle is a secondarily acquired trait, resulting from reduction or complete loss of the ability to form multicellular structures. Within Ascomycota, this reduction in complexity can be observed in several lineages of the Taphrinomycotina (Schizosaccharomycetes, Taphrinomycetes, Pneumocystidomycetes), and Pezizomycotina (black yeasts and related groups in the Eurotiomycetes and Dothideomycetes; symbiotic *Ophiocordyceps* in the Sordariomycetes and *Symbiotaphrina* within Xylonomycetes), and it represents a major evolutionary transition in Saccharomycotina. However, it must be noted that filamentous lineages within the Taphrinomycotina do not diverge much in terms of genome size or gene numbers from their yeast-forming relatives. Taphrinomycotina is the sister group to a clade comprising both the filamentous Pezizomycotina and the yeast-forming Saccharomycotina. Inferring the ancestral genomic characteristics of early Ascomycota is difficult, with the only trait that we can infer with certainty being their filamentous nature. Unicellular or mostly unicellular forms are very common across the Basidiomycota. In this group, it is generally acknowledged that thallus reduction has occurred in groups that are primarily biotrophic parasites (Begerow *et al.*, 2014; Wang *et al.*, 2015a,*b*; McLaughlin *et al.*, 2017; Oberwinkler, 2017). This lifestyle generally implies a high degree of genome compaction, reduction of many signalling and structural components, and loss of secondary metabolism pathways.

## (2) The hyphal cell as a living pipe

The basic cellular unit for most described fungi is the hypha, a walled cylindrical multinucleated cell that is highly polarized. Cell polarization is necessary for hyphal growth, although not all fungal polarized cells are hyphae (e.g. the yeast *Saccharomyces cerevisiae*). Polarized growth has been widely studied in *S. cerevisiae*, and a core of proteins have been

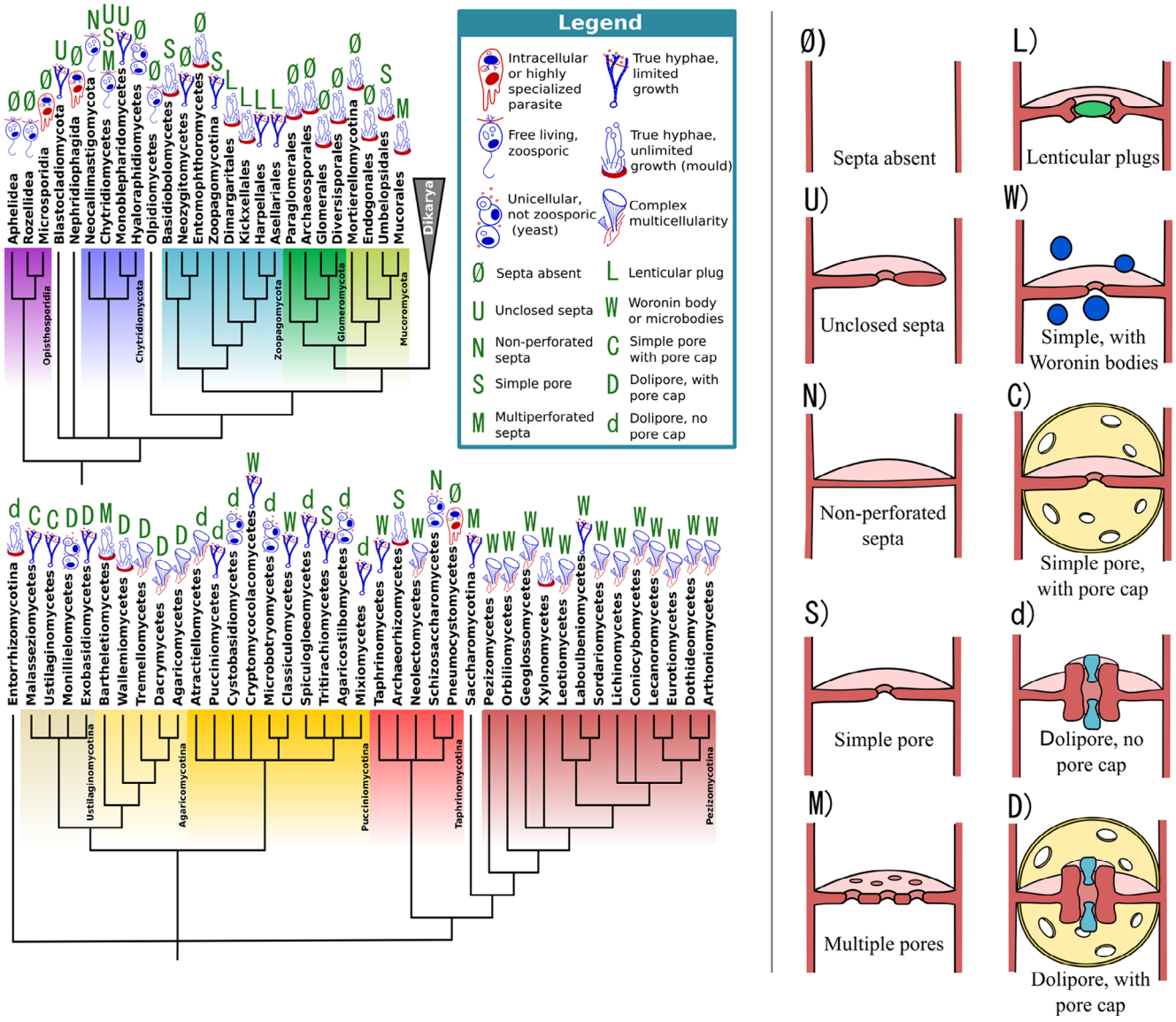


**Fig. 1.** Cellular complexity and septal pore structure across the kingdom Fungi. Phylogenetic tree showing the main fungal lineages and their evolutionary relationships. Each group is associated with an icon and one or more letters. Icons show the highest level of cellular complexity described within the group. Letters show the type of pore structures described within the group; these are illustrated on the right of the figure. Ø, several groups are not known to produce septa, including various zoosporic and parasitic groups, as well as certain zygomycetous lineages. N, non-perforated septa are rare in fungi, restricted mostly to the Neocallimastigomycotina, where they appear at the base of rhizoids. U, unclosed septa appear in certain groups of zoosporic fungi, either within true hyphae or as pores separating the main cellular body and the rhizoid. They typically present a central pore in addition to the unclosed septal division. S, simple septa with a main central pore. M, septation with multiple pores of variable size. L, lenticular plugs with variable morphology are a synapomorphic trait of the Kicxellomycotina. W, simple pores associated with small organelles that are able to block the pore. The most common form of this type of pore architecture is Woronin bodies of the Pezizomycotina, although other lineages have developed morphologically similar structures independently. C, d, D, most members of the Basidiomycota possess either dolipores and/or parenthesomes (also known as pore caps). Dolipores are barrel-like swellings of the septal wall that delimit a pore. The pore is often blocked by occlusive bodies. Parenthesomes are membranous structures derived from the endoplasmic reticulum that surround the septal pore. Their morphology and ultrastructure is highly variable and has been used as a taxonomic trait.

identified (Arkowitz & Bassilana, 2011; Riquelme, 2013; Martin & Arkowitz, 2014; Diepeveen *et al.*, 2018). This core toolkit seems to be relatively well conserved across all fungal lineages, although no individual component appears to be completely essential (Diepeveen *et al.*, 2018). Within the kingdom, true hyphal growth is an evolutionary novelty of the

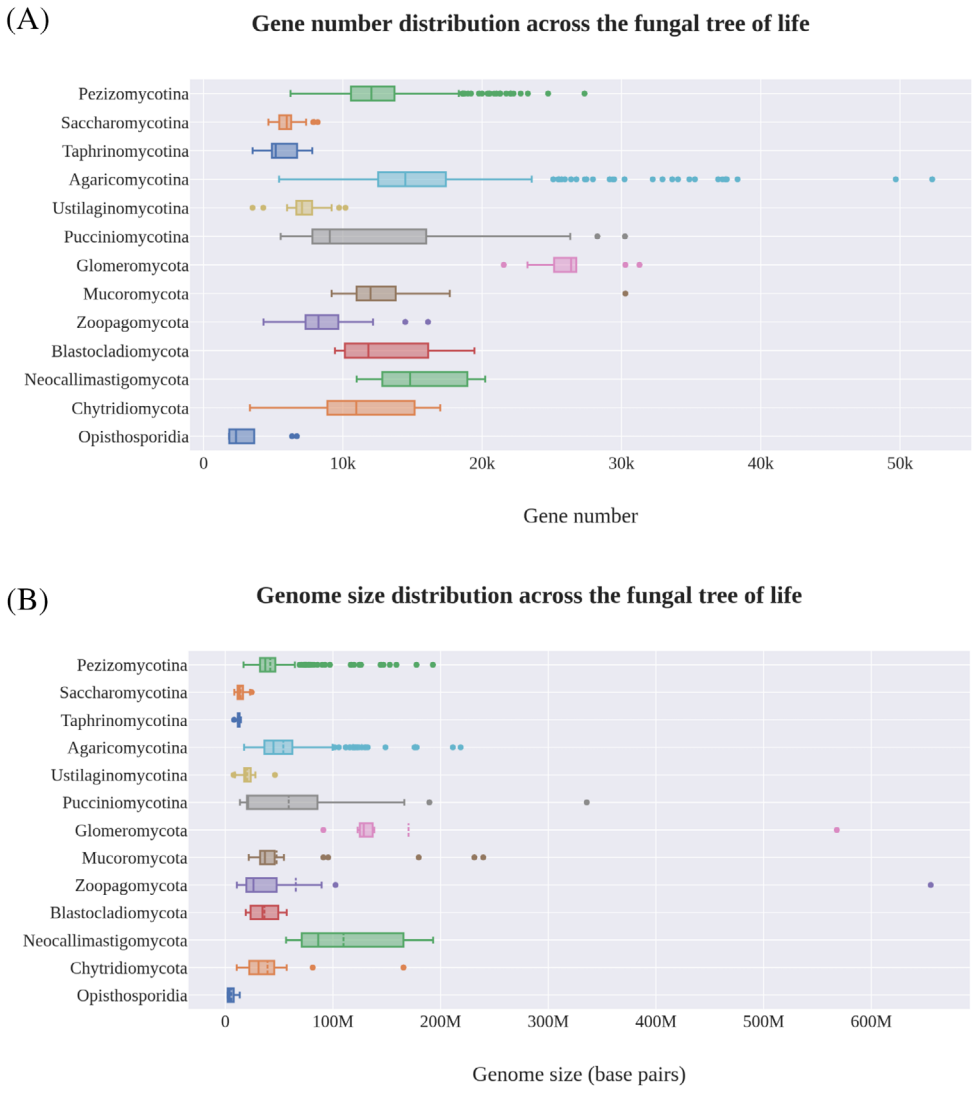


**Fig. 2.** Gene number and genome size across the fungal kingdom. (A) Distribution of the number of genes per genome across different lineages. (B) Distribution of genome size across different lineages. All numbers were obtained from Mycocosm, accessed in June 2019.

'terrestrial fungi', a monophyletic clade that includes the phyla Zoopagomycota, Mucoromycota, Glomeromycota, Ascomycota and Basidiomycota. True mycelial growth is also observed in some members of the Blastocladiomycota (e.g. *Allomyces*) (James *et al.*, 2014) and the Monoblepharidomycetes (e.g. *Gonapodya*) (Dee *et al.*, 2015). Due to controversies regarding the phylogenetic placement of Blastocladiomycota (Tanabe, Watanabe & Sugiyama, 2005; Sekimoto *et al.*, 2011; Ebersberger *et al.*, 2012; Tretter *et al.*, 2013; Ren *et al.*, 2016; Spatafora *et al.*, 2016), it is currently unknown whether the ability to form hyphae in this group has a shared evolutionary origin with the terrestrial fungi. By contrast, hyphal growth in Monoblepharidomycetes clearly has an independent origin (Dee *et al.*, 2015).

The hypha of most filamentous fungi is organized around an organelle called the Spitzenkörper (SPK) (Steinberg, 2007; Arkowitz & Bassilana, 2011; Riquelme & Sánchez-León, 2014; Lin *et al.*, 2014b; Takeshita, 2016; Steinberg *et al.*, 2017b; Riquelme *et al.*, 2018). The SPK is composed of a collection of vesicles originating in the Golgi apparatus that contain the enzymes, lipids and polysaccharides required for the synthesis of membranes and cell wall. Comparative studies have revealed the conservation of this molecular machinery across all Dikarya, regardless of whether they present hyphal growth or not, but information outside this group is very limited. For instance, most zygomycetous fungi present a less-organized aggregation of vesicles named the apical vesicle crescent (AVC) (Fisher & Roberson, 2016). This structure has been studied mostly using electron microscopy, and thus equivalence between SPK and AVC components at the molecular level is poorly known (Roberson *et al.*, 2011; Henk & Fisher, 2012; Fisher *et al.*, 2018). The SPK

seems to be present in *Basidiobolus* (Roberson *et al.*, 2011) and *Conidiobolus* (Fisher *et al.*, 2018), which are early-diverging lineages within the Entomophthoromycotina. Members of the Blastocladiomycota (e.g. *Allomyces*, *Blastocladiella*) present a morphologically recognizable SPK (Vargas, Aronson & Roberson, 1993; Srinivasan, Vargas & Roberson, 1996; McDaniel & Roberson, 1998; James *et al.*, 2014). The presence of the organelle in these lineages suggests that the last common ancestor of all terrestrial fungi could have had an SPK that was subsequently lost or modified into an AVC in the zygomycetous fungi, although it is currently impossible to rule out whether the SPK in these lineages arose independently.

Another widespread trait in filamentous fungi is the presence of septa, which are transversal modifications of the cell wall that allow the selective passage of cytoplasmic components between adjacent cells. At least in Pezizomycotina, septa-divided cells show a certain degree of biochemical and regulatory autonomy (Bleichrodt *et al.*, 2012; Steinberg *et al.*, 2017b; Tegelaar & Wösten, 2017), which is a prerequisite for complex multicellularity. Septal structure varies widely among groups (Fig. 1), ranging from incomplete pseudosepta in some Blastocladiomycota (Meyer & Fuller, 1985) to highly sophisticated membranous barriers in Agaricomycetes (Orlovich & Ashford, 1994; Muller *et al.*, 1998; van Driel *et al.*, 2009; McLaughlin *et al.*, 2015). The distribution and function of these structures within the mycelium is also highly variable, and many lineages within the zygomycetous fungi lack them or restrict their presence to specific structures or senescent hyphae (Benny, Humber & Voigt, 2014; Redecker & Schüβler, 2014). The formation of septa requires the activity of actin rings and chitin synthases (Harris, 2001; Rittenour, Si & Harris, 2009; Lin *et al.*, 2014b; Riquelme *et al.*, 2018). Most filamentous members of Dikarya possess seven genes encoding chitin synthases (Pacheco-Arjona & Ramirez-Prado, 2014). However, some plant-pathogenic fungi have expanded this repertoire, while yeasts tend to reduce it (Pacheco-Arjona & Ramirez-Prado, 2014). Outside Dikarya, however, the number and distribution of these enzymes is highly variable, with no recognizable pattern (Pacheco-Arjona & Ramirez-Prado, 2014). Septal barriers in their different forms have emerged independently in several lineages, deriving from different cellular components (peroxisome-derived Woronin bodies in Pezizomycotina, endoplasmic reticulum-derived dolipores in most Basidiomycota), although the ontology of these structures is not fully understood for some groups (Benny *et al.*, 2014; Redecker & Schüβler, 2014; Nguyen *et al.*, 2017). *Neolecta* is a genus of filamentous Taphrinomycotina that has septal pores that are morphologically similar and perhaps homologous to Woronin bodies (Landvik *et al.*, 2003; Healy *et al.*, 2013; Nguyen *et al.*, 2017). The Kickxellomycotina have sophisticated septal plugs of unclear ontogeny whose morphology varies among the different clades (Tretter *et al.*, 2014).

Fungi must grow in an expansive way to explore and exploit their territory, a complex task at which they are extremely proficient (Bebber *et al.*, 2007; Asenova *et al.*, 2016). To achieve this, simple cylindrical hyphae are not sufficient, both in terms of exploiting the available space and in growth speed (Simonin *et al.*, 2012; Fricker *et al.*, 2017). Instead, fungi grow by forming branching patterns by generating novel cylindrical hyphae from already established ones. Very little is known about the molecular intricacies of this process (Harris, 2008, 2011; Lin *et al.*, 2014b; Riquelme *et al.*, 2018). Establishment of a new branching hyphal tip seems to share many components with yeast budding (Harris, 2008, 2011), but there are considerable differences between the main tip and the branches that stem from it (Momany, 2002; Riquelme & Bartnicki-Garcia, 2004; Harris, 2011; Lin *et al.*, 2014b). Additionally, the establishment of a true network requires the ability to grow in a convergent pattern through hyphal tip fusion, or anastomosis. This process requires complex cell recognition mechanisms, preventing fusion between genetically dissimilar hyphae during vegetative growth (Saupe, 2000; Glass & Kaneko, 2003; Hall *et al.*, 2010; Ishikawa *et al.*, 2012; Zhang *et al.*, 2014; Fleißner & Herzog, 2016; Daskalov *et al.*, 2017). After fusion, the genetic compatibility of the newly formed heterokaryon is evaluated, resulting in programmed cell death if certain requirements are not met. In Pezizomycotina, this check point is based on the presence of highly polymorphic *het* loci, which have homologs in organisms as distant as Basidiomycota (Van der Nest *et al.*, 2014). A minimum of 24 different proteins are known to be involved in this process in *Neurospora*, including proteins involved in vesicular transport, membrane components, cell wall integrity, mitogen-activated protein kinase (MAPK) cascades and numerous transcription factors (Aldabbous *et al.*, 2010; Fu *et al.*, 2011; Jonkers *et al.*, 2014). However, while some of these components such as *het* appear to be conserved over long evolutionary distances, others are taxonomically restricted to Pezizomycotina (Riquelme *et al.*, 2011; Herzog, Schumann & Fleißner, 2015). Hyphal fusion is essential for fungal sex (Ni *et al.*, 2011; Teixeira *et al.*, 2017). In zygomycetous fungi, this fusion generates meiotically reduced zygospores, with the two original hyphae acting as *de facto* gametes (Benny *et al.*, 2014; Lee & Heitman, 2014; Lee & Idnurm, 2017). In Dikarya, fusion establishes dikaryotic hyphae that later will initiate meiotic recombination (Lee *et al.*, 2010; Ni *et al.*, 2011; Heitman, Sun & James, 2013). Homologs of mating (MAT) systems and meiotic machinery can also be found in the genomes of Microsporidia, Chytridiomycota, Blastocladiomycota and even Glomeromycota, for which sexual structures have never been observed (Lee *et al.*, 2010; Heitman *et al.*, 2013; Tang *et al.*, 2016).

### (3) The mycelium as a living network

Hyphae acquire a network organization once they reach a critical size, through generation of lateral branches and anastomoses. The structure of this network is typically highly dynamic, and responds to fluctuations in the environment or biotic interactions (Simonin *et al.*, 2012). The whole mycelium should be considered an independent organism that

presents global and local responses to stimuli. Fungi, like many other eukaryotes, undergo apoptosis and senescence (Hamann, Brust & Osiewacz, 2008; Sharon *et al.*, 2009; Shlezinger, Doron & Sharon, 2011; Shlezinger, Goldfinger & Sharon, 2012). Apoptosis helps the mycelium to dismantle and reuse components of network regions that are not useful, such as those that have already depleted the nutrients in their immediate surroundings (Hamann *et al.*, 2008; Sharon *et al.*, 2009; Shlezinger *et al.*, 2012). The fungal apoptotic machinery shows deep homology with that of metazoans, and thus it is safe to assume that this process also exists in non-Dikarya fungi (Sharon *et al.*, 2009; Shlezinger *et al.*, 2012).

Unlike plants, nutrient transport in filamentous fungi is performed entirely through cytoplasmic currents, which can also transport cellular components, including fresh nuclei for growing hyphal tips (Tlalka *et al.*, 2007; Fricker *et al.*, 2008, 2017; Lew, 2011; Simonin *et al.*, 2012). While transport in vascular plants has clear directionality (water and inorganic nutrients are absorbed in the roots and travel to the rest of the plant, while photosynthetic products flow in the opposite direction), fungi are able to create a more flexible flux. This allows fungi to allocate different limiting nutrients from distant sources across heterogeneous environments (Fricker *et al.*, 2008, 2017; Simonin *et al.*, 2012; Boberg *et al.*, 2014), akin to the movement of goods and people along roads (Bebber *et al.*, 2007). Movement of cytoplasmic components throughout the mycelial network is an active process, which uses cytoplasmic waves to transport over large distances (Tlalka *et al.*, 2007; Fricker *et al.*, 2008, 2017; Lew, 2011) and cytoskeleton-based movement for short-range movements or against the main cytoplasmic current (Fricker *et al.*, 2008; Lichius, Berepiki & Read, 2011; Takeshita, 2016). Septate fungi can exert an additional layer of control over the flux, as they can selectively block nodes of the network to limit the harm caused by injuries or to regulate the movement of cellular components (Palma-Guerrero *et al.*, 2008; Jedd & Pieuchot, 2012; Fricker *et al.*, 2017; Steinberg *et al.*, 2017a,*c*).

Like any multicellular organism, the mycelium must be able to sense a wide array of physical and chemical signals. Fungal sensory systems are functionally very similar to those found in plants. For instance, fungi are able to detect the ratio of different wavelengths of light to adjust to their surroundings, similar to phototropin-mediated signalling in plants (Fuller, Loros & Dunlap, 2015; Fischer *et al.*, 2016; Schumacher, 2017). In many fungi, light can affect expression of genes, including those involved in important processes such as reproduction, morphogenesis, virulence and metabolism (Corrochano & Garre, 2010; Kamada *et al.*, 2010; Idnurm, 2013; Fuller *et al.*, 2015; Fischer *et al.*, 2016; Schumacher, 2017; Adam *et al.*, 2018; Wang *et al.*, 2018). Fungi possess well-studied circadian clocks, too (Dunlap & Loros, 2004, 2006; Liu & Bell-Pedersen, 2006; Salichos & Rokas, 2010; Fuller *et al.*, 2015). Whether seasonal cycles exist in fungi remains unclear, but a combination of wavelength-ratio sensing and circadian clocks, both of which exist in fungi, are involved in such processes in plants (Searle & Coupland, 2004; Andrés & Coupland, 2012; Johansson & Staiger, 2015). Transcriptomic changes in response to light, including circadian cycles, are mediated in all studied fungi by white collar complex proteins (He *et al.*, 2002; Dunlap & Loros, 2004; Olmedo *et al.*, 2013; Fuller *et al.*, 2015; Fischer *et al.*, 2016). These are zinc-finger transcription factors that include chromophore-binding domains, similar to the non-homologous phototropins in plants. White collar proteins are found in all main lineages of the kingdom (Corrochano & Garre, 2010; Fuller *et al.*, 2015), while some yeast and specialized parasitic lineages have lost them secondarily. These are not the only light-sensitive proteins in fungi. Opsin-like proteins in fungi are involved in regulation of the sexual cycle and in pathogenesis in some species, including *Fusarium fujikuroi* (Hypocreales) (García-Martínez *et al.*, 2015; Adam *et al.*, 2018) and *Blastocladiella emersonii* (Blastocladiomycota) (Scheib *et al.*, 2015). Despite the ancient nature of this protein family, information about the biological roles of its members is still very fragmented.

Fungi are able to sense gravity and show, in some cases (e.g. aerial sporangia), strong gravitropism or gravity-based morphogenic patterns. Gravity perception in fungi has been studied extensively in *Phycomyces blakeensianus* (Mucorales), where it is mediated by a combination of statoliths made of oxalate crystals and buoyant lipid structures (Schimek *et al.*, 1999; Eibel *et al.*, 2000; Göttig & Galland, 2014). Gravitropism in *Phycomyces* is apparently mediated by a differential flux of $H^+$ and $Ca^{2+}$ in the mycelium (Živanović, 2005, 2012, 2013; Göttig & Galland, 2014). However, statoliths in this fungus seem to have originated from a recent bacterial gene transfer (Nguyen *et al.*, 2018). In the absence of crystalline structures in other lineages, it has been proposed that nuclei themselves might act as statolith-like structures in Agaricomycotina (Monzer, 1995, 1996; Moore *et al.*, 1996; Kern, Mendgen & Hock, 1997). However, biophysical data suggest that the density of the nuclei in Ascomycota might not be sufficient for them to function as statoliths (Grolig, Döring & Galland, 2006). Buoyancy systems have been identified in Ascomycota, Basidiomycota, Mucoromycotina, Mortierellomycotina and Glomeromycota (Grolig *et al.*, 2006) and the identified components seem to be well conserved across long evolutionary distances. Fungi are also able to detect electric fields and respond to them in a $Ca^{2+}$-dependent manner (Gow, 1984; Lever *et al.*, 1994). These responses are well described in both filamentous and zoosporic fungi, suggesting a considerable degree of evolutionary conservation, but unfortunately little is known about their molecular mechanisms.

Structural damage is another important factor to which fungal organisms must respond appropriately. At a local level, fungi respond to mycelial breakage by closing their septa to constrain cytoplasmic loss, a response which is often followed by the promotion of branching and sporulation (Maruyama, Escaño & Kitamoto, 2010; Hernández-Oñate *et al.*, 2012; Medina-Castellanos *et al.*, 2014, 2018). Injury is able to induce coordinated responses across the mycelium, such as increasing the production of toxic metabolic

compounds, as shown by arthropod grazing experiments (Rohlfs *et al.*, 2007; Yin *et al.*, 2012; Caballero Ortiz, Trienens & Rohlfs, 2013; Döll *et al.*, 2013; Rohlfs, 2014; Atriztán-Hernández *et al.*, 2018; Künzler, 2018). There are several injury-signalling pathways described in fungi. Reactive oxygen species (ROS) are one of the most important responses to any kind of damage in fungi (Hernández-Oñate *et al.*, 2012; Medina-Castellanos *et al.*, 2014, 2018; Hernández-Oñate & Herrera-Estrella, 2015). Not only do ROS induce responses in the fungus, but they are also used as a chemical weapon against invasive biological agents. ROS also play important roles in cell differentiation signalling, as discussed below (Section II.4). Extracellular ATP is another important injury-response molecule that acts through a $Ca^{2+}$-mediated cascade (Hernández-Oñate *et al.*, 2012; Medina-Castellanos *et al.*, 2014, 2018). ATP in the surrounding medium is rare, and thus the presence of this molecule can be used by the fungus as a signal of cytoplasm leakage. It is well established that the presence of cell wall components induces defence responses in plants, but such reactions in response to the enzymatic degradation of their own cell walls are not described in fungi. However, we consider that chitosans, partially deacetylated forms of chitin, are likely recognized by fungi as a signal of cell wall damage. Chitosan itself is known to have antifungal properties (Palma-Guerrero *et al.*, 2008, 2009; Lopez-Moya & Lopez-Llorca, 2016). However, fungi that are specialized mycoparasites, arthropod pathogens or nematophagous are virtually impervious to this compound. Due to their trophic lifestyle, these fungi possess high chitinolytic activities, and thus are unlikely to respond to the presence of chitin-derived products in the surrounding medium as if they were a signal of damage to their own cells. The fungus *Rhizopus* also has a high tolerance to chitosan (Lopez-Moya & Lopez-Llorca, 2016) and, as in other members of the Mucorales, possesses high concentrations of chitosan in its own cell walls (Battaglia *et al.*, 2011). Chitosan is not toxic to animals, indeed, in humans chitosan is marketed as weight-loss supplement (Saper, Eisenberg & Phillips, 2004; Mhurchu *et al.*, 2005), but it can elicit innate immune responses in both animals (Zaharoff *et al.*, 2007; Li *et al.*, 2013) and plants (Benhamou & Thériault, 1992; Sathiyabama, Akila & Charles, 2014; Malerba & Cerana, 2016). Thus, we propose that the antifungal activity of chitosan could result from over-activation of fungal defence mechanisms rather than inherent toxicity. Oxylipin signalling also plays an important role in damage responses in fungi (Brodhun & Feussner, 2011). Importantly, all of these signalling pathways are well conserved among fungi, plants and animals (Hernández-Oñate *et al.*, 2012; Hernández-Oñate & Herrera-Estrella, 2015). Finally, complex multicellular fungi have been shown to possess action potential-like electric signals that travel across large distances in response to direct damage (Adamatzky, 2018); a similar phenomenon is well studied in plants (Fromm & Lautner, 2007; Katicheva *et al.*, 2014; Vodeneev, Akinchits & Sukhov, 2015).

Besides responding to external stimuli, fungi can generate a wide array of extracellular chemicals that are used to coordinate mycelial behaviour. Oxylipins are a diverse class of molecules derived from poly-unsaturated fatty acids that play important signalling roles in virtually all eukaryotes, including animals (Andreou, Brodhun & Feussner, 2009), plants (Mosblech, Feussner & Heilmann, 2009; Wasternack & Feussner, 2018) and fungi (Brodhun & Feussner, 2011). However, we still have a very incomplete knowledge about the role of oxylipins in fungal biology. It is clear that these compounds regulate important processes, including morphological switches, secondary metabolism, pathogenesis, the sex cycle, and defence against grazing (Brodhun & Feussner, 2011; Kretschmer, Wang & Kronstad, 2012; Künzler, 2018). Additionally, parasitic fungi can synthesise oxylipins that exert biological activity in their hosts (Noverr, Erb-Downward & Huffnagle, 2003; Wilson *et al.*, 2004; Tsitsigiannis & Keller, 2007; Brodhun & Feussner, 2011; Christensen & Kolomiets, 2011; Fischer & Keller, 2016). Expansions in the genes encoding oxylipins have been proposed to be important developments in the ability of some fungal species to invade plant tissues (Tsitsigiannis & Keller, 2006, 2007; Gao *et al.*, 2011). Screening for conidiation-defective mutants in *Aspergillus* led to the discovery of regulatory polyketide synthetases (PKSs) and non-ribosomal peptide synthetases (NRPSs) (Lee & Adams, 1994, 1995; Lo *et al.*, 2012; Soid-Raggi *et al.*, 2016; Riquelme *et al.*, 2018). These regulatory secondary metabolites were subsequently described in other filamentous Ascomycota, such as *Fusarium fujikuroi* (Wiemann *et al.*, 2012; Riquelme *et al.*, 2018). Since these classes of compounds are known to possess a wide range of biological activities, the possibility that some fungi might have adapted their own regulatory extracellular metabolites to disrupt the biology of other fungi is intriguing, particularly in terms of the search for novel antimycotic agents. However, PKS and NRPS biosynthetic clusters are reduced or absent in some lineages, such as yeasts (Dujon, 2010, 2015) and certain biotrophic plant pathogens (Kämper *et al.*, 2006; Perlin *et al.*, 2015).

### (4) Complex multicellularity

The ability to form multicellular structures emerged independently in several lineages of eukaryotes. Complex multicellularity, which implies the coordination of different cell types to form tissues, has emerged in Metazoa, Streptophyta, Chlorophyta, Rhodophyta, Ochrophyta and Fungi (Niklas, 2014). Fungi are peculiar in this regard, as their complex multicellularity is almost always restricted to fruiting bodies, i.e. reproductive structures that are usually intermittent. In all cases, fruiting bodies are formed from dikaryotic mycelium, generating a vegetative hyphal tissue that protects fertile hyphae, where meioisis takes place. These structures are named ascomata in the Ascomycota (Pöggeler, Nowrousian & Kück, 2006; Engh & Nowrousian, 2010; Lord & Read, 2011; Kües *et al.*, 2018) and basidiomata in the Basidiomycota (Kües, 2000; Kües & Liu, 2000; Hibbett *et al.*, 2014; Kües & Navarro-González, 2015; Kües *et al.*, 2018). Even in fungi that produce fruiting bodies, these structures

are not indispensable for reproduction and dispersal, given the possibility to propagate asexually. Multicellular structures have evolved independently at least twice in fungi (Nguyen *et al.*, 2017; Kües *et al.*, 2018; Nagy *et al.*, 2018) and is only present in three lineages: Neolectomycetes, Pezizomycotina and Agaricomycetes.

The first and least well-known group to have developed complex multicellularity is the class Neolectomycetes (Taphrinomycotina) (Landvik *et al.*, 2003; Healy *et al.*, 2013; Kurtzman & Sugiyama, 2015). The Taphrinomycotina is an early-branching lineage of Ascomycota that is sister to the group formed by the Pezizomycotina (which tend to be filamentous and often possess complex fruiting bodies) plus the Saccharomycotina (which possess a highly reduced thallus). Genomic analysis of *Neolecta irregularis* shows a very reduced genome, comparable to other members of the Taphrinomycotina (Nguyen *et al.*, 2017). Despite having a yeast-like genome size and number of protein-coding genes, *Neolecta* form true, albeit simple, fruiting bodies (Landvik *et al.*, 2003; Healy *et al.*, 2013). *Neolecta* shares approximately 1000 genes with filamentous Pezizomycotina that are absent in yeast-like members of the Taphrinomycotina, with this set mostly enriched in genes relating to endomembrane systems (Nguyen *et al.*, 2017). Some studies have suggested that the fossil *Prototaxites* [420–370 million years ago (Mya)] (Hueber, 2001; Selosse, 2002) is affiliated to Neolectomycetes based on structural characters (Honegger *et al.*, 2018). Under that interpretation, *Prototaxites* represents fruiting bodies or vegetative thalli of an unspecified lineage within the Ascomycota, and is probably a member of the Taphrinomycotina. Thus, either modern members of Neolectomycetes are secondarily simplified, or the lineage leading to *Prototaxites* evolved considerably increased complexity.

Multicellular fruiting bodies are known in most classes within the Pezizomycotina (Liu & Hall, 2004; Schmitt, 2011), with the lack of correlation between morphological complexity and phylogeny suggesting they are an ancestral trait. Some of the most complex fruiting bodies within this subphylum belong to the Pezizomycetes, which are recovered as sister to the rest of the group or to the rest of the group minus Orbiliomycetes by most phylogenies (Liu & Hall, 2004; Spatafora *et al.*, 2006; Prieto *et al.*, 2013). It is unclear whether the molecular basis of multicellular fruiting bodies in Pezizomycotina is homologous to that of the complex structures in Neolectomycetes, but if so, this would imply a multicellular common ancestor for all Ascomycota. The basic fruiting body morphology in Pezizomycotina is a cup-like structure with asci oriented towards the concavity (apothecia). This basic body plan has become elaborated in many groups to form a bottle-like (perithecia) or completely closed (cleistothecia) architecture (Liu & Hall, 2004; Schoch *et al.*, 2009; Kües *et al.*, 2018). Cleistothecia often act as both protective and dissemination structures. It is important to note that sex or sexual structures have never been described for many Pezizomycotina, with the literature referring to these fungi as *fungi imperfecti* or Deuteromycetes. Genomic evidence of meiotic recombination suggests that sex does occur in these fungi, albeit under unknown circumstances (Lee *et al.*, 2010; Ni *et al.*, 2011; Heitman *et al.*, 2013). This was confirmed with the discovery of sexual cycles in *Penicillium* (Houbraken, Frisvad & Samson, 2010) and *Aspergillus* (O'Gorman, Fuller & Dyer, 2009; Swilaiman *et al.*, 2013), widely studied fungi that were thought to be asexual for more than a century. Ascomata size is highly variable, ranging from less than a millimeter to several centimeters (Schmitt, 2011; Kües *et al.*, 2018). The relationships between phylogeny and fruiting body morphology are poorly understood in Pezizomycotina, although it is generally acknowledged that closed ascomatas (Pezizomycetes and lichen-forming Lecanoromycetes) are derived forms (Liu & Hall, 2004; Schoch *et al.*, 2009; Schmitt, 2011). The genetics of fruiting body development have been well studied in several model species, allowing the identification of developmental mutants (Nowrousian *et al.*, 2007; Dirschnabel *et al.*, 2014; Teichert *et al.*, 2017; Trail *et al.*, 2017). Comparative transcriptomic analyses in the Sordariomycetes (Trail *et al.*, 2017) and Pezizomycetes (Murat *et al.*, 2018) suggest that the regulatory machinery of the fruiting body is well conserved, at least within these groups. Many questions remain regarding ascomata development in Pezizomycotina. Similarly to *Neolecta*, some ascomata-forming Pezizomycotina have gene numbers similar to those of yeast species. For instance, the Périgord truffle *Tuber melanosporum* possesses approximately 7500 protein-coding annotated genes (Martin *et al.*, 2010), not dissimilar to the approximately 6000 genes of *S. cerevisiae*. Lichen-forming fungi tend to produce a macroscopic thallus that includes their symbionts, often in an organized layered structure. This organization, in many cases resulting in a well-defined morphology, has been interpreted as complex multicellularity by some authors (Grube & Hawksworth, 2007; Sanders & de los Rios, 2012, 2017). Lichen genomics is still in its infancy, and to date there is no comprehensive study of developmental programs in lichen species. It is likely that lichen thalli will share regulatory pathways with the ascomata developmental program, a hypothesis that will undoubtedly be addressed in the near future.

Agaricomycotina is the other main group with complex multicellularity, and the one whose fruiting bodies (basidiomata or basidiocarp) are most familiar to humans (de Mattos-Shipley *et al.*, 2016). We can differentiate between two main fruiting body architectures (Hibbett, 2006; Millanes *et al.*, 2011; Shirouzu *et al.*, 2013; Hibbett *et al.*, 2014; Oberwinkler, 2014; Weiss *et al.*, 2014; Kües & Navarro-González, 2015). Gelatinous fruiting bodies are morphologically more simple and are found in several lineages (Tremellomycetes, Dacrymycetes, Cantharellales, Auriculariales), probably with independent origins. These fruiting bodies lack a true tissue organization and tend to form very simple amorphous structures. By contrast, the Holobasidiomycetes are a monophyletic group that includes most members of the Agaricomycetes and whose fruiting bodies have true tissues and often distinct morphologies. The tissue of the basidiocarp is formed by several different types of hyphae embedded in an extracellular matrix. These cell types differ

from vegetative assimilative hyphae in the thickness of their cell walls, the frequency of lateral branching, and the distribution of clamp connections, etc. (Manocha, 1965; Volz & Niederpruem, 1969; Kennedy & Larcade, 1971; States, 1975; Mol, Vermeulen & Wessels, 1990; Nakagiri & Ito, 1991). The proportion of these different hyphae varies between the stipe and the cap, and determines the mechanical properties of the basidioma. Different forms of organization are known in certain species, typically corresponding with morphologically distinct regions of the fruiting body. Virtually nothing is known regarding the molecular basis of this cell differentiation or if there are other cell types identifiable (e.g. by biochemical or immunological markers). Most descriptions of tissue organization in mushroom-forming fungi come from historical works that make use of often outdated and inconsistent terminology, greatly hindering comparisons among species. Comparative analyses show that fruiting body-forming Agaricomycetes have expanded sets of genes encoding kinases and several families of ubiquitin-signalling pathways, and have an increased frequency of alternative splicing (Krizsan *et al.*, 2019). Similar traits have evolved independently in multicellular metazoans and plants. There is evidence for a conserved developmental program in Agaricomycotina (Stajich *et al.*, 2010; Plaza *et al.*, 2014; Cheng *et al.*, 2015; Nowrousian, 2018), which emerged independently from that found in Ascomycota (Nguyen *et al.*, 2017; Nagy *et al.*, 2018; Kües *et al.*, 2018). Transcriptomic analyses in *Coprinopsis cinerea* suggest that gene expression in fruiting bodies follows a highly conservative pattern early in fruiting body development, compared with production of the vegetative mycelium or late basidioma (Cheng *et al.*, 2015). The development of the fruiting body shows wide differences in gene expression compared with the development of the vegetative mycelium, including overexpresion of many genes involved directly or indirectly in cell wall remodelling, DNA synthesis, ribosomes, lipid metabolism and hydrophobins (Ohm *et al.*, 2010b; Krizsan *et al.*, 2019). Environmental factors influence fruiting body development through cyclic AMP (cAMP), rat sarcoma (Ras) and MAPK cascades (Palmer & Horton, 2006; Nowrousian, 2018; Sakamoto, 2018). Additionally, some groups (e.g. the genus *Armillaria*) are able to form truly multicellular vegetative structures called rhizomorphs, which are thread-like aggregations of vegetative hyphae that allow the relocation of nutrients over very large distances (Motta, 1969; Agerer & Iosifidou, 2004; Morrison, 2004). Transcriptomic analyses of *Armillaria* rhizomorphs suggest an origin *via* redeployment of the fruiting body developmental program (Sipos *et al.*, 2017).

## III. GENOME COMPLEXITY

The main driver for the acquisition of morphological complexity in fungi is protection of the sexual structures and dissemination of spores. For Ascomycota and Basidiomycota, the dikaryotic stage involves several phenotypic traits that sets them apart from the monokaryon, although in a different way for each group. Sexual recombination in fungi is typically sporadic, and sexual stages have not been identified for many fungal lineages. The existence of sexual and parasexual cycles opens the possibility for recombinant lineages, including the formation of inter-species hybrids (Peter *et al.*, 2018). Hybridization is starting to be recognized as an important source of genetic diversity in fungal species. This has deep implications, particularly in the fields of fungal epidemiology and fungus–plant interactions (Stukenbrock, 2016; Möller & Stukenbrock, 2017; Feurtey & Stukenbrock, 2018; Giordano *et al.*, 2018). The typically clonal nature of many fungal populations imposes another type of challenge: if sex is uncommon in these fungi, how do they adapt to an ever-changing environment? While spontaneous mutations and horizontal gene transfer might provide a certain level of variability, none of these phenomena seem to be as prevalent in fungi as they are in prokaryotes. Mutations in particular need to become fixed in a population, which in many fungi would mean a whole mycelium. However, fungi seem to be able to tolerate high levels of chromosomal mutations such as polyploidies and aneuploidies, particularly under stressful conditions (Cogliati *et al.*, 2012; Li *et al.*, 2012; Bennett, Forche & Berman, 2014; Kravets *et al.*, 2014; Gerstein & Berman, 2015; Berman, Wertheimer & Stone, 2016; Todd, Forche & Selmecki, 2017). From a phenotypic point of view, impairment in regulatory networks caused by chromosomic aberrations has the potential to affect signalling pathways controlling morphological complexity. This gene dosage alteration also has the potential to induce changes in metabolism, which might in turn generate new phenotypes. Chromosomal aberrations emerge spontaneously and are reversible, and thus could help fungi to adapt to new conditions in a rapid and transitory way. It is important to note that sex and chromosomal aberrations are interconnected. Aberrations to chromosomes can potentially impair meiotic recombination, or by contrast might be responsible for the stabilization of highly divergent hybrid genomes (Aminnejad *et al.*, 2012; Forche, 2012; Morrow & Fraser, 2013). Genomics is starting to explore these processes, revealing new challenges and opportunities in this field. Figure 3 illustrates the different sources of genomic variability that can be identified within a single mycelium. In this section we discuss all these chromosome alterations, as well as their physiological and evolutionary relevance.

### (1) Hybridization

The use of *S. cerevisiae* as a research model in genetics and biochemistry led to the identification of their sexual cycle and of metabolic traits that could be used as makers for different lineages. This enabled the discovery that several *Saccharomyces* strains, classified as independent species, were in fact hybrids (Dujon, 2010; Borneman *et al.*, 2011; Morales & Dujon, 2012; Hittinger, 2013; Kumaran, Yang & Leu, 2013; Walther, Hesselbart & Wendland, 2014; Leducq *et al.*, 2016). Due to the difficulty of defining species boundaries

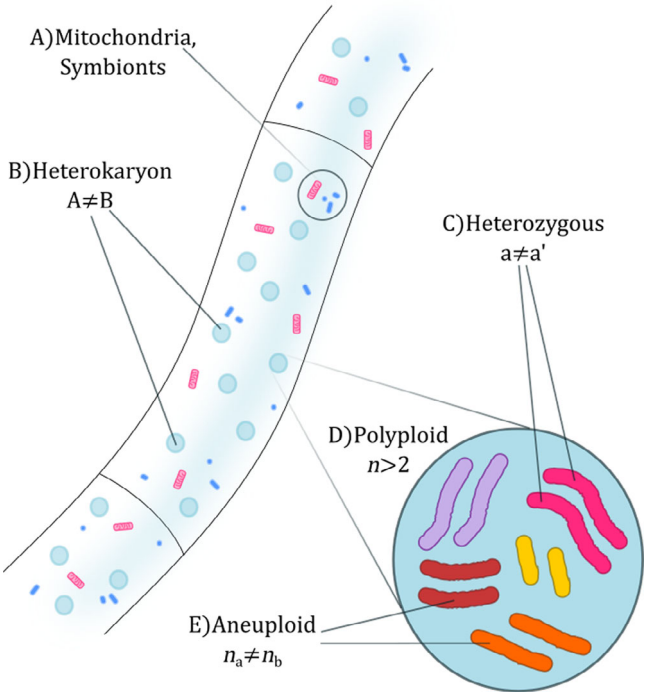


**Fig. 3.** Deviations from standard genome structure in fungi. A, Many fungi harbour symbiotic associations with bacteria or other eukaryotes whose DNA is sequenced alongside the fungal DNA. B, Filamentous fungi can possess populations of nuclei with sequence differences, a phenomenon known as heterokaryosis. C, Sequence differences between recombinant chromosomes are possible, known as heterozygosis. D, Most eukaryotes possess a number of chromosome copies equal to either one (haploid) or two (diploid). Copy numbers above two are known as polyploidies. E, Chromosome number might vary among chromosomes (aneuploidies). All these phenomena carry important biological consequences and might occur at the same time, making genome assembly and analyses more difficult.

in fungi, the definition of hybrids is similarly unclear. Here, we refer to hybrids as any fungal lineage that has emerged from mating between two lineages whose divergence exceeds that typically found across the most distant strains of well-recognized species (e.g. ~1% in *S. cerevisiae*; Peter *et al.*, 2018). The advent of genome sequencing led to a revolution in yeast research, and showed that the ability of *Saccharomyces* to hybridize was not exceptional within Saccharomycotina. Hybrid yeasts seem to be common in industrial environments and some of them are particularly relevant as fermenters in the food and beverage industry (James *et al.*, 2005; Hellborg & Piskur, 2009; Morales & Dujon, 2012; Walther *et al.*, 2014; Borneman *et al.*, 2014). Hybrid yeasts can also be found among clinical isolates; the *Candida parapsilosis* species complex is a particularly interesting example, with numerous described hybrid isolates that apparently possess higher pathogenic capabilities than their non-hybrid relatives (Pryszcz *et al.*, 2014, 2015; Gabaldón, Naranjo-Ortíz & Marcet-Houben, 2016; Mixão & Gabaldón, 2018). The inability to identify the parental strains for some hybrids might reflect the increased success of the hybrid in taking over the ecological niche of the parental strains (Pryszcz *et al.*, 2015; Depotter *et al.*, 2016). Hybridization is thus likely to be a powerful driver for adaptation to novel environments, including new hosts. However, it is important to note that we still know very little about the physiology of yeasts in natural environments, and while this hypothesis is indeed attractive, it is currently very difficult to demonstrate.

Hybridization outside Saccharomycotina has been described, although sampling in other groups is certainly not as extensive. The *Cryptococcus neoformans* species complex contains several hybrids between distantly related strains (Aminnejad *et al.*, 2012; Cogliati *et al.*, 2012; Li *et al.*, 2012). For the AD serotypes of this species complex, one of the parental species appears to be geographically restricted to certain areas in Africa, while the hybrid has spread all over the world, suggesting that hybridization provided the pathogen with a selective advantage (Cogliati *et al.*, 2012; Li *et al.*, 2012). Mating between *Cr. neoformans* and *Cr. gatti* is possible in laboratory conditions, producing a viable offspring that possesses a highly unstable genome (Aminnejad *et al.*, 2012). The hybrid rapidly loses and rearranges chromosomes in a manner similar to the parasexual cycle of *Candida albicans*, suggesting that hybridization could promote rapid adaptation by generating highly volatile genomic configurations (Aminnejad *et al.*, 2012; Forche, 2012; Morrow & Fraser, 2013). Population analysis in *Coccidioides* (Eurotiomycetes), another genus including human pathogens, detected recent hybridization (Neafsey *et al.*, 2010). Hybridization is common in the grass endophyte *Epichlöe/Neotyphodium* (Sordariomycetes) (Hamilton, Faeth & Dowling, 2009; Saari & Faeth, 2012; Shoji *et al.*, 2015), and it has been shown that some of these events enhance its ability to colonize grass under stressful conditions. Numerous examples of hybridizations, both *in vitro* and in natural populations, have been described for plant pathogens in the Basidiomycota and Ascomycota (Park & Wellings, 2012; Stukenbrock *et al.*, 2012; Sriswasdi *et al.*, 2016; Stukenbrock, 2016). In this regard, introduction of crops to new territories, global trade, and movement of people around the globe provide routes for new contacts between otherwise geographically isolated populations that may potentially favour the formation of novel hybrid strains that could become emergent pathogens (Gonthier *et al.*, 2004; Stukenbrock *et al.*, 2011; Stukenbrock, 2016; Möller & Stukenbrock, 2017; Mixão & Gabaldón, 2018).

## (2) Heterokaryosis

The number of nuclei in a fungal colony can easily be in the order of thousands (Roper *et al.*, 2012, 2013). Hence, the assumption that all nuclei are genotypically identical is likely to be an oversimplification. The coexistence of two or more genetically distinct nuclear populations within a syncytium is referred to as heterokaryosis. If the phenotypic characteristics of these different populations of nuclei are different, variations in their proportions could translate into phenotypic

variation in the whole colony. This was proposed and demonstrated on the basis of experiments using wild heterokaryotic *Penicillium* (Jinks, 1952; Strom & Bushley, 2016). As mentioned above, fungal mycellia can cover large areas while maintaining cytoplasm continuity (Sipos, Anderson & Nagy, 2018). Heterokaryosis would then affect local responses to stimuli within different areas of the same mycelium (Jany & Pawlowska, 2010; Roper *et al.*, 2012).

At least theoretically, heterokaryons are expected to be unstable (Hallatschek & Nelson, 2008; Roper *et al.*, 2012, 2013). If nuclear populations spread differentially based on their relative fitness and simple diffusion, then one of the populations eventually should be out-competed by the other or disappear due to stochastic effects, in a similar manner to alleles within a population. 'Nuclear death' in filamentous fungi has been described; nuclei from senescent mycelia enter apoptosis and their nutrients are recycled (Maheshwari, 2005). This implies that nuclei with low fitness will not simply become diluted within a population. Phenotypic heterogeneity in nuclei sharing the same cytoplasm can be better understood in terms of population dynamics. For example, under the right conditions, such as growth in supplemented media, mutant nuclei can out-compete the wild phenotype (Ryan & Lederberg, 1946; Maheshwari, 2005). On the other hand, nuclei carrying different mutations may complement each other, as shown for the carotenoid biosynthetic pathway in *Phycomyces* (De la Guardia *et al.*, 1971; Sanz *et al.*, 2002; Strom & Bushley, 2016). Mixed nuclear populations with distinct genetic backgrounds might, in theory, become stable under so-called Black Queen scenarios (Morris, 2015) (Fig. 4). In this scenario, in a simple community of two members (A and B), if A loses the ability to perform a certain essential task that can be fulfilled sufficiently by B, then B will be 'trapped' and unable to lose that function, as this would mean the collapse of the community. If the same happens for another essential function, but this time in B, A and B would be mutually dependent of each other for survival. This situation was artificially generated in a classic experiment with *Neurospora* (Beadle & Coonradt, 1944; Strom & Bushley, 2016). The population nature of the heterokaryon adds a new layer of phenotypic complexity without involving the development of complex regulatory mechanisms (Maheshwari, 2005; Roper *et al.*, 2012, 2013, 2015; Anderson *et al.*, 2013; Dundon *et al.*, 2016; Strom & Bushley, 2016) or increasing effective genome size, since each nucleus contains roughly the same genetic information. Experimental evidence in *Neurospora tetrasperma* suggests that, at least in this species, nuclear populations are kept at controlled proportions that vary during the life cycle of the fungus (Roper *et al.*, 2012, 2013, 2015; Johannesson & Samils, 2014). Despite the astounding growth speed of this mould, reaching >5 mm/h in optimal conditions (Ryan, Beadle & Tatum, 1943), and its asynchronous nuclear division, the heterokaryon is stable over long periods of time. It is important to note that nuclear division in *Neurospora* is not restricted to hyphal tips, and active cytoplasmic currents provide the growing tip with fresh nuclei generated throughout the colony (Maheshwari, 2005; Roper *et al.*, 2012, 2015). Cytoplasmic currents prevent stochastic extinction by actively mixing the cytoplasm of the whole colony (Roper *et al.*, 2013, 2015; Johannesson & Samils, 2014). In *Eremothecium*, however, nuclear migration is mediated by the cytoskeleton (Gladfelter, 2006; Anderson *et al.*, 2013; Dundon *et al.*, 2016; Gibeaux *et al.*, 2017). The ability to transport nuclei from distant regions in the network would provide a steady supply of nuclei, maintaining directed growth even if comparatively less-fit nuclei are present, as is likely to be the case to some degree in any nuclear population (Nobre *et al.*, 2014; Anderson *et al.*, 2015). It is important to mention here that, despite cytoplasm continuity, nuclei seem to control cytoplasmic territories with considerable autonomy, a situation also known as 'cells within cells' (Nair *et al.*, 2010; Roper *et al.*, 2012, 2013; Anderson *et al.*, 2013; Roberts & Gladfelter, 2015). Classic protoplasm fusion experiments force this autonomy to the point of allowing nuclei from even different fungal phyla to share a cytoplasm (Peberdy, 1979, 1989; Kavanagh & Whittaker, 1996; Strom & Bushley, 2016).

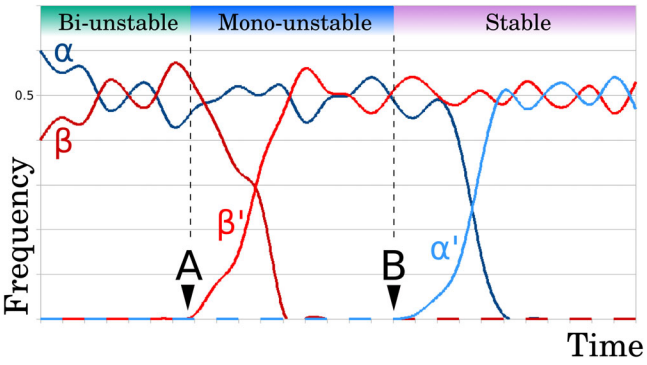


**Fig. 4.** Black Queen population dynamics. Assume a hypothetical population of two types of nuclei, α and β within a single cytoplasm. If the frequency at which each type of nucleus divides is the same, the population would become bi-unstable and would tend to collapse into a single type due to stochastic variation alone (drift). At point A in time a β mutant nucleus (β') appears that has a deletion in some key cellular function. Since both α and β can encode the mutated function, β' can survive. However, since β' presents the same characteristics as β, but makes savings in terms of the resources that were originally required for the function, β' would eventually out-compete β. Once β has disappeared from the population, α and β' reach a new unstable equilibrium. β' should divide faster than α, but β' it still needs α to maintain a minimum level of the mutated cellular function. The population at this stage is mono-unstable, as the only possible course is that drift drives β' extinct. At point B, a second cellular function deletion occurs within the α population (α'). Again, α' tends to out-compete α. However, since α' and β' present complementary mutations, the new population is stable. Once this stage has been achieved, the system can only evolve towards further complementary reduction of its pair of components or towards the generation of a new nuclear population that restores the mutated functions by recombination of α' and β'.

Filamentous fungi can fuse their hyphae during their normal sexual cycle, and formation of dikaryotic hyphae is a defining trait of Dikarya. If the fused hyphae are too divergent these mixtures might become trapped, unable to undergo meiosis. Fungi have genetic mechanisms to prevent such unions (Saupe, 2000; Glass & Kaneko, 2003; Micali & Smith, 2006; Ishikawa *et al.*, 2012; Van der Nest *et al.*, 2014; Daskalov *et al.*, 2017), although these barriers are not insurmountable. As mentioned above, compatibility is evaluated by check-point mechanisms that can induce apoptosis. Sporadically, however, this system could be overcome and inter-species heterokaryons may be formed. Furthermore, environmental factors, such as certain mycoviruses (Wu *et al.*, 2017), are able to lower the thresholds of these recognition systems. The presence of short haploid regions in an apparently diploid genome is suggestive of the existence of two non-recombining sub-genomes and is compatible with heterokaryosis. Additionaly, significant deviations in the expected 1:1 proportions for reference *versus* alternative alleles might be used to identify heterokaryotic genomes in some cases. Successive formation of heterokaryons might allow the fungus to 'update' its genome dynamically, fusing its cytoplasm with new individuals as conditions change (Beadle & Coonradt, 1944; Strom & Bushley, 2016). However this carries the risk of being invaded by a faster dividing nuclear population, as well as being exposed to viruses and other infectious elements (Saupe, 2000; Aanen *et al.*, 2008; Johannesson & Samils, 2014; Strom & Bushley, 2016). Even temporary, exotic unions might have long-lasting effects by promoting genome rearrangements and transfer of genetic material (Kinsey, 1990; James *et al.*, 2008; Van Der Does & Rep, 2012; Soanes & Richards, 2014). Heterokaryosis might emerge spontaneously without the need for mating or high heterozygosity, for instance through ploidy changes (Anderson *et al.*, 2015). This is the case for the filamentous saccharomycotine *Eremothecium gossypii* (syn. *Ashbya gossypii*), which possesses hyphae whose nuclei divide independently (Gladfelter, 2006; Nair *et al.*, 2010; Anderson *et al.*, 2013; Dundon *et al.*, 2016) and form populations with varying karyotypes. The proportion of nuclei carrying abnormal chromosome numbers varies under stressful conditions and with mycelial age (Fisher *et al.*, 2012). Under environmental conditions that positively select for chromosome aberrations, the presence of normal nuclei within the cytoplasm might help buffer any deleterious effects (Toledo-Hernández *et al.*, 2013). While most experimental work has been carried out in filamentous Ascomycota, the dikaryon phase in these organisms is usually short lived. In Basidiomycota, on the other hand, the dikaryon forms most of the vegetative thallus. In most cases, the fungus controls nuclear division tightly by forcing synchronization through clamp connections (Shepherd, Orlovich & Ashford, 1993; Iwasa, Tanabe & Kamada, 1998; Maheshwari, 2005; Raudaskoski & Kothe, 2010). Even so, nuclear competition and population dynamics have been described and studied in *Heterobasidion* (Garbelotto *et al.*, 2004; James *et al.*, 2008; James, Johansson & Johannesson, 2009; Garbelotto & Gonthier, 2013; Giordano *et al.*, 2018) and *Termitomyces* (Nobre *et al.*, 2014). Arbuscular mycorrhizal fungi also seem to show high levels of heterokaryosis in nature (Bever & Wang, 2005; Boon *et al.*, 2015; Wyss *et al.*, 2016; Mathieu *et al.*, 2018), forming nuclear populations that are mantained over time through the production of highly multinucleated spores (Bever & Wang, 2005; Jany & Pawlowska, 2010; Chagnon, 2014; Boon *et al.*, 2015). However, there are considerable discrepancies among studies and methods and in the amount of estimated divergence (Kuo *et al.*, 2014; Lin *et al.*, 2014a; Ropars & Corradi, 2015). In these fungi, nuclear populations vary depending on the nature of the fungal host, which might explain the apparent low specificity of mycorrhizae–plant interactions (Angelard *et al.*, 2014; Chagnon, 2014).

### (3) Aneuploidy

Aneuploidy is the presence of different ploidy levels within the same genome, usually affecting entire chromosomes or large chromosomal regions. Aneuploidies can emerge spontaneously within populations (Torres, Williams & Amon, 2008) and tend to have dramatic fitness effects due to imbalances in gene dosage and in the formation of multipolar meiotic and mitotic divisions (Torres *et al.*, 2008; Oromendia, Dodgson & Amon, 2012; Kumaran *et al.*, 2013; Bonney, Moriya & Amon, 2015; Dodgson *et al.*, 2016). However, under certain conditions aneuploidies might provide a selective advantage (Kravets *et al.*, 2014; Bennett *et al.*, 2014; Gerstein & Berman, 2015; Berman *et al.*, 2016; Todd *et al.*, 2017). For instance, in a medium containing a toxic compound, aneuploid cells that increase the dosage of genes related to detoxification could tolerate higher concentrations, thereby being fitter than their euploid counterparts. This has been observed in fungal pathogens acquiring resistance to antifungal drugs (Sionov *et al.*, 2010; Farrer *et al.*, 2013; Morrow & Fraser, 2013; Sun *et al.*, 2014; Harrison *et al.*, 2014; Anderson *et al.*, 2017; Ksiezopolska & Gabaldón, 2018). While the same phenotypic effect would be possible with tandem gene duplications, the frequency of these mutations is much lower. Aneuploidies can easily revert to a euploid state if the stressful condition is transitory. If not, mutations that reduce the deleterious effects of the altered ploidy state while keeping the advantageous phenotype will be selected. Thus, aneuploidies serve as transitory, intermediate states during the process of adaptation to novel conditions (Farrer *et al.*, 2013; Morrow & Fraser, 2013; Harrison *et al.*, 2014; Hirakawa *et al.*, 2015; Berman *et al.*, 2016; Anderson *et al.*, 2017). Finally, aneuploidies can result from unstable polyploidies. The best-studied example of this is the parasexual cycle of *C. albicans* (Saccharomycotina) (Whelan *et al.*, 1985; Forche *et al.*, 2008; Forche, 2012; Brown *et al.*, 2014; Hickman *et al.*, 2015). This process is not related to mating in filamentous fungi that leads to the formation of a heterokaryon, also known as the parasexual cycle (Pontecorvo, 1956; Daskalov *et al.*, 2017) (Fig. 5). In *C. albicans*, fusion of two diploid cells by non-meiotic mating results in an effective tetraploid state. The tetraploid is genomically unstable, and suffers concerted

chromosome loss that recovers stability. Thus, the parasexual cycle promotes aneuploidies and helps this pathogenic yeast to adapt to the host immune system, as well as to pharmacological treatments (Bennett *et al.*, 2014; Harrison *et al.*, 2014; Gerstein & Berman, 2015). A parasexual cycle in *C. albicans* has apparently evolved through loss of part of the meiotic recombinatory machinery, but aneuploidy might still be an important genome stabilizer in cases in which meiotic recombination is impaired, such as hybridization (see Section III.1). Aneuploid populations are also well known for other members of Saccharomycotina isolated from industrial environments, such as *Saccharomyces* (Borneman *et al.*, 2011; Walther *et al.*, 2014; Zhu, Sherlock & Petrov, 2016) and *Brettanomyces* (Hellborg & Piskur, 2009; Borneman *et al.*, 2014; Avramova *et al.*, 2018), as well as in the frog-killing chytrid *Batrachochytrium dendrobatidis* (Joneson *et al.*, 2011; Rosenblum *et al.*, 2013).

Over short evolutionary timescales, chromosome aberrations possess some other emergent ecological properties. Even in highly homogeneous environments, such as liquid laboratory cultures, small microniches that impose differential selective pressures might emerge (Rosenzweig *et al.*, 1994; Ibarra, Edwards & Palsson, 2002; Wortel *et al.*, 2016). If that is the case, two or more reversible chromosome states might coexist. Polyploidies might produce meiotic and mitotic impairments and involve higher nitrogen and phosphorus costs per cell division, which should slow growth under optimal conditions (Otto, 2007; Schoenfelder & Fox, 2015; Scott *et al.*, 2017). It is important to note that such conditions are met almost exclusively in laboratory settings. It is then reasonable to assume that putative polyploids or aneuploids that have been grown in axenic cultures for long periods could have streamlined their genome towards a haploid or diploid state that maximizes growth rate. Non-canonical chromosome conformations in environmental fungi might even prevent growth in experimental conditions, thus contributing to plate count anomalies (Staley & Konopka, 1985; Zak & Visser, 1996; Bridge & Spooner, 2001; Anderson & Cairney, 2004). This could explain why culture-based diagnostic methods of fungal infections are prone to negative results (Ostrosky-zeichner, 2012). Genome sequencing projects tend to focus on reference strains or on strains that a particular laboratory uses as a model. In both cases, it is very likely that these strains have been grown for years in non-limiting conditions. Even in cases in which an isolate with chromosome aberrations can be sequenced, this requires specialized experimental and computational approaches that are far from standard, involving expertise and increased costs. Polyploid strains, particularly allopolyploids, produce highly fragmented assemblies that often present an inflated assembly size, due to their high heterozygosity (Kajitani *et al.*, 2014; Safonova, Bankevich & Pevzner, 2015; Pryszcz & Gabaldón, 2016; Huang, Kang & Xu, 2017). The same holds for supernumerary chromosomes, which might pass unnoticed as a collection of highly fragmented scaffolds within an otherwise typical assembly. Because of this, many hybrids, polyploids and aneuploids might have been already sequenced but still not described (M. A. Naranjo-Ortiz, M. Molina-Marín, V. Mixào & T. Galbadón, in preparation).

### (4) Polyploidy

As in plants, fungi are able to undergo autopolyploidization, in which all chromosomes have the same genotype at the moment of duplication; or allopolyploidization, in which the chromosomes are genetically distinct (Otto, 2007; Albertin & Marullo, 2012; Todd *et al.*, 2017). Over longer timescales, these events provide plenty of opportunities for innovation through extensive gene duplication followed by subfunctionalization and neofunctionalization (Conant & Wolfe, 2008; Albertin & Marullo, 2012; Magadum *et al.*, 2013). However, autopolyploidization does not provide genotypic innovation in the short term, a necessity for fixing this mutation within a population. Despite the lack of genotypic novelty, autopolyploidy might still provide advantages. This process usually produces larger cells with a reduced surface area to volume ratio (Otto, 2007; Schoenfelder & Fox, 2015). This has implications for membrane transport, which in turn affects general metabolism. An increased size might be selectively advantageous against certain selective pressures, such as phagocytic predation. This seems to be the case for titan cells in *Cryptococcus*, which are polyploid vegetative cells resistant to attack by the vertebrate immune system, from which infectious diploid and aneuploid cells emerge (Okagaki & Nielsen, 2012; Gerstein *et al.*, 2015). Finally, a putative tetraploid state has been described for a widespread strain of the microsporidian *Nosema ceranae*, although the putative selective advantages in this case remain unclear (Pelin *et al.*, 2015).

Unlike in plants, for which many ancient polyploidization events have been identified, very few have been identified in fungi (Campbell *et al.*, 2016). There is evidence of an ancient allopolyploidization event that occurred 100 Mya in the Saccharomycetaceae (Saccharomycotina), affecting the common ancestor of the genera *Saccharomyces*, *Nakaseomyces*, *Kazachstania* and *Naumovozyma* (Wolfe & Shields, 1997; Hittinger, 2013; Marcet-Houben & Gabaldón, 2015). The order Mucorales (Mucoromycotina) seems to have experienced at least two well-characterized events of this kind, an ancient event affecting the ancestor of *Mucor* and *Phycomyces* (Corrochano *et al.*, 2016), and a more recent one within the genus *Rhizopus* (Ma *et al.*, 2009). The apparent scarcity of ancient polyploidization in fungi, compared with animals or plants, is at odds with their expected higher plasticity and is likely the result of greater difficulty in detecting them (Campbell *et al.*, 2016). Finally, an additional whole-genome duplication event has been described for the hyperhalotolerant black yeast *Hortaea werneckii* (Lenassi *et al.*, 2013; Sinha *et al.*, 2017). This event has contributed to the expansion of cationic transporters, important in surviving high salinity. The origin of this whole-genome duplication has been ascribed to an inter-species hybridization event (Gostinčar *et al.*, 2018). We are confident that many ancient

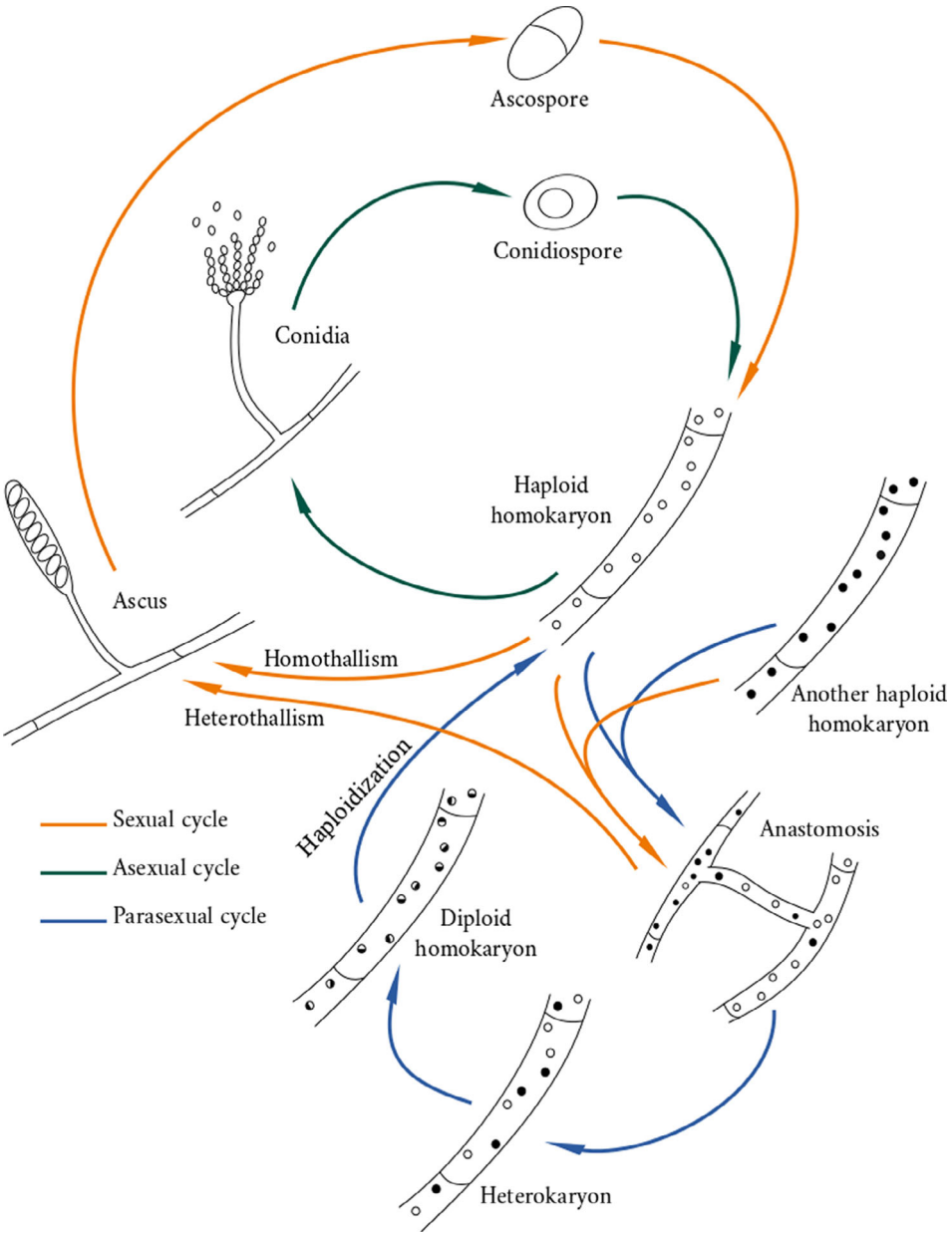


**Fig. 5.** Life cycle of a generic Pezizomycotina. In most cases the vegetative thallus is formed by a homokaryotic mycelium. Sexual cycle: a homokaryotic mycelium might transform into an ascoid mycelium, where nuclei undergo meiosis and form ascospores in asci. This change might occur after fusion with another compatible mycelium, producing recombination between two strains (heterothallism), or occur in the nuclear population within the mycelium without genetic exchange (homothallism). Asexual cycle: a vegetative mycelium can form conidia that produce conidiospores by simple mitosis. Parasexual cycle: two compatible vegetative mycelia might fuse through anastomosis, interchanging nuclei and forming an haploid heterokaryon. At some point, the different nuclei might fuse to form a diploid homokaryon that undergoes concerted chromosome loss to regain a haploid state in the absence of meiosis. This process returns the mycelium to a haploid homokaryon state.

whole-genome duplication events resulting from either auto- or allopolyploidization events, are yet to be identified and will be discovered once sufficient genome sampling is available for enough fungal clades. Very likely, some of these events will correlate with the emergence of important traits and ecological transitions within the group, just as has been observed for plants and metazoans. However, cytogenetic studies in fungi are much less prevalent than in plants and animals, and require more costly approaches such as pulse-field electrophoresis. In comparison with these groups, fungi tend to have shorter generation times and larger population sizes, higher ecological dependency on the speed their nuclei can complete meiosis, more active haploid estates and an absence of embryonic programs. All these traits translate into

much faster evolutionary rates, higher chromosome plasticity and higher selective pressures for a reduced genome, while having less freedom in this regard due to higher genome compaction. These methodological and biological factors make the detection of footprints of ancient polyploidies such as synteny, chromosome numbers or widespread and phylogenetically restricted gene duplication more difficult than in plants (Jiao *et al.*, 2011; Leitch & Leitch, 2012; Carretero-Paulet *et al.*, 2015; Del Pozo & Ramirez-Parra, 2015; Soltis *et al.*, 2015) and animals (Van de Peer, Taylor & Meyer, 2003; Van de Peer, 2004; Dehal & Boore, 2005; Kenny *et al.*, 2016; Schwager *et al.*, 2017; Li *et al.*, 2018).

## IV. METABOLIC COMPLEXITY

The last cornerstone defining the complexity of fungal life lies in the diversity of their metabolic pathways. This enzymatic diversity, coupled with their cellular versatility, gives fungi access to a vast array of substrates. Additionally, fungi are often able to synthesize bioactive compounds that play key roles in their interactions with the rest of the biosphere. One of the main physiological achievements of fungi is their ability finely to localize these biochemical pathways within their mycelial networks. An illustrative example concerns the appresoria of many parasitic fungi. The appresorium itself is a form of hypha, with a particular structure that enables it to exert pressure at a highly localized point. Many fungi complement this physical assault with hydrolytic enzymes that weaken the host cell walls to facilitate invasion. From an evolutionary perspective, new metabolic capabilities typically emerge by some form of gene duplication, followed by functional differentiation between the duplicates. In this regard, chromosomal aberrations and other genome architecture changes have a great impact on gene dosage and can lead to the stabilization of gene duplicates. Gene loss and duplication is a powerful way to increase metabolic diversity, but it is limited by the requirement for pre-existing genes. Acquisition of novel genes through horizontal gene transfer (HGT), often from distantly related genomes, could provide a source of immediate and radical novelty. In addition, novelty might emerge through the establishment of new regulatory networks, often through changes in the physical organization of the genome. Finally, recent studies focusing on intraspecific genomic variation offer a new perspective on the dynamic nature of fungal genomes, as genes are gained, lost and exchanged across partially isolated populations. In this section we will discuss the evolutionary processes that shape the biochemical dimensions of fungal biology with special emphasis on the origin, diversification and functional implications of their vast secondary metabolism.

### (1) Secondary metabolites in fungal biology

The filamentous nature of most fungi allows these organisms to explore and control a certain territory. This control requires some form of dissuasion, that in the case of fungi is achieved through limiting nutrient access to competitors and, more importantly, through the production of toxic secondary metabolites (Keller, 2015, 2018; Bills & Gloer, 2016). These toxins protect the fungus from invertebrate grazers (Caballero Ortiz *et al.*, 2013; Rohlfs, 2014), delimit exclusion areas for other competing mycelial networks (Boddy & Hiscox, 2016), and regulate the so-called 'mycosphere' (Boer *et al.*, 2005; Warmink & van Elsas, 2008; Boersma *et al.*, 2010; Nazir *et al.*, 2010; Haq *et al.*, 2014), i.e. the microbial populations associated with the hyphal surface and its immediate proximity. In parasitic fungi, secondary metabolites can be used to inflict direct damage to the host (necrotrophic strategies) (Arunachalam & Doohan, 2013), mitigate host immune responses (Williams *et al.*, 2011), induce changes in host tissues (Bömke & Tudzynski, 2009) or, in the case of animal parasites, induce behavioural changes (Boyce *et al.*, 2019). Not all secondary metabolites are toxins, however. Other known functions include cell signalling, pigmentation, osmotic protection or metal chelation (Bills & Gloer, 2016; Rokas, Wisecaver & Lind, 2018). Although the diversity of bioactive compounds synthesized by fungi is enormous, they ultimately fall into a few broad categories of enzymatic pathways (Zhong & Xiao, 2009; Keller, 2015; Bills & Gloer, 2016). The main groups of secondary metabolites are small nuclear-encoded peptides, non-ribosomal peptides (NRPs), polyketides (PKs), terpenoids and derivatives from the shikimate pathway (Bills & Gloer, 2016; Rokas *et al.*, 2018). Innovations in secondary metabolism might emerge by duplication and modification of existing pathways or by acquisition of novel enzymes. Secondary metabolites might confer important selective advantages to Fungi even when produced at very low concentrations, albeit only under certain conditions. On the other hand, production of these compounds usually implies an important investment in terms of energy and nutrient cost, not to mention the potential effects of the toxin itself on the producer fungus (Chanda *et al.*, 2009; Brakhage, 2013; Keller, 2018). Notably, most of these functions are dependent on responses to these compounds by other organisms, implying that their selective advantages might disappear if the target organisms respond differently. This has important consequences from the perspective of population genetics. Whenever the ability to synthesize a successful secondary metabolite appears in a genome, the associated selective advantage would drive the fixation of these genetic components in the population. Such evolutionary dynamics are ideal for the proliferation and establishment of rare evolutionary events, including HGT (Richards *et al.*, 2011; Wisecaver, Slot & Rokas, 2014; Wisecaver & Rokas, 2015). Analogously, if the conferred benefit is restricted to uncommon circumstances, it is very likely that the absence of selection will result in loss of the ability to produce the compound in some subpopulations (Spatafora & Bushley, 2015; Bills & Gloer, 2016; Rokas *et al.*, 2018). This volatility further complicates evolutionary studies, as it will lead to patchy distributions in signals that are commonly used to discern putative gene duplications and transfers (Wisecaver *et al.*, 2014).

### (2) Metabolic gene clusters

A peculiarity of fungal genomes is the tendency to group together genes that are functionally related, particularly those encoding enzymes from the same metabolic pathway. Clustering in non-metabolic genes has also been described and seems to be an important evolutionary process in many fungal lineages (Marcet-Houben & Gabaldón, 2019). There are clear differences regarding the evolutionary dynamics between metabolic and non-metabolic gene clusters (Marcet-Houben & Gabaldón, 2019), but most studies have focused on the former. Metabolic gene clusters exist in other eukaryotes, particularly in plants (Boycheva *et al.*, 2014; Nützmann, Huang & Osbourn, 2016), but not in the diversity and abundance found in fungal genomes. Some important pathways can be found clustered in most Fungi (Slot & Hibbett, 2007; Slot, 2017), while others appear clustered only in some species or strains (Inglis *et al.*, 2013; Slot, 2017; Rokas *et al.*, 2018). Secondary metabolism pathways require the coordinated action of a wide set of enzymes, which has been invoked to explain why these pathways appear clustered in fungal genomes (Bills & Gloer, 2016; Rokas *et al.*, 2018). However, some pathways that are clustered in fungi appear unclustered in other eukaryotes, suggesting that clustering itself carries an associated selective advantage in fungi (Wisecaver *et al.*, 2014; Slot, 2017; Rokas *et al.*, 2018; Marcet-Houben & Gabaldón, 2019). Metabolic gene clusters often include more than enzyme-encoding genes, and may involve other genes such as transporters or transcription factors. The presence of genes in the same cluster should facilitate coordinated expression of the different components, similarly to the situation for bacterial operons (Fischbach, Walsh & Clardy, 2008; Brakhage, 2013; Keller, 2018). Intermediate compounds in these pathways and many final products that will be exported extracellularly are often highly toxic, and coordinated expression might be necessary to avoid hazardous accumulation in the cytoplasm (Wisecaver *et al.*, 2014; Keller, 2015; Bills & Gloer, 2016; Slot, 2017; Rokas *et al.*, 2018). This same logic applies when considering events that might break the cluster apart. For instance, accumulation of toxic intermediates has been proposed to ensure cluster completeness during HGT events (Lawrence, 1999; Fischbach *et al.*, 2008; Wisecaver *et al.*, 2014; McGary, Slot & Rokas, 2013; Slot, 2017; Krause *et al.*, 2018). In addition, if the pathway genes are scattered across the genome, aneuploidies or chromosome loses could affect its components differentially, rendering the pathway unbalanced or incomplete. Horizontally transferred bacterial operons or polycistrons would necessarily appear tightly clustered (Lawrence, 1999; Fischbach *et al.*, 2008), although relatively few clusters seem to have this origin (Wisecaver *et al.*, 2014; Marcet-Houben & Gabaldón 2019). Importantly, many gene clusters contain genes that protect the fungus from the toxicity of the cluster products (Bills & Gloer, 2016; Slot, 2017; Rokas *et al.*, 2018). There are some cases in which more than one cluster is required for the synthesis of a particular compound, representing an exception to the otherwise general rule of 'one cluster, one secondary metabolite' (Lo *et al.*, 2012; Bills & Gloer, 2016).

Due to the aforementioned factors, tight regulation of cluster expression appears essential (Brakhage, 2013; Slot, 2017). Epigenetic mechanisms have emerged as key regulators of fungal secondary metabolism, a situation probably facilitated by the physical proximity of their components (Gacek & Strauss, 2012; Brakhage, 2013; Slot, 2017; Keller, 2018). Based on this, mutation or inhibition of chromatin signalling components are beginning to be used to induce the expression of cryptic metabolic clusters (Cichewicz, 2010; Brakhage & Schroeckh, 2011; Yin & Keller, 2011; Brakhage, 2013; Keller, 2018). Global regulators affect the expression of a wide array of clusters in response to external or internal stimuli in Pezizomycotina. The best-studied global regulators are transcription factors from the Velvet complex (Sarikaya Bayram *et al.*, 2010; Yin & Keller, 2011; Bayram & Braus, 2012; López-Berges *et al.*, 2013; Lan *et al.*, 2014; Schumacher *et al.*, 2015; Estiarte *et al.*, 2016; Akhberdi *et al.*, 2018). Velvet complex proteins are present across all groups of fungi, but their role in regulating secondary metabolism has barely been studied outside Pezizomycotina (Bayram & Braus, 2012; Todd *et al.*, 2014). Velvet complex is also important for sexual development in both Ascomycota and Basidiomycota. External factors include nutrient availability, light, pH or injury, while internal factors refer to specific cell types, senescence or the sexual cycle (Bok & Keller, 2004; Yin & Keller, 2011; Brakhage, 2013; Estiarte *et al.*, 2016; Keller, 2018). These regulators allow the fungus to coordinate the cost-effective production of secondary metabolites under specific conditions, and in a coordinated manner. Some of these regulators seem to be evolutionarily conserved across large phylogenetic distances, although functional differences might exist (Bok & Keller, 2004; Brakhage, 2013; Jain & Keller, 2013; Estiarte *et al.*, 2016). Similar regulators might exist outside Pezizomycotina that remain to be discovered. Additionally, to prevent the organism producing its whole arsenal at the same time, each cluster must respond differentially to many other regulatory elements (Brakhage, 2013; Bills & Gloer, 2016; Keller, 2018). Many clusters contain transcription factors that regulate their own expression (Brakhage, 2013; Bills & Gloer, 2016; Slot, 2017; Rokas *et al.*, 2018; Marcet-Houben & Gabaldón, 2019). This provides greater independence in terms of the complexity hypothesis (Jain, Rivera & Lake, 1999), and enhances the chances of successful HGT (Wisecaver & Rokas, 2015; Rokas *et al.*, 2018). It has been found that transcriptional factors included in a cluster can sometimes affect the expression of other clusters (Martín, 2017; Keller, 2018). Such cluster cross talk has important evolutionary implications, as the phenotypic effects of a recently acquired cluster are potentially far greater than the mere production of its metabolite. Fungal genomes reveal a much broader diversity of gene clusters than described secondary metabolites, indicating that many fungi encode clusters that are only expressed under unknown conditions (Chiang *et al.*, 2009; Brakhage, 2013; Gerhards *et al.*, 2015; Bills & Gloer, 2016; Keller, 2018). Some of these

clusters might even be inhibited by others (Brakhage, 2013; Keller, 2018), and thus deletion of known clusters could be an overlooked strategy for mining novel compounds (Gerke & Braus, 2014).

Quite often, clusters show conservation across different fungi. Such clusters show a set of genes that appear physically linked within a given chromosome region, but whose order is often highly variable. This phenomenon is known as mesosynteny and seems to be a peculiarity of genomes in the Pezizomycotina (Hane *et al.*, 2011). Many evolutionarily widespread gene clusters present patchy taxonomic distributions, which has sometimes been explained as being the result of HGT (Khaldi *et al.*, 2008; Marcet-Houben & Gabaldón, 2010; Slot & Rokas, 2011; Wisecaver *et al.*, 2014; Wisecaver & Rokas, 2015; Slot, 2017; Rokas *et al.*, 2018; Marcet-Houben & Gabaldón, 2019) or convergent evolution (Marcet-Houben & Gabaldón, 2019). Gene loss is likely common in gene clusters, which can explain patchy distribution patterns. Even different species of the same genus might contain radically different repertoires of metabolic clusters, as observed in *Penicillium* species (Malmstrøm, Christophersen & Frisvad, 2000; Marcet-Houben *et al.*, 2012; Julca *et al.*, 2016; de Vries *et al.*, 2017; Koul & Singh, 2017). A particular gene cluster might exist in a given species, but be absent in the analysed strain (Kelly & Ward, 2018; Plissonneau, Hartmann & Croll, 2018; Syme *et al.*, 2018; McCarthy & Fitzpatrick, 2019). Finally, the ability to produce particular metabolites might arise independently through convergent evolution. For instance, a recent study has found that cicada pathogens in the genus *Massospora* (Entomophthorales) are able to produce the psychotropic psilocybin, previously known only from 'magic mushrooms' in the Agaricomycetes (Boyce *et al.*, 2019). Inability to detect certain expected intermediate compounds suggests that *Massospora* have probably acquired the ability to synthesize psychotropic compounds through an independent pathway. The composite nature of gene clusters opens many evolutionary possibilities. Clusters might mutate, duplicate, divide into two, combine, or lose or gain new genes, occasionally through HGT (Fischbach *et al.*, 2008; Martín & Liras, 2016; Slot, 2017; Rokas *et al.*, 2018; Olarte *et al.*, 2019). Each of these possibilities is rife with methodological complications for evolutionary studies (Bull *et al.*, 1993; Castresana, 2007; Fischbach *et al.*, 2008). However, it is important to note that most clusters are *in silico* predictions, detected based on co-linearity. This clearly biases our knowledge against unclustered biosynthetic pathways, as those must be detected using more laborious techniques. Even worse, it is difficult to estimate how many of the predicted clusters are genuine. While this has not been evaluated in Fungi, analyses on plant metabolic clusters using patterns of transcriptional coexpression suggest that most of the predicted clusters are false positives (Wisecaver *et al.*, 2017).

Pezizomycotina are the best known group of fungi that produce secondary metabolites, and most of the information regarding the evolutionary dynamics of clusters, their regulatory expression and even their derived pharmacology comes from members of this clade. Free-living Pezizomycotina tend to possess a higher diversity of PKS and NRPS gene clusters (Rokas *et al.*, 2018). HGT seems to play a much more important role in the evolution of metabolic diversity in Pezizomycotina than in other fungi (Schmitt & Lumbsch, 2009; Fitzpatrick, 2012; Wisecaver *et al.*, 2014; Rokas *et al.*, 2018), and there is convincing evidence for a high frequency of cluster gene transfer among members of this subphylum (Wisecaver *et al.*, 2014; Bills & Gloer, 2016). Lichen-forming fungi produce an even greater diversity of compounds, with several classes not found in other filamentous Ascomycota (Boustie & Grube, 2005; Stocker-Wörgötter, 2008; Molnár & Farkas, 2010). One peculiarity of these organisms is that their secondary metabolites often accumulate in crystalline forms in extracellular spaces. However, due to the paucity of available lichen genomes (McDonald *et al.*, 2013; Meiser *et al.*, 2017) and the recent discovery of several groups of novel endolichenic organisms (Spribille *et al.*, 2016), assigning metabolic pathways to a particular mycobiont is not straightforward, and thus the full scope of cryptic secondary metabolism is much less understood than for non-lichenic fungi (Stocker-Wörgötter, 2008; Molnár & Farkas, 2010; Bills & Gloer, 2016).

Members of the Agaricomycotina are the other main group of secondary metabolite-producing fungi (Schüffler & Anke, 2009; Zhong & Xiao, 2009; Quin, Flynn & Schmidt-Dannert, 2014; Stadler & Hoffmeister, 2015; Lin *et al.*, 2019). HGT seems to be relatively rare among this group, and cluster gene duplication appears to be the main evolutionary force behind metabolic diversification (Wisecaver *et al.*, 2014). Agaricomycetes produce a relative abundance of alkaloid and terpenoid compounds and a reduced amount of NRPs, compared to Pezizomycotina (Brakhage, 2013; Bills & Gloer, 2016; Rokas *et al.*, 2018). The diversity of secondary metabolites in Agaricomycetes is not fully explored, mostly due to limitations on *de novo* gene prediction strategies that are optimized for the Pezizomycotina (Quin *et al.*, 2014), although thousands of compounds have been chemically identified from this group (Schüffler & Anke, 2009; Zhong & Xiao, 2009; Stadler & Hoffmeister, 2015). Information regarding genetic regulation of secondary metabolism in Agaricomycetes is very limited. Genomic analyses for *Ganoderma sinense* suggest that global regulatory proteins control secondary metabolism through epigenomic mechanisms, including Velvet complex proteins similar to those found in Pezizomycotina (Zhu *et al.*, 2015).

Gene cluster composition and evolutionary dynamics is markedly different in other fungal lineages. Within Ascomycota, the Saccharomycotina are notable for having lost virtually all their secondary metabolism arsenal. This reduction even affects the Velvet complex, whose components are completely absent in *S. cerevisiae* and *C. albicans*, but present in *Yarrowia lipolytica* (Bayram & Braus, 2012). This metabolic reduction is shared by other yeast-forming groups in the Taphrinomycotina and Basidiomycota mostly due to genome changes associated with their biotrophic lifestyles, although the complete loss of Velvet complex seems rare (Bayram & Braus, 2012).

Secondary metabolite production is poorly studied in zygomycetous and zoosporic lineages. Arbuscular mycorrhizae fungi in the Glomeromycotina are known to produce secondary metabolites (e.g. isoprenoids) that mediate communication with plant roots (Strack *et al.*, 2003). Little is known regarding the diversity, structure or regulation of these metabolic clusters, but genome sequencing suggests that these fungi have a reduced repertoire of secondary metabolic pathways compared to other zygomycetous lineages (Morin *et al.*, 2019), similar to biotrophic plant parasites in the Dikarya. Most members of the Mucoromycotina and Mortierellomycotina have a typical mould lifestyle (filamentous, saprotrophic, free-living) and as such they are capable of secreting secondary metabolites. However, the predicted metabolic diversity in these groups lags behind that of Pezizomycotina and Agaricomycotina (Lebreton *et al.*, 2018; Rokas *et al.*, 2018). For example, comparative analyses of five *Mucor* species revealed only one NRPS and one PKS gene cluster. Surprisingly, though, the genome of *Mortierella alpina* (Mortierellomycotina) contains an expansion of small secreted nuclear encoded peptides (defensines) (Wu, Gao & Zhu, 2014). Small peptides are very difficult to predict accurately by *de novo* gene prediction models and it is entirely possible that their diversity, particularly in zygomycetous fungi, has been largely overlooked. Many zygomycetous fungi exhibit associations with cytoplasmic bacteria with the ability to produce secondary metabolites (Partida-Martinez *et al.*, 2007). Little is known regarding the metabolic production of members of the Zoopagomycota or the zoosporic lineages. Alkaloid compounds have been described in several members of the Entomophthoromycotina, with different activities in their insect hosts (Claydon, 1978; Wrońska *et al.*, 2018; Boyce *et al.*, 2019). However, very little is known regarding the genomic organization of these pathways. Most analysed species (Zoopagomycotina, Kickxellomycotina, Blastocladiomycota and Chytridiomycota) present no more than one or two NRPS genes, although the mycoparasite *Dimargaris cristalligena* (Kickxellomycotina) is remarkable for possessing 27 of these genes (Ahrendt *et al.*, 2018). Most analysed species in this study show highly reduced thalli and a biotrophic lifestyle, which seems to be common in this group and could explain their reduced secondary metabolism. It is well known that secondary metabolism is highly compartmentalized in Pezizomycotina (Chanda *et al.*, 2009; Martín, Ullán & García-Estrada, 2010; Roze, Chanda & Linz, 2011; Kistler & Broz, 2015), which should help the fungus to limit self-toxicity. Thus, the absence of a septal apparatus in most zygomycetes might limit the development of their metabolic repertoire. It is noteworthy that *Dimargaris* belongs to the only zygomycetous group that shows well-developed septa. Zoosporic lineages seem to contain a secondary metabolism pool similar to that of zygomycetous fungi (Spatafora & Bushley, 2015) and Velvet complex proteins (Bayram & Braus, 2012), but very few details are known. Interestingly, methylation patterns in zygomycetous lineages and the Neocallimastigomycotina are unusual, as they show widespread gene activation mediated by adenine N6 methylation (Mondo *et al.*, 2017). This would suggest that global epigenetic regulators others than Velvet complex might be capable of regulating secondary metabolism in early-diverging fungi.

### (3) Genes on the move: horizontal gene transfer in Fungi

After the publication of the first drafts of the human genome, the field of HGT in eukaryotes entered its 'Dark Age'. The human genome paper included the claim that more than 200 genes were putatively acquired from bacteria *via* HGT (Lander *et al.*, 2001). However, this finding was later rejected as an artefact resulting from insufficient sampling in the genomic comparisons (Stanhope *et al.*, 2001; Salzberg, 2017). This led to a decade in which HGT detection in eukaryotic genomes was faced with severe skepticism, with most genome studies not even exploring that possibility. Yet, evidence began to accumulate supporting a not-uncommon occurrence of HGT in some eukaryotic lineages, including fungi. The detection of HGT events usually requires finding incongruences between a gene phylogeny and the known species tree (Galtier & Daubin, 2008; Leigh *et al.*, 2011; Grant & Katz, 2014; Wisecaver & Hackett, 2014; Katz, 2015; Nguyen *et al.*, 2015; Soucy, Huang & Gogarten, 2015; Szöllősi *et al.*, 2015; Naranjo-Ortíz *et al.*, 2016; Wisecaver *et al.*, 2016; Dupont & Cox, 2017). This requirement has been traditionally difficult to meet for most eukaryotic lineages, since genomic studies have long been focused on just a few economically important species, limiting taxonomic coverage. However, fungi were an early exception to this. With a taxonomically robust backbone of sequenced genomes and DNA generally coming from axenic cultures, HGT claims in Fungi are relatively robust. Once it became possible to search for HGT in a wide taxonomic range of Fungi, it was revealed that these evolutionary phenomena affect Pezizomycotina preferentially (Marcet-Houben & Gabaldón, 2010; Wisecaver *et al.*, 2014; Gluck-Thaler *et al.*, 2015), at least compared with Saccharomycotina and Basidiomycota. Furthermore, in some cases, HGT has been shown to have been key in the appearance of important adaptations, as shown in Neocallimastigomycotina and its outstanding carbohydrate-degrading enzymatic pool (Garcia-Vallvé, Romeu & Palau, 2000; Rosewich & Kistler, 2000; Murphy *et al.*, 2019).

Despite the increasing evidence for HGT in Fungi, a key question remains unsolved. The exact mechanism that allows transference and integration of external genetic material into the genome of a fungus is not understood (Andersson, 2005, 2009; Richards *et al.*, 2006, 2011; Soanes & Richards, 2014; Husnik & McCutcheon, 2017). Fungal cells are surrounded by a thick cell wall and do not have phagotrophic capabilities, thus ingested microbes cannot be a source of HGT, as posited by the 'you are what you eat' hypothesis (Doolittle, 1998). However, reports of *in vitro* recombination between bacteria and yeasts have been published (Heinemann & Sprague, 1989, 1991; Inomata, Nishikawa & Yoshida, 1994; Sawasaki, Inomata & Yoshida, 1996; Moriguchi

*et al.*, 2013; Suzuki, Moriguchi & Yamamoto, 2015). *Agrobacterium*-like bacteria can be used to transform filamentous fungi in the laboratory, suggesting that a similar process could mediate HGT in nature (Lacroix *et al.*, 2006; Jiang *et al.*, 2013; Lacroix & Citovsky, 2016). HGT can span long portions of a chromosome, or even whole chromosomes, which allows the transfer of groups of genes that are clustered together. Some of these genetic elements might have evolved for mobility, acting as transferable cassettes of functionally linked genes. Such is the case for mobile chromosomes in certain plant pathogens, such as *Fusarium* and *Zymoseptoria* (Akagi *et al.*, 2009; Coleman *et al.*, 2009; Mehrabi *et al.*, 2011; Van Der Does & Rep, 2012; Vlaardingerbroek *et al.*, 2016; Mehrabi, Mirzadi Gohari & Kema, 2017). These regions contain many genes related to host-specific pathogenicity, and their acquisition allows non-pathogenic strains to be infective in a new host. While the mechanisms of these genetic exchanges are not fully understood, we are starting to have a better picture of what type of genes are transferred. The 'complexity hypothesis' (Jain *et al.*, 1999) describes the gene content of an organism in terms of network connectivity and posits that new members can be more easily added to the boundaries of existing networks. This implies that simple transporters, simple enzymatic pathways or secondary metabolism genes are more likely to be transferred than highly interconnected proteins in the network. Indeed, some types of enzymes, such as amino acid racemases seem particularly prone to HGT in fungi and other microbial eukaryotes, although their physiological role in the receiving organisms remains to be clarified (Marcet-Houben & Gabaldón, 2010; Naranjo-Ortíz *et al.*, 2016). At the other extreme, genes related to information processing, such as translation or transcription, are among the most recalcitrant genes in terms of HGT. Comparative genomic studies support the paradigm of the complexity hypothesis (Marcet-Houben & Gabaldón, 2010; Wisecaver *et al.*, 2014; Wisecaver & Rokas, 2015).

Given the difficulties in detecting HGT, it is likely that a fair portion of HGT events are simply not detected. In general, it is far easier to detect an event if the resulting phylogenetic incongruence is large, such as that caused by interdomain transfers (Galtier & Daubin, 2008; Marcet-Houben & Gabaldón, 2010; Leigh *et al.*, 2011; Haegeman *et al.*, 2014; Naranjo-Ortíz *et al.*, 2016). In the hypothetical scenario of HGT between relatively closely related species (for instance, members of the same family), alternative hypotheses such as differential gene loss or incomplete lineage sorting cannot be ruled out easily. In addition, ancient HGT events might have an untraceable phylogenetic signal, perhaps to be expected given that transferred genes may undergo periods of rapid accumulation of changes to accommodate to their new environments, or that databases might lack adequate representation of the donor group. HGT might occur several times independently for the same gene, either through sequential transfers or by independent transfers from a phylogenetically close donor. These routes would create complex phylogenetic patterns that could prove difficult to interpret. In addition, some protein families evolve in ways that result in intricate molecular phylogenies that are difficult to resolve. For example, NRPSs are modular multidomain enzymes that can evolve by losing, duplicating or shuffling functional domains, rather than simply by point mutations (Weber & Marahiel, 2001; Marahiel, 2009; Hur, Vickery & Burkart, 2012). Many protein families display extremely low sequence conservation, which makes the reconstruction of accurate molecular phylogenies difficult, even over small evolutionary distances (Ponting, 2017). This is true for secreted peptidases in Fungi (Poppe *et al.*, 2015; Krishnan *et al.*, 2018). Both NRPSs and peptidases are well-known virulence factors in many fungi or have roles relevant to certain niches, are compatible with the complexity hypothesis, and have a huge diversity in filamentous fungi, making them prime candidates for HGT events.

HGT can play important roles in the adaptation of species to novel niches or lifestyles, and has been shown to be involved in short-term evolutionary transitions. For example, the acquisition of a toxin-encoding gene by *Pyrenophora tritici-repentis* from *Stagonospora nodorum* turned a fungus causing occasional spots in wheat leaves into a devastating pest in a matter of decades (Friesen *et al.*, 2006; Oliver & Solomon, 2008). HGT between plant pathogens seems to be fairly widespread and, in certain cases, patterns of repeated HGT between the same groups have been reported (Khaldi *et al.*, 2008; Armijos-Jaramillo, Sukno & Thon, 2014; Bettini *et al.*, 2014; Gluck-Thaler *et al.*, 2015; Qiu *et al.*, 2016; Yin *et al.*, 2016). HGT has been involved in drastic shifts in lifestyle, such as the acquisition of an entomopathogenic habit from a grass endophyte lifestyle in the genus *Metarrhizium* (Zhang *et al.*, 2019). This mounting evidence suggests that HGT is an important factor promoting the rise of novel plant pathogens. Another example of recent acquisition of novel genes with functional implications concerns fungi involved in beverage and food-production environments. Wine strains of *S. cerevisiae* contain genes that are not present in beer strains and are probably related to adaptation to their particular industrial environment (Novo *et al.*, 2009; Galeote *et al.*, 2010; Borneman *et al.*, 2011). Similarly, several *Penicillium* species growing on cheese have been shown to contain recently acquired genes that are adaptive in this particular environment (Ropars *et al.*, 2015). These examples highlight the power of HGT in enabling microbial adaptation to novel niches, including those related to domestication.

While ancient events are difficult to detect, there is clear evidence that some fungal groups have been affected by HGT over long evolutionary timescales. Many yeasts in the Saccharomycotina possess a horizontally transferred cytoplasmic dihydroorotate dehydrogenase that allows for the biosynthesis of pyrimidines in anoxic conditions (Gojkovic *et al.*, 2004). HGT of high-affinity nitrate transporters from Oomycota has been proposed to be an important feature for the land hegemony of Dikarya (Slot & Hibbett, 2007). A large fraction of the polyketide synthase genes in Lecanoromycetes seem to arise from Actinobacteria, followed by gene expansions (Schmitt & Lumbsch, 2009). Some of these genes are involved in the synthesis of ecologically relevant

secondary metabolites such as mycotoxins or antibiotics. Terpenoids and alkaloids are also widespread families of secondary metabolites whose biosynthetic pathways have dispered across the fungal kingdom through HGT (Marcet-Houben & Gabaldón, 2016; Reynolds *et al.*, 2018; Jia *et al.*, 2019). However, some studies suggest that these may be exceptional findings, and that, overall, HGT events in eukaryotes are evolutionarily short lived (Katz, 2015). Many such events might remain undetected, either because of the lack of a sufficient phylogenetic signal or because they have been lost in the sampled extant lineages, but it is safe to assume that HGT was as important in past evolutionary transitions as it apparently is for short-term adaptations in recent times.

### (4) From genomes to pangenomes

The concept of pangenome arises from the realization that gene content differs among strains or isolates within a defined taxonomic unit, usually a species (Tetz, 2005). The pangenome refers to the complete gene pool of a single species, including copy number variations, horizontally acquired genes and mobile genetic elements, such as plasmids. For example, the different strains of *Escherichia coli* have genomes typically containing 3500–4000 protein-coding genes, but with more than 2000 sequenced strains, the known pangenome of the species contains over 18000 genes (Jang *et al.*, 2017). The pangenome can be divided into two distinct subsets: the core genome refers to the set of genes that are universally present in all analysed genomes of a given species, while the variable (also known as accessory or flexible) genome comprises genes which may be absent or present, depending on the analysed strain. Obviously, the composition of the pangenome and the core and accessory subsets depends on the number of analysed strains. Similar to HGT, this concept has been widely studied in Bacteria, while its impact is less recognized in eukaryotes. However, the concept can be applied to eukaryotes, including plants (Springer *et al.*, 2009; Golicz, Batley & Edwards, 2016a; Golicz *et al.*, 2016b), animals (Gerdol *et al.*, 2019) and fungi.

Pangenome studies require the sequencing and comparison of multiple strains of the same species, and no other fungus has been studied in more detail than *S. cerevisiae* (Engel & Cherry, 2013; Strope *et al.*, 2015; Gallone *et al.*, 2016; Legras *et al.*, 2018). Compared with other Fungi, particularly with moulds, the secretome and secondary metabolism of yeast is very limited. Even so, a significant number of genes are not fixed in the global yeast population. Comparative analyses of 100 strains characterized the patterns of presence/absence of several genes associated with highly variable phenotypic traits, such as resistance to copper, sulfite or cycloheximide (Strope *et al.*, 2015). Some of these genes seem to have been acquired by introgression from other *Saccharomyces* species, mainly *S. paradoxus*, and quite often show copy number variation across isolates. A recent comparative analysis of over 1000 *S. cerevisiae* strains from diverse environments provided a reliable pangenome estimate of almost 7800 genes, of which approximately 4940 are core and 2860 are accessory (Peter *et al.*, 2018). Accessory genes tend to be concentrated in subtelomeric regions, and are enriched in functions related to cell–cell interactions, secondary metabolism and stress responses. Furthermore, these genes have a higher tendency to show copy number variation and hemizygosity. Wine yeasts have a high tendency to form hybrids, and some HGT associated with adaptations to this niche have been described (Galeote *et al.*, 2010; Borneman *et al.*, 2011; Marsit *et al.*, 2015; Legras *et al.*, 2018). The same can be said for the sake strain K7. This strain is very similar to the reference S288c except for the presence of certain subtelomeric regions that include up to 48 open reading frames (ORFs) that are absent in the reference; 49 ORFs that are found in the reference are absent in K7 (Akao *et al.*, 2011). Sequencing of the laboratory strain CEN.PK113-7D revealed the absence of 83 genes that are present in S288c, and a small number of genes that appeared only in CEN.PK113-7D (Nijkamp *et al.*, 2012). Among the latter was the surprising finding of a functional biotin biosynthetic pathway (Nijkamp *et al.*, 2012). All these studies illustrate that *S. cerevisiae* has a relatively small pangenome that, nonetheless, has a profound effect in shaping the phenotypic diversity of this species. It should be noted that most of these studies treat yeast hybridization as an anomaly, when instead we should consider the scope of yeast hybrid diversity as part of its total genetic pool. *S. cerevisiae* has some peculiar feaures compared to other yeast species, particularly regarding the frequency of sexual mating (Zeyl, 2009; Ni *et al.*, 2011; Hittinger, 2013; Dujon & Louis, 2017), which probably makes it a poor model for Saccharomycotina as a whole with regard to pangenome dynamics.

Pangenomes have been studied for a handful of filamentous Ascomycota. *Beauveria bassiana* is an entomopathogenic member of Hypocreales (Sordariomycetes) with a wide host range. Valero-Jiménez *et al.* (2016) compared five isolates with varying virulence phenotypes against mosquitoes. For *B. bassiana*, the core genome comprised around 7300 genes, with the pangenome size estimated at around 13000 genes. In the most virulent strain, 163 genes were strain specific, mostly containing secondary metabolic clusters located near telomeric regions. It is noteworthy that some of these strain-specific genes show homology to other entomopathogenic Hypocreales or bacteria, suggesting an HGT origin. *Aspergillus* and *Penicillium* are two widely studied genera of Eurotiales (Eurotiomycetes) that produce a broad diversity of secondary metabolites and exhibit a wide range of genome and proteome sizes (de Vries *et al.*, 2017; Nielsen *et al.*, 2017). Several comparative genomics studies have shown that each strain carries a significant number of specific genes (Ropars *et al.*, 2015; Julca *et al.*, 2016; Gilbert *et al.*, 2018). Pangenomic studies are of great relevance to understanding the emergence of virulent traits in plant pathogens. In this regard, accessory chromosomes in *Fusarium* spp. and *Zymoseptoria tritici* are a well-known part of their pangenome. *Fusarium* in particular possesses a mitochondrial pangenome (Brankovics *et al.*, 2018), with evidence of mitochondrial

recombination between strains. Comparison of subtelomeric regions among six strains of *Fusarium fujikuroi* revealed the presence of lineage-specific secondary metabolic pathways, some of which have emerged from HGT events (Chiara *et al.*, 2015). Analysis of 60 *F. graminearum* isolates form North America identified an accessory genome close to 1700 genes that seems to concentrate in AT-rich regions, probably centromeres or telomeres (Kelly & Ward, 2018). Similar results have been obtained for *F. fujikuroi* (Chiara *et al.*, 2015; Niehaus *et al.*, 2017), and *F. oxysporum* (Armitage *et al.*, 2018). Together, these studies have focused either on geographically delimited isolates or have compared a handful of isolates. The pangenome of the wheat pathogen *Z. tritici* has recently been extensively investigated (Plissonneau *et al.*, 2016, 2018) and it is probably the only filamentous fungus for which a reasonably complete pangenome has been described to date. *Z. tritici* contains a pangenome comprising more than 17400 protein-coding genes. All analysed isolates possessed around 12000 genes, while the core genome for all analysed strains was around 9100 genes. This fungus has large effective population sizes and shows frequent genetic exchange between populations (Zhan, Pettway & McDonald, 2003). Finally, McCarthy & Fitzpatrick (2019) analysed the pangenome of four model fungal species: *S. cerevisiae*, *C. albicans*, *Cr. neoformans* and *Aspergillus nidulans*. Their study recovered an accessory genome ranging from almost 10% in *C. albicans* to almost 20% in *Cr. neoformans*. This probably represents a reasonable range for most fungi, although it is likely that particular species might have much greater or smaller pangenomes.

The development of a proper pangenomic paradigm for fungal genomics has been severely limited by the use of resequencing technologies in eukaryotes, where a single reference genome is used to map sequencing libraries from other strains. Applying *de novo* sequencing techniques to all strains in a given study is much more expensive, but should still be a feasible goal. However, a *de novo* assembly approach can still be limited by the fact that accessory genes tend to concentrate in AT-rich regions such as telomeres, centromeres, genomic islands and transposable element-rich regions, which in turn tend to be very difficult to assemble, at least without the use of long read-sequencing technologies. As an alternative, RNA sequencing (RNAseq) techniques might be used to identify genes missing in specific strains, as well as novel transcripts without homology in the reference sequence. Accessory genes, however, tend to evolve at a faster rate than the rest of the genome (Dong, Raffaele & Kamoun, 2015), which of course further limits homology-based annotation approaches. In any case, as more fungal genomes accumulate, the concept of the pangenome is starting to become more widely adopted, and the field is likely to expand in future years. The examples given here show that fungal pangenomes vary greatly in size and functional relevance across different lineages. The existence of an extensive pangenome requires efficient mechanisms for genetic exchange, which may or may not be sexual in nature. Our current knowledge in this area is severely lacking. Sex is only indirectly inferred from genomic data for many groups and mechanisms of HGT in Fungi are still unknown. Regarding the later, the pangenome concept forces us to reevaluate the hypothesis that HGT drives gene clustering in Fungi, as HGT among closely related Fungi might be much more prevalent than previously thought. It is important to point out the possible relationship between mesosynteny and pangenomes (Hane *et al.*, 2011). Mesosynteny seems to be particularly prominent among Dothideomycetes (Hane *et al.*, 2011), the group to which *Z. tritici* belongs.

The pangenome of the model arbuscular mycorrhizal fungus *Rhizophagus irregularis* has been studied only recently, and the results are controversial (Mathieu *et al.*, 2018). After comparing just six laboratory strains, the results show that only 50% of the genes are shared among all of them, and the remaining, accessory genome contains over 150 000 genes (Chen *et al.*, 2018). It remains to be seen whether these results can be interpreted in the context of the heterokaryotic nature of these fungi. First, the existence of such a large pangenome can only be explained in the light of rampant gene flow, either by sexual or sexual-like interchange among strains or, alternatively, by high levels of HGT. Second, if these fungi are heterozygous, what are the implications for their intracytoplasmic pangenomes? How are these accessory genes distributed across the nuclear population within a certain mycelium? If distinct nuclei possess accessory genes that are not present in the entire cytoplasmic population, this would greatly affect genome assembly and annotation, as sequencing would be highly variable in these regions and reads spanning these regions would be incongruent. The large size of this pangenome might well be related to the fact that arbuscular mycorrhizal fungi have a species diversity and endemicity that is orders of magnitude lower than that of land plants, their obligate hosts. *R. irregularis* is currently the only member of Glomeromycota that can be cultured in laboratory. Assuming that the findings in this species can be extrapolated other members of the phylum, the genetic pool accessible to these fungi may be truly enormous (Mathieu *et al.*, 2018).

## V. CONCLUDING REMARKS

Despite the relevance of several species of fungi as model organisms, traditional genetics approaches during the last century have provided limited information about the peculiarities of fungal cell biology. Fungi have served well as model organisms for biochemistry and eukaryotic cell biology, but comparatively fewer studies have focused on understanding fungi themselves. Fungi exist in all shapes and sizes, contributing to their astounding evolutionary success. Unicellular fungi thrive in the environment mostly as saprobes and parasites, where their small size contributes to their successful dispersal and their ability to colonize specialized niches. The main multicellular organization in fungi, the mycelium, has a highly versatile cylindrical reticulated

organization. The hyphal tip is able to exert physical force and can thus grow through solid substrates, while most microbes can access only the surface of such resources. Their network organization allows fungi to colonize their environment in a very flexible way. For example, they can simultaneously exploit spatially separated resources, using their network structure to transport nutrients and cell components across the whole colony. Efficient nutrient exploitation and secondary metabolite production generates a 'territory' for the fungus in which it exerts ecological control over other microorganisms. All of these traits require the fungus to regulate its gene expression in time and space, a feat that necessitates a complex network of sensory and signalling pathways, which in turn is a prerequisite for the emergence of complex multicellularity.

Genomics provides a powerful comparative and functional framework from where to start unravelling the intricacies of fungal biology. Comparative genomics is beginning to identify universal features over long evolutionary timescales. For example, the prevalence, evolution and global epigenetic regulation of gene clusters by the Velvet complex across the fungal kingdom was completely unknown three decades ago. The dynamic nature of fungal genomes over short evolutionary timescales is also receiving considerable attention due to its relevance to fungal diseases and industrial processes. Hybrids, polyploids, aneuploids and heterokaryons are an important and often overlooked dimension of fungal genetics whose importance to the kingdom can only be hypothesized at present. Heterokaryosis in particular is a relatively unexplored phenomenon with direct relevance to fungal physiology, potentially allowing new layers of phenotypic complexity without the need for complex regulatory pathways. As such, the effects of heterokaryosis should be considered for many aspects of the biology of fungi, as well as other syncytial eukaryotes.

Despite major advances in our understanding of fungi brought about by comparative genomics, sequencing approaches alone are not sufficient to solve most biological problems. The power of a comparative approach depends on previous functional knowledge, which can then be extrapolated to other organisms. Most functional knowledge in fungi derives from a few model species, and it is very limited outside Ascomycota. It is necessary to obtain direct empirical information from a wider diversity of species. Not only will this increase our ability to infer function based on homology, but it also will allow us to explore the realm of lineage-specific genes. This is particularly relevant when dealing with secondary metabolism. Inferring the function and chemical nature of these products from exclusively *in silico* approaches is virtually impossible. Indeed, the extremely dynamic evolution of these genes imposes particular challenges for homology-based methodologies. The recent technical revolution represented by novel genome editing technologies, which allow manipulation in non-model species, promises further advances in our understanding of fungal biology (Ohm *et al.*, 2010a; Nødvig *et al.*, 2015; Deng *et al.*, 2017) for both ancestral and taxonomically restricted traits.

## VI. CONCLUSIONS

(1) Hyphal growth is the most common form of cellular organization found in the kingdom Fungi. Fungi were ancestrally unicellular and flagellated, and hyphal organization has been lost secondarily in several lineages independently. Mycelial growth requires the establishment of polarized cell extension, branching and anastomosis. While the cellular machinery required for cell polarization seems to be well preserved across the whole kingdom, little is known regarding the regulation and establishment of the latter two processes. Additionally, certain lineages in the Taphrinomycotina, Pezizomycotina and Agaricomycotina have developed complex structures consisting of different types of hyphae. The genetic mechanisms underlying complex multicellularity in fungi are starting to be revealed by comparative genomic approaches, uncovering many peculiarities and convergences among the different lineages.

(2) The mycelial network is able to exert considerable control over a territory. To achieve this, the mycelium must be able to coordinate global reactions to local stimuli. Most known sensory systems in fungi seem to be functionally similar to those found in plants, although the majority have, when known, an independent evolutionary origin.

(3) Most filamentous fungi can compartmentalize their cytoplasm by means of transverse perforated sections of their cell wall, known as septa. Septated hyphae should, in theory, be able spatially to restrict the biosynthetic machinery of secondary metabolites, which are often toxic or selective only under specific conditions. Non-septated lineages tend to encode fewer secondary metabolism pathways.

(4) Genomic plasticity in Fungi is an essential aspect of adaptation to ever-changing environments and it is one of the bases for long-term evolutionary change. Chromosome aberrations act as unstable intermediates during adaptation to new conditions, and their deleterious consequences can be buffered in heterogeneous multinucleated mycelia. Genetic exchange between distantly related strains has been shown to be important in ecological adaptation for many species. However, studying these phenomena is challenging, due to the presence of artifacts in many standard genomic analyses.

(5) The metabolic diversity of fungi, particularly with regards to their secondary metabolism, is key to explaining their evolutionary success. This biochemical toolbox can evolve through gene loss, gene duplication and horizontal gene transfer. Many of these secondary metabolic pathways appear physically clustered in fungal genomes, a situation that appears to be much more common than in any other eukaryotic group. The selective pressures that cause gene clustering are not fully understood, and it has been proposed that it is caused by the need to coordinate the expression of their components or by frequent lateral gene transfer. Finally, genomic analyses of intraspecific variability has proved the value to fungal biology of the prokaryotic concept of a pangenome.

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