MOLECULAR ECOLOGY

Molecular Ecology (2014) **23**, 753–773 doi: 10.1111/mec.12631

INVITED REVIEWS AND SYNTHESES

Fungal evolutionary genomics provides insight into the mechanisms of adaptive divergence in eukaryotes

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Abstract

Fungi are ideal model organisms for dissecting the genomic bases of adaptive divergence in eukaryotes. They have simple morphologies and small genomes, occupy contrasting, well-identified ecological niches and tend to have short generation times, and many are amenable to experimental approaches. Fungi also display diverse lifestyles, from saprotrophs to pathogens or mutualists, and they play extremely important roles in both ecosystems and human activities, as wood decayers, mycorrhizal fungi, lichens, endophytes, plant and animal pathogens, and in fermentation or drug production. We review here recent insights into the patterns and mechanisms of adaptive divergence in fungi, including sources of divergence, genomic variation and, ultimately, speciation. We outline the various ecological sources of divergent selection and genomic changes, showing that gene loss and changes in gene expression and in genomic architecture are important adaptation processes, in addition to the more widely recognized processes of amino acid substitution and gene duplication. We also review recent findings regarding the interspecific acquisition of genomic variation and suggesting an important role for introgression, hybridization and horizontal gene transfers (HGTs). We show that transposable elements can mediate several of these genomic changes, thus constituting important factors for adaptation. Finally, we review the consequences of divergent selection in terms of speciation, arguing that genetic incompatibilities may not be as widespread as generally thought and that pleiotropy between adaptation and reproductive isolation is an important route of speciation in fungal pathogens.

Keywords: *Coccidioides*, competition, effector, gene regulation, genetic incompatibilities, genomic islands, local adaptation, *Neurospora*, *Penicillium*, positive selection, *Saccharomyces*, yeast

Received 13 September 2013; accepted 4 December 2013

Introduction

Understanding the genetic and genomic processes behind adaptive phenotypes remains a holy grail in biology (Olson-Manning *et al.* 2012; Alfoeldi & Lindblad-Toh 2013). This exercise is not purely academic; it is also crucial for predicting the ways in which organisms will respond to global crises, such as climate change, changes in landscapes and ecosystems, the spread of invasive species, the emergence of pathogens, resistance to drugs and vaccines and increasing food demand. Key challenges currently include identifying the genes involved in ecologically relevant traits and understanding the nature, timing and architecture of the genomic changes governing the origin and

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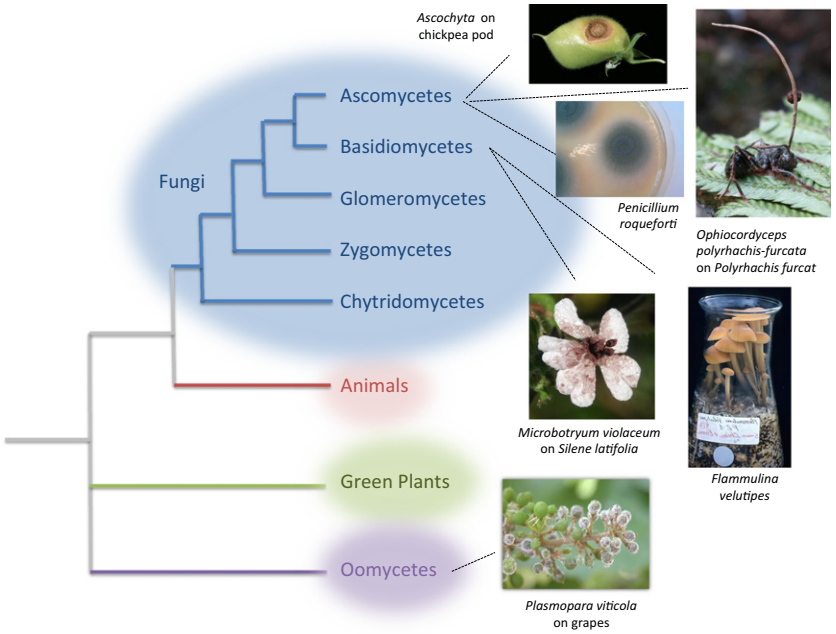

Fig. 1 The tree of life, including the main fungal clades, with illustrative images: for ascomycetes, *Ascochyta* on chickpea pod, *Penicillium roquefor* on a Petri dish, *Ophiocordyceps polyrhachis-furcata* on *Polyrhachis furcat*; for basidiomycetes, *Microbotryum violaceum* on *Silene lafolia* and *Flammulina velupes*; for oomycetes, *Plasmopara vicola* on grapes. Oomycetes were long considered to be fungi, because of convergent fungal-like traits, such as a filamentous form, for example, but they are actually more closely related to brown algae and are not considered in this review.

processes of local adaptation, lineage divergence and ecological speciation. These processes will be grouped together below under the umbrella term 'adaptive divergence'. The possibility of sequencing thousands of related genomes has opened up new possibilities for tackling these crucial issues from a new perspective, providing unprecedented insight into the genomic bases and processes of adaptive divergence (Luikart *et al.* 2003; Alfoeldi & Lindblad-Toh 2013; Fu & Akey 2013; Leducq 2014).

The sequencing of multiple genomes can reveal the relative prevalence of amino acid substitutions, genomic rearrangements, gene gains, gene losses and introgressions as sources of genomic change. However, it remains difficult to address these questions in most eukaryotes, due to their large genomes, phenotypic complexity, long generation times and the difficulty of validating computational inferences by setting up genetic transformation protocols. In this respect, fungi are ideal model organisms. They have a simple morphology, inhabit contrasting and well-identified ecological niches and display considerable diversity, including a huge variety of lifestyles (from saprotrophs to pathogens, mutualists and even predators). Fungi have small genomes and tend to have short generation times and to be amenable to experimental approaches, making it possible, for example, to validate gene functions or to conduct experimental evolution studies (Dettman *et al.* 2007; Schoustra *et al.* 2009; Ajouz *et al.* 2010; Anderson *et al.* 2010; Schoustra & Punzalan 2012; Barrick & Lenski 2013).

Furthermore, the hundreds of genomes available make it possible to use similarity data from public databases for gene annotation, based on information gained from the dissection of gene function in model fungi, such as the baker's yeast *Saccharomyces cerevisiae* and the orange bread mould *Neurospora crassa*. Systematic gene deletion and phenotype screening have been carried out in these models (Winzeler *et al.* 1999; Giaever *et al.* 2002; Colot *et al.* 2006; Hillenmeyer *et al.* 2008). More than 160 sequenced fungal genomes have been published to date and more than 250 are available in total. Although fungi are often considered to be microbes, they are actually phylogenetically close to animals (Fig. 1), thus sharing physiological complexity and similar modes of genomic architecture and evolution with metazoans and other eukaryotes (Tirosh *et al.* 2006; Stajich *et al.* 2009). Inferences drawn from fungi can therefore provide information that can be extrapolated to the genomic processes of adaptive divergence in eukaryotes (Tirosh *et al.* 2006). Fungi thus have considerable potential for use as tractable models of agronomic, medical, industrial and ecological importance (Stajich *et al.* 2009; Gladieux *et al.* 2010a).

There are millions of fungal species, spanning billions of years of evolution and displaying diverse lifestyles that evolved on multiple occasions in the tree of life (James *et al.* 2006), and playing extremely important roles in both ecosystems and human activities. The process of adaptive divergence can be studied in (i) domesticated fungi, used for the production of food and beverages and for bioindustry in general (Fay & Benavides 2005; Liti *et al.* 2009; Libkind *et al.* 2011), (ii) pathogens, which frequently adapt to new hosts, causing emerging diseases that have a major negative impact on human welfare, through agricultural and eco-

nomic losses, and threats to biodiversity (Fisher *et al.* 2012), (iii) symbiotic fungi, including endophytes, that protect their hosts against herbivory or enhance plant growth and resistance to stress (Zuccaro *et al.* 2011), and mycorrhizal fungi, which provide nitrogen and phosphate to wide range of plants, and (iv) saprotrophic fungi, the only organisms capable of breaking down lignin to any great extent (Floudas *et al.* 2012).

We review here recent insights into the genomic mechanism of adaptive divergence gleaned from fungi, ranging from adaptive polymorphism to speciation, and improving our understanding of these processes in eukaryotes. We first outline the various ecological sources of divergent selection acting on fungi, with the aim of providing an overview for nonmycologists of the selection agents promoting adaptive divergence in these organisms. We then review evidence for the roles of different types of genomic changes, showing that gene loss and changes to gene expression and genomic architecture are important mechanisms of adaptation, in addition to the more widely recognized processes of amino acid substitution and gene duplication. We also review interspecific sources of novel genomic variation on which selection can act and suggest that introgression, hybridization and horizontal gene transfer (HGT) are of much greater importance than is often suggested. In addition, we show that transposable elements can influence all these processes, serving as important adaptation factors. Finally, we review the evidence relating to the direct translation of divergent selection into reproductive isolation, through either pleiotropy between adaptation and reproductive isolation or the appearance of genetic incompatibilities between species due to rapid evolution. We argue that the contribution of classical epistatic incompatibilities, although real and important, may be less pervasive than currently thought. Specific fungal terms are defined in the glossary.

Sources and targets of ecological divergence

Ecological divergence in fungi may be due to abiotic and biotic factors, including intra- and interspecific interactions, or artificial selection (domestication).

Abiotic factors

Environmental factors, such as temperature and edaphic conditions, are drivers of ecological differentiation in diverse fungi. Differences in temperature regimes, for instance, maintain differentiated populations of crop pathogens, adapted to different climates or seasons (Enjalbert *et al.* 2005; Frenkel *et al.* 2010; Mboup *et al.* 2012), and also strongly affect the distribution of forest pathogens (Vacher *et al.* 2008). Climate change has been implicated in the recent emergence and probable expansion in the future of several diseases caused by fungi (Fisher *et al.* 2000; Bergot *et al.* 2004; Fabre *et al.* 2011). In *Neurospora crassa,* a population genomics approach revealed that temperature and latitude were important drivers of local adaptation. Indeed, genome scans have detected islands of genomic differentiation including genes involved in both the response to cold temperatures and the circadian cycle, and growth rate assays have confirmed differences in fitness between populations (Ellison *et al.* 2011). In addition, carotenoid accumulation in *Neurospora* has been correlated with latitude (Luque *et al.* 2012). Carotenoids protect against UV irradiation and their production is induced by light. Pigment levels may therefore be subject to selection and may underlie population differentiation in these fungi.

Edaphic factors have been found relevant in the niche requirements of forest mutualists and decomposers, with species showing clear preferences based on soil chemistry (Frankland 1998; Branco 2010). Humidity and other abiotic factors associated with elevation also act as strong selection agents in tree pathogens and symbionts, affecting their distributions (Cordier *et al.* 2012).

There may be trade-offs between different types of performance subject to selection by different abiotic agents. For instance, trade-offs may have led to different strategies in closely related pathogenic fungal species, some being better at overwintering, whereas others are better at sporulating late in the season (Giraud *et al.* 1997; Feau *et al.* 2012).

Pathogens and mutualists: the host as a selective agent

Unlike abiotic factors, biotic agents evolve and constitute discrete ecological niches in sympatry, therefore causing strong disruptive selection. This makes fungal pathogens, which are dependent on their living hosts, attractive systems for the study of adaptive divergence. Host shifts have been associated with multiple cases of recently diverged sibling species in numerous pathogens (Giraud *et al.* 2008; de Vienne *et al.* 2013), and ecosystems modified by humans continually provide examples of new fungal diseases emerging on new hosts (Anderson *et al.* 2004; Gladieux *et al.* 2010a; Fisher *et al.* 2012), providing ample opportunity to investigate the early stages of adaptive divergence. The strong selection imposed by hosts is conducive to ecological differentiation in fungal pathogens, through an increase in the frequency of locally advantageous alleles and prevention of the immigration of locally deleterious ancestral alleles (Giraud *et al.* 2010). Furthermore, specialist pathogens are more efficient in the arms race with their hosts (Whitlock 1996). Most fungal pathogens are indeed specialists, evolving by host shifts (de Vienne *et al.* 2013).

In pathogens of animals, virulence reflects a capacity to neutralize or resist the somatic adaptive immune system of the host (Upadhya *et al.* 2013) and, for pathogens of homeothermic animals, an ability to cope with temperatures of 37 °C or higher (which is usually a strong barrier for fungi). Amphibians, which are cold-blooded, act as hosts to several species of fungal pathogens; the recent emergence and spread of chytridiomycosis, caused by the chytrid *Batrachochytrium dendrobatidis*, has attracted much attention as it poses a threat to amphibians worldwide (Fisher *et al.* 2009).

By contrast to the situation in animals, plant defenses are based on the innate immunity of each cell and on systemic signals emanating from sites of infection (Jones & Dangl 2006). Plant immune responses can be broadly grouped into two major layers: responses triggered by general microbe-associated molecular patterns (*e.g.* chitin) and those triggered by isolate-specific pathogen effectors, recognized by specific nucleotide-binding and leucine-rich repeat (NB-LRR) resistance proteins (Schulze-Lefert & Panstruga 2011). The specific defense response typically involves localized cell death, which completely prevents microbial growth, thus exerting strong selection on fungi (Giraud *et al.* 2010). Over the last 100 years, plant breeders have mostly used resistance genes of major effect – usually encoding NB-LRR proteins – to control infectious fungal diseases, as they are associated with a phenotype that can be easily selected and display simple Mendelian inheritance (Crute & Pink 1996). However, with only a few exceptions, such resistances have rapidly broken down (McDonald 2010), providing spectacular examples of adaptive evolution (Brown 1994; Guerin *et al.* 2007; Terauchi & Yoshida 2010; Xhaard *et al.* 2011). More generally, widely distributed, high-density and genetically uniform populations, such as those of cultivated crops, regularly select for new pathogens (Stukenbrock & McDonald 2008). Population genetics and phylogenetics have provided evidence that many fungal pathogens have emerged through host shifts, host-range expansion or host tracking over the last 10 000 years, following the domestication of the affected crops (Couch *et al.* 2005; Munkacsi *et al.* 2006; Stukenbrock *et al.* 2007; Zaffarano *et al.* 2008; Frenkel *et al.* 2010; Gladieux *et al.* 2010b, 2011; Silva *et al.* 2012). By contrast, host plants do not seem to exert strong selective pressure on mycorrhizal fungi, and there are few examples of strict mycorrhizal host specificity (Bruns *et al.* 2002).

Ecological interactions between fungi

Ecological interactions between competitors also act as strong biotic selection agents and may be involved in processes of ecological divergence. Competition can favour the exploitation of underused resources, leading to character displacement and niche expansion, resource polymorphism and speciation (Bono *et al.* 2013). Intraspecific competition and interspecific competition in natural conditions have been documented in ectomycorrhizal and saprotrophic fungi (Boddy 2000; Kennedy 2010) and in fungal pathogens (Koskella *et al.* 2006; Lopez-Villavicencio *et al.* 2007; Staves & Knell 2010; López-Villavicencio *et al.* 2011). The mechanisms involved in competitive interactions include the production of toxins inhibiting competitors (Kaiserer *et al.* 2003; Sass *et al.* 2007), vegetative incompatibility and hyphal interference, resulting in the death of incompatible hyphae after somatic fusion (Glass *et al.* 2000; Silar 2005). Competition between fungi shapes the distribution of species in the field and can play an important role in species divergence. In addition, many of the virulence traits in fungal pathogens also have a function in competition outside of the host (Morris *et al.* 2009; Stergiopoulos *et al.* 2012). Predation can also play a selective role in divergence, and several authors have suggested that many emerging animal pathogens might actually have acquired virulence traits, such as resistance to phagocytosis, through their initial selection for the avoidance of predation by amoebas or nematodes (Casadevall *et al.* 2003; Greub & Raoult 2004).

Sexual selection and assortative mating

Sexual selection is another biotic source of divergence. It acts on traits involved in mate recognition, conditioning mate preference and influencing the genetic architecture passed on to progenies. The existence of strong consistent biases in nucleus fertilization in crosses between decomposers of the species *Schizophyllum commune* has suggested that sexual selection may be of relevance in fungi (Nieuwenhuis *et al.* 2010). Also, yeasts display a preference for higher levels of pheromone production, which might result from sexual selection (Jackson & Hartwell 1990; Rogers & Greig 2009). However, it remains unclear how widespread sexual selection is or how it promotes divergence in fungi.

Another important force underlying adaptive divergence is selection against maladaptive hybrids, that is, reinforcement or selection for assortative mating in sympatry. Several cases of reinforcement have been reported, particularly in toadstools (Kohn 2005; Giraud *et al.* 2008; Giraud & Gourbiere 2012), but also in ascomycetes of the genus *Neurospora* (Turner *et al.* 2011).

Domestication

Domestication is a specific case of adaptive divergence in response to artificial selection. Diverse fungi have

been domesticated for the fermentation of food products, such as wine, beer, bread (*Aspergillus oryzae, Saccharomyces sp.*), dried sausages (*Penicillium nalgiovense*), red fermented rice (*Monascus purpureus*) and cheeses (*Penicillium sp.,* Fig. 1). Additional characteristics have also been selected, including growth, mycelium thickness, colour or lipolytic and proteolytic activities in cheese *Penicillium* species. Other domesticated fungi (i) have organoleptic properties that are appreciated (e.g. the button mushroom *Agaricus bisporus,* the shiitake *Lentinula edodes,* the jelly ear *Auricularia auricula-judae*), (ii) produce secondary metabolites useful for medical purposes, such as penicillin (*Penicillium rubens*), or (iii) are a source of enzymes useful for the biodegradation of plant polysaccharides in biofuel production (*Trichoderma reesei*).

Genetic bases of adaptation: within-species changes

We have outlined above the different types of selection agents potentially involved in adaptive divergence in fungi. The genomic bases of such adaptations are beginning to be dissected in fungi, and we review below the exciting findings obtained to date, focusing first on intraspecific genomic changes, that is, mutations leading to amino acid substitutions, gene regulation and gene gains and losses.

Amino acid substitutions

Amino acid changes can occur due to errors in DNA replication or the addition of nucleotides after the insertion and excision of transposable elements (TEs) (Daboussi & Capy 2003), as shown, for instance, for genes controlling spore colour (Colot *et al.* 1998) and encoding effectors (Farman 2007; Rep & Kistler 2010).

Candidate gene analyses have shown that amino acid changes are pervasive in underlying fungal adaptation (reviewed in Aguileta *et al.* 2009; Stergiopoulos *et al.* 2007; Stergiopoulos & de Wit 2009; Stukenbrock & McDonald 2009). We focus here on the most recent findings stemming from the analysis of genomic sequence variation in natural populations/species. Genomic approaches have the advantage of not requiring a priori information on the genes involved in adaptation and can therefore be used to elucidate the functions involved in host/habitat specialization and the environmental factors driving adaptive divergence, through a 'reverse-ecology' approach.

Genes under diversifying selection have been identified from analyses of expressed sequence tags (ESTs) collected in closely related species with different ecological profiles. In the *Microbotryum* and *Botrytis* pathogen species complexes and in *Saccharomyces* yeasts, for instance, this approach has identified several dozens of genes that have been subject to recurrent selection, generating repeated adaptive amino acid changes in the same gene or even at the same site in different variants (Li *et al.* 2009; Aguileta *et al.* 2010, 2012). A large proportion of these genes under positive selection have been annotated as transmembrane proteins, putative secreted proteins or cell wall proteins presumably involved in transporter activities and establishing communication with the host cell and the external environment. Interestingly, most of the genes that have been through episodes of adaptive diversification between *Microbotryum* species specialized on different hosts appeared to have subsequently evolved under strong functional constraints in the lineages remaining specialized on a given host plant (Gladieux *et al.* 2013), indicating they are not involved in the arms race against their host.

Whole-genome sequencing in plant pathogens has revealed the existence of an arsenal of effectors expressed during infection, revolutionizing our understanding of plant–fungus interactions (reviewed in (de Jonge *et al.* 2011; Oliver 2012; Stergiopoulos & de Wit 2009). Effectors are generally defined as secreted proteins that manipulate host innate immunity, enabling infection to occur (Dodds & Rathjen 2010). Resequencing data for the wheat pathogens *Blumeria graminis* and *Zymoseptoria tritici* have identified several hundred putative effector genes displaying signatures of positive selection (Stukenbrock *et al.* 2011; Wicker *et al.* 2013). Such a pervasive rapid evolution of effectors in fungal pathogens is consistent with a permanent arms race, with increases in the complexity of recognition systems in hosts being matched by the development of new systems for escaping recognition in the pathogen. Other examples of adaptive amino acid change consistent with rampant coevolution with hosts or competitors in fungal lineages include toxin biosynthesis gene clusters (Ward *et al.* 2002; Carbone *et al.* 2007) and secreted proteins in the amphibian-killing fungus *B. dendrobatidis* (Farrer *et al.* 2013; Rosenblum *et al.* 2013).

More generally, with the availability of larger genome-wide data sets for multiple members of same genus or family, it is becoming increasingly possible to identify the gene-specific or genome-wide effects of selection associated with changes in life history traits or ecological strategies. For instance, comparison of the genomes of human pathogens of the genus *Coccidioides* genomes with those of closely related species has revealed lineage-specific accelerations in the amino acid substitution rate in a set of about 70 genes displaying functional enrichment in genes associated with biopolymer metabolic processes and RNA metabolic processes

(Sharpton *et al.* 2009). Footprints of positive selection, in terms of amino acid changes, have also been found in domesticated fungi, due to the strong selection exerted by humans. In the fungus used for sake production for instance, *A. oryzae*, one of the genes with the strongest signal of positive selection with respect to its wild relatives encodes a glutaminase catalysing the hydrolysis of L-glutamine, a widely used food flavour enhancer present at high levels in sake (Gibbons *et al.* 2012).

The genetic code itself can also provide unexpected adaptive amino acid changes. Many fungi have altered their genetic code to incorporate serine residues at sites at which leucine was previously incorporated. This may sound highly deleterious, but experiments in *Candida albicans* have shown that such misincorporation is well tolerated (Bezerra *et al.* 2013). Basic growth rates were lower, but many novel phenotypes were retrieved, including enhanced growth on novel media, drug resistance and response to human immune cells.

Gene family size changes, gene deletions

As amino acid changes, gene duplication was identified early on as a possible mechanism of adaptive innovation (Ohno 1970). The sequencing of a large number of fungal genomes has made it possible to identify gene families that have been expanded, but also gene families that have been reduced in particular lineages or that have become species specific (Ames *et al.* 2012; Han *et al.* 2013; Leducq 2014) (Fig. 2). Species- or population-specific genes may be derived from within-group innovation by such rapid divergence that homology is not recognized (Kellis *et al.* 2004) or may be obtained by horizontal or lateral gene transfer through the non-vertical acquisition of genome fragments containing coding sequences (Keeling 2009). The reduction or complete loss of gene families has also often been found to reflect ecological shifts (Casadevall 2008).

Gene family expansion. Expanded gene sets are widespread and have received special attention due to their role in adaptive divergence. Duplication allows functional diversification or an adaptive increase in enzyme production. For example, families of genes encoding secreted proteins (often regarded as potential effectors), nutrient transporters and enzymes acting on carbohydrates are commonly expanded in fungal obligate parasites and mutualist symbionts, such as mycorrhizal fungi (Martinez *et al.* 2004; Martin *et al.* 2008; Powell *et al.* 2008; Butler *et al.* 2009; Duplessis *et al.* 2011; Ohm *et al.* 2012). Families of membrane-bound transporters, including amino acid permeases and sugar transporters, allow the uptake of nutrients by pathogens and of carbohydrates by symbiotic fungi from their host plants in exchange for nitrogen and phosphate compounds. Expanded sets of effectors produced in large amounts during plant colonization are involved in the establishment of symbiosis or the development of disease, avoiding the triggering of host defences, whilst the fungus is growing within living cells (Martin *et al.* 2008; Zuccaro *et al.* 2011).

Gene family expansion has led not only to improvements in nutrient uptake and host infection in fungal pathogens and symbionts, but also to adaptations for more efficient catabolism and drug resistance. In the human pathogens *Malassezia globosa* and *Candida* yeasts and in the amphibian pathogen *B. dendrobatidis*, expanded families of proteases or hydrolases may play a role in the ability of the pathogens to degrade host tissues (Xu *et al.* 2007; Joneson *et al.* 2011). In white-rot* fungi, the gene families encoding the enzymes involved in wood decay (oxidases, peroxidases and hydrolytic enzymes) have been expanded (Martinez *et al.* 2004). In the human pathogen *Cryptococcus neoformans*, recent amplification of a gene encoding an arsenite efflux transporter has enhanced arsenite resistance, the degree of enhancement being correlated with the copy number of the repeat (Chow *et al.* 2012).

The expansion of gene families has also contributed to genomic innovation in domesticated fungal species, enhancing their enzyme production or particular aspects of metabolism. In the domesticated species *Penicillium rubens* (previously known as *P. chrysogenum*), the penicillin biosynthesis gene cluster shows footprints of tandem duplication events, whereas this cluster is present as a single copy in the wild type (Fierro *et al.* 1995). The genomic regions specific to the domesticated *A. oryzae*, which is used for sake or enzyme production and is derived from a plant pathogen, are enriched in genes involved in the synthesis of secondary metabolites, and specific expansions of genes encoding secreted hydrolytic enzymes, proteins involved in amino acid metabolism and amino acid/sugar uptake transporters have been reported (Machida *et al.* 2005). Expanded families of transporters have also contributed to the evolution of various degrees of sensitivity to drugs or anaerobic fermentation in yeasts (Dunn *et al.* 2005; Marcet-Houben *et al.* 2009; Lin & Li 2010).

A number of gene expansions have been facilitated by mobile genetic elements. TEs can acquire cellular genes or gene fragments between their terminal inverted repeats and replicate them throughout the genome (Manning *et al.* 2013). Such TE-mediated duplications have contributed to the amplification of toxin production and increased the copy number of effectors, and their diversification, in the pathogen *Pyrenophora tritici-repentis* (Manning *et al.* 2013). In natural yeast populations, transposon-mediated genome rearrangements

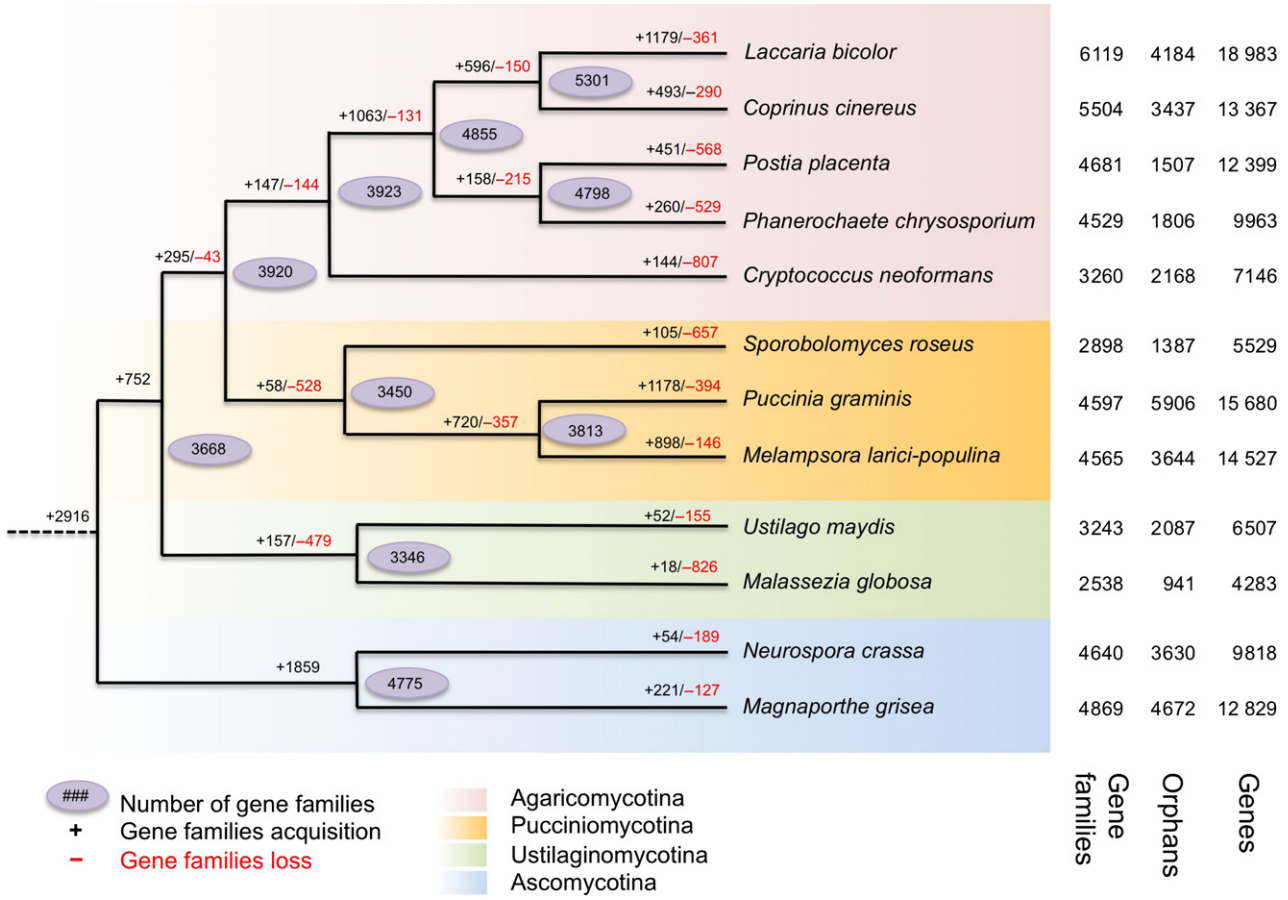

Fig. 2 Predicted pattern of gene family gain and loss in representative fungal genomes. The figure represents the total number of protein families in each species or node estimated by the Dollo parsimony principle. The numbers on the branches of the phylogenetic tree correspond to the numbers of expanded (left, black), contracted (right, red) or inferred ancestral (oval) protein families in each lineage, determined by comparison with the putative pan-proteome. For each species, the number of gene families, orphan genes and the total number of genes are indicated on the right. Reproduced with permission from Duplessis *et al.* (2011).

have resulted in the duplication of genes governing the regulation of the copper pathway, enhancing copper tolerance (Chang *et al.* 2013).

Whole-genome duplication has also created duplication events in yeasts, with about 500 duplicate genes known to have been retained in *Saccharomyces cerevisiae* (Kellis *et al.* 2004). Some of these duplicated genes diversified and became specialized, encoding, in particular, enzymes controlling metabolism in aerobic and hypoxic conditions, enabling *S. cerevisiae* to grow without oxygen, by fermenting glucose anaerobically (Wolfe 2004). In most cases of diverging paralogs, neofunctionalization commonly occurs where one copy evolved slowly, retaining the ancestral function, whereas the other copy evolved much more rapidly, acquiring a novel function (Kellis *et al.* 2004), as predicted before the advent of genome sequencing (Ohno 1970). By contrast, other duplicate genes have remained identical by gene conversion, conferring advantages through greater protein production, as in the case of ribosomal protein genes (Kellis *et al.* 2004).

Gene losses. Gene losses are a common landmark of the switch to an obligate biotrophic or symbiotic lifestyle in fungi, with a decrease in the numbers of plant cell wall degradation proteins, secreted toxins and genes controlling the machinery redundant with that of their hosts (Kamper *et al.* 2006; Martin *et al.* 2008; Spanu *et al.* 2010; Duplessis *et al.* 2011; McDowell 2011; Spanu 2012). The mutualist endophyte *Piriformospora indica*, for instance, lacks the pathways required for the synthesis of toxic secondary metabolites and some essential genes involved in nitrogen assimilation (Zuccaro *et al.* 2011). The human *Malassezia* pathogens have no fatty acid synthase gene, instead producing multiple secreted lipases, which they use to obtain fatty acids from human skin (Xu *et al.* 2007). An extreme case of genome reduction in pathogens is provided by the fungus-related

microsporidia. These obligate intracellular parasites have lost many genes, resulting in a high degree of dependence on the host genome (Peyretaillade *et al.* 2011). Cases of adaptive gene reduction have also occurred during the evolution of ectomycorrhizal biotrophy* and brown rot* saprotrophy from lignin-degrading white-rot* ancestors (Eastwood *et al.* 2011; Floudas *et al.* 2012). The reduction of specific protein families (lignin-degrading peroxidases) in these fungi represents a considerable saving in terms of the production of expensive machinery completely unnecessary for their lifestyles. Similarly, the biocontrol agent *Pseudozyma flocculosa*, which antagonizes powdery mildew, is not a plant pathogen, and it lacks the secreted proteins involved in the pathogenicity of its close relative *U. maydis* (Lefebvre *et al.* 2013).

Gene deletion is an important mechanism of adaptation not only because it saves energy due to the elimination of unnecessary enzymatic machineries, but also because it allows pathogens to avoid detection by host defences. For example, recent sequencing of the genome of the wheat powdery mildew *Blumeria graminis* revealed large deletions in some individuals, with most of the deleted genes identified as candidate effectors (Wicker *et al.* 2013). Another example is provided by the emergence of *Magnaporthe oryzae* on rice, which was probably facilitated by the loss of an effector (Couch *et al.* 2005), mediated by transposable elements.

Regulatory change

Looking at the presence of specific genes or alleles is not sufficient for a full understanding of adaptive divergence, as the specific regulation of genes may also play an important role (Wolbach *et al.* 2009; Spanu & Kämper 2010). Genes may be regulated by *cis*-acting modulators of single genes or *trans*-acting modulators of multiple genes. *Cis*-acting sites (i.e. the DNA-encoded nucleosome organization of promoters) evolve much more rapidly than coding sequences (Borneman *et al.* 2007; Tuch *et al.* 2008). In the budding yeast, *trans*-acting loci affecting the expression of up to 100 genes each have been identified, with related functions displaying coregulation (Brem *et al.* 2002).

A first line of evidence for the importance of gene regulation in adaptation comes from genomic scans looking for signs of selection. Analyses of EST data in closely related plant pathogens have identified several genes involved in *trans* regulation among those undergoing rapid diversification (Aguileta *et al.* 2010, 2012). In *S. cerevisiae*, selective sweeps have been identified on several *cis*-regulatory mutations downregulating the levels of interacting proteins involved in endocytosis in pathogenic strains, thereby increasing virulence (Fraser *et al.* 2009, 2013). More generally, genome-wide scans have revealed widespread positive selection, affecting expression levels in yeasts (Fraser *et al.* 2009; Bullard *et al.* 2010).

A second line of evidence supporting the role of regulatory changes in adaptation has been obtained from a combination of genome sequencing and expression data. These studies have revealed that genes encoding proteins involved in growth and general metabolism have conserved expression patterns, whereas those involved in responses to external and internal signals (e.g. stress response and effectors) or with nonessential functions display divergent patterns of expression between species (Tirosh *et al.* 2006; Thompson & Regev 2009). The proximal mechanism allowing such differences in the rate of expression to evolve is linked to promoter organization. Genes displaying divergent expression harbour promoters that are particularly sensitive to chromatin remodelling, a particular nucleosome organization and the presence of a TATA box (Tirosh *et al.* 2006; Field *et al.* 2009; Thompson & Regev 2009). These observations suggest that there is selection for stable promoters for essential and housekeeping genes, whereas the promoters for genes controlling responses to stresses or encoding effectors are more labile. This situation favours stability and robustness to mutation for essential genes, and the rapid evolution of stress-response and effector genes (Tirosh *et al.* 2006).

Some important changes in gene regulation have been found to be caused by the insertion of transposable elements. TE-mediated rearrangements have, for instance, been implicated in changes to the regulation of genes conferring sulphite resistance in yeast strains used for wine production (Perez-Ortin *et al.* 2002).

The exceptional genetic tractability of the yeast *S. cerevisiae* has made it possible to investigate the role of gene regulation in adaptation by experimental evolution experiments. After evolution over thousands of generations of cultures in various suboptimal media (glucose, sulphate or phosphate limitation) or with novel nutrient sources, adaptation has been shown to involve the massive remodelling of gene expression, demonstrating the importance of genetic regulation for adaptation (Ferea *et al.* 1999; Gresham *et al.* 2008).

Genomic architecture of adaptation

The genomic changes underlying adaptive phenotypes appear to be nonrandomly distributed within the genomes, with some regions more prone to the accumulation of changes. Genome sequencing in fungi has, indeed, revealed many cases of genomic heterogeneity, with gene-dense and gene-sparse repeat-rich regions, the latter often evolving more rapidly and carrying

genes under divergent selection between closely related species. This phenomenon has been referred to as 'two-speed genomes'. Gene-sparse regions may constitute genomic islands enriched in ecologically important genes (e.g. effectors), and displaying higher rates of evolution, in terms of presence/absence, copy number or nonsynonymous substitutions (Hatta *et al.* 2002; Gout *et al.* 2006; Cuomo *et al.* 2007; Fedorova *et al.* 2008; Martin *et al.* 2008; Ma *et al.* 2010; Schirawski *et al.* 2010; Stajich *et al.* 2010; Klosterman *et al.* 2011). The islands with high rates of evolution may be subtelomeric (Chuma *et al.* 2011), AT-rich isochore-like regions (Van de Wouw *et al.* 2010; Rouxel *et al.* 2011), small dispensable chromosomes (Coleman *et al.* 2009; Ma *et al.* 2010; Goodwin *et al.* 2011; Croll & McDonald 2012; Croll *et al.* 2013), dynamic gene clusters (Schirawski *et al.* 2010; Schardl *et al.* 2013) or regions of extensive chromosomal reshuffling (de Jonge *et al.* 2011).

The genes underlying adaptive phenotypes can thus be clustered on supernumerary chromosomes, such as those of the pathogen *Fusarium solani,* carrying genes involved in pathogenicity, antibiotic resistance and the use of unique carbon/nitrogen sources (Coleman *et al.* 2009). Similarly, genomic islands in the human pathogen *Aspergillus fumigatus*, which may be as large as 400 kb, contain mostly repetitive DNA and species-specific genes involved in metabolic processes conferring adaptation to specific ecological niches (Fedorova *et al.* 2008). The genomic islands of *A. fumigatus* are preferentially located in subtelomeric regions prone to frequent nonhomologous recombination between paralogs, duplications, sequence variability (Brown *et al.* 2010) and gene transfers (Kavanaugh *et al.* 2006). There may be selection for the location of effector genes in regions in which frequent transposable element movements and rearrangements induce high rates of mutation, as these genes frequently evolve under positive selection (Gout *et al.* 2006; Klosterman *et al.* 2011; Rouxel *et al.* 2011). Sequencing of the genomes of several strains of the cereal pathogen *Fusarium graminearum* has revealed that the gene-sparse regions with species-specific genes are also the most polymorphic within species (Cuomo *et al.* 2007).

Other types of 'genomic islands' involved in adaptation include those strongly differentiated between closely related species adapted to different ecological niches. Genomic islands displaying strong differentiation have been detected in closely related fungi by genome resequencing, which has made it possible to identify regions involved in adaptation to contrasting environments by a 'reverse-ecology' approach, that is, with no a priori candidate gene or assumed function (Li *et al.* 2008). A striking example is provided by the detection of a region displaying high levels of differentiation between *Neurospora* species, harbouring genes shown to be involved in adaptation to temperature (Ellison *et al.* 2011) (Fig. 3).

Chromosomal rearrangements constitute another kind of genomic architecture that can be involved in adaptation by changing gene regulation or triggering gene duplication for example (Adams *et al.* 1992; Perez-Ortin *et al.* 2002; Gresham *et al.* 2008). Transposable elements have been implicated in many adaptive chromosomal rearrangements (Gioti *et al.* 2012), and some have even been recruited for the promotion of regular mating-type switching (Butler *et al.* 2004; Barsoum *et al.* 2013). Genetic engineering in yeasts has even shown that chromosomal rearrangements can promote enhanced fitness in the absence of other polymorphisms (Colson *et al.* 2004; Teresa Avelar *et al.* 2013). Similarly, experimental evolution and genetic engineering in yeast have revealed that a whole-genome duplication and a frameshift mutation were sufficient to induce a dramatic change in behaviour, generating a fast-sedimenting, multicellular phenotype (Oud *et al.* 2013).

Another feature of the genomic architecture of adaptation in fungi is the clustering of genes involved in the same biosynthesis pathway, such as those encoding proteins involved in the production of secondary metabolites, in particular (Slot & Rokas 2010). The genes within clusters are coregulated, facilitating their coinduction in response to particular conditions, such as plant colonization or stresses, and preventing the accumulation of intermediate toxic compounds (McGary *et al.* 2013). Clustering has been reported, for example, for the genes responsible for mycotoxin production in *Fusarium* (Ma *et al.* 2010), secreted proteins involved in virulence in *Ustilago maydis* (Kamper *et al.* 2006), for the galactose utilization pathway (Slot & Rokas 2010) and for the genes involved in nitrate assimilation (Slot & Hibbett 2007). Conversely, cluster fragmentation may facilitate metabolic retooling and the subsequent host adaptation of plant pathogens (Bradshaw *et al.* 2013).

Genetic bases of adaptation: genomic novelties of trans-specific origin

We have reviewed above the genomic bases of adaptation resulting from genomic changes occurring within species, that is, amino acid substitutions, regulation, gene content and genomic architecture. In this section, we will focus on adaptations extending across species boundaries (i.e. hybridization and HGTs). Recent findings suggest that these sources of adaptive change may have made a substantial contribution to evolution, rather than being merely anecdotal, as initially thought (Roper *et al.* 2011).

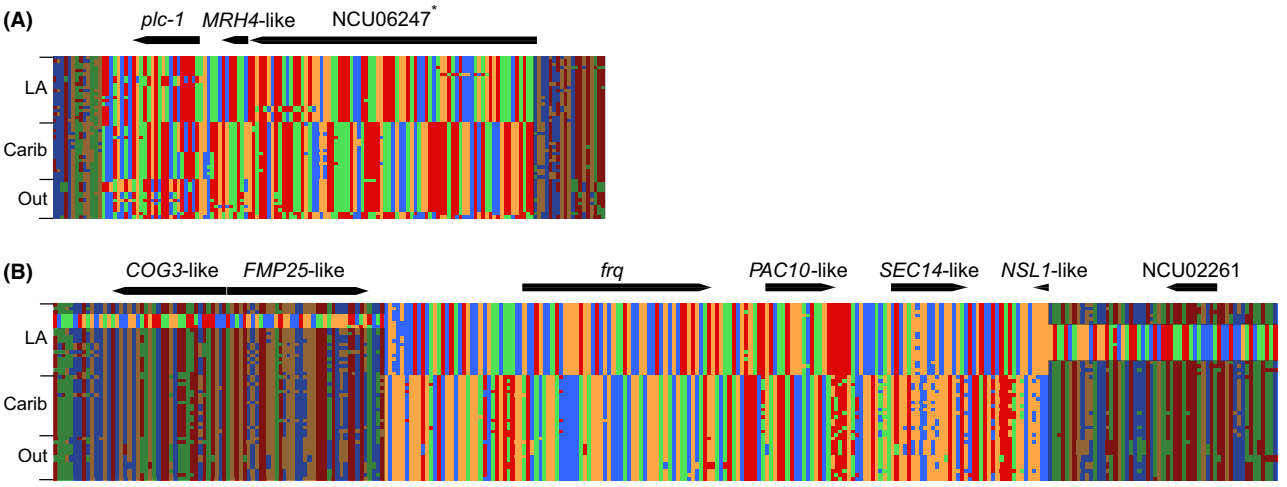

Fig. 3 Genomic islands of divergence in *Neurospora crassa*. Each column is a polymorphic site, and each row contains the genotype for a particular strain. The flanking regions surrounding the divergence outliers are shaded and accentuate the distinct patterns of nucleotide polymorphism within the divergence outlier regions. Strains are grouped by population of origin. LA, Louisiana; Carib, Caribbean (Florida, Haiti and the Yucatan); Out, outgroups from Central America, South America and Africa. The matrix in A is a 10-kb divergence island on chromosome 3. The matrix in B is a 27-kb divergence island on chromosome 7. Reproduced with permission from Ellison *et al.* (2011). MRH4-like RNA helicases are key factors in the microbial cold response. *frq* is a circadian oscillator gene frequency.

Hybridization and introgression

Hybridization is generally deleterious, as it breaks up adaptive combinations of alleles and may bring together incompatible alleles. However, introgression*, the transfer of genetic material between hybridizing taxa through backcrossing, can sometimes be important in adaptation, by incorporating innovation, as reported in several cases in fungi. For example, population genomic analyses of resequencing data have also revealed widespread recent introgressions between the human pathogens *Coccidioides immitis* and *C. posadasii* (Neafsey *et al.* 2010) (Fig. 4). The genomic regions introgressed in *C. immitis* may confer a selective advantage, as they are enriched in coding sequences, accounting for about 8% of the genes in *C. immitis*. In another human pathogen, *Cryptococcus neoformans*, a genomic fragment containing 14 genes from the variety *grubii*, has introgressed in the variety *neoformans* (Kavanaugh *et al.* 2006). The adaptive nature of this introgression is indicated by the spread of the island throughout almost the entire gene pool of the variety *neoformans* and by its duplication.

Widespread recent introgressions have also been identified in several *Saccharomyces* yeasts (Naumova *et al.* 2005; Liti *et al.* 2006). For instance, it has been suggested that a subtelomeric introgression between *S. paradoxus* and *S. cerevisiae* containing 12 genes is adaptive, based on the invasion of the entire European population of *S. paradoxus* by the introgressed fragments (Liti *et al.* 2006). One of the candidate genes for the selective advantage identified encodes resistance to toxin killing (Liti *et al.* 2006). Genome sequencing has also revealed the introgression of three large regions between the distantly related wine yeasts *S. cerevisiae* and *Zygosaccharomyces bailii*. Two of these regions are subtelomeric, and the three together encompass 34 genes involved in key wine fermentation functions (Novo *et al.* 2009). These recent introgressions might be due to the close association of the species concerned with human populations, as humans are known to have mixed previously isolated species and to exert strong selection for novel phenotypes.

Another type of adaptive introgression involves the regeneration, by introgression, of alleles that have accumulated deleterious mutations. In phylogenetic lineages of the filamentous ascomycete *Neurospora tetrasperma* for instance, comparative genomics studies have revealed the presence of a large introgression tract (>4 Mb) in the region of suppressed recombination of the mating-type chromosome (Sun *et al.* 2012). This introgression from freely recombining species of *Neurospora* has been shown to be associated with a lower level of degeneration of the mating-type chromosome and may therefore contribute to the reinvigoration of genomic regions subject to suppressed recombination.

Hybridization can even promote the emergence of new species, by creating transgressive phenotypes* allowing adaptation to new ecological niches (Brasier 2001; Schardl & Craven 2003). Examples of transgressive phenotypes in hybrids can also be found in domes-

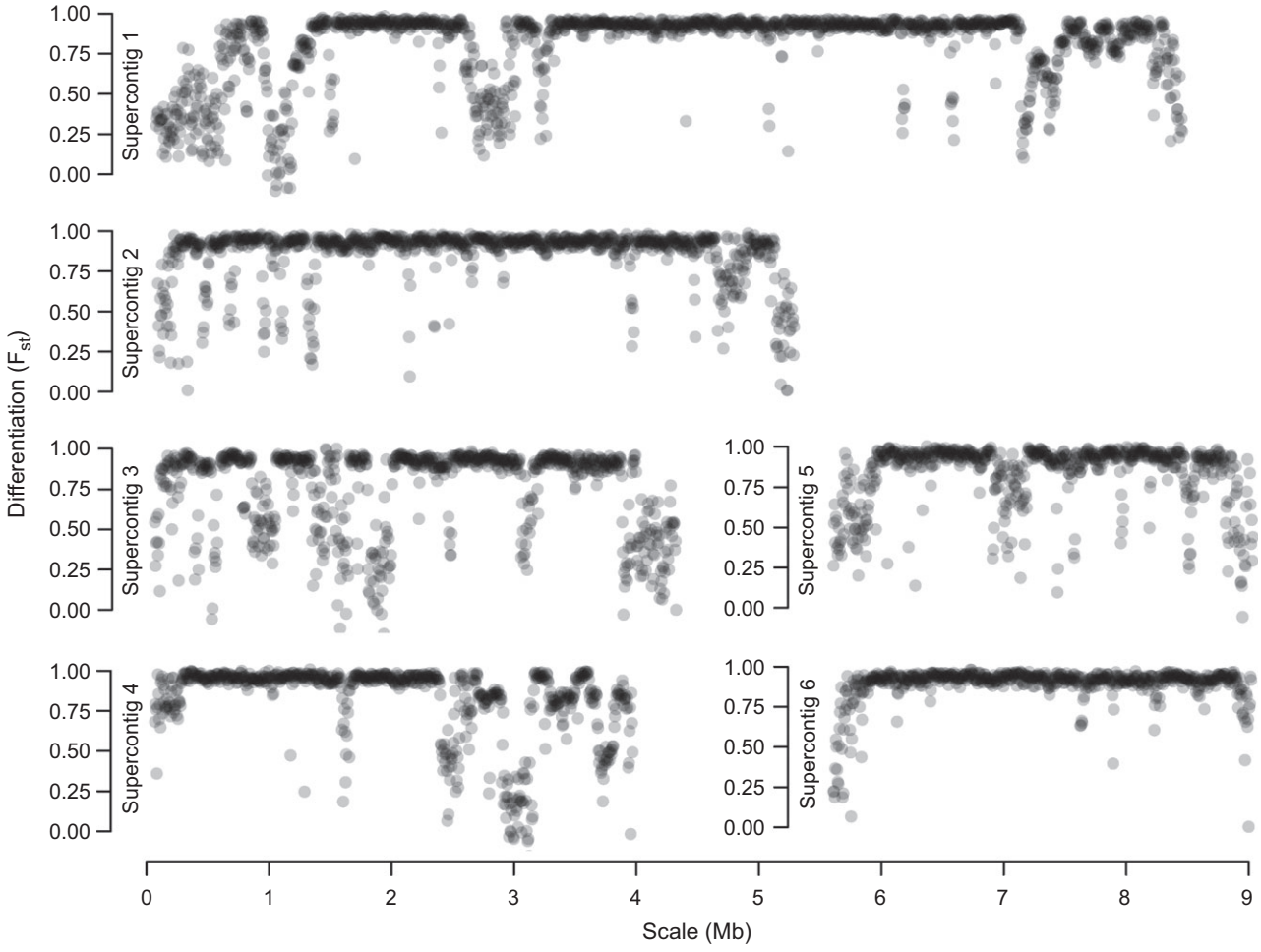

Fig. 4 Illustration of introgression between fungi: the case of the human pathogens *Coccidioides immitis* and *C. posadasii*. Sliding-window analysis of species divergence (F_{ST}). Each circle represents the F_{ST} calculated for a nonoverlapping 5-kb window. Low F_{ST} values indicate introgressed genomic regions. Reproduced with permission from Neafsey *et al.* (2010).

ticated fungi. The lager-brewing yeast, *S. pastorianus*, is an allotetraploid obtained by the fusion of *S. cerevisiae* with the cryotolerant species *S. eubayanus* (Libkind *et al.* 2011). The production of lager requires a particular low-temperature fermentation that can only be achieved efficiently by *S. pastorianus*. Transgressive phenotypes* have also been demonstrated in certain growth conditions for artificial interserotype hybrids of the human pathogen *C. neoformans* (Shahid *et al.* 2008). Together, these cases suggest that transgressive hybridization could promote adaptation at the margin of species distributions.

Horizontal gene transfer

Unlike introgression and hybridization, HGT results in the transmission of genetic material between species in the absence of sexual reproduction. HGT has been long acknowledged as a major driver of prokaryotic evolution and is increasingly recognized as a prominent source of adaption in eukaryotes (Keeling & Palmer 2008; Keeling 2009; Syvanen 2012). Within eukaryotes, fungi are the group for which the largest number of HGT events has been described. This may be explained by the large number of genomes sequenced and the performance of large-scale phylogenomic analyses specifically for the detection of HGT in fungi (Marcet-Houben & Gabaldon 2010). For instance, a systematic survey of 60 fungal genomes from various clades has shown that more than 700 genes of prokaryotic origin were acquired by HGT (Marcet-Houben & Gabaldon 2010). The finding that most of the known HGTs in eukaryotes involve prokaryotic genes probably reflects the abundance of prokaryotes in all environments (Keeling & Palmer 2008) and the relative ease of detecting such HGT events, due both to the wealth of bacterial genomes publicly available and the marked differences between eukaryotic and prokaryotic genomic features.

Eukaryote-to-eukaryote gene transfers may prove to be more frequent when more genome sequences become available. A number of HGT events have been facilitated by mobile genetic elements (Friesen *et al.* 2006). There are now many convincing examples of HGT conferring a selective advantage on the recipient fungal host, as outlined below.

HGT promoting pathogenicity on plants. Fungal pathogens have provided several examples of horizontal transfers, including the acquisition of new virulence factors by HGT. For example, the toxin-encoding gene *ToxA* was transferred in the 1940s from the wheat pathogen *Stagonospora nodorum* to another pathogenic fungus, *Pyrenophora tritici-repentis* (Friesen *et al.* 2006). This HGT, mediated by TEs, allowed *P. tritici-repentis* to acquire virulence on wheat. Another study on the same genus revealed the presence of numerous genes acquired by HGT from bacteria and plants and directly associated with virulence factors, that is, genes encoding proteins that interfere with plant-defence responses or enzymes that can degrade plant cell walls (Sun *et al.* 2013). Another example is provided by the acquisition, by fungal pathogens infecting cereal hosts, of novel virulence factors from bacteria also present in grains (Gardiner *et al.* 2012).

The acquisition of virulence factors by whole-chromosome HGT has also been reported in fungi. In *Fusarium oxysporum*, a whole 'pathogenicity chromosome' bearing a collection of genes encoding small proteins involved in virulence has been horizontally transferred between otherwise genetically isolated strains. The possibility of transferring a whole chromosome between strains was confirmed experimentally by simply incubating strains together (Ma *et al.* 2010). In *Alternaria alternata*, a small extra chromosome is present only in strains pathogenic on tomato. Genetic divergence patterns suggest that this chromosome was also acquired by HGT (Akagi *et al.* 2009). The acquisition of pathogenicity chromosomes by HGT can thus mediate the evolution of pathogenicity in fungi.

HGT of secondary metabolic clusters. In addition to horizontal transfers of single genes or whole chromosomes, several transfers of gene clusters have been described, involving, in particular, clusters controlling the biosynthesis of secondary metabolites. For instance, the ascomycetous mould *Trichoderma reesi* has acquired a cluster of nitrate assimilation genes from a distantly related fungus from the phylum Basidiomycota (Slot & Hibbett 2007). It has been suggested that this transfer facilitated a niche shift in fungi and may have been a key acquisition for the colonization of dry land by Dikarya, the group formed by ascomycete and basidiomycete fungi. Another example is provided by the intact transfer of a 23-gene cluster involved in the biosynthesis of a highly toxic secondary metabolite pathway between ascomycetes from different taxonomic classes: from a Eurotiomycete (*Aspergillus* species) to a Sordariomycete (*Podospora anserina*) (Slot & Rokas 2011). This HGT increased the toxicity of the receptor species and highlights the importance of HGT for metabolic diversity of fungi.

It has even been suggested that the organization of secondary metabolite genes into clusters in fungi is a consequence of their acquisition by HGT (Walton 2000; Slot & Rokas 2010), by analogy to the 'selfish operon' theory in prokaryotes (Lawrence & Roth 1996). If transfers are frequent, then the organization of genes into clusters is selectively advantageous for the cluster itself, because it increases its dispersal and its probability of survival. The presence of multiple virulence-related genes on pathogenicity chromosomes that are transferred horizontally may result from the same type of selection.

HGT and adaptation to extreme environments. Some HGTs in fungi have been shown to be involved in the adaptation of species to extreme environments. This is the case for the wine yeast *S. cerevisiae* EC1118, which can tolerate harsh wine fermentation conditions characterized by high sugar and alcohol content, hypoxia, low nitrogen, vitamin and lipid contents (Novo *et al.* 2009). Three genomic regions of foreign origin have been detected in this wine yeast strain; one of these regions was probably acquired by HGT from *Zygosaccharomyces bailii*, a yeast contaminant of wine that is known to be able to survive the entire fermentation process. Several prokaryotic glycosyl hydrolases have also been acquired via HGT by fungi inhabiting the rumen of herbivorous mammals (Garcia-Vallvé *et al.* 2000), allowing the colonization of this new environment in which cellulose and hemicellulose are the main carbon sources.

A striking example of HGT associated with domestication is provided by cheese-associated *Penicillium* species (Cheeseman *et al.* 2014), in which multiple, independent, recent transfers of a long genomic tract of about 500 kb have been detected. The screening of hundreds of different strains and species from diverse environments revealed the presence of the transferred regions only in *Penicillium* strains associated with dairy environments. This transfer might confer a competitive advantage in the complex and highly nutritive cheese environment, as it contains the gene encoding the *Penicillium* antifungal protein (Marx *et al.* 2008), which has been shown to have cytotoxic activity against various filamentous fungi in vitro (Kaiserer *et al.* 2003).

HGT thus seems to be a significant source of evolutionary novelty in fungi and is often associated with

major adaptive transitions, such as the acquisition of pathogenicity, the infection of new hosts and, more generally, adaptation to new environmental conditions. The publication of larger numbers of genome sequences may reveal that HGT is of general importance in eukaryotes.

Conversion of divergent adaptation into reproductive isolation

The nature of the mechanisms responsible for the transition between adaptive polymorphism and speciation remains one of the central questions in evolutionary biology. The mechanisms of reproductive isolation in fungi have been reviewed elsewhere (Kohn 2005; Giraud *et al.* 2008), including at the genomic level (Stukenbrock 2013; Leducq 2014). We focus here exclusively on the two principal phenomena converting adaptation directly into speciation: pleiotropy between adaptation and reproductive isolation, and Bateson–Dobzhansky–Muller incompatibilities (BDM), in which rapidly evolving genes cause deleterious interactions in hybrids.

Pleiotropy and linkage

When adaptive divergence occurs in the face of gene flow due to divergent selection, recombination impedes the construction of adaptive allelic combinations (Rice 1987), unless specific mechanisms keep the alleles together. These mechanisms include recombination suppression (Kirkpatrick & Barton 2006) and the evolution of assortative mating, with the most favourable situation for adaptive divergence being a locus pleiotropically inducing adaptation to a specific niche and assortative mating (Maynard Smith 1966). Such traits controlling both local adaptation and assortative mating have long been considered as exceptions, but might be more widespread than previously thought, as several cases have recently been reported (Servedio *et al.* 2011). A particular case of interest is host specificity in pathogenic ascomycetes: as these fungi mate within their host after growing and obtaining resources, mating can only occur between individuals adapted to the same host, so host specificity also controls assortative mating (Giraud *et al.* 2010). Ecological divergence in pathogenic ascomycetes is further facilitated by the small number of genes involved in host specificity, with a single toxin gene or virulence allele being able to confer the ability to colonize the host. This, combined with the billions of spores produced, provides opportunities for mutation and a high selective load (Giraud *et al.* 2010). One well-studied example is *Venturia*, the fungus responsible for apple scab, in which population divergence between hosts and within apple orchards in sympatry has been associated with a single virulence locus, causing instant adaptive speciation (Giraud *et al.* 2010; Gladieux *et al.* 2011). As host specificity can pleiotropically cause reproductive isolation, interfertility can be retained long after speciation, without the development of incompatibility (Giraud *et al.* 2008; Le Gac & Giraud 2008). A genome scan comparing closely related *Venturia* pathogens revealed no genes under selection other than the gene involved in the ability to infect the host plant and no incompatibility footprints, with the entire genetic structure explicable by the presence or absence of virulence alleles (Leroy *et al.* 2013). Such traits controlling host specificity and assortative mating pleiotropically are therefore not only conducive to adaptive divergence but also leave specific genomic footprints.

Genetic incompatibilities

Reproductive isolation can arise directly from genes responsible for adaptation to divergent ecological niches, but it can also evolve as a by-product of rapidly evolving genes in closely related species that will become incompatible when brought together in hybrids. Epistatic interactions between alleles at different loci that are deleterious in hybrids, causing intrinsic nonviability or sterility, constitute a form of BDM incompatibility often observed in hybridizing species (Orr & Turelli 2001). Alternatively, hybrid nonviability may result from poor suitability for growth in parental environments, also referred to as 'extrinsic isolation' (Egan & Funk 2009).

According to the BDM genetic incompatibility model, epistatic interactions at two or more loci in hybrids tend to be negative, causing sterility or nonviability (Coyne & Orr 2004). This model is widely accepted and has been supported both theoretically and experimentally (Presgraves 2010). However, only a few genes involved in such incompatibilities have been identified in a handful of model species (Presgraves 2010). Several of these 'speciation genes' were identified in fungi and, strikingly, many involve mitochondrial–nuclear incompatibilities and display rapid evolution (Lee *et al.* 2008; Anderson *et al.* 2010; Chou *et al.* 2010). One elegant study used chromosome replacement lines in two yeast species and identified a genetic incompatibility between an *S. bayanus* nuclear gene and *S. cerevisiae* mitochondria, resulting in F2 hybrid sterility (Lee *et al.* 2008). The rapid evolution of a mitochondrial gene impedes the interactions of its RNA with a protein encoded by the nucleus, preventing its translation. Another systematic screening of incompatibilities between yeast species also identified mitochondrial–nuclear incompatibilities (Chou *et al.* 2010). It has been suggested that some

incompatibilities in yeasts are more complex than mere interactions between two loci (Kao & Sherlock 2008).

BDM genetic incompatibilities are often considered in opposition to ecological speciation, but these two processes may actually be associated. The most detailed examples of this association have been provided by laboratory studies with saprotrophs. In a now classic experiment, the initial stages of speciation were provoked by growing replicate *Saccharomyces cerevisiae* populations under different suboptimal growth conditions, on high-salinity or low-glucose minimal medium (Dettman *et al.* 2007). After 500 generations, postzygotic isolation had evolved, in the form of a lower fitness of hybrids due to antagonistic epistasis, as a direct consequence of divergent adaptation. Whole-genome sequencing revealed that postzygotic isolation was caused by a BDM incompatibility between the evolved alleles of genes conferring higher fitness in high-salt and low-glucose media, respectively (Anderson *et al.* 2010). This work neatly demonstrates how divergent selection can drive the evolution of intrinsic genetic incompatibilities between populations and shows that adaptive divergence is not limited to the evolution of inherently ecological forms of reproductive isolation, such as ecological selection against migrants or hybrids (Nosil 2012).

Divergent adaptation was also found to promote reproductive isolation directly in an experiment in *Neurospora* (Dettman *et al.* 2008), indicating that this process may be widespread among fungi and illustrating the convenience of the experimental models available in this kingdom for the testing of evolutionary hypotheses. In this study, two incompatibility loci (*dfe* and *dma*) consistent with the BDM model were identified and shown to cause severe sexual reproduction defects in the hybrids of evolved populations, and in naturally occurring hybrids of *N. crassa* and *N. intermedia.*

BDM incompatibilities are powerful mechanisms known to be involved in isolation, but they may not be as widespread as generally thought. Some genome-wide analyses in fungi have failed to find BDM incompatibilities despite the screening of almost the entire genome by chromosome replacement experiments (Greig 2007; Kao & Sherlock 2008; Lee *et al.* 2008). Furthermore, studies investigating the shape of the decrease in fungal hybrid fitness as a function of genetic distance between species found no evidence of the snowball pattern expected under the hypothesis of a predominance of BDM genetic incompatibilities (Gourbiere & Mallet 2010; Giraud & Gourbiere 2012). The linear or slowing decrease in fitness appeared more consistent with reinforcement, sterility due to karyotypic variation or a lack of ecological suitability of hybrids (Gourbiere & Mallet 2010; Giraud & Gourbiere 2012).

Conclusion and future prospects

We have reviewed the numerous insights into the genomic processes of adaptive divergence in eukaryotes provided by studies on fungi. Many predictions have been validated, such as the role of gene duplication in novel functions, the positive impact of TEs on evolvability, the importance of changes in gene regulation, the clustering of some adaptive changes in particular genomic regions and the occurrence of BDM incompatibilities. Other processes, previously considered anecdotal, have been shown to feature prominently among the drivers of adaptive divergence. These processes include gene deletions, introgressions, changes in genomic architecture and HGTs. The strength and nature of ecologically based divergent selection or life cycle characteristics have also been shown to be important. The genomic heterogeneity in rates of evolution in some fungi, with regions differing in their susceptibility to mutations, may facilitate the resolution of an apparent 'conflict of interest' between different classes of genes. Isochore-like structures, for instance, make it possible to cope with trade-offs in which there is a need to maintain some functions under strong constraints, with others evolving rapidly in response to positive selection. This trade-off may also be resolved by gene regulation, with promoters differing in evolvability according to the type of function.

Increasingly affordable sequencing will continue to contribute to genomic studies of fungal adaptation and speciation, making it possible to address a new range of questions. Future challenges include understanding how the selective pressures on phenotypes are reflected in genome evolution and the extent to which coding and noncoding sequence differences between species are adaptive. Large-scale genome resequencing projects will also improve our understanding of local adaptation and diversification within species. Population genomics studies will make it possible to identify the genomic regions that have experienced selective sweeps without the need for a priori gene candidates, thereby revealing the relative importance in adaptation of regulatory changes versus changes in coding sequences, and, more generally, the genomic features underlying adaptive phenotypes. Dramatic improvements in the functional annotation of fungal genomes should facilitate real progress in the use of such reverse-ecology approaches, which are just beginning to be applied to fungi. Increasing the number of sequenced species will make it possible to assess the actual extent of eukaryote-to-eukaryote HGT. We are also just beginning to unravel the genomic architecture of adaptive divergence, and many processes occurring at the genome scale are still probably not understood or not even predicted.

Studies of the genomic processes allowing adaptive divergence in the face of gene flow are also required, for which fungal models will be ideal. In particular, domesticated fungi, recently emerged pathogens and experimentally evolved populations will make it possible to investigate the earliest stages of divergence in the face of gene flow, before they become confounded with other species differences. Experiments associated with genome sequencing will be required for investigations of the relative importance of BDM incompatibilities in speciation, the traits inducing pleiotropically adaptation and reproductive isolation, the intrinsic ecological barriers to gene flow (selection against immigrants and hybrids) and genomic rearrangements. In particular, the role of rearrangements as a protection against recombination for accumulating a suite of coadapted alleles allowing local adaptation in the face of gene flow is still debated (Navarro & Barton 2003), and this aspect could be investigated with fungal genome sequences. Improvements in assembly technology will be required for this, and optical mapping appears to be particularly promising in this respect (Hood *et al.* 2013).

New methods for analysing genomes are continually becoming available, making it possible to test new hypotheses. For instance, recently developed methods have made it possible to investigate the co-evolution of protein-encoding genes within genomes through the use of machine learning processes (de Vienne & Aze 2012) or to generate testable hypotheses from phylogenetic profiles for lineage-specific functional modules in the form of information about the correlated gain and loss of protein families (Pellegrini 2012). These approaches are based on a rationale of identifying gene families with correlated or coupled evolution. Advances in theoretical population genomics have also increased power for the inference of demographic parameters (Gutenkunst *et al.* 2009; Excoffier *et al.* 2013), determinations of the relative importance of natural selection and random genetic drift for shaping molecular evolution (Messer & Petrov 2013), and the identification of genes under natural selection (Eilertson *et al.* 2012). More generally, systems biology is another fascinating perspective for studying fungal genomes. Systems biology studies on genomes have mostly focused on deciphering molecular networks and biochemical pathways so far (Costanzo *et al.* 2010; Altelaar *et al.* 2013; Mitra *et al.* 2013); however, this approach could be useful for understanding genome evolution and adaptation and even for predicting evolutionary trajectories (Papp *et al.* 2011).

Acknowledgements

This work was supported by the ANR Grant 12-ADAP-0009-02-GANDALF and the ERC starting grant, GenomeFun 309403 to TG, the ANR FROMA-GEN Grant ANR-12-PDOC-0030 to AB, the National Science Foundation Grant DBI 1046115 to SB and Marie Curie postdoctoral fellowships to PG [FP7-PEOPLE-2010-IOF-No.273086], GA [FP7-PEOPLE-2010-IEF-No.274223] and RRDLV [FP7 COFUND PRES-SUD No. 246556]. We thank François Delmotte, Tobin Peever, the Mycology Laboratory BIOTEC and Jacques Guinberteau (INRA) for the pictures in Fig. 1.

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All authors contributed to writing the review. TG supervised the writing.
