

Interspecific hybridization as a primary force inevolutionary transformation of fungi

ABSTRACT

Gene transfer across species is often linked to bacteria, which have developed a lot of approaches to promote horizontal DNA exchange. But whole-genome sequencing has shown that fungal species exchange DNA as well, resulting in interwoven lineages, unclear species boundaries, or even the emergence of new species. The interspecific hybridization (IH) that occurs in fungi, as opposed to prokaryote DNA exchange, results in a polyploid genome that is very unstable and quickly develops into more stable derivatives. Genotypic and phenotypic diversity may be combined in creative ways to improve fitness and facilitate the colonization of different habitats in the resultant hybrids. IH led to the formation of major pathogens for plants and humans (for example, numerous "powdery mildew" and *Candida* species, respectively), as well as important industrial yeasts, including *Saccharomyces* hybrids that are vital in the manufacturing of cold-cellared Belgian beers and cold-fermented lagers. In this review, we explore the genetic mechanisms and evolutionary consequences of IH in fungi, as well as some of the most well-studied instances of this phenomenon. It's also possible to research the molecular processes that underlie evolution, speciation, and adaptation by using hybrids; this may also lead to the creation of novel varieties for commercial use.

Keywords: Horizontal gene transfer; transcriptome shock; heterosis; interspecific hybridization; reproductive barriers

1. INTRODUCTION

The idea that organisms from distinct species do not share DNA has largely been disproven. As far back as 1928, Frederick Griffith demonstrated experimentally how genetic information may be transmitted horizontally across *Streptococcus pneumoniae* strains [1]. It was later discovered that the sharing of genomic information was not limited to transfers between species. Multiple independently developed asexual mechanisms, on the other hand, allow for horizontal gene transfer (HGT) across distinct species [2]. For certain bacterial lineages, the idea of "species" is no longer relevant because of HGT, which has a dramatic effect on the evolution and adaption of bacteria [3].

Contrary to this, genetic material transfer across eukaryotic species has traditionally been seen as a rare occurrence with limited evolutionary significance due to the fact that the ensuing progeny are almost always sterile. Some plant species may interchange DNA and these occurrences, albeit uncommon, have long been recognized by botanists as key factors in plant evolution [4–6]. Lately, an increasing number of sequenced genomes has shown that most eukaryotic genomes include loci that derive from different species, indicating that interspecific exchange of DNA exists throughout all kingdoms of life [7,8], including fungi [9–11]. [12,13]. A process known as "interspecific hybridization" (IH) is responsible for the majority of the exchange of fungal genomic material across species.

The most well-known method of HGT between organisms is sexual hybridization. In order to produce a zygote that incorporates the DNA from both parents, meiosis must produce a variety of mating kinds of gametes, a suitable mating partner must be identified, and finally, the two cells must fuse. These fundamental characteristics are seen throughout the tree of life, although fungi have developed a wide

range of specialized processes and a significant diversity is observed at the time of karyogamy [14]. Karyogamy occurs rapidly in Zygomycota and Chytridiomycota, often followed by meiosis directly [15]. Basidiomycota and Ascomycota, on the other hand, have karyogamy that may be delayed, leading to cell lineages that retain the nuclei of each parent. In some species (such as *Saccharomyces cerevisiae*), karyogamy is rapidly induced after mating, while in others (such as Basidiomycota), the dikaryotic phase lasts until the beginning of the next sexual cycle [16].

Parasexuality, contrary to the sexual cycle, is a phenomenon that is only seen in fungi and some other microorganisms. Without the necessity for meiosis, parasexual processes allow for the transmission of genetic material. The process begins with the merging of hyphae, which results in the formation of multinucleated cells known as "heterokaryons". Genetic instability, as well as poor fitness, may lead to the reversion of heterokaryons to homokaryons [17]. Alternatively, mitotic crossover and nuclear fusion may occur in heterokaryons, resulting in diverse groups of heteroploid hybrids, which are commonly followed by chromosomal losses [18,19].

As a starting point for this review, we present an outline of the numerous kinds of reproductive barriers as well as their strengths. Although these hurdles may be surmounted, hybrids are not certain to succeed in the long run due to their intrinsic instability, fitness problems, and the potential for severe genetic alterations. Next, we will look at the short- and long-term effects of IH on the genome, proteome, phenome, and transcriptome of the organism. We demonstrate how genetic instability may ultimately lead to a unique adaptive potential, enabling hybrids to rapidly acquire traits that allow them to colonize habitats that are unavailable to either of the parent species. We end by discussing the origins and evolutionary histories of several noteworthy fungal hybrids that have emerged and thrived in habitats that have been influenced by humans. For instance, several new studies indicate how hybridization fueled the creation of significant plant pathogens, but also highlight how numerous benign yeasts employed in the manufacturing of fermented items such as bread, wine, and beer have a complicated genealogy of hybridization.

2. RESOLVING REPRODUCTIVE BARRIERS IMPEDING HYBRIDIZATION

The traditional perspective on the concept of biological species is that species are depicted as different populations that are also reproductively segregated from one another [20]. Hybridization is prevented when reproductive barriers exist between species, limiting the flow of genetic material. Nevertheless, even if these barriers to reproduction are resolved and a hybrid is created, the evolutionary result is dependent on the existence of boundaries among the parent species and the newly produced hybrid. When the hybrid and the parent species are restricted from crossing, the chances of the hybrid evolving into a unique population increase. As a result, when these reproductive barriers are missing or permissive, newly produced hybrids often participate in recurrent backcrossing with one of the parent species, which results in a reduction of the alternative parent subgenome and is referred to as "introgression" [21].

Reproductive barriers are generally separated into postzygotic and prezygotic barriers in plants, animals, and Ascomycota. However, in species with a lengthy dikaryotic stage (such as Basidiomycota), this term may be confusing, therefore we will just use the terms "premating" and "postmating" in this article.

2.1 Premating barriers

The first need for hybridization is that species must exist in the same location at the same period of time. A strong premating barrier is one that isolates the parent species geographically, ecologically, and temporally. Temporal isolation is rare in fungi, unlike ecological and geographical isolation, which are widespread in fungi. *Ampelomyces* spp., which are slow-growing pycnidial fungi and well-known intracellular mycoparasites that prey on phytopathogens, are a good illustration of how temporal isolation may help preserve genetic differentiation [22].

Additional premating barriers, such as preferred selfing and assortative mating, may persist even if the species are neither separated in space nor time. *Microbotryum violaceum* [23] and *Saccharomyces paradoxus* [24] have been shown to exhibit preferred selfing, which reduces the frequency of interspecific mating in these organisms. Gametes, which are produced in fungi during assortative mating, can distinguish between heterospecific and conspecific individuals. This is achieved, for example, by the use of pheromones and receptors that are species-specific [25].

As a result of the rise of large-scale agriculture, globalization, industrialization, and climate change, several obstructions to hybridization have been removed. In the case of pathogens, this barrier elimination is particularly crucial, and globalization is considered to be a primary cause of their growing prevalence [9,26]. As an example, *Batrachochytrium salamandrivorans* and *Batrachochytrium dendrobatidis* are the causal agents of the disease chytridiomycosis, which has caused catastrophic damage to about half of the amphibian species [27,28]. It is believed that both of these species emerged on the Asian continent [29], but human activities have contributed to their global dispersal, allowing for the creation of novel, highly infectious genotypes via hybridization among divergent lineages.

2.2 Postmating Barriers

A variety of conditions, many of them interrelated, may reduce the viability and sterility of newly generated hybrids after mating. "Bateson–Dobzhansky–Muller incompatibilities" (BDMIs) may arise when two species that developed separately acquire variations that are not compatible with one another (BDMIs). Due to the adverse epistatic linkages that destabilize co-adapted gene structures, BDMIs are detrimental, and their appearance is determined by parent populations' evolutionary history [37]. *Saccharomyces*, for example, had a more rapid emergence of mutations that resulted in BDMIs compared to parent populations that developed in similar habitats [19,38]. In one instance, the incompatibilities were traced back to an antagonistic epistatic impact between mutations present in both parents, more precisely between allelic variations of MK1 and TPMA1 [19]. In parent lineages, the discrete mutations are beneficial, but in hybrids, the combination of mutations leads to a decreased glucose absorption rate. When competing alleles of certain loci known as 'vic' (vegetative) or 'het' (heterokaryon) are expressed in the adjacent hyphal cytoplasm, vegetative incompatibility may occur in parasexual reproduction. This can lead to the induction of apoptosis [39].

Antirecombination may be responsible for as much as 98% of hybrid infertility in *Saccharomyces*, according to two recent studies [40,41]. Whole-genome duplication in the hybrid may occasionally resolve this kind of sterility, providing homologous chromosomes with proper meiotic pairing [42–45]. However, due to the fact that fungal hybrids are able to proliferate asexually, even total infertility does not always restrict the evolutionary capacity of these organisms. This fundamental distinction from the majority of complex eukaryotes, especially mammals, is a major contributor to the widespread occurrence of fungal hybrids.

3. Physical Superiority of Hybrids

A phenomenon known as "heterosis" or "hybrid vigor" describes situations in which hybrids exhibit superior performance compared to their parents regarding certain characteristics. Hybridization of distinct species' genomes has long been recorded, but scientists have been unable to come up with a single explanation for how this process works for over 100 years. There are a variety of models that have been discussed. Models such as these are not completely incompatible, and their respective importance may vary depending on the genotype and phenotype. According to the prevailing theory in the area, heterosis is caused by the increase of pathways that promote growth [50]. Charles Davenport, who coined the word "dominance" in 1908, was the first to suggest this idea. According to this theory, advantageous dominant alleles inherited from one parent can mask the potentially harmful recessive alleles inherited from another parent. The 'overdominance' idea was proposed by geneticists George Shull and Edward East in the same year. According to this idea, heterosis is caused by greater rates of heterozygosity throughout

the hybrid. This phenomenon is known as "heterozygote advantage," and it suggests that hybrids possess a duplicate of "the best" parent allele for every gene and environment. This model has evolved over the years, with the most popular variation being the "pseudo-overdominance" model. In the phenomenon known as pseudo-overdominance, conjugation occurs for separate recessive alleles expressed in tight association but on opposing members of a set of homologous chromosomes, giving the appearance that overdominance is functioning, but in reality, it is not [50]. Finally, heterosis may be caused by newly developed favorable linkages in the hybrid across alleles from distinct loci, referred to as "epistasis" [51].

Even though these theories have been generally accepted, they fail to explain all documented occurrences of heterosis [50,51]. The notion that "heterosis" and "genetic incompatibility" are two distinct processes was called into question by a model that was presented in the year 2017 [52]. Because of incompatibilities within the hybrids, regulatory systems that have developed to guard cells against harm or to equip them for the challenges of the future are hampered in their work in this model. For instance, the checkpoints that regulate the cell cycle no longer work properly, and as a direct result of this, cells of a hybrid do not slow their growth in exposure to moderate stimuli. This approach has been scientifically proven in engineered *Saccharomyces* hybrids; nevertheless, it is unknown to what degree such flaws in safety systems are significant over prolonged evolutionary periods and for longevity in natural habitats that are prone to change.

4. GENOTYPIC INSTABILITIES IN HYBRIDS

It's vital to keep in mind that improved hybrid fitness doesn't always appear right away after hybridization. When two different genomes are brought together in a single nucleus, the immediate consequence of this might be ineffective. Natural selection has refined the genomes of both parents; therefore, this malfunction, although not fatal, may lead to lower fitness [49,54]. Interspecific hybrids, on the surface, seem to be unable to compete with their parent species. Conversely, the genotypes of freshly produced interspecific hybrids are very unstable, and they rapidly spawn new variations via a variety of molecular processes that may shuffle, augment, delete, or otherwise change the acquired genetic blocks [21]. As a consequence of this extraordinary flexibility, harmful associations across the two subgenomes may be reduced or eliminated, leading to an improved fitness-enhancing genotype, a process known as "genome stabilization" (Fig. 1).

4.1 Mitonuclear pairing

The outcome of hybrids may be determined by the genome of the mitochondria and the way that it interacts with the genome of the nucleus. Within the kingdom of fungi, there is a wide range of variations in mitochondrial inheritance throughout hybridization. Uniparental inheritance occurs in most Basidiomycetes during hybridization, and the mitotype that is inherited may have a significant impact on the traits of the hybrid [79]. *Heterobasidion annosum*, among the world's most destructive tree pathogens, is an example of a fungus in which virulence is directly linked to its hereditary mitotype [80]. In ascomycetes, biparental inheritance occurs, and hybridization may result in chimeras that include both nuclear and mitochondrial DNA [81,82]. Vegetative segregation, on the other hand, results in the hybrid lineage having just one mitotype when it has been fixed. Genetic drift may influence the mitotype that is kept, but more commonly, there is a selection of a particular mitotype [59]. Mitonuclear abnormalities, which are widespread in fungi [83–86], may be eliminated by eradicating a mitotype, although positive selection has also been shown. Lager yeasts, for example, have been shown to carry mitochondria from *S. eubayanus*, which is compatible with the evolution of artificial hybrids under a lager-like environment [59,87]. The primary advantage of these mitochondria is cold resilience, which is essential for the lager fermentation process [88,89,90].

4.2 Whole-genome duplication

Whole-genome duplication is one more typical outcome of IH, and it has been frequently observed throughout plants [42–46,78]. It can repair chromosomal pairing, allowing meiosis to begin [42]. IH has been proposed as the root source of the well-documented whole-genome duplication in the *Saccharomyces cerevisiae* lineage [44,45]. It was once thought that this early duplication included autopolyploidization, which occurred millions of years ago. However, new investigations show that the whole-genome duplication was caused by a historical IH process, possibly between two haploid species or between two diploid species that autodiploidized to regain fertility [45].

4.3 Aneuploidy

Another mechanism that occurs regularly during genetic stability is aneuploidy, i.e., the removal or addition of whole chromosomes. Aneuploidies developing during meiosis may lead to impotence and hence impose a reproduction barrier. Nonetheless, aneuploidies could potentially provide an evolutionary benefit by modifying gene load or eliminating dominant detrimental alleles, thereby permitting fast adaptability to stressors [71–74]. In those instances, aneuploidy is regarded as a temporary stage, and the organism typically switches back to euploidy if a more effective genetic mechanism, e.g. a mutation, is obtained [75]. An additional benefit of aneuploidy is that it may assist in the elimination of genetic incompatibilities. As a result, aneuploidy is prevalent in many fungi that are hybridized. For instance, the amplified expression of chromosome 13 in the human pathogenic fungi *Cryptococcus gattii* × *Cryptococcus neoformans* (serotype AD) has been associated with enhanced virulence [76]. The chromosomal copy number varies widely across strains of the *Saccharomyces cerevisiae* × *S. eubayanus* brewing yeast hybrid, with a total of 45 to 79 per cell [77]. This diversity is functionally significant because variations that vary from one another solely in the number of chromosomal copies may display considerable changes in phenotypes that are relevant to industry, including flocculation and the formation of the off-flavor chemical compound diacetyl [78].

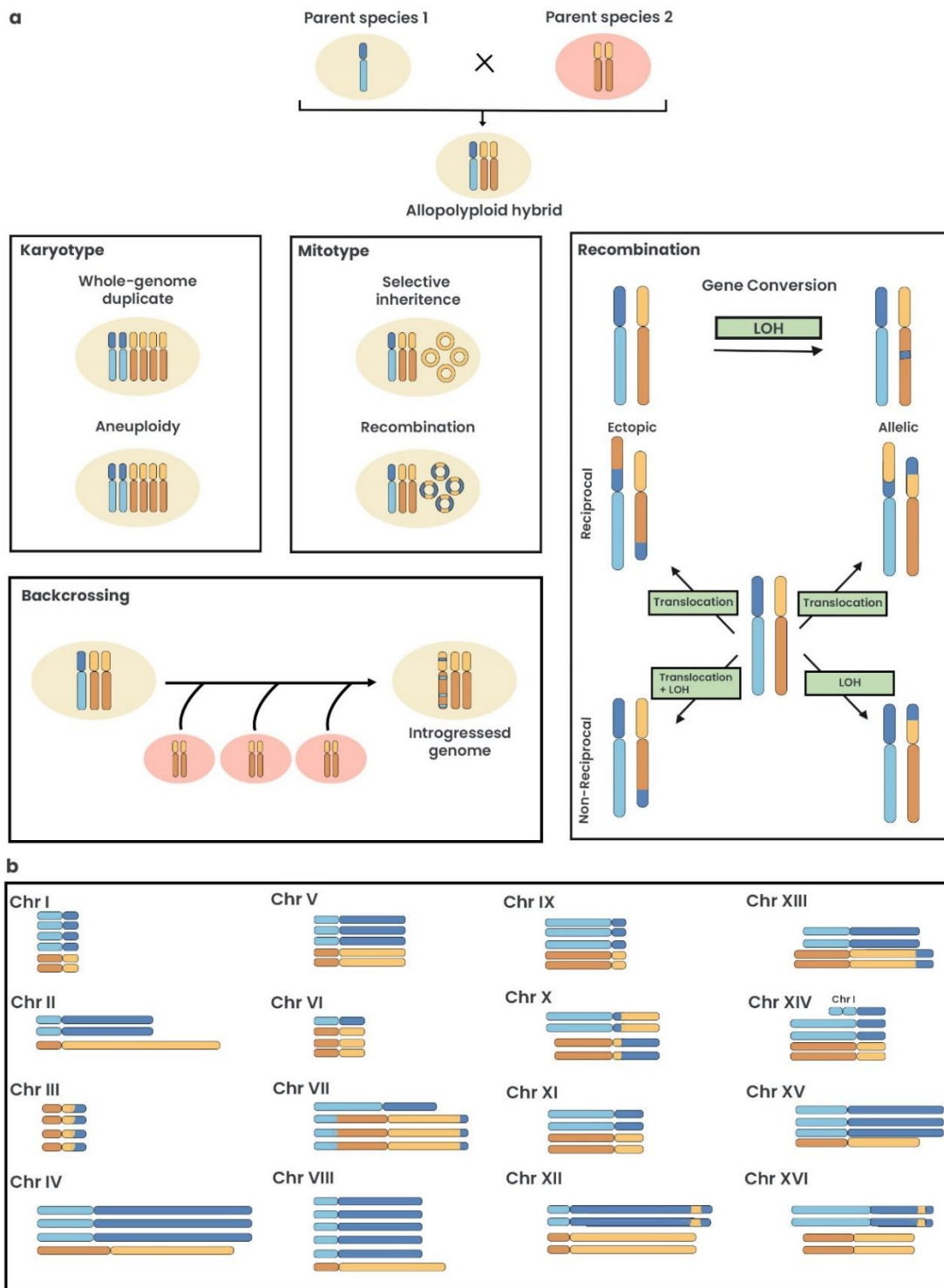


Figure 1. Genome Stabilization after hybridization

5. HYBRIDIZATION-INDUCED TRANSCRIPTOME SHOCK

Different genomes combined within one nucleus alter the parent species' transcription regulatory system, which affects both gene regulation and absolute expression levels. In plants and animals, these expression adjustments have been extensively studied and can involve subgenome dominance [91–93], homoeologue expression bias [93–95], chromatin accessibility adjustments [96], and interspecies transcriptional rewiring [97–99], commonly referred to as "transcriptome shock" [100–102].

When it comes to natural hybrids, it might be difficult to determine if the transcriptional modifications are a result of polyploidization or hybridization. In addition, the transcriptional response prior to genome stabilization differs from long-term changes brought on by genome restructuring or selection because of the varied pace at which some changes develop after hybridization. However, a number of recent studies have started to shed light on the phenomenon of transcriptome shock in fungus by using both artificial and natural hybrids [52,101–109]. Unlike plants and animals, fungal hybrids appear to have a milder reaction to this shock, and the variations in expression levels among parents are mainly retained after hybridization [105,109]. This lack of transcriptional interaction between the two species' networks may explain the substantial divergence across the two parents' transcriptional resilience [110]. For instance, in engineered *S. uvarum* × *S. cerevisiae* hybrids, 87% of homoeologous genes inherited similar expression levels of the respective orthologous genes as in the parent species. There was only a 10% genetic difference across homoeologues in the hybrids and orthologues of the parent species, while the rest of 3% exhibited larger homoeologue expression differences than orthologues [106]. Some plant hybrids, such as rapeseed [112] and cotton [113], have a substantially greater number of genes exhibiting gene expression modifications, with one-third of orthologues indicating homoeologue expression blending or bias. However, the percentage of genes exhibiting gene expression variations in certain plant hybrids is substantially higher, with around one-third of orthologues in cotton [112] and rapeseed [113] hybrids exhibiting homoeologue expression bias.

6. PATHOGENIC AND INDUSTRIAL HYBRIDS

In terms of evolutionary adaptability to abrupt environmental and ecological changes, it might not be unexpected that IH has been essential in fungal adaption to new niches established by humans. Some examples of these niches include the manufacturing of cheese, beer, and wine as well as naive populations that have been afflicted by emergence of new pathogens.

6.1 Pathogenicity

It is especially important for fungi involved in symbiotic associations, such as mutualistic symbionts, endophytes, and pathogens, to have the capability to invade novel habitats or swiftly adjust to changes in their environment [9,140]. Pathogens, in particular, must be able to adapt quickly in order to keep up with the ever-changing immune systems of their hosts. Therefore, the fact that hybridization plays such a large role in these processes and yields variants with varying levels of virulence or host specificity is not surprising [9,11]. A serious concern is posed by certain hybridization-driven host range expansions, which may lead to epidemic outbreaks [10]. This section focuses on two genera that demonstrate the importance of hybridization throughout the evolution of pathogens, one of which affects crops (*Blumeria*) and another that affects elm trees (*Ophiostoma*).

6.1.1 Powdery Mildews

In addition to the fact that fungi are major human pathogens, infections caused by fungi are responsible for up to one-third of all agricultural losses caused by pests [28]. Powdery mildew is among the most common plant diseases that may affect a broad variety of plant species [149]. The name "powdery mildew" is a general term that describes pathogenic fungi that induce similar symptoms following infection. The pathogen *Blumeriagraminis*, which has received the most attention, infects a wide range of

grasses, including cereals like barley, wheat, and rye. Host-specific sub-lineages (*formaespeciales*) of *B. graminis* have been identified, with hybridization serving as a major driving force for host range expansion. For instance, powdery mildew that attacks wheat (*B. graminis* f. sp. *tritici*) is thought to have originated from an ancient IH activity [111]. This event was projected to have taken place soon after the development of wheat bread roughly ten thousand years ago, which suggests that these pathogens are able to swiftly exploit novel host possibilities generated by agriculture. The appearance of triticales pathogens is another illustration of the swift adaptation that has taken place. With the grain and yield quality of wheat and the environmental resilience of rye, Triticale is a synthetic cross between the two, and it is tolerant to powdery mildews that affect *Triticum* species. Nonetheless, the virulent *B. graminis* strain *B. graminis* f. sp. *triticales* appeared in 2001, which resulted in significant losses of triticales [79]. *B. graminis* f. sp. *tritici* was once thought to have been a result of minor gene mutations, but a detailed genomic examination found that the pathogen evolved through a minimum of two separate hybridization events among wheat-specific and rye-specific mildews, with subsequent recurrent backcrossing events to the wheat-specific mildews, indicating how pathogen adaptation may swiftly track host evolution [132].

6.1.2 Dutch elm disease

The Dutch elm disease (DED) pathogen complex is made up of three different lineages: *Ophiostoma ulmi*, *Ophiostoma novo-ulmi* subsp. *americana* (SSAM), and *Ophiostomanovoulmi* subsp. *novo-ulmi* (SSNU). DED is usually regarded to be among the most destructive plant pandemics. This is due to the fact that two successive pandemics of this fungus have occurred in the last century, resulting in the mortality of around a billion elm trees around the globe [141]. Early in the twentieth century, the first *O. ulmi* pandemic decimated 10–40% of the North American and European elm trees. In the early 1940s, a far more devastating pandemic arose on the same continents, which was driven by the highly aggressive SSAM and SSNU lineages and devastated most of the remaining elm trees. In 2020, a study of 97 DED-causing fungi found that the enhanced virulence of SSAM and SSNU was linked to hybridization [142]. It is clear from the amount of mosaicism across their genomes that interbreeding between SSAM and SSNU was prevalent. Additionally, there were varying levels of introgression with *O. ulmi*, with *O. ulmi* genomic material accounting for 0–8% of the genomes of the two SSAM and SSNU populations. Although functional assessments of these areas are currently limited, they are favored for genes related to virulence and survival.

6.2 Industrial Biotechnology

Fungi are capable of producing a diverse range of fermented products, which the human race has traditionally used for various purposes. Standardized fermentation processes developed in fungi gave humanity a new, reliable supply of nutrients. The initial and most significant element of standardizing fermentation techniques is to transfer material from a finished fermentation to commence another batch, a method known as "backslopping" [127]. Adaptation to a completely novel niche was necessary for the continuous proliferation of microbes in these demanding conditions. IH aided this domestication, or adaption, in multiple cases [10,59,128,129].

In fermentation conditions, hybrids derived from a diverse collection of fungal species have been successfully isolated. IH, on the other hand, is particularly widespread in the *Saccharomyces* genus, where about 50% of the known species have been implicated in hybridization occurrences. Some hybrids even reveal an ancestry that includes four different species (*S. kudriavzevii* × *S. uvarum* × *S. eubayanus* × *S. cerevisiae*) [59]. Strains utilized to make lager-type beers comprise a unique allopolyploid hybrid lineage called "*Saccharomyces pastorianus*", which includes two sublineages named after the regions from where they were initially isolated: "Frohberg" and "Saaz". Molecular clock examinations of the *S. cerevisiae* genome found that it is closely linked to the beer yeast from the European continent, which coincided exactly with the start of Bavarian lager brewing during the sixteenth century [11].

Since hybrids are so prevalent in industrial environments, IH has become a well-established approach for generating improved yeasts [134]. As a result, hybrids produced in a lab are now accessible for a variety of products, including beer, wine, sake, cider, baking, biofuel, and the manufacturing of commercial enzymes. These hybrids have a wide range of applications in industrial operations. Increasing stress tolerance or fermentation vigor may give a competitive advantage in certain cases, but most of the time the benefit is related to the development of novel metabolite profiles. There are a number of benefits associated with carrying out hybridization procedures in a laboratory environment. First, premating obstacles are eliminated, allowing for a greater variety of species pairings. In addition, alternative hybridization methods, such as protoplast fusion, may be applied, which can allow intergeneric crossover.

7. CONCLUSION

In contrast to animal hybridization, which seems to be hampered by substantial genetic distances between parental species, fungal hybridization appears unhindered. As an example, hybrids of *Saccharomyces* with an estimated orthologous protein variation of about 20% have been discovered, which is approximately identical to the gap between humans and chicken species [117]. A large portion of this aggressive hybridization is explained by the tendency of fungi to reproduce asexually following hybridization (enabling infertile hybrids to mature and develop mutations and adaptability that may help overcome any incompatibilities across the subgenomes), as well as by the strikingly identical chromosomal synteny and karyotype across species of the identical species complex [37]. However, despite an increase in incidences of IH and introgressions, they are likely simply the tip of the iceberg.

While hybridization has been exhibited to be a widespread occurrence in the fungal tree of life, it is not yet apparent how often it occurs in populations. In addition, the majority of hybrids are discovered in industrial or clinical settings, which are also the niches that have been sampled the most extensively. In order to better understand the evolutionary significance of IH, a more extensive sampling of additional, more natural settings, especially those with harsh or variable circumstances, is necessary. Moreover, a combination of extensive gene loss, incomplete lineage sorting, and low divergence between parent species may effectively disguise hybridization, particularly for ancient instances. As a result, precise and effective identification of hybridization events across genomes remains a challenge.

When comparing our knowledge of animal or plant ecology, for instance, our current understanding of the ecology of fungi is still in its early stages. When it comes to the geographic range of fungi, the Baas Becking hypothesis, i.e. "everything is everywhere, but the environment selects", is the most widely accepted theory. However, human-associated dispersion of fungal taxa or populations (for instance, fungal pathogens and fermentation-linked species) certainly facilitates hybridization in some circumstances [11,142]. Thus, a more methodical study of fungal biodiversity and how this is influenced by globalization and similar phenomena, including climate change, agriculture, human travel, and pollution, might assist in explaining ancient hybridizations and forecasting future hybridization events.

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