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Review

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Understanding the molecular mechanisms of human diseases: the benefits of fission yeasts

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ABSTRACT The role of model organisms such as yeasts in life science research is crucial. Although the baker's yeast (*Saccharomyces cerevisiae*) is the most popular model among yeasts, the contribution of the fission yeasts (*Schizosaccharomyces*) to life science is also indisputable. Since both types of yeasts share several thousands of common orthologous genes with humans, they provide a simple research platform to investigate many fundamental molecular mechanisms and functions, thereby contributing to the understanding of the background of human diseases. In this review, we would like to highlight the many advantages of fission yeasts over budding yeasts. The usefulness of fission yeasts in virus research is shown as an example, presenting the most important research results related to the Human Immunodeficiency Virus Type 1 (HIV-1) Vpr protein. Besides, the potential role of fission yeasts in the study of prion biology is also discussed. Furthermore, we are keen to promote the uprising model yeast *Schizosaccharomyces japonicus*, which is a dimorphic species in the fission yeast genus. We propose the hyphal growth of *S. japonicus* as an unusual opportunity as a model to study the invadopodia of human cancer cells since the two seemingly different cell types can be compared along fundamental features. Here we also collect the latest laboratory protocols and bioinformatics tools for the fission yeasts to highlight the many possibilities available to the research community. In addition, we present several limiting factors that everyone should be aware of when working with yeast models.

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Abbreviations:
AA - amino acid,
AS - alternative splicing,
ECM - extracellular matrix,
FBS - fetal bovine serume,
GO - gene ontology,
HIV-1 - Human Immunodeficiency Virus Type 1,
MDR - multidrug resistance,
MMP - matrix metalloproteinase,
MTHFR - methylenetetrahydrofolate reductase,
NHEJ - non-homologous end joining,
NuRD - nucleosome remodeling and deacetylase,
PPI - protein-protein interaction,
RNAi - RNA interference,
SAP - secreted aspartyl protease,
Y2H - yeast-two-hybrid

INTRODUCTION

The use of model organisms to understand essential processes is a well-known strategy in life science research. If we take a look at the publication statistics in repositories like PubMed, we can see that there are a substantial number of studies using different model organisms. For example, a quick search in the aforementioned repository resulted in (accessed on 2023.10.16) 142,277 matches for the keywords '*Saccharomyces cerevisiae*', 429,254 for '*Escherichia coli*', 1,945,515 for '*Mus musculus*', 92,105 for '*Arabidopsis thaliana*', 62,541 for '*Drosophila melanogaster*', 36,775 for '*Caenorhabditis elegans*' just a few to mention. This leads us to conclude that the contribution of model organisms to our understanding of basic biological processes is indispensable.

The yeasts have a special place among model organisms because these tiny fungal cells have provided many useful models for different studies. For example, *Candida albicans* and *Cryptococcus neoformans* emerged as models for studying fungal pathogenesis, while *S. cerevisiae* and *Schizosaccharomyces pombe* are useful models for studying the eukaryotic cell cycle and other countless fundamental biological processes. Accordingly, thousands of research articles related to these species are published every year (Fig. 1). Although *S. cerevisiae* is the most popular yeast model, we would like to concentrate on the fission yeasts (*Schizosaccharomyces*) as models in this particular review. The

fission yeasts are widely established models of the eukaryotic cell cycle, cell size maintenance, cellular aging, gene expression and epigenetics, autophagy, and apoptotic processes, just a few to mention.

To our best knowledge, the fission yeast genus consists of six species to date: *S. japonicus*, *S. pombe*, *S. octosporus*, *S. cryophilus*, and the recently described species *S. osmophilus* and *S. lindneri*, and other variants [1–6]. *S. japonicus* has two main varieties: var. *japonicus* and var. *versatilis*, which have recently been proposed to be considered as two different lineages [7]. In our opinion, the two most divergent branches of the genus (*S. japonicus* and *S. pombe*) have tremendous potential (not just) as model organisms.

FISSION YEASTS? FOR WHAT?

Someone may ask the legitimate question: why do we need fission yeasts when we already have well-established and widely used yeast models such as *S. cerevisiae* and *C. albicans*? What can fission yeasts provide that cannot be provided by the aforementioned ones? Most importantly, could a fission yeast be a good (or better) alternative for studying human diseases than budding yeasts? We try to provide answers to these questions while revealing some fundamental differences among the yeast models (Table 1).

Fundamental considerations

At first, we should take a close look at the phylogenies of the fission yeasts. Since they are a basal lineage of the Ascomycota (subdivision Taphrinomycotina), they have a closer phylogenetic relationship with the Metazoa lineage [10, 44–47]. Besides, the fission yeast genus has remarkably conserved common gene content, which is maintained through a relatively long divergence time [10, 48, 49]. Maybe that is one of the reasons for them to preserve many common features with the higher eukaryotes. The fission yeasts are already considered "micro-mammalian" model organisms since they share various fundamental features with the metazoan species, such as chromosomal structure and metabolism, relatively large chromosomes and centromeres, low-complexity replication origins, epigenetic mechanisms for regulation of gene expression and centromere maintenance, G2/M control of cell cycle, cytokinesis, mitosis and meiosis, DNA repair and recombination, the mitochondrial translation code, spliceosome components with functional alternative splicing, post-translational modifications, and RNA interference (RNAi) [10, 11, 50–53].

Chromosomes, centromeres and heterochromatin

The haplontic chromosomal state facilitates genetic modifications and makes the phenotypic association of the mutation more comprehensible. Although both *S. cerevisiae* and *S. pombe* are able to maintain haplontic and diplontic chromosomal states as well, in contrast to *S. cerevisiae*, the fission yeasts preferred the haplontic state. While it seems to be a tendency that the lab strains of *S. cerevisiae* drive towards diploidization after a few generations, the fission yeasts naturally maintain their haplontic form even in the wild [20, 21, 53–57]. Despite possessing similar genome sizes, *S. cerevisiae* has many small chromosomes with short (125 bp) point-like centromeres, while the fission yeasts have few but long chromosomes with large centromeres containing repetitive sequences that are more similar to mammalian centromeres [23, 58]. Nevertheless, the larger chromosome sizes allow for more efficient microscopic examination. Moreover, the fission yeast genome contains regions of centromeric heterochromatin, which is maintained by H3K9 methylation of nucleosomes and RNAi, unlike the budding yeasts that do not have the necessary molecular toolkit for either one [10, 26, 58–60]. Although both *S. pombe* and *S. cerevisiae* have silent chromatin at telomeres, at the mating-type loci, and rDNA regions, only *S. pombe* has silent chromatin at centromeres [40, 61]. In humans, the methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in the folate metabolic pathway, loss of function mutations of which are associated with several human conditions, such as cancer, congenital heart disease, and maybe Down and Turner syndrome, too [62–66]. Lim and co-workers examined the fission yeast equivalent of MTHFR, the Met11, and they revealed that it functions to maintain centromeric integrity to ensure precise chromosome segregation in mitosis and meiosis, as the Δ *met11* null mutant showed increased missegregation of chromosomes in mitosis and increased transcription from centromeric heterochromatic regions [67]. They also observed heterochromatic derepression at subtelomeric and rDNA regions, accompanied by a disruption of H3K9me2 and HP1 protein (Swi6) at all these loci [67]. The human nucleosome remodeling and deacetylase (NuRD) complexes sustain specific gene expression programs required for lineage specification, so they have an important role in development and aging [68, 69]. In many cases of cancer, the subunits of the NuRD complex contain mutations [70] and some of the mutations can also have detrimental effects on neurological and cognitive development [71]. To understand the fundamental function and operation of this heterogenic complex, examination of the fission yeast counterpart Snf2/Hdac Repressive Complex (SHREC) and its interacting partners can be a good alternative [72–75]. Wei and co-workers studied the TOR signaling pathway, and they showed that this cascade targets a conserved nuclear RNA elimination network to dynamically control gene expression by promoting RNA decay and facultative heterochromatin assembly [76]. Since RNA elimination factors are involved in proper meiotic progression during oogenesis and/or spermatogenesis in mammals, their result may shed light on the epigenetic reprogramming during development [76–79]. Thus, the fission yeasts proved to be a very powerful model for the investigation of heterochromatin assembly and epigenetic gene silencing [53]. Surprisingly, unlike higher eukaryotes, and many other fungal species, neither *S. pombe* nor *S. cerevisiae* have DNA methylation processes [40, 41]. However, the heterologous expression of a murine DNA methyltransferase in *S. cerevisiae* resulted in methylated DNA at specific sites [80].

Telomere maintenance

All eukaryotic organisms have precisely defined regions called telomeres at both ends of their chromosomes. Telomere malfunction can cause several problems, from genome rearrangements to several diseases like premature aging, dyskeratosis congenita, and cancer amongst many other

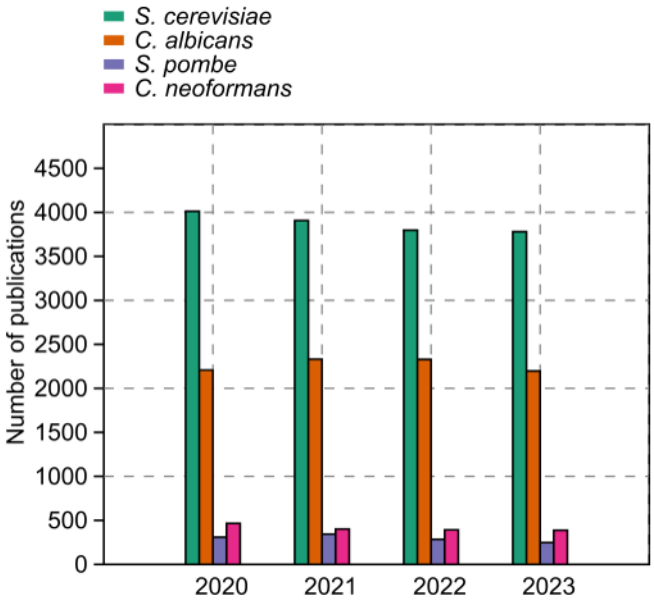

FIGURE 1 ● **Number of published papers at the PubMed repository from 2020 to 2023.** *S. cerevisiae* is for the baker's yeast *Saccharomyces cerevisiae*, and *C. albicans* stands for the opportunistic human pathogen *Candida albicans*. *C. neoformans* represents the medically important species *Cryptococcus neoformans*, and *S. pombe* is for the fission yeast model *Schizosaccharomyces pombe*.

diseases [81, 82]. One of the protein complexes, the heterotrimeric CST complex plays a key role in the regulation of telomere extension, which can be examined in both the budding and the fission yeast systems [83]. The other complex, which contains up to six different proteins, the shelterin-complex has a crucial role in the maintenance of telomeres, as it is responsible for telomere protection and telomerase regulation [83–85]. Strikingly, *S. pombe* has a shelterin-like telomere complex, which lacks in *S. cerevisiae* [83, 84]. Although the fission yeast shelterin-like complex has "only" three obvious protein orthologues with the vertebrates, the overall structure seems to be quite similar [83, 84, 86–89]. Thus, fundamental processes can be investigated in the fission yeasts also in the case of shelterin function [90–92]. As an example, Irie and co-workers observed in *S. pombe* that simultaneous inactivation of the shelterin complex subunits Taz1 (TERF1 in humans) and Rap1 (TERF2IP in humans) enables a substantially higher number of gross chromosomal rearrangements per cell division, not just in the telomeric regions but also in the whole genome [93]. This is also remarkable because extensive chromosomal rearrangements have been reported in many cancers with mutations in the human shelterin complex [81, 94].

Introns and splicing

Since the fission yeasts have thousands of introns in their genes compared to the few hundred introns of *S. cerevisiae*, and have degenerate splice site sequences and exonic splicing enhancers, the former species is again a better choice for investigating maturation of mRNA and misregulated splicing [28, 53]. Although spliceosome components are available in fission yeasts, functional alternative splicing (AS) has been debated because of the low amount of unequivocal evidence. Montañés and co-workers provided exact proof for functional AS and they showed that it is more prevalent in *S. pombe* than it was previously thought [29]. They have identified 332 alternative isoforms affecting 262 coding genes, 97 of which occur with frequencies >20%. The overwhelming majority of the events (~80%) were intron retention, besides intron inclusion, the use of alternative splicing sites, and exon skipping. According to Zheng and co-workers, the phenomenon of intron retention is one of the least understood forms of alternative splicing in the human genome, even though it can be associated with serious diseases, such as Alzheimer's disease and cancer [95].

Protein interactions

Thanks to modern sequencing techniques, we were able to identify thousands of mutations associated with diseases and disorders in humans. However, it is still a serious problem to filter out the noise and find the true causes of the observed phenotypes. Moreover, the International Rare Disease Research Consortium (IRDiRC) also acknowledged that different model organisms are an effective experimental system for investigating the impact of gene variants on protein activity, determining their biological function, and identifying potential therapies [96]. Thus, yeasts as a system seem to be good candidates for this task too [97–99]. To establish binary protein-protein interactions (PPI) and to find out which mutation causes loss of function or reduced functionality, the yeast two-hybrid (Y2H) system is a well-established method [100–102]. For example, a SARS-CoV2 – human protein interactome was examined in a recent study with the combined usage of Y2H and mass spectrometry [103]. Yeasts can also be used for heterologous expression of other eukaryotic proteins, as well as for studying the impact of the foreign protein on the yeast transcriptome and proteome or the effect of different drugs on the proteins to be tested [104–107]. However, these tasks are easier when the interactome of the host is more similar to the tested one. Vo and co-

TABLE 1 ● Fundamental differences of yeast models.

Genome stats/ Biological features	*C. albicans*	*S. cerevisiae*	*S. pombe*	*S. japonicus*
Genome size (Mb)	~ 14.28 (SC5314)	~ 12.24 (S288c)	~ 12.59 (L972)	~ 16.6-18.12 (ATCC10660)
Chromosome number (haploid set)	8	16	3	3
Chromosome sizes (Mb)	0.95-3.19	0.23-1.55	3.5-5.7	~ 3.8-5.75
Coding gene number	6030	5850	5134	4942
Common orthologues with humans	~ 3400	~ 3427	~ 3422	~ 3316
Disease-associated transcripts	YTBD*	~ 1000	1521	YTBD*
Genetic code	CTG	Standard	Standard	Standard
Whole Genome Duplication	pre	post	pre	pre
Preferred chromosomal state	2n	2n	1n	1n
Centromere sizes	3-4.5 kb	125 bp	35-110 kb	610-738 kb
Centromere type	Unique DNA sequence, without repetitive elements	Small, point-like	Large, repetitive sequences	Large, repetitive sequences and transposons
RNAi components	Yes	No	Yes	Yes
RNAi-mediated splicing	No	No	Yes	Yes
Percent proportion of introns	4-6%	2-6%	>50%	>50%
Spliceosome components	Yes	Reduced	Yes	Yes
Alternative splicing	Obscure	Obscure	Frequent	YTBD*
Generation time (hours)	1.7-3.6	1.25-2.0	2.0-3.0	1.0-1.5
Working time of genetic cross (days)	Not applicable	7	4	2.5
Pathogenicity	Yes	Can be	No known cases	No known cases
Hyphae production	Yes	Pseudo	No**	Yes
Cell division	Budding	Budding	Fission	Fission
Mitosis	Closed	Closed	Closed	Semi-open
DNA methylation	Yes	No	No	YTBD*
H3K9 methylation	No	No	Yes	Yes

'Genome size' ref.: [8, 9]. 'Chromosome number' ref.: [10–13]. 'Chromosome sizes' ref.: [9, 11–13]. 'Coding gene number' ref.: [8, 14, 15]. 'Common orthologues with humans' ref.: [14–16]. 'Disease associated transcripts' ref.: [14, 17]. 'Genetic code' ref.: [18]. 'Whole Genome Duplication' ref.: [19]. 'Preferred chromosomal state' ref.: [10, 20–22]. 'Centromere sizes' and 'Centromere type' ref.: [9, 23–25]. 'RNAi components' and 'RNAi mediated silencing' ref.: [10, 26, 27]. 'Percent proportion of introns' and 'Spliceosome components' and 'Alternative splicing' ref.: [10, 28–31]. 'Generation time' ref.: [20, 32–34]. 'Working time of genetic cross' ref.: [32, 35]. 'Pathogenicity' ref.: [36, 37]. 'Mitosis' ref.: [38, 39]. 'DNA methylation' ref.: [40–42]. 'H3K9 methylation' ref.: [10, 26, 43]. * YTBD – Yet to be determined. ** Under standard circumstances, *S. pombe* does not form hyphae.

workers created a proteome-wide binary interaction network for *S. pombe*, and they compared the result with previous data concerning the *S. cerevisiae* and human interactomes [108–111]. Interestingly, they found that only ~40% of *S. pombe* interactions are conserved in *S. cerevisiae*, but ~65% of *S. pombe* interactions are conserved in humans despite the overall higher sequence similarity between *S. pombe* and *S. cerevisiae* [108]. Their results therefore suggest that many of the interactions between humans and *S. pombe* are conserved, but specifically lost in the *S. cerevisiae* lineage. Besides, they tested whether known disease-causing mutations that disrupt PPIs in humans also disrupt PPIs in *S. pombe*. Their results showed that in the three tested cases (NMNAT1-NMNAT1, PCBD1-PCBD1, and SNW1-PPIL1), the introduced mutations in the *S. pombe* counterparts also disrupted PPIs.

Disease-associated genes

The idea that yeast might be a useful model of human diseases has already emerged right after the completion of the sequencing of both *S. cerevisiae* and *S. pombe* [11, 12]. Based on data from Heinicke *et al.*, *S. cerevisiae* has approximately 1000 genes, which have orthologues in gene families associated with human diseases [17]. In the case of *S. pombe*,

we have an up-to-date and relevant information source on this topic, since the PomBase database is in connection with the Monarch Initiative [112, 113] and Mondo database [114]. According to PomBase (https://www.pombase.org accessed on 2024.01.13), *S. pombe* has 1514 transcripts (proteins and ncRNAs) that are considered orthologues of human disease-associated transcripts [14].

THE ADVANTAGES OF FISSION YEASTS IN VIRUS RESEARCH

Viruses can cause various and often fatal diseases. Effective prevention and treatment of these diseases require extensive knowledge about the molecular mechanism of the infection and the changes caused by the viral proteins in the host cells. Various model organisms are used as hosts to reveal consequences of viral infections. The yeasts belong to these model organisms [115], because of their attractive features, such as eukaryotic cell structure, small genome, widely available molecular tools, and the ability of several eukaryotic viruses to replicate in their cells [20, 116, 117]. That is, yeast cells are suitable for heterologous expression and the study of viral proteins.

Here, we would like to provide a brief insight into the research results of viral proteins produced in the fission yeast *S. pombe*, with particular attention to the Human Immunodeficiency Virus type 1, (HIV-1) Vpr protein, which has been extensively studied in this yeast species.

HIV1 causes Acquired Immunodeficiency Syndrome (AIDS) by damaging the immune system, which is a life-threatening condition. The HIV-1 genome contains several genes, and each protein encoded by these genes has a special role [118, 119]. Cloning of these viral genes into *S. pombe*-specific vectors allowed the researchers to determine the exact cellular localization of the GFP (Green Fluorescent Protein)-tagged viral proteins in the yeast cells [119]. The localization of many proteins was revealed for the first time, while further results demonstrated that the intracellular localization of the viral proteins was the same in the yeast and human cells [119].

The Vpr gene (Virus protein R) which encodes a component of virus particles that promotes virus infectivity, has been studied in detail [118]. One of the goals was to find out which cellular processes of the host cells are affected by the Vpr protein and whether the same processes are inhibited in the yeast cells and the human cells. Since the *S. pombe* genomic sequence [14], and the genetic background of its cell processes were well-known, and in addition, a large number of mutant strains were available in this species, it was possible to express the Vpr gene both in the wild-type and various mutant strains. The overproduction of the Vpr gene product revealed that the Vpr protein caused multiple effects on the host cells. The expression of the viral protein resulted in small colonies, growth delay, abnormal cell morphology, arrest in the G2 phase of the cell cycle, and cell death [120–124]. Besides, the Vpr protein caused depletion of the glutathione, and oxidative stress, stimulating the production of reactive oxygen species (ROS) [124–126]. In addition, the direct interaction of the Vpr protein with the proteosome complex, which is responsible for ubiquitin-mediated protein degradation, has also been demonstrated (Fig. 2) [127].

To find out how a single viral protein can destroy various cellular processes, the phenotypic changes of the transformed yeast cells were investigated. Examination of cell morphology of the Vpr-transformed cells showed that the changes were caused by several cellular abnormalities, such as disruption of actin cytoskeleton or altered cell polarity [121]. Cloning and transformation of the mutant Vpr genes enabled the detection of the effect of a given mutation on the Vpr function. The results obtained in *S. pombe* showed highly similar changes to the human cells that confirmed the conservation of the Vpr functions. Besides, the truncated genes also revealed that the C-terminal end of the Vpr protein was particularly important for the cell cycle (G2) arrest, while the N-terminal region was required for nuclear localization [128]. Chen's report also demonstrated that the nuclear localization of the Vpr protein was not required for G2 arrest, while it was necessary for cell killing, suggesting that the G2 arrest and cell death caused by Vpr could be independent functions [128].

The investigation of the Vpr-expressing yeast cells shed also light on the molecular background of the cell cycle arrest. The experiments proved that cell cycle arrest correlated well with increased phosphorylation of the Cdc2 kinase, which is the key regulator of mitosis [120, 129]. These experiments showed that the regulators of the Cdc2, such as *wee1* (encodes an M-phase inhibitor protein kinase) and the *cdc25* (encodes a phosphatase, M-phase inducer) were important in the Vpr-induced cell cycle arrest [130, 131]. According to the data, the Vpr protein promoted the cytoplasmic compartmentalization of Cdc25 and inhibited its function, which required the Srk1 kinase [123]. Since there are differences in cell cycle regulation between *S. pombe* and *S. cerevisiae* (the G2/M transition is more important in *S. pombe* than *S. cerevisiae*) [53], it was better to choose the fission yeast for the analysis of Vpr-mitosis relation.

The further results also showed that the Vpr protein might affect the cell cycle through different pathways because the *rad24* gene (which plays a role in the DNA damage pathway) was also involved in the Vpr-associated cell division defect [131]. Based on these results a putative mechanism of the Vpr-induced cell cycle arrest could also be determined [131]. The genetic screens, where checkpoint and mitotic regulator mutants were used, have confirmed the complexity of the viral effect, and shed light on the role of further genes, such as *rad25*, *wos2*, and *hsp16*, *ef2* that enhanced or suppressed the cell cycle defect or cell death caused by the Vpr protein [124, 130, 132, 133]. Examination of Vpr-induced cell death demonstrated that it resembles apoptosis and correlates with changes in mitochondrial morphology. This study described well the pro-apoptotic effects of Vpr [123].

The *S. pombe* cells were also suitable for finding agents that can reduce the negative effects of the Vpr protein. The H_2O_2 treatment for example promoted the survival of the Vpr-expressing yeast cells [134], while a simple fission yeast-based screening system allowed to find small molecules that specifically inhibit HIV-1 Vpr [135].

In summary, this simple model organism allowed researchers to reveal the effects of the multifunctional Vpr protein on the host cells. The researchers were able to discover the cellular processes disturbed by the viral protein and their molecular background, while a comparison with the results obtained in mammalian cells showed the conserved characteristics of the viral infection. These results could

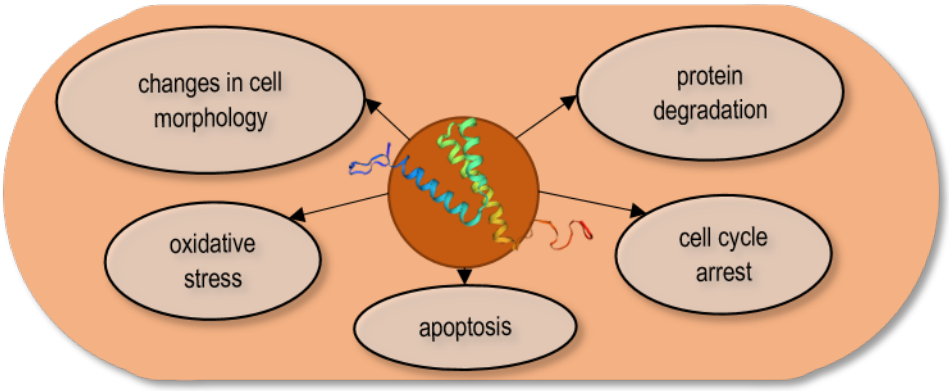

FIGURE 2 ● The Vpr protein caused multiple effects on the *S. pombe* cells.

contribute to a better understanding of the mechanism of viral infection and HIV-1 pathogenesis. Although *S. cerevisiae* is also used as a model to study the HIV-1 Vpr effects [136, 137], there are some major differences that make *S. pombe* superior to *S. cerevisiae* in this regard. Besides the aforementioned cell cycle control point, the Vpr-induced changes in mitochondrial morphology more closely resemble those observed in human cells compared to *S. cerevisiae*. *S. pombe* exhibits a greater degree of similarity to humans with respect to mitochondrial features [138]. *S. pombe* displays cell death induced by Vpr that shares some characteristics with apoptosis in human cells, potentially making it a more relevant model for studying this aspect [123].

POMBE FOR PRION BIOLOGY?

Prions are amyloid forms of cellular proteins and are implicated in many incurable and fatal neurodegenerative disorders. Prion disease can be transmitted from organism to organism and is characterized by the accumulation of PrP^{Sc} (scrapie isoform of the prion protein). The disease has many forms, such as genetic, sporadic, and acquired [139].

Prions seem to be more widespread than currently appreciated because the research data revealed that yeasts can also have heritable elements transmitted via proteins [140, 141]. Since many yeast genome sequences are available, they allow the *in silico* identification of prion-like genes/proteins in different species [142, 143]. In this way, genes with various functions, such as transcriptional regulators, genes involved in sporulation, copper-transport, and translation were identified as prion-associated proteins [141, 143]. Structural analyses also showed that asparagine/glutamine-rich domains are linked to amyloidogenesis [140].

In *S. pombe* 295 PrD (prion-forming domain) containing proteins were identified [143] . One of the prion-like proteins is encoded by the *ctr4* gene, the study of which, placed *S. pombe* on the prion map [143, 144]. The overexpressed form of this copper transporter protein was proteinase K-resistant and conferred sensitivity to oxidative stress [143]. In addition, overexpression of a *S. cerevisiae* gene (Sc*Sup35*) in *S. pombe* also demonstrated that this fission yeast can support the formation and propagation of the *S. cerevisiae* prion [143]. Experimental examination of the other genes mentioned above may lead to many new results.

Further characterization of chaperons and heat shock proteins (HSP), as the latter genes are linked to protein folding [139], may reveal especially the new details of prion aggregation. A study has revealed for example that the C-terminal region of HSP104 plays an essential role in prion propagation [145], while the results of Reidy and co-workers confirmed the role of other chaperons in prion propagation [146]. As also *S. pombe* has many *hsp* genes and genes with GO term "heat shock protein binding" (GO:0031072) (PomBase), their investigation can significantly expand our knowledge of prion disease.

THE DARK HORSE OF EUKARYOTIC CELL RESEARCH: *SCHIZOSACCHAROMYCES JAPONICUS*

The most divergent branch of the fission yeast genus is the dimorphic *S. japonicus* [10, 44, 147], which has several features that make it an interesting prospect among other model organisms [32, 148, 149].

First and foremost, *S. japonicus* is able to switch between a unicellular yeast form and a true invasive hyphal form [150–154]. Hyphal switching can occur through different stimuli: nutrient deprivation [150], DNA damage [153, 154], the presence of fetal bovine serum (FBS) or fruit extracts [155, 156], and negatively regulated by quorum sensing [157]. *S. japonicus* is not pathogenic to humans, despite its ability to form invasive hyphae that penetrate solid surfaces like agar or gelatine [150, 156, 158]. Moreover, hyphal extension is initiated in the presence of FBS even in liquid media, and elevated transcription levels of certain protease-coding genes can be observed in the hyphae [155, 159]. Thus, it can be a good non-pathogenic model to study the fungal dimorphism. However, some unique features distinguish it from other dimorphic species such as *C. albicans*. *S. japonicus* hyphae does not have a Spitzenkörper, undergoes complete cell divisions, and remains mononuclear [156]. Additionally, one of the master regulators of the yeast-to mycelia transition, the transcription factor Nrg1 behaves differently in *S. japonicus*. In *C. albicans*, NRG1 represses morphological transition [160, 161], while in *S. japonicus*, it rather acts as an activator of the hyphal switch [157, 159]. Further differences can be observed as nitrogen starvation is a signal that induces a morphological switch in *C. albicans*, but it is not effective in *S. japonicus* [162, 163]. In this regard, it seems that the MAPK

signal transduction pathways contribute somewhat differently to hyphal induction in *S. japonicus* than in *C. albicans* [157, 163]. Besides, the hyphae of *S. japonicus* are photoresponsive, which is also an unusual feature among most of the other yeasts [164].

However, *S. japonicus* is also quite different from its closest relative. While a handful of studies suggest *S. pombe* can produce adhesive and invasive hyphae-like phenotypes under specific conditions or certain genetic backgrounds [165–170], *S. japonicus* remains the definitive dimorphic species within the genus. Furthermore, *S. japonicus* utilizes a semi-open form of mitosis, while *S. pombe* undergoes closed mitosis, they differ in the regulation of chromatin-nuclear envelope interactions during mitosis, moreover they exhibit discrepancies in their dynamics of cytokinesis and gene regulation too [38, 171–186]. For example, while *S. pombe* assembles the actomyosin ring in metaphase and requires a mechanism to prevent its premature constriction, *S. japonicus* initiates ring assembly only at the mitotic exit, similarly to metazoan cells [149, 176, 187]. Although all the fission yeasts have large, centromeric regions with repetitive sequences, *S. japonicus* does not have specialized pericentromeric repeat sequences as *S. pombe* has, but it has a larger complement of retrotransposons clustered at centromeric and telomeric regions [10, 60, 188]. The *S. japonicus* centromeres consist of arrays of retrotransposons, which is reminiscent of the human centromeric structure, moreover, the RNAi pathway is indispensable for both *S. japonicus* and mammalians [188–191]. In *S. japonicus*, RNAi-mediated silencing of retrotransposons is essential to maintain centromere function and genome integrity, while the other fission yeasts rely on the CENP-B proteins and use RNAi exclusively for heterochromatin maintenance [10, 60, 188, 192]. They exhibit discrepancy in their cell-wall composition too: the O-glycans on the cell surface of *S. pombe*, *S. octosporus*, and *S. cryophilus* mainly composed of tetra-saccharides, whereas those of *S. japonicus* mostly consist of trisaccharides (Gal-Man-Man) [193, 194]. Besides, *S. japonicus* has a wider temperature tolerance: the growth of *S. pombe* is largely restricted above 37°C, *S. japonicus* can even grow at 42°C and the generation time is somewhat shorter of *S. japonicus* than that of *S. pombe* [32, 148]. Strikingly, *S. japonicus* is well-adapted to anaerobic conditions as it has respiratory deficiency and is able to grow anaerobically without sterol supplementation, which is an unusual ability among eukaryotic organisms [195–198]. In this context, *S. japonicus* can grow much faster under fermentative conditions than *S. pombe*, and produces ethanol even at 42°C [197]. Alam and co-workers showed that in spite of the fact that *S. japonicus* does not respire oxygen, it is capable of efficient NADH oxidation, amino acid synthesis, and ATP generation via modification of metabolic pathways [199]. *S. japonicus* is also a suitable model to study membrane bilayer properties and dynamics in anoxic environments, knowing that numerous changes can occur in the membrane lipidomes under hypoxic conditions, for example, in a tumor microenvironment [200–202].

The phylogenetic distance within the *Schizosaccharomyces* genus is uniquely large, despite the fact, that they possess remarkably conserved gene content, gene order and gene structure. According to Sipiczki and Rhind *et al.*, at the level of protein sequence identity (~55%), *S. japonicus* is as distant from *S. pombe* as the platypus is to humans [10, 44]. Interestingly, there might be no genus of Ascomycota that exhibits such a high degree of gene content conservation and sequence divergence at the same time [48, 49, 203]. Such sequence divergence, besides the high amount of common gene content, really provides an excellent model pair to study the same cellular processes in different genetic backgrounds. Since most of the laboratory protocols developed for *S. pombe* can also be used (with slight modifications) for *S. japonicus*, the parallel investigation of these two species provides an unprecedented opportunity [174, 201, 204–215].

After we showed that *S. japonicus* is a remarkable model organism by itself or in comparison with other species, we can ask the question: what is *S. japonicus* able to bring to human disease research? The answer is not so trivial.

S. JAPONICUS HYPHAL GROWTH AS A MODEL TO STUDY THE INVADOPODIA OF TUMOR CELLS

Besides the above-mentioned advantages of *S. japonicus*, so far no comparisons have been made between mammalian cells and hyphal growth. This is not surprising because mammalian cells do not form structures such as hyphae, do they? We can say that mammalian cells do not have structures corresponding to hyphae, except for one that resembles its behavior: the invadopodium.

Generally, invadopodia can be described as membrane protrusions, which play a key role in cancer metastasis. These actin-rich structures can reach a diameter of 3 μm and extend several micrometers in length [216]. It can digest the surrounding tissues by proteases, to help disseminate the cancerous cells.

One could say that both invadopodia and hyphae are very specialized structures with different roles. However, invasive cell growth may have a deep origin, in which particular features are common among the different lineages [217]. Thus, comparisons can be made along five main aspects: polarized growth, actin cytoskeleton, vesicle trafficking, substrate degradation, and environmental sensing (**Fig. 3**).

Polarized growth

Both fungal hyphae and invadopodia grow in a polarized way. When *S. japonicus* cells switch from the yeast phase to hyphal growth, they switch from bipolar to unipolar (polarized) growth [151, 156]. Similarly, the invadopodium is formed in a specific part of the cell, where the early invadopodium precursors have accumulated [218]. The data suggest that this protrusion is often found near the nucleus and Golgi system [219]. In addition, not only the position of protrusions themselves but also the polarized exocytosis of matrix metalloproteinases (MMPs) are the indicators of the polarized growth of invadopodia [220–222]. Polarized growth is maintained by the continuous balance of exocytosis and endocytosis [221], and requires an alteration in the actin cytoskeleton in the hyphae too [151, 156].

Actin cytoskeleton

Both invadopodia and hyphae have the same core mechanism, which drives their growth. In the case of invadopodia, the main core structure is F-actin with its regulators (WASP, N-WASP, Arp2/3) [223, 224]. The activation of the Arp2/3 complex is a critical step in invadopodia formation, which is responsible

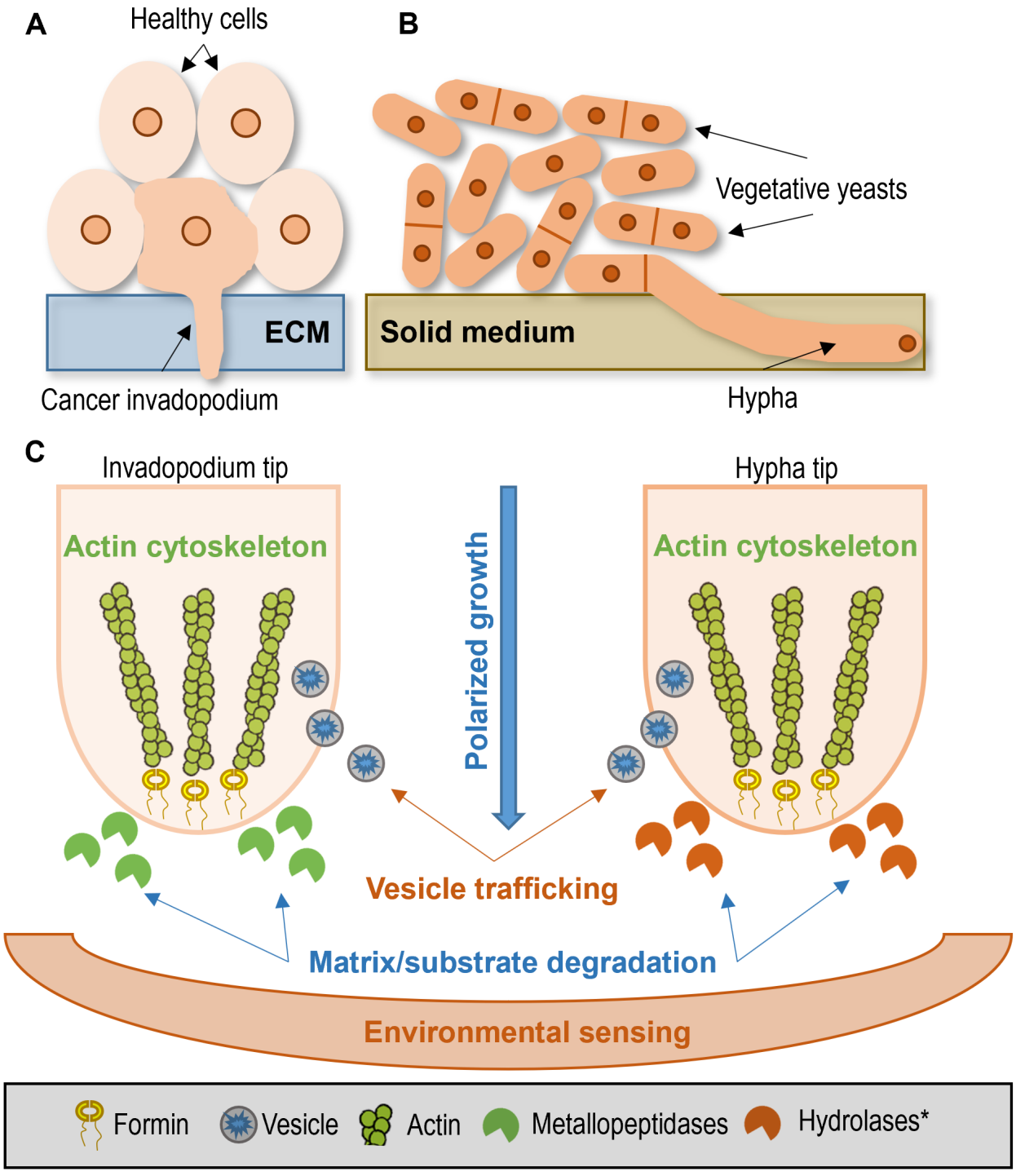

FIGURE 3 ● **Common features of tumor invadopodia and hyphal growth.** (A) Tumor invadopodium invades the extracellular matrix (ECM) among healthy cells. (B) Extension of invasive hypha of the fission yeast *S. japonicus* in the solid medium among normal vegetative yeast cells. (C) Common features enable a direct comparison between cancer invadopodia (left side) and the fungal hyphae (right side). Polarized growth: both fungal hyphae and invadopodia grow in a polarized way. Actin cytoskeleton: the polarized growth is primarily driven by actin polymerization, and it needs changes in the cytoskeletal structure. Vesicle trafficking: invadopodia formation or hyphae growth is unimaginable without vesicle transport. Matrix/substrate degradation: to continue expansion and acquire nutrition, both the invadopodia and the hyphae need to release enzymes that degrade their surrounding environment. Environmental sensing: signals from the environment have a substantial impact on the behavior of cells. Invadopodia formation and yeast-to-hyphae transition are affected by environmental factors like nutrient availability, pH, temperature, or CO_2. ⁎Although transcriptome analysis of the hyphae of *S. japonicus* suggested that several coding genes responsible for the production of vacuolar hydrolases were upregulated during hyphal extension [159], further studies are required to assess the extent of substrate degradation in *S. japonicus*.

for the nucleation of actin [223]. Similarly, the accumulation of actin structures at the tips of the growing hyphae was noticed in *S. japonicus* [151, 156]. In addition, Arp2/3 complex activation (presence) was also required for *C. albicans* hyphae formation [225].

The polarized growth is primarily driven by actin polymerization, which is initiated by the polarisome protein complex [226]. Its components play an important role in the polymerization of F-actin into cables, which is required for the proper hyphae formation of *C. albicans* [226]. Similarly, actin polymerization occurs in the invadopodium maturation, in its third step [218]. In the case of the fission yeasts, the formin For3 is responsible for actin cable assembly [156, 227]. In *S. japonicus*, actin polymerization is essential for polarized growth as the cells did not show polarized growth at all in the absence of For3 [156]. Besides, actin depolymerization abolished all vesicle trafficking and cell tip localization of Ypt3 (Rab11 family GTPase), which has a role in cytoskeleton organization [156].

Cortactin, which is another important nucleation-promoting factor, has an important role in the stabilization of the branched actin network and it has a major role in all steps of invadopodia formation [228]. Interestingly, the downregulation of cortactin via the p38 pathway resulted in the inhibition of the function and formation of invadopodia in colon cancer [229]. In S. *japonicus*, sty1, which is the orthologue of p38, negatively regulates the induction and progression of hyphal growth [157]. The latter indicates that the regulation of certain genes may be similar in invadopodia and hyphae. Therefore, there are critical points that share similarities in mechanism and are also conserved at the gene level.

Vesicle trafficking

Invadopodia formation or hyphae growth is unimaginable without vesicle transport. Soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNARE) are key components of vesicle transport which enable fusion between two membranes in an effective and coordinated way, thus allowing delivery of vesicle contents to the target site [230]. Gorshtein and co-workers recently reviewed that the inhibition of vesicle trafficking and SNARE family members inhibit invadopodia formation [231].

Similarly, SNARE family members are required for appropriate transport of the cargo vesicles which is essential for hyphal extension and leads to abolished or reduced virulence in pathogenic fungi [230, 232]. These data are supported by the strong vacuolization of the *S. japonicus* hyphae [151, 155, 156]. Ypt3 vesicles accumulate at the growing hyphal tips of *S. japonicus* with a greater intensity than in the yeast cell tips. This probably reflects an increase in membrane trafficking to maintain growth rate of the hyphae [156]. In conclusion, the growth of *S. japonicus* hyphae relies on the transport of vesicles on actin filaments for polarized growth with increased rates of vesicular transport.

Substrate degradation

To continue expansion and acquire nutrition, the hyphae need to release enzymes that degrade their surrounding environment. For example, the *C. albicans* hyphae produce the secreted aspartyl proteases (SAP), similarly to the cancer cells that digest the host proteins to acquire nutrients [36, 233, 234]. In the case of tumor cells, extracellular matrix (ECM) degradation is a crucial step in invading new organs, thus metastasizing [235]. Invadopodia release MMPs, which degrade the ECM, facilitating the invasion process [220]. It is not clear whether invadopodia formation is also driven by nutrient availability, however, according to van Horssen and co-workers, the metabolic activity of the cancer cell regulates matrix degradation [236].

Although *S. japonicus* does not have *C. albicans*-like SAP orthologues, transcriptome analysis of the hyphae of *S. japonicus* suggested that several coding genes responsible for the production of vacuolar hydrolases were upregulated during hyphal extension (Supplementary Table S1) [159]. This finding parallels observations in *C. albicans* and invadopodia, where hyphal growth is associated with the secretion of hydrolytic enzymes that degrade their surroundings [237–239]. Although further studies are required to assess the extent of substrate degradation in *S. japonicus*, the elevated expression levels suggest that these enzymes play a role in hyphal elongation, likely in a manner similar to that observed in *C. albicans*.

Environmental sensing

Signals from the environment have a great impact on the behavior of cells. In most cases, the yeast-to-hyphae transition is affected by nutrient availability, pH, and temperature. In *S. japonicus*, acidic pH and 37°C, along with different types of nitrogen sources, have a significant impact on filamentous growth [150, 155]. In *C. albicans*, besides the aforementioned factors, CO_2 and adherence have triggered filamentous growth [240].

Invadopodia formation is also affected by similar factors, such as pH, CO_2, and glucose availability [223, 241]. In general, the microenvironment of the tumor plays a crucial role in invadopodia formation and thus in metastasis [242].

Common orthologues and gene regulation

As we have seen in these subchapters, yeast-to-hyphae transition and invadopodia formation have many features in common and are comparable to each other. Despite their distinct functionality, the core mechanisms are very similar. To determine whether these two processes share common genes, we compared the RNA sequencing data from *S. japonicus* hyphae and invadopodia, without claiming completeness [159, 243]. In the case of the *S. japonicus* hyphae, 1337 genes were significantly upregulated, of which 112 genes showed expression above $\log_2$ fold change 2 [159]. 1484 genes were significantly downregulated, among which 109 had $\log_2$ fold changes below 2 [159]. In the cancer invadopodia, 5873 genes showed elevated expression, while 5467 genes showed decreased expression levels [243]. Based on the data of JaponicusDB (accessed on 2024.07.02.), *S. japonicus* and humans share ~3500 common orthologues (https://www.japonicusdb.org/data/orthologs/). According to our more stringent approach, strict reciprocal BLASTp analyses (E value $\leq 1 \times 10^{-30}$) revealed 1774 common putative orthologues between *S. japonicus* and *H. sapiens* (Supplementary Table S2) [16]. The list of common orthologues was compared to the gene lists of the RNA seq obtained from *S. japonicus* hyphae [159] and human invadopodia [243],

TABLE 2 ● Common orthologues of *S. japonicus* and humans, whose expression levels are changed in the hyphae and invadopodia in a similar way.

S. japonicus gene identifier	human gene	log2 inva	log2 hyph	Intersecting GO categories
SJAG_04499	P54868	2.052	0.888	acetyl-CoA metabolic process (GO:0006084)
SJAG_03763	Q5TDH0	1.073	0.383	proteolysis (GO:0006508)
SJAG_04224	Q12788	1.049	0.288	endonucleolytic cleavage to generate mature 5'-end of SSU-rRNA from (SSU-rRNA, 5.8S rRNA, LSU-rRNA) (GO:0000472)
SJAG_03961	P22557	0.964	1.126	protoporphyrinogen IX biosynthetic process (GO:0006782)
SJAG_03693	O95373	0.916	0.203	protein import to nucleus (GO:0006606)
SJAG_01209	Q15124	0.857	0.510	carbohydrate metabolic process (GO:0005975)
SJAG_03401	Q9BXP2	0.813	0.941	monoatomic ion transport (GO:0006811)
SJAG_03866	A0A2R8Y635	0.761	0.457	transmembrane transport (GO:0055085)
SJAG_00451	Q9UI42	0.757	0.476	proteolysis (GO:0006508)
SJAG_0230	Q9UNX4	0.669	0.478	maturation of SSU-rRNA (GO:0030490)
SJAG_04204	P08708	0.662	0.548	translation (GO:0006412)
SJAG_01438	P13639	0.607	0.540	translation (GO:0006412)
SJAG_00911	Q9BZJ0	-0.597	-0.718	spliceosomal complex assembly (GO:0000245)
SJAG_04821	Q96F25	-0.603	-0.792	dolichol-linked oligosaccharide biosynthetic process (GO:0006488)
SJAG_04308	Q9NVU7	-0.662	-0.349	ribosomal large subunit export from nucleus (GO:0000055)
SJAG_00272	P40938	-0.668	-0.938	DNA replication (GO:0006260)
SJAG_00111	Q149N8	-0.669	-2.141	protein polyubiquitination (GO:0000209)
SJAG_01924	Q9Y5U8	-0.761	-0.363	mitochondrial pyruvate transmembrane transport (GO:0006850)
SJAG_04540	Q13216	-0.775	-0.604	protein polyubiquitination (GO:0000209)
SJAG_04307	A0A8Q3WKR8	-0.866	-0.400	isoprenoid biosynthetic process (GO:0008299)
SJAG_03436	Q81Y18	-0.931	-0.605	double-strand break repair via homologous recombination (GO:0000724)
SJAG_02625	Q14997	-0.972	-0.452	DNA repair (GO0006281)
SJAG_00851	O75037	-1.080	-1.207	microtubule-based movement (GO:0007018)
SJAG_16456	Q96GW9	-1.289	-0.795	translation (GO:0006412)
SJAG_04068	P11168	-3.039	-0.696	carbohydrate transport (GO:0008643)
SJAG_03434	P80404	-3.543	-1.596	gamma-aminobutyric acid metabolic process (GO:0009448)

Each row corresponds to an orthologous protein pair, includes their *S. japonicus* and human identifiers, and their log2-transformed values, which show their mRNA levels in invadopodia (log2 inva) and hyphae (log2 hyph). Besides, the intersection of Gene Ontology (GO) terms, and the associated GO categories are listed in it. To create this table, we downloaded the human proteome from UniProt (https://www.uniprot.org/ accessed on 12.27.2023.) and the *S. japonicus* proteome from JaponicusDB (https://www.japonicusdb.org/ accessed on 12.27.2023.). Reciprocal BLAST analysis was carried out using blast+ (ver. 2.13.0) [16]. The cutoff value was set to $E \leq 1 \times 10^{-30}$. Based on these data, we found 1774 common orthologues between *S. japonicus* and *H. sapiens*. Then this list was further filtered using the data from [243] and [159], resulting in a total of 86 genes. These genes were subjected to categorization by GO terms (https://www.ebi.ac.uk/QuickGO/help/slims accessed on 12.27.2023.), specifically focusing on the terms associated with biological processes. Only the terms that were present in both species were retained. At last, 26 genes remained, whose belonged to the same GO categories and expressed in a similar way.

which resulted in a total of 85 common genes (Supplementary Table S3). These genes were subjected to categorization by Gene Ontology (GO) terms, considering mainly the common biological processes. In this way, the common orthologue number was reduced to 53 (Supplementary Table S4). 26 genes out of 53 exhibited similar regulation in both hyphae and invadopodia (**Table 2**), whereas 27 genes showed opposite regulation (Supplementary Table S4). Several gene pairs belonged to the GO categories of transport or metabolic processes (**Table 2** and Supplementary table S4). Although the number of common orthologues is quite small and half of the genes were differently regulated, they might still be good indicators or starting points for further investigation of regulatory mechanisms.

We should bear in mind that this is only one pairwise comparison from one-on-one specific conditions, data from different circumstances might result in substantially different gene sets. Moreover, we should also consider the fact that invadopodia are formed in cells that carry severe genetic mutations, in contrast to the normal genetic background of *S. japonicus* in which the hyphae were produced. Taking these considerations into account, we would consider it particularly interesting to examine the *S. japonicus* hyphae production in such a mutational genetic background that resembles the genetic background of the invadopodia. In particular because some *S. japonicus* cell cycle mutant strains produced somewhat

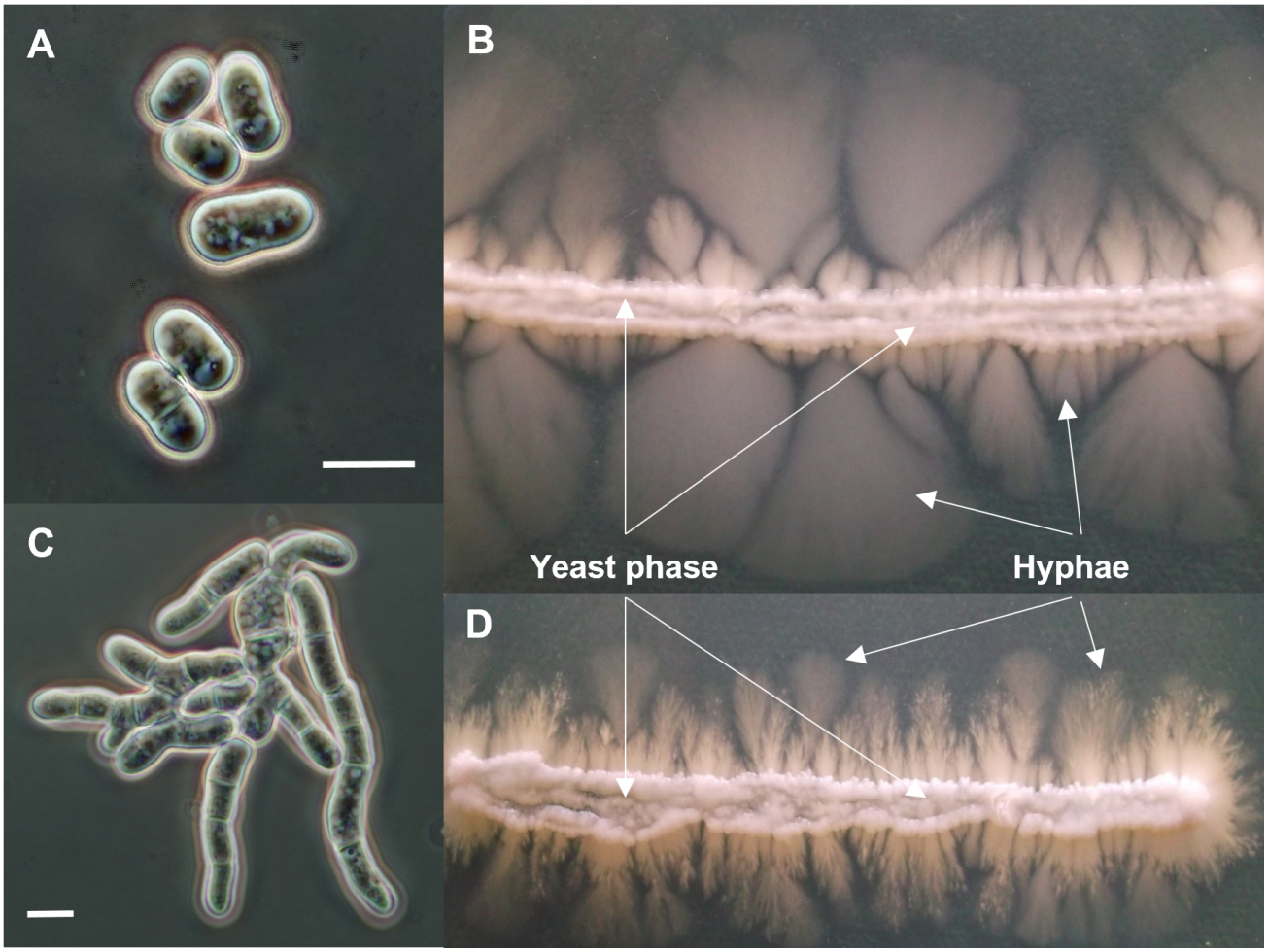

FIGURE 4 ● **Microscopic and macroscopic morphologies of different *Schizosaccharomyces japonicus* strains.** Microscopic morphology of the wild-type *S. japonicus* cells (**A**) and colony morphology of the yeast phase and hyphae on agar plate (indicated with white arrows and labels) (**B**). Cell morphology of a yet unidentified cell separation mutant strain (**C**) and its yeast phase and hyphae production (**D**). Cell sizes in (A) and (C) are not to scale, the images concentrate on the cell morphology. Scale bars represent 10 μm. Microscopic images were captured with an Olympus DX-40 microscope and an Olympus DP-70 camera. Photos were taken in different focal planes and stacked with the program Combine ZP.

different hyphae (**Fig. 4 C, D**), compared to the wild-type strain (**Fig. 4 A, B**).

LABORATORY USE AND TOOLKITS

Although there is a tendency for most molecular toolkits to be developed for *S. cerevisiae* first, then adapt to the fission yeasts, sometimes the latter species proves to be a better subject in terms of practical implications. Many wild-type *S. cerevisiae* strains are used as laboratory models, and because of this, it often happens that the same mutation causes different phenotypes in different wild-type strains [244, 245]. This often makes the comparison of the results difficult. In contrast, almost every lab working with *S. pombe* uses the same strains: the L968 h^{90} homotallic, the L972 h^- and the L975 h^+ heterotallic strains isolated by Urs Leupold [246]. As a result, majority of the studies using *S. pombe* can be directly compared and contrasted. Furthermore, L968 is a natural isolate, which does not behave differently compared to the other natural isolates [247].

Numerous useful databases, protocols and toolkits have arisen through the years for the fission yeasts. Virtually, all the molecular biology tools available were adapted or can be adapted to fission yeasts, from standard gene replacements to CRISPR-Cas9 and from FISH to Hi-C systems [248–252]. Since Herrera-Camacho and co-workers have presented many useful applications for *S. pombe*, here we just focus on the recently described methods, online tools and algorithms (**Table 3** and **4**) [251].

Both *S. pombe* and *S. japonicus* have their own dedicated databases: PomBase and JaponicusDB, which are community-curated (**Table 3**) [14, 15]. These platforms summarize the results reported by the researchers working with the fission yeasts; they enable a rapid overview of the recent developments in many topics.

LIMITATIONS

Despite all good features of yeasts, they also have their own limiting factors. Since all the fission yeast species have their unique elements of metabolic pathways and protein interaction networks, most of the biological processes can only be "similar" to their human counterparts. Although we could gain useful information about human diseases using fission yeast

TABLE 3 ● Online platforms and bioinformatic tools for the fission yeasts.

Databases/Tools	Links	
Pombase	https://www.pombase.org/	
Forsburg lab	https://dornsife.usc.edu/pombenet/	
Bähler lab	https://www.bahlerlab.info/resources/	
EnsemblFungi	http://funig.ensembl.org/Schizosaccaromyces_pombe/Info/Index	
EnsemblFung	https://funig.ensembl.org/Schizosaccaromyces_japonicus/Info/Index	
JaponicusDB	https://www.japonicusdb.org/	
Oliferenko lab	http://www.oliferenkolab.uk/protocols.html	
Japonet	https://shigen.nig.ac.jp/yeast/japonet/	
Methods/Tools	**Description**	**Reference**
Protein function prediction	Phenomics and machine-learning approaches to predict protein function	[253]
pomBseen	Analysis pipeline for the quantitation of fission yeat micrographs containnig bright-field channel and up to two fluorescent channels	[254]
DeepEdit	A powerful tool for the study of RNA editing	[255]
DeePiCt	An open-source deep-learning framework for supervised segmentation and macromolecuar complex localization in cryo-electron tomography	[256]
3D models of chromosomes	Building 3D models from raw Hi-C data	[257]
YEASTRACT+	Tool for the analysis, prediction and modelling of transcription regulatory data	[258]
PTMint	Manually curated complete experimental evidence of the PTM regulation on protein-protein interactions	[259]
Metabolic modelling	Computational modeling of metabolic networks	[260]
Photo Phenosizer	Machine learning-based method to measure cell dimensions	[261]
3D-SIM pipeline	Three-dimensional structured illumination microscopy (3D-SIM) image analysis pipeline for nuclear pore complex quantitation	[262]
Serine phosphorylation prediction	A computational predictor was proposed to predict serine phophorylation sites mapping on *S. pombe*	[263]
Yesprit and Yeaseq	Applications for designing primers and browsing sequences in four fission yeast species	[264]
GproDIA	A framwork for the proteome-wide characterization of intact glacopeptides from data independent acquisition (DIA) data with comprehensive statistical control	[265]
Spindle elongation dynamics	An ImageJ plugin that can automatically track *S. pombe* spindle length over time and replace manual or semi-automated tracking of spindle elongation dynamics	[266]
ChroMo	An interactive, unsupervised cloud application specifically designed for exploring chromosome movement datasets from live imaging	[267]

models [297–305], there will always be differences that we should be cautious about. At the same time, complex processes cannot be investigated because of the lack of multicellular phenotypes. But beyond the trivial, there are other factors to consider.

The creation of auxotrophic mutant strains is a widely used procedure in yeast genetics. Auxotrophic mutant strains enable researchers to easily verify the success of a gene deletion or plasmid vector introduction into the cells, for example. However, there is emerging evidence that a knockdown of even a simple metabolic gene could produce a pleiotropic effect, which causes a complex phenotype leading to false conclusions. For instance, a defect in certain amino acid (AA) biosynthetic pathways may activate the general AA control and suppress the TOR pathway, depending on the growth conditions [306–308]. In the case of *S. pombe*, leucine (Leu) auxotroph strains have been used for decades [309], although Leu auxotrophy can cause altered intracellular response compared to the prototrophic wild-type strain [307]. Similarly, the use of the *URA3* gene as a selective marker caused decreased virulence in *C. albicans*, thus, it resulted in misleading phenotypes [310, 311]. The effect could be more severe in the case of strains that have two or more auxotrophies. The situation is not much better when using antibiotic-resistant genes as genetic markers. To ensure a sufficient expression of the marker gene, constitutive promoters are generally used. Those promoters sometimes act bidirectional or might elevate the expression levels of the neighboring genes too [312]. In that particular case, we are again facing a pleiotropic phenotype. It is also common practice to knock out one of the members of the non-homologous DNA end joining (NHEJ) repair system to enhance gene targeting efficiency. Without efficient NHEJ, the cells ideally use the homologous recombination repair system, which enables precise integration of the foreign DNA into the target genome. Despite NHEJ-deficient strains showing normal phenotypes in standard circumstances, NHEJ members have many other roles that go beyond just joining DNA ends. In *S. pombe*, the Pku70-Pku80 heterodimer plays a critical role in telomere length maintenance and recovery from replication stress [313, 314].

TABLE 4 ● Recent experimental tools and protocols for the fission yeasts.

Methods/Tools	Description	References
Quantifying turgor pressure	Experimental approach to access turgor pressure in yeasts based upon the determination of isotonic concentration using protoplasts as osmometers	[268]
POMBOX	Modular tools for generating plasmids with up to 12 transcriptional units	[269]
New vectors	New *S. pombe* vector systems employing *lys1* and *arg3* as markers	[270]
CRISPRi	CRISPR interference method to study essential genes in *S. pombe*	[271, 272]
BiFCo	Introduction of bimolecular fluorescent cohesin to monitor cohesin complex assembly and disassembly	[273]
CRISPR-Cas13d	Implementation of the CRISPR-Cas13d system in fission yeast for RNA knockdown	[274]
Kinetochore nanostructure	Construction of a nanometer-precise in situ map of the human-like regional kintetochore of *S. pombe* using multi-color single-molecule localization microscopy	[275]
Heterothallic strains	Creating heterothallic strains of *S. pombe*	[276]
SLIPT	Introduction of self-localizing ligand-induced protein translocation (SLIPT) system in *S. pombe*	[277]
SILAC	Stable isotope labeling by amino acids (SILAC) to apply for protein identification and quantification	[278]
TCP-seq	Translation-complex profiling of fission yeast cells	[279]
Visualizing tropomyosins	Tools to visualize tropomyosins in four different organisms/cell types using an mNG fusion strategy	[280]
Barcoded mutant arrays	Construction of a *S. pombe* transposon insertion library	[281]
Mulitcopy suppressors	A protocol for carrying out 'multicopy suppression'-based genetic screen in *S. pombe*	[282]
Fluorescnece exclusion	A rapid, accurate and powerful method for measuring yeast cell volume	[283]
Protein-RNA interactions	Quantitative analysis of protein-RNA interactions	[284]
DNA Curtain Technique	DNA curtain is a hybrid technique that combines lipid fluidity, microfluidics, and total internal reflection fluorescence microscopy (TIRFM) to provide a universal platform for real-time imaging of diverse protein-DNA interactions	[285]
PDE inhibitors	Platform for expressing cloned cyclic nucleotide phosphodiesterases (PDEs) and robust screening for small molecule inhibitors that are cell permeable	[286]
Cell cycle stage	Detecting cell cycle stage and progression in fission yeast	[287]
Cell cycle synchrony	Cell cycle synchrony methods for fission yeast	[288]
Mitotic inheritance of histone modifications	A framework to successfully implement an inducible heterochromatin establishment system and evaluate its molecular properties	[289]
DRIP assay	Antibody-based DNA:RNA immunoprecipitation (DRIP) strategy	[290]
Near-infrared imaging	Easy use of multiplexed live-cell imaging in fission yeast with a broader color palette	[291]
Protein interactions	Introduction of an efficient and convenient method termed the Pil1 co-tethering assay to detect binary, ternary, and quaternary protein interactions	[292]
Local protein accumulation kinetics	A detailed protocol for determining protein accumulation kinetics at the division site in *S. pombe* and *S. cerevisiae*	[293]
G-Quadruplex-DNA-Disrupting Small Molecules	*In vitro* assays to reliably identify molecules able to destabilize G-quadruplex-DNA	[294]
New vectors	New vectors to simplify the genome editing protocols	[295]
Hyphal RNA isolation	Simple method to grow hyphae and isolate quality RNA from hyphal tips	[158]
AID vectors	Two plasmids that facilitate the introduction of the mini auxin-inducible degron (mAID) tag with a FLAG epitope or GFP by the conventional PCR-based gene targeting method	[296]

In *S. japonicus*, disruption of the Ligase 4 (*lig4*) gene resulted in a seemingly normal phenotype [315]. However, increased sporulation on complete medium, decreased hyphal growth, faster chronological aging, and higher sensitivity to heat shock, UV light, and caffeine can be observed in the *lig4*-disrupted strains [315]. Thus, gene characterization conducted in an NHEJ-deficient strain could also lead to incorrect conclusions.

Although we are able to track dynamic cellular processes by using chemical inhibitors, many drugs are not efficient enough for fission yeasts because of their multidrug resistance (MDR) [316–318]. Thus, finding a new therapeutic agent or investigating the performance of a candidate might not work well in the fission yeast (or in other yeasts). However, there are several counterexamples, of course [319, 320]. It is even possible to make fission yeasts sensitive to drugs by engineering their MDR-related genes [318], but the effect of those gene deletions might resemble the gene deletion effects of other metabolic or DNA repair pathway genes.

In fact, any gene knockdown could cause secondary gene mutations or overall genomic imbalance, which initiates adaptive genomic changes [321]. Of course, the purpose of many studies is exactly to understand these changes. But we should bear in mind, that all the yeasts have a very short generation time, and the continuous inoculation of their cells could result in multiple bottlenecks and in parallel, forced genome evolution. There is a lot of anecdotal evidence circulating among researchers when they experience that a mutant yeast strain completely changes its behavior after a certain number of rounds of inoculation. To provide experimental evidence, Szamecz *et al.* showed that many knockout strains have recovered and exhibited almost as good fitness as the wild-type strain did after certain rounds of generation [322]. Although they performed their experiments with *S. cerevisiae*, their result could easily be true for the fission yeasts too.

CONCLUSIONS

With this particular review, we would have liked to emphasize the importance of the fission yeast models, as we are convinced that they still have many unexploited benefits. Although the number of researchers using fission yeasts is relatively high, the size of the fission yeast community is nowhere near the size of the budding yeast community. Obviously, in many cases, it is easier to work with *S. cerevisiae*, but the fission yeasts share substantially more fundamental biological processes with the metazoans. Therefore, we wanted to highlight some of the differences between budding and fission yeast models, without claiming completeness. Besides, we also wanted to promote *S. japonicus* as a less-known, but emerging model organism with unique features. As we have shown, *S. japonicus* is more similar to mammalian cells in certain features than *S. pombe* is. Moreover, in our view, *S. japonicus* can easily be a non-mammalian model for tumor invadopodia studies, since the fundamental processes of invadopodia formation and hyphae formation can be rationally compared. Although it is obvious that none of the yeasts can be used as equivalent models of human diseases, we believe that the fission yeasts could substantially contribute to our understanding of the molecular background of human diseases.

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SUPPLEMENTAL MATERIAL

All supplemental data for this article are available online at www.microbialcell.com.

CONFLICT OF INTEREST

The authors declare no competing interests.

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