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Why is Yeast Such a Widely Used Eukaryotic Model Organism? A Literature Review

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Abstract

Introduction: The use of yeasts in various fields dates back to thousands of years ago, but their biological significance has only recently been discovered. Genomes of many members of this relatively small group have been sequenced, and the consequent studies on them and on various cell processes have revealed similarities between yeast species *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*, and other eukaryotes, suggesting that they may be used as eukaryotic model organisms.

Methods: A literature search was conducted investigating general yeast characteristics, genetics and physiology, as well as modern applications in biomedical research as model organisms.

Results: Yeasts have many traits that make them especially favorable in research: they can easily be cultivated in laboratory conditions where their metabolism may be altered by tweaking the growth medium properties. Additionally, analyzing the yeast and human genome sequences has revealed astonishing similarities, with many successfully mapped homologous genes.

Discussion: By varying environmental conditions of a *S. cerevisiae* culture, it was found that such treatments could affect respiration in yeast. Proving useful in research of antifungal drugs and interactions between fungal pathogens and hosts, yeast was also used as a model for studying prion related diseases, Alzheimer's disease and cancer, amongst others.

Conclusion: With all the yeast characteristics—their simple requirements for growth, their genome and metabolism similar to other eukaryotes, and their use in studying varying disease conditions—it is understandable and clear why yeasts are such widely used model organisms. Considering recent advancements, their application in biomedical research will inevitably increase over time.

Keywords: yeast; *S. cerevisiae*; *Schiz. pombe*; model organism; gene homologs

Introduction

It often happens in biological and biomedical sciences that performing research on specific organisms, especially humans, is difficult due to ethical and practical reasons. In such cases, *in vivo* and *in vitro* procedures are performed using other organisms which exhibit similar patterns or phenomena. Such organisms are called model organisms and are dispersed all around the phylogenetic tree, including the fruit fly *Drosophila melanogaster*, nematode *Caenorhabditis elegans*, zebrafish *Danio rerio*, mouse *Mus musculus*, and, notably, yeast species, *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe* [1].

Long before performing research or finding their application in biotechnology, humans have used yeast in food production, including in the fermentation of beers, ciders, wines, cheese, and other products [2]. While they are still used in such cases and in agriculture, novel biomedical applications of yeasts have created new opportunities for research. This is well illustrated by the fact that four Nobel Prizes were awarded between 2001 and 2013 for discoveries involving yeast research [3]. Historically, it was Louis Pasteur (1822-1895) who recognized that microorganisms were responsible for creating alcohol from sugar and observed the difference in alcoholic fermentation by yeasts and their aerobic growth. *Saccharomyces cerevisiae* was first isolated at the end of the 19th century [4], while Emil Fischer and Eduard Büchner started investigating its metabolism about a century earlier.

There are 1,500 species of yeast and they are all unicellular organisms alternating between haploid and diploid phases, both of which can exist as stable laboratory cultures [5]. They vary in types of reproduction, making them suitable for exploring different phenomena. For instance, when studying cell division, fission yeast (*Schizosaccharomyces pombe*) is preferred to budding yeast (*S. cerevisiae*), given that "pombe" cells split into two cells similar to human cells, unlike budding yeast, which use buds for reproduction (Figure 1).

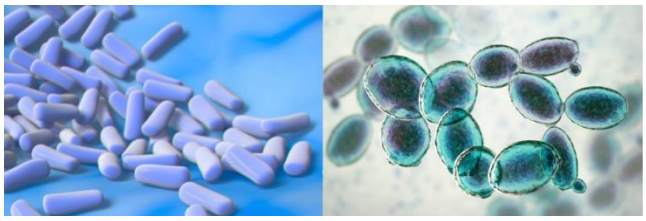

Figure 1. *Schiz. pombe* (left) and *S. cerevisiae* (right) cell shapes resulting from different means of division

The first ever eukaryotic genome to be sequenced is that of *S. cerevisiae* [6] and the other yeasts followed: *Schiz. pombe*, *Schiz. japonicus*, *Schiz. cryophilus*, and *Schiz. octosporus* [7]. Upon further analysis of their genomes, it was revealed that budding yeast's genome has undergone large duplications during evolution, resulting in the total of 16 total chromosomes, unlike the fission yeast whose karyotype has only three chromosomes [8].

When a model organism is being chosen for a human study, the choice is made depending on the process being researched. In aging, for example, cell cultures would not be preferred as cellular senescence mechanisms cannot be accurately extrapolated to human aging. Invertebrates *C. elegans* and *D. melanogaster* are chosen in this case. Ziehm et al. [9] proposed an uncommon approach for studying aging using these invertebrates—they used what is known about molecule-binding in higher organisms from the available data to transfer knowledge to the invertebrates which were then used to assess effects of compounds on organisms' viability. This enabled them to avoid testing the chemicals on higher organisms directly. The opposite approach is used in drug testing which is based on similarities between a simpler organism and humans. This allows the researchers to predict what would occur in humans with high certainty.

But of all the model organisms more closely related to humans than yeast, why would someone choose to use this unicellular fungus to study a human process? This paper aims to explore and compare why and how yeast can be used to model, and research human physiological conditions compared to other existing model organisms, and why it is so commonly used.

Methods

A literature search was conducted for articles describing basic yeast characteristics and historical uses, their physiology, genetics, more recent discoveries, and where different yeast species are used in research. Also, a search was conducted for literature describing other model organisms. The search engine used was Google Scholar, and the key words used include "yeast," "*Saccharomyces*," "*Schizosaccharomyces*," "model organism," "gene homology," and "cultivation conditions." The years of publication for the literature used ranged from 1991 to 2021.

Results

General characteristics of yeast

Key characteristics of some of the most commonly used model organisms are outlined in Table 1.

Table 1. Commonly used model organisms

Model organism	Characteristics	Cultivation conditions	Advantages
Escherichia coli	Gram-negative bacterium, facultatively anaerobic [10], human pathogen.	In growth media, the optimal temperature is between 35 and 40°C, pH ranges from 4.4 to 10.	The most extensively studied microorganism, not difficult to cultivate, sequenced genome, fast reproduction cycle.
Saccharomyces cerevisiae	Unicellular fungus, "baker's" yeast, divides by budding, used in food industry [11].	In growth media, the optimal temperature is between 25 and 35°C, and the pH is between 4.5 and 6.5.	Eukaryotic, easily cultivated and genetically manipulated, cultures can be either haploid or diploid, sequenced genome (*Saccharomyces* Genome Database), fast reproduction cycle.
Caenorhabditis elegans	Nematode, 1 mm long [12].	In a medium, often with bacteria as a food source [13].	Eukaryotic, relatively simple cultivation, fast reproduction cycle.
Drosophila melanogaster	The "fruit fly," insect.	Cultures are kept in "population cages" [14] and the process is more complex than having a cell culture.	Fast reproduction cycle, commonly used in genetics (used to prove the chromosomal theory of inheritance [15]).
Mus musculus	Rodent (mammal).	Many factors need to be considered: temperature and humidity, ventilation and air quality, illumination, acoustics, amongst others.	99% gene homology with humans [16], a mammal—more closely related to humans and even exhibits some of the same conditions.

External environment and yeast growth conditions can be modified in different ways through varying chemical and environmental factors [7]. In the study on effects of different cultivation conditions on *S. cerevisiae* mitochondria, Visser et al. [17] found that varying glucose and ethanol concentrations in the medium influenced the repression of respiratory enzymes, leading to morphological changes in their mitochondria. This study reinforces the use of chemostat cultivation as a way of studying the regulation of respiratory activity in yeasts. The method is based on keeping the volume of the medium constant by continuously adding and removing the fluid containing biomass, products, and nondepleted nutrients [18].

Yeast in genetic research

Another important yeast characteristic is that its genome is well suited for genetic analysis, with different techniques shown to be successful in accurately replacing wild type genes with mutant alleles [19]. Despite having significant differences in cell and tissue organization, motility, metabolism, and external environment, with the most recent common ancestor from around one billion years ago [20], humans and yeasts have more than a thousand homologous genes [21]. The genome of *Schiz. pombe* contains protein-encoding genes approximately every 2.3 kb [22], compared to another commonly used model organism, *C. elegans*, where such can be found on average every 6 kb [23]. Even with a small genome compared to that found in humans, 12 Mb compared to 3,200 [24], the key processes in yeasts including autophagy, protein translocation and secretion, heat shock, protein folding, chaperone functions, and endoplasmic reticulum-associated protein degradation are highly conserved [25]. Further genetic analyses have contributed to our knowledge of yeast-human gene homology. Soon after sequencing the *Saccharomyces* genome, by creating deletions in most of the open reading frames, a deletion library was created [26]. This set the ground for the discovery of biological roles of most of the yeast genes, which is known for more than 85% of them, higher than for any other eukaryote. Only 34% of the entire set of genes with mammalian homologs have no function listed in the Saccharomyces Genome Database (SGD), compared to less than 25% of the genes having the strongest homology [26]. While the reason for this is largely unknown, there is a possibility that scientists studying yeast have concentrated on the most important genes which are more likely to be conserved. At least 71 human genes complement yeast mutations, but this is certainly an underestimate [26]. Due to these features, yeasts have been used as model organisms for studying various diseases and conditions, examples of which can be found in Table 2.

Table 2. Diseases studied by using *S. cerevisiae* as a model organism; adapted from [2]

Disease	Reference
Prion related diseases	27
Alzheimer's disease	28
Parkinson's disease	29
Cancer	30
Aging	31

Discussion

While there are other organisms that also have genetic homologies with humans similar to the baker's yeast, there are impediments in using them for research purposes. If two potential model organisms exhibit the same trait, the simpler one will be chosen. For example, 99% of *M. musculus* genes have their homologs in humans, higher than any other organisms [16]. But given that it is a mammal, it must be housed and handled following specific conditions, which are more complex compared to those used to develop a microbial culture. Also, there are ethical and legislative barriers to using "higher organisms," making individuals and institutions seek alternatives for their research. Bacteria, much simpler organisms, come as a good alternative. The Ames test is an excellent reminder of how they are be used to assess mutagenicity, instead of a cell line [32]. However, they do not come without drawbacks of their own—namely, there are species of bacteria are referred to as viable, but nonculturable, meaning that their metabolism functions slowly and they do not divide. Performing research on them is extremely difficult. Additionally, prokaryotes are much simpler than eukaryotes including humans and yeasts, and this drastically limits what can concluded about more complex eukaryotes from findings in such experiments. For example, given that bacterial DNA is not organized in chromosomes, gene regulation is simpler than in eukaryotes where chromatin has an important role among other factors. This is where *S. cerevisiae* and *Schiz. pombe* come as exceptional model organisms. As mentioned earlier and similar to many bacteria, they are easy to cultivate and their growth media can be adjusted to modify their metabolism. While *E. coli* is simpler to cultivate, the yeast cell culture is still easier to maintain compared to other commonly used eukaryotic model organisms.

Given the observed gene homology, *S. cerevisiae* and *Schiz. pombe* have been utilized as models to explain various phenomena in humans. Despite having a smaller genome, *Schiz. pombe* has proportionally more genes preserved in animals [6], although *S. cerevisiae* is preferred when studying some cellular functions—namely, it was key in exploring physiology of the peroxisome [33].

Nonetheless, using a compare and contrast approach, both yeasts have been used to characterize genes involved in regulating normal events in cell cycle progression [6]. Utilizing yeast as a model has led to other discoveries. Given that it lacks endogenous nuclear receptor and receptor regulatory proteins found in mammalian cell lines [2], a great use has been made of it for studying activation of human receptors by anti-estrogens [34]. *S. cerevisiae* has also been used for developing diagnostics and to better understand mechanisms of various antifungal drugs [35] and interactions between fungal pathogens and hosts [36] As mentioned earlier, a yeast culture can be either haploid or diploid and each type can be applied for different studies. Haploid cultures can be useful in screening as mutant phenotypes are expressed in such cases. On the other hand, diploid cultures are a good tool in performing complementation tests, exploring gene interactions, or "silencing" deleterious mutations. Considering the homology observed between yeast and other eukaryotes, findings of such experiments can suggest what occurs in higher organisms.

Considering cultivation conditions and the extent to which the genome is studied—it is of no surprise that yeast is such a widely used model organism. Its characteristics and genetic similarities with other organisms make it suitable and easily adaptable for researching metabolism, gene expression, and other common eukaryotic processes, as well as for processes unique to higher groups but with the same genetic basis.

Conclusions

Morphological, physiological, and genetic characteristics of yeasts, namely *S. cerevisiae* and *Schiz. pombe*, give researchers a variety of biological tools they can use: the cultivation environment can be tweaked to modify the yeast metabolism in a certain way, and by knowing its genome sequence and having different databases, it is possible to use the yeast for different genetic research and understand its metabolism on a molecular level. Genetic analysis also revealed that many of its genes have been preserved in evolutionary younger organisms, resulting in many cellular processes being similar or same, and making yeast a great model organism for other eukaryotes. This has allowed for them to be used for studying prion related diseases, Parkinson's disease, and aging, amongst others.

List of Abbreviations Used

S. cerevisiae: *Saccharomyces cerevisiae*
Schiz. pombe: Schizosaccharomyces pombe
Schiz. japonicus: Schizosaccharomyces japonicus
Schiz. cryophilus: Schizosaccharomyces cryophilus
Schiz. octosporus: *Schizosaccharomyces octosporus*
C. elegans: Caenorhabditis elegans
D. melanogaster: Drosophila melanogaster
SGD: Saccharomyces Genome Database
M. musculus: Mus musculus
E. coli: Escherichia coli

Conflicts of Interest

The author declares that he has no conflict of interests.

Ethics Approval and/or Participant Consent

The study required no ethics approval or participant consent.

Authors' Contributions

DP: contributed to the design of the study, the review of literature and collection of data, interpretation and analysis of the data, and revised the manuscript.

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