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REVIEW ARTICLE OPEN ACCESS

The Power of Yeast

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ABSTRACT

Yeasts have been intimately connected with human civilization for millennia, originally used for fermentation in food and beverage production. This article explores the multifaceted roles of yeasts—particularly *Saccharomyces cerevisiae*—as both a model organism and a cell factory. The historical journey of yeast research is chronicled from early fermentation practices to its central role in the molecular biology revolution. Notable discoveries using yeast have led to numerous Nobel Prizes, demonstrating its power in elucidating fundamental biological processes such as the eukaryal cell cycle, protein trafficking, transcription, and autophagy. The deep conservation of cellular pathways between yeast and humans, such as AMPK/Snfl and TORC1/Tor1 signaling, further underscores yeast's value in biomedical research. Beyond its use in basic science, *S. cerevisiae* has become a preferred host for industrial biotechnology due to its genetic tractability, safety status, and ability to scale fermentation processes. Yeast has been engineered to produce a broad range of chemicals, fuels, and pharmaceuticals. Advanced tools in metabolic engineering—including genome-scale metabolic models, multi-omics analyses, and adaptive laboratory evolution—have driven remarkable improvements in yield, productivity, and strain robustness. These tools also offer insights into fundamental metabolic regulation and cellular adaptation. As the article discusses, yeast has not only illuminated the molecular workings of eukaryal life but also transformed industrial biotechnology. Its legacy and continued evolution affirm its indispensable role in science and technology.

1 | Introduction

Yeast and human civilization have co-developed since ancient times, with the first reported production of beer using yeast in China dating back to around 7000 BCE, and a similar technique was used in Mesopotamia and Egypt around 3500 BCE (P. E. McGovern et al. 2004). Similarly, the use of yeast for the production of wine dates back to around 6000 BCE in Georgia (P. McGovern 2017), but there are strong indications that yeast was already used to raise bread around 10,000 BCE (Money 2018). The application of yeast for the production of bread and fermented beverages has therefore clearly been closely related to early agricultural developments of human civilization. Even though Antonie van Leeuwenhoek, generally considered as the founder of microbiology as a discipline, started to observe microorganisms in his microscope in the 1670s, it was first in the 19th century that Louis Pasteur clearly showed that production of beer and wine was the result of a

fermentation process involving a microorganism. In 1861, he presented results from his classical experiments that clearly showed that fermentation is not a spontaneous process but requires “contamination” of the wine must with yeast. Already before Pasteur's discovery, the term yeast, from the old English word *gist*, had been used for the description of the bubbling and foaming of bread dough and alcoholic beverages, and it was therefore naturally for Pasteur to give reference to the microorganism responsible for the alcohol production as yeast. Pasteur later also found bacteria in wine, but only when the fermentation had gone bad. Another major contribution was made in 1883 when the Danish researcher Emil Chr. Hansen was the first to isolate yeast. Hansen was employed at Carlsberg but was given freedom to do research by the Carlsberg founder, Jacob C. Jacobsen, and this led to the isolation of the yeast strain used for the production of lager beer at Carlsberg. For this reason, the

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Summary

- Yeast has been part of human civilization for millennia.
- Yeast is widely used as a model organism for studying the biology of eukaryal cells, and the mechanisms underlying many different human diseases have been identified using yeast as a model organism.
- Yeast is widely used as a cell factory for the production of fuels, beverages, foods, food ingredients, chemicals, and pharmaceuticals.

yeast was named *Saccharomyces carlsbergensis* but was later re-named to *S. pastorianus* as well as it was discovered that this yeast is in fact a hybrid between *S. cerevisiae* and *S. eubayanus*.

Today, yeasts are widely used as model organisms as well as for industrial production of bread, beer, wine, chemicals, and pharmaceuticals. The term yeast is often taken as a synonym for *S. cerevisiae*, even though yeast encompasses a phylogenetically diverse group of fungi belonging to two different phyla: Ascomycota and Basidiomycota. Both the budding yeasts, including *S. cerevisiae*, and the fission yeast, *Schizosaccharomyces pombe*, belong to the Ascomycota phyla, and have served as important model organisms, but *S. cerevisiae* has at the same time served as an important cell factory. Today, several other yeast species are used as cell factories, for example, *Komagataella phaffii*, formerly known as *Pichia pastoris*, which is widely used for recombinant protein production, and *Yarrowia lipolytica*, which is used for the production of lipids and here-off derived chemicals. Here, I will briefly discuss the historical developments that led to yeast, predominantly *S. cerevisiae*, becoming an important model organism as well as an important cell factory. Based on some lessons from the past, I will end with a discussion of how these lessons may shape the future of the yeast research community.

2 | Yeast as a Model Organism

Yeast has evolved as a very important model organism for studying eukaryal biology (Botstein and Fink 2011). This is clearly demonstrated by successful conference series like International Congress on Yeast that is held every fourth year and organized by International Commission of Yeast (ICY), International Specialized Symposia on Yeast (ISSY) that is held annually except for years where the large international congress is held (also organized by ICY), and the International Conference on Yeast Genetics and Molecular Biology that is held every second year and dates back to the 1960s. Also, yeast research is covered by two prominent international journals: Yeast and FEMS Yeast Research, which combined publish about 200 papers on yeast research annually. However, the strength of the international yeast research community is also seen by many papers on yeast research in leading journals like *Cell*, *Nature*, *Science*, and *PNAS*.

The use of model organisms has been around for a long time, but the idea of using microorganisms for studying basic

molecular mechanisms in cells started in the 1950s with the studies of Francois Jacob and Jacques Monod, who used the bacterium *Escherichia coli* for studies of how lactose metabolism is regulated. In 1961, this culminated in their landmark paper published in the *Journal of Molecular Biology* that describes the operon model and the genetic regulatory mechanisms underlying expression of β -galactosidase (or lactase) that is responsible for cleavage of lactose into glucose and galactose (Jacob and Monod 1961). Based on this work, they received the Nobel Prize in Physiology or Medicine in 1965 together with André Lwoff, who had studied how bacteriophages incorporate their genetic material into bacteria's genomes but remain latent until a trigger factor causes a new phage to be formed. This seminal work resulted in much focus on using *E. coli* as a model organism for molecular biology studies, but there was, however, need for also having a model of eukaryal molecular and cell biology.

In the late 1960s and early 1970s, Fred Sherman addressed this by developing a simple, almost one-step, method for purification of the Iso-1-cytochrome *c* protein from yeast, which enabled mapping how mutations in the *CYC1* gene linked to variants of the protein (Fink 2014). These studies enabled Sherman to show that the genetic code in yeast, and hence eukarya, is the same as in bacteria, and he also deduced that whereas operons are typical of bacteria, they are not used by eukarya. In 1974, Sherman established a course on yeast genetics at Cold Spring Harbor and ran this intensive 3-week course for 17 years. The course was instrumental in solidifying experimental methods, and much of these is captured in his paper in *Methods in Enzymology* (Sherman 2002). An important outcome of the course and Sherman's dedication to developing methods for studying yeast was the isolation of laboratory strains that were suitable for genetic studies, and this resulted in consolidation on the use of relatively few strains in different research laboratories, which has been a significant advantage for the field, as this has enabled easy sharing of strains for comparative studies. Today, this has even consolidated further with the wide use of strains like S288C and W303, as well as the later addition CEN.PK that was developed in the 1990s by crossing various laboratory strains (Entian and Kötter 2007). A collection of strains with gene deletions is available for all these strains, but only with an almost complete collection available for BY, which was derived from one of Sherman's original yeast strains, FY1679, and which is isogenetic to S288C but carries deletion in four metabolic genes that can be used as markers for genetic transformations.

The importance of yeast as a model organism is well illustrated by the number of yeast researchers who have received Nobel Prizes in Physiology or Medicine for their work (Hohmann 2016). In 2001, Paul Nurse, Leland Hartwell, and Tim Hunt received the Nobel Prize for their discoveries of key regulators of the eukaryal cell cycle. Using classical forward genetics, using *S. cerevisiae*, Hartwell had identified hundreds of genes engaged in the cell cycle. Similarly, Nurse, who had used *S. pombe* in his studies, also used forward genetics, identified the protein kinase Cdc2 (later he also identified the homologous human protein CDK1) that plays an important role in the cell cycle. Hunt, who was using sea urchins for his studies, discovered that several proteins are degraded in different phases of the cell cycle and that this protein degradation plays an important role in the regulation of the cell cycle. In 2013, James Rothman,

Randy Scheckman, and Thomas Südhof received the Nobel Prize for their discoveries of how proteins are transported and delivered to their right location within eukarya. As eukarya contains multiple compartments, it is important that proteins are transported to their proper destination, and using yeast as a model organism, Scheckman identified a large number of genes involved in protein translocation within the cell. Rothman identified proteins involved in the docking and fusion of vesicles that transport proteins in mammalian cells, and many of these proteins were found to be the same as those identified by Scheckman, showing that the protein translocation pathway is highly conserved in eukarya. Südhof was also studying vesicle transport but did this in neuronal cells, where this process is important for the release of neurotransmitters. The protein translocation pathway is very important for protein secretion, and these basic discoveries have hereby enabled mapping of this pathway to the level where advanced mathematical models have been reconstructed for both yeast cells (F. Li et al. 2022) and mammalian cells (Feizi et al. 2017; Gutierrez et al. 2020). As will be discussed later, these models have enabled improved design of cell factories applied for recombinant protein production, which today is a billion USD industry. Again in 2016, the Nobel Prize in Physiology or Medicine was given to a yeast researcher, namely to Yoshinori Ohsumi, for his discovery of the mechanisms for autophagy. Using a similar approach as applied by Hartwell and Scheckman, he identified all the proteins involved in autophagy, an important process for the degradation of cellular material in the lysosomes. Also in this case, it was found that there is complete conservation of this pathway between yeast and mammalian cells, pointing to the power of using yeast as model organism.

Yeast has also been used as a tool for several other discoveries that have resulted in researchers receiving the Nobel Prize. Thus, in 2006, Roger Kornberg received the Nobel Prize in Chemistry for his discovery of the molecular basis of eukaryal transcription, and in his research, he used expression of the *GAL* genes in yeast, and in 2009, Elizabeth Blackburn, Carol Greider, and Jack Szostak received the Nobel Prize in Physiology or Medicine for their discovery of how chromosomes are protected by telomers. Blackburn, who had originally performed her studies on protozoa, started to collaborate with Szostak, who was a yeast geneticist, on how the linear chromosome of yeast is protected from degradation. Aaron Ciechanover, Avram Hershko, and Irwin Rose, who got the Nobel Prize in Chemistry in 2004 for the discovery of the mechanism of ubiquitin-mediated protein degradation, did their work on mammalian cell extracts, but through collaboration with Alexander Varshavsky, this process was mapped to function in yeast. Finally, Osamu Shimomura, Martin Chalfie, and Roger Y. Tsien received the Nobel Prize in Chemistry in 2008 for their discovery and development of the green fluorescent protein (GFP), and Tsien used yeast to demonstrate how GFP could be used as a marker for intracellular location and trafficking of proteins.

The extensive use of yeast as a model organism resulted in the organism playing a central role in the genomics revolution. Thus, Chromosome III of yeast was the first complete chromosome to be sequenced (Oliver et al. 1992), 3 years before the genome sequence becoming available of the first bacterium. Also, the complete sequence of the yeast genome was published already in 1996 (Goffeau et al. 1996), only 1 year after the genome sequences of the first two bacteria had been presented. These early yeast sequencing projects were carried out using

traditional Sanger sequencing and could therefore only be carried out due to organized efforts engaging many different yeast laboratories around the world. Following publication of the complete yeast genome, 35 laboratories worldwide engaged in a large and coordinated functional characterization of the identified yeast genes (Goffeau 2000), and this resulted in the establishment of a library of single gene deletion mutants, which represents a unique collection that has later been used in a number of functional studies. With the first eukaryal genome being available, pioneering studies were first carried out using yeast as a model organism, for example, genome-wide transcription analysis (DeRisi et al. 1997), extensive proteomics analysis (Washburn et al. 2001), protein-protein interaction analysis (Uetz et al. 2000), extensive mapping of protein localization (Huh et al. 2003), enzyme catalysis (Martzen et al. 1999), and the first genome-scale metabolic model for an eukaryal organism was reconstructed for yeast (Förster et al. 2003). This model has consistently been updated resulting in continuous releases of better models, for example, recent releases of Yeast8 (Lu et al. 2019) and Yeast9 (C. Zhang et al. 2024), as well as it has formed the basis for development of completely new genome-scale modeling concepts like enzyme-constrained models that can describe key phenotypes such as the Crabtree effect (Sánchez et al. 2017; Chen and Nielsen 2019). In recent years, many different yeast isolates have been sequenced (Peter et al. 2018; Caudal et al. 2024), and this has enabled the generation of the pan-genome of *S. cerevisiae* as well as building genome-scale metabolic models for the different isolates and using these to show how yeast metabolism has adapted to different ecological niches, for example, that oxidative phosphorylation is down-regulated in oxygen-limited niches (Wang et al. 2025). With all these developments, the Saccharomyces Genome Database (SGD) (www.yeastgenome.org) has played a central role in gathering, curating, and organizing information. SGD was founded by J. Michael Cherry in 1993 together with a group of researchers at Stanford University, with David Botstein playing a prominent role (Cherry 1998), and today it represents one of the most comprehensive databases on genomic and physiological information for any organism.

As already mentioned above, there is a high degree of conservation of processes between yeast and human cells, and indeed about 1000 human disease genes exhibit functional conservation by their ability to complement the yeast ortholog (Heinicke et al. 2007). This has enabled mapping of complex regulatory pathways in yeast and later used these pathway maps for identifying corresponding processes in human cells. In particular pathways involved in nutrient sensing have been extensively studied in yeast, and many lessons have then subsequently been used to gain insight into nutrient sensing in human cells. This is well illustrated by the key regulatory roles of AMPK (yeast ortholog Snf1) and TORC1 (yeast ortholog Tor1) (Figure 1). Thus, Snf1 (sucrose non-fermenting) was first discovered in yeast in 1981 (Yang et al. 1994) but has later been extensively studied in mammalian cells, where it has been identified to be associated with controlling the development of many different diseases (Hardie et al. 2012). AMPK (AMP-activated kinase) senses the glucose level indirectly through the levels of AMP (or ADP) and then controls a large number of metabolic processes related to energy metabolism, for example, activation of glycolysis, β -oxidation, and mitochondrial biogenesis, as well as processes related to cell proliferation and maintenance (Figure 1). AMPK is

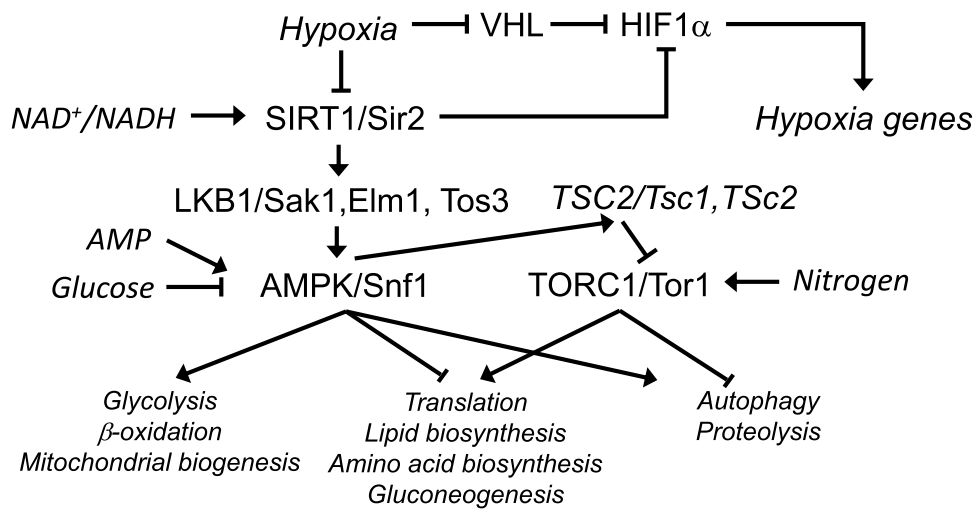


FIGURE 1 | Highly conserved pathways between yeast and human cells for controlling important cellular processes. Human gene names are listed first and yeast gene names last. AMPK/Snf1 and TORC1/Tor1 are two key protein kinases that regulate a number of cellular processes associated with cellular growth and maintenance. Regulation of hypoxia is currently known and not conserved between yeast and human cells. The two central protein kinases integrate information about nitrogen availability, energy (glucose) availability, and redox state of the cell, and based on this, regulate energy production, energy consumption in biosynthetic processes, and degradation of cellular components.

highly conserved in the eukaryal kingdom, and mapping of its functions in yeast therefore generally translates to a wide range of other organisms, and in a study using controlled growth conditions involving multi-omics analysis, it was possible to generate a global map of Snf1/AMPK regulation in yeast (Usaita et al. 2009). Snf1 is also activated upstream by three protein kinases, Sak1, Tos3, and Elm1, whereas AMPK only seems to be activated by two protein kinases, LKB1 and CaMKK β , where LKB1 is a tumor suppressor kinase for which there has so far not been identified any upstream protein kinase. However, LKB1 is activated by SIRT1 (Figure 1) through de-acetylation, and as the de-acetylation activity of SIRT1 requires NAD⁺, there is an indirect regulation of the redox level in the cells, and therefore also linked to the level of oxygen in the cells. Hereby, Snf1/AMPK is regulated by the levels of carbon/energy source as well as oxygen levels in the cells, and integrates this information to control energy metabolism as well as metabolic pathways associated with cell production that are highly energy demanding (Figure 1).

Also, Tor1/TORC1 (target of rapamycin complex) was first discovered in yeast by screening for resistance towards rapamycin (Heitman et al. 1991), and this kinase has also later been extensively studied in mammals, where it has been found to be an important drug target. TORC1 senses the nitrogen levels in the cells, and through activation stimulates protein synthesis and reduces the activity of protein degradation pathways, including autophagy (J. Zhang et al. 2011). TORC1 is regulated by the upstream kinase TSC2, which is again regulated by AMPK (Figure 1), and AMPK and TORC1 hereby jointly ensure that energy metabolism is balanced with pathways required for cellular proliferation, in particular protein synthesis and degradation. In cancer cells, there is a dramatic shift towards rapid cell proliferation, and these two pathways play a key role in regulating the dramatic metabolic shift required for this. And for this reason, these pathways are extensively studied in human cells with the objective of identifying new cancer drugs. The initial discovery of many of the components of these pathways in yeast is yet another strong manifestation of the important role yeast has played as a model organism in the past.

3 | Yeast as a Cell Factory

As mentioned in the introduction, yeast has been used as a cell factory since ancient times (Figure 2). For thousands of years, yeast was only used for the production of bread, beer, and wine, but already in the late 19th century yeast was used for the production of ethanol to be used as transportation fuel. However, ethanol was rapidly replaced by gasoline, and it was first during the oil crisis in the late 1970s that the first large-scale plants for ethanol production were established, and a wider use of ethanol as a transportation fuel was established. Also, during World War I, yeast was used to produce glycerol by the so-called Neuberg fermentation process, where bisulfite was added to the medium, resulting in yeast producing glycerol. In the 1910–1920s, the incremental feed process, or generally referred to as the fed-batch process, was developed by the Danish scientist Sak for the production of Baker's yeast, often referred to as the Danish method (or Zulaufverfahren). In this method, there is slow feeding of sugar to the bioreactor such that the sugar concentration is kept low and thereby prevents the onset of the Crabtree effect, resulting in the production of ethanol. This leads to a high yield of Baker's yeast from the fed sugar, and this method is today widely used in many fermentation processes.

With the development of recombinant DNA technology in the 1970s and the development of yeast as a widely used model organism, yeast was also exploited for the production of pharmaceuticals. Among the first applications was for the production of virus-like particles that accumulate intracellularly in yeast, and this led to the development of vaccines for Hepatitis B and Infectious Bursal Disease Virus (IBDV) in 1986 and 1990, respectively. Already in 1982, Genentech, in collaboration with Eli Lilly, developed a process for recombinant production of insulin using *E. coli* as a cell factory. In this process, the two peptides forming human insulin were produced individually as inclusion bodies, that is, accumulating intracellularly, and following purification, the two peptides were then connected via two sulfur-bridges, resulting in human insulin in an *in vitro*

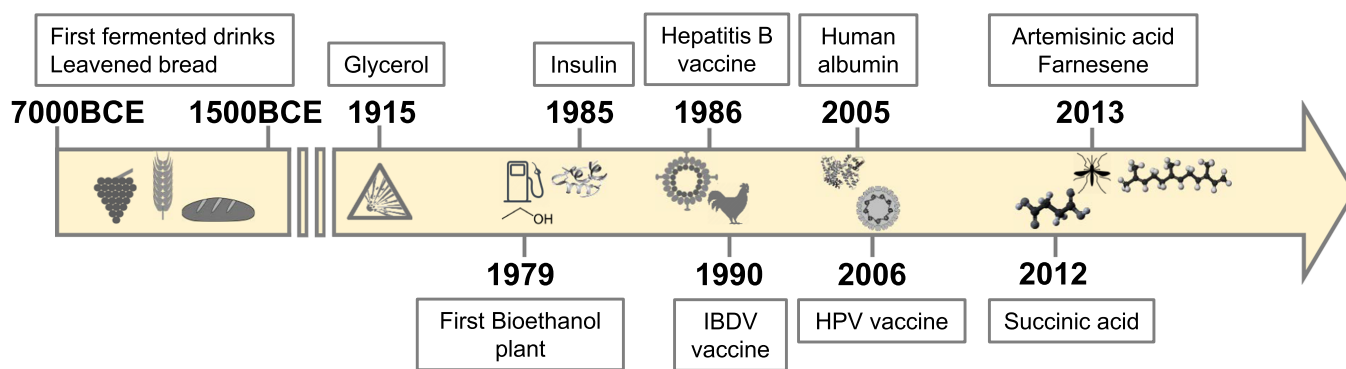


FIGURE 2 | Key historical events in the history of industrial application of yeast.

process. This process represents a landmark in terms of production of recombinant proteins to be used as pharmaceuticals, but it is quite complex, and it was therefore a breakthrough when Novo (now Novo Nordisk) launched a process for the production of human insulin using recombinant *S. cerevisiae* in 1985. This process is cost-effective and easy to scale as the product is secreted by yeast, and this has therefore resulted in *S. cerevisiae* becoming the platform cell factory of Novo Nordisk, used also for the production of many of their other peptide drugs, including the peptide part of Semaglutide, the active ingredient in Ozempic and Wegovy. In 2005, Delta Biotechnology, UK, launched a process for the production of human serum albumin (HSA) using recombinant yeast. HSA contains 17 sulfur-bridges, and the fact that this protein folds efficiently and easily gets secreted by a heterologous host is quite remarkable, but it turns out that *S. cerevisiae* does not efficiently secrete all proteins (Huang et al. 2014). There has therefore been much interest in engineering the secretory pathway of yeast in order to improve recombinant protein production. However, the protein secretory pathway is quite complex, involving many different steps, that is, translocation of the protein into the endoplasmic reticulum, proper disulfide bond formation, glycosylation, further translocation to the Golgi and secretory vesicles, before the protein is secreted (F. Li et al. 2022). A certain modification of the secretory pathway that works well for the secretion of one protein does, therefore often does not work for another protein. Using a fungal α -amylase as a model protein, we developed a microfluidic screening system for rapid screening of mutants having increased protein secretion, and through genome sequencing and systems biology characterization of isolated mutants, we identified a large number of targets for improving protein secretion (Huang et al. 2015; Huang et al. 2017). Many of these targets were later proved to enable a 2.5-fold improved production of α -amylase (Huang et al. 2018).

S. cerevisiae also has a number of advantages as a cell factory for the production of chemicals. Among these are: (1) extremely well characterized with extensive knowledge of nutrient sensing and gene regulation; (2) availability of SGD as a highly curated database that provide information about genomics, literature and different datatypes; (3) easy to genetically engineer with a wide range of synthetic biology tools available; (4) availability of detailed metabolic models that maps all known elements of metabolism; (5) easy to obtain GRAS (Generally Regarded As Safe) status for products produced by yeast; (6) yeast is a robust industrial microorganism with high tolerance to various chemicals, for example, a very high ethanol tolerance, low pH and

a relatively wide temperature range; (7) yeast fermentations have demonstrated to scale consistently, both for anaerobic and aerobic processes, which makes it relatively easy to develop a new process. In many cases, these advantages make *S. cerevisiae* a superior choice as a cell factory compared with other widely used cell factories such as *E. coli*, *Corynebacterium glutamicum*, and *Aspergillus niger* (Nielsen 2019). However, the choice of cell factory should always be considered carefully, and the choice will depend on the chemical to be produced. Thus, for any process, it is important to ensure that a techno-economic analysis is performed, and here the evaluation of possible titer, rate, and yield (TRY) with a given cell factory plays an important role (Konzock and Nielsen 2024). As an example, *E. coli* is excellently suited for the production of 1,3 propanediol and 1,4 butanediol, where commercial processes have been developed, as it is possible to obtain very high rates, which ensures efficient use of capital investments in the production facility.

Today *S. cerevisiae* has been engineered for the production of a wide range of fuels and chemicals (Shi et al. 2025), and it is therefore widely used as a cell factory (Figure 3A). Among some of the chemicals produced by yeast fermentation and launched as commercial products are farnesene by Amyris (Meadows et al. 2016), resveratrol by Evolva (M. Li et al. 2016), santalene by DSM-Firmenich (Scalciati et al. 2012), spermidine by Chrysea (Qin et al. 2021), and thebaine by Antheia (Galanie et al. 2015). In all of these cases, a heterologous pathway was inserted to ensure conversion of an intermediary of yeast metabolism to the product of interest, but even more importantly, the resulting yeast strain had undergone several rounds of engineering using the design, build, and test cycle (Figure 3B) (Nielsen and Keasling 2016). As an example the production of farnesene and santalene, both so-called sesquiterpenes, involves only a few enzymatic steps from farnesyl pyrophosphate (FPP), but in order to ensure a high flux towards the products it was necessary to both engineer the enzymes in this conversion to be more efficient (Meadows et al. 2016) as well as perform multiple engineering of the central carbon metabolism to ensure a high flux directed towards FPP (Tippmann et al. 2016; Meadows et al. 2016). In particular, engineering of the central carbon metabolism for ensuring high flux towards the precursor for the product of interest is often complicated, as yeast has evolved extensive regulatory mechanisms to maintain homeostasis of metabolism, and redirecting flux therefore generally requires several rounds in the design, build, and test cycle. In this cycle, advanced genome-scale metabolic models mentioned above are being used, both for the identification of new design strategies

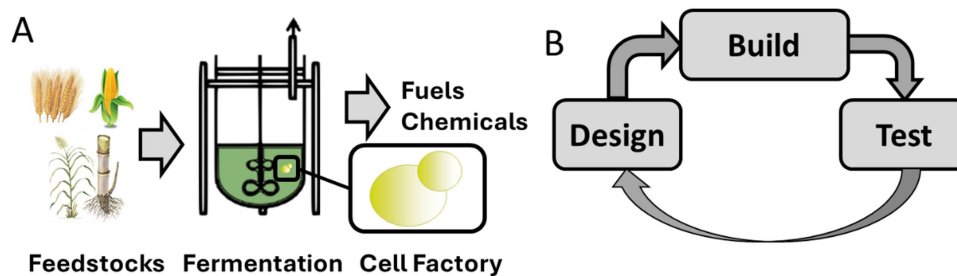


FIGURE 3 | Concepts of metabolic engineering of yeast. (A) Through engineering of yeast, it is possible to obtain a cell factory that can be used to convert various feedstocks, for example, corn, wheat, or sugar cane, into fuels and chemicals through fermentation. (B) The design, build, test cycle that is generally used in metabolic engineering for the construction of a yeast strain that meets the requirements for cost-effective production of fuels and chemicals.

(Domenzain et al. 2025) and for analysis of strains when they are being tested (Oftadeh et al. 2021).

In some cases, an engineering strategy results in strains with reduced growth, and here adaptive laboratory evolution can be useful for isolation of mutants with improved properties. Following isolations of mutants and characterization of these using genome sequencing and omics analysis, it may be possible to identify causal mutations that can then be implemented in the engineered strains, where strains are obtained with only well-defined genetic mutations. A good example of this was the use of adaptive laboratory evolution of yeast to grow at elevated temperatures, that is, 40°C. Hereby, several mutants were identified, and through genome sequencing, transcriptome analysis, and genome-scale metabolic flux analysis, a causal mutation in *ERG5* was identified to result in loss of function of *Erg5*, an enzyme involved in the biosynthesis of ergosterol (Caspeta et al. 2014). This loss of function resulted in a shift in production of ergosterol to production of fecosterol, which causes the membrane to maintain proper function at higher temperatures (Caspeta et al. 2014). In another study, yeast was engineered to shift from producing ethanol to free fatty acids, but this resulted in a significant reduction in the specific growth rate (Yu et al. 2018). Through adaptive laboratory evolution of the engineered strain, faster-growing mutants were identified, and through genome sequencing of several isolated mutants, a causal mutation was identified in *Pyk1*, a key glycolytic enzyme (Yu et al. 2018). Through attenuation of *Pyk1* activity, the cell is better balancing flux through glycolysis with the lower flux capacity pathway leading to free fatty acids, and hereby cellular homeostasis is recovered (Yu et al. 2018). In another strategy to overcome the Crabtree effect in yeast, an alternative glycolytic pathway was reconstructed using phosphoketolase that converts xylose-5-phosphate to acetyl-phosphate and glyceraldehyde-3-phosphate, and glycolysis was blocked through deletion of *PFK1* and *PFK2* (Qin et al. 2023). The resulting strain grew very slowly, but again, adaptive laboratory evolution could be used to identify faster-growing mutants. In this case, a causal mutation was identified in *OCA5*, but the function of *Oca5* was not known at the time. However, through further studies, it was identified that *Oca5* is involved in adjusting the level of 5-diphosphoinositol 1,2,3,4,6-pentakisphosphate that engages with transcription factors that regulate glycolysis and respiration (Qin et al. 2023). Also, in this study, the cells found a strategy to regulate flux through glycolysis and the tricarboxylic cycle to the flux of the artificial glycolysis and thereby ensure homeostasis. Even though the objective of the study was to engineer the central carbon metabolism, the result was that completely new insight into the

regulation of the central carbon metabolism in yeast was obtained. But, also when the causal mutation in *Oca5* was inserted into the engineered strain, it was possible to use this strain for very efficient production of free fatty acids, as the acetyl-phosphate derived from the pathway could efficiently be converted to acetyl-CoA, the key precursor for biosynthesis of fatty acids (Qin et al. 2023).

4 | The Future of the Yeast Research Community

It is obvious that yeast has served as a very important model organism as well as an important cell factory for the production of fuels and chemicals. It is undisputable that yeast will continue to serve as a key cell factory, as it has many advantages compared with other cell factories, as discussed here. However, will *S. cerevisiae* remain as an important model organism for studies of eukaryal biology? With the advancement of experimental techniques, including CRISPR technology, it has become relatively easy to use human cell lines directly for studies of key processes involved in eukaryal cell biology; however, many different cell lines are being used for these studies, and it is therefore difficult to get the same cumulative knowledge as holds for yeast. Also, the infrastructure available for yeast researchers is beyond what is available for any other organism, for example, the SGD database, availability of gene-deletion libraries of strains, availability of many different strain libraries, and availability of large datasets of multi-omics analysis. This, combined with a strong and dedicated yeast research community organizing regular dedicated yeast conferences and driving specialized yeast journals, makes me confident that yeast will maintain as an important model organism in parallel with its expanded use as a cell factory. Thus, in the future I am certain that the yeast research community will maintain strong as it will shape around: (1) Use of yeast as a cell factory and through metabolic engineering construction of yeast strains that can be used for production of a wide range of complex natural products; (2) Use of yeast as model organism for synthetic biology where the function of different regulons can be tested in an eukaryal cell; (3) Use for studies of how eukaryals cell evolve in different ecosystems and adapts to different environmental conditions; (4) Use for studies about how eukaryal cells interacts with bacteria and archaea in microbial communities; (5) Use as a classic model organism for studies of complex regulatory pathways and discovery of new regulatory features. Many of these studies will probably arise as part of some of the other four applications mentioned above, but also by its own right,

I am certain that yeast will remain an important model organism in the years to come.

Author Contributions

Jens Nielsen conceived the idea behind the paper and wrote the paper.

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Conflicts of Interest

Jens Nielsen is co-founder of Melt&Marble that is a yeast synthetic biology company that produces ingredients for cosmetics and food, and co-founder of Chrysea that is a yeast synthetic biology company that produces bioactive ingredients for human health and nutrition.

Data Availability Statement

The author has nothing to report.

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