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A review on sustainable yeast biotechnological processes and applications

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ABSTRACT

Yeast is very well known eukaryotic organism for its remarkable biodiversity and extensive industrial applications. *Saccharomyces cerevisiae* is one of the most widely used microorganisms in biotechnology with successful applications in the biochemical production. Biological conversion with the focus on the different utilization of renewable feedstocks into fuels and chemicals has been intensively investigated due to increasing concerns on sustainability issues worldwide. Compared with its counterparts, *Saccharomyces cerevisiae*, the baker's yeast, is more industrially relevant due to known genetic and physiological background, the availability of a large collection of genetic tools, the compatibility of high-density and large-scale fermentation, and optimize the pathway for variety of products. Therefore, *S. cerevisiae* is one of the most popular cell factories and has been successfully used in the modern biotech industry to produce a wide variety of products such as ethanol, organic acids, amino acids, enzymes, and therapeutic proteins. This study explores how different sustainable solutions used to overcome various environmental effects on yeast. This work targets a broad matrix of current advances and future prospect in yeast biotechnology and discusses their application and potential in general.

1. Introduction

Saccharomyces cerevisiae is one of the widely industrially used microorganisms in microbial production of proteins, chemicals and metabolites. This is because genetic manipulation of *S. cerevisiae* is relatively easy and established of large collection of genetic tools compared to other microorganisms. *S. cerevisiae*, a unicellular eukaryote is most intensively studied and also used as industrial microorganism for biochemical production and heterologous protein expression (Mattanovich et al., 2014). Synthetic biology makes the yeast cell factories as more efficient and more controlled process such that the novel organism derived from *S. cerevisiae* might work according the requirement/s or demand. Synthetic biology is an advanced definition of framework for design, conceptualization and manufacture of biological systems such that genetic engineering, genomics and systems biology are used to make control and program the biological device to create predictable properties and control the cell behavior which was previously not found in the system. This will give a clear picture where genetic engineering makes a unique solution for a specific problem and therefore, with the help of genome editing techniques, of next generation sequencing and gene synthesis plus with the help of different modelling using large datasets and bioinformatics tools, synthetic biology solves the design of industrially relevant strains for producing biochemical products specifically novel chemicals.

S. cerevisiae is most industrially intensively studied unicellular eukaryote for biochemical production. *S. cerevisiae* is being used to produce many industrially relevant chemicals and heterologous protein production apart from traditional applications in alcohol fermentations, baking or bio-ethanol processes. There are a lot of *S. cerevisiae* strains exist as library and therefore, it will be easier to find a suitable host from the library based on the product and other parameters like productivity, yield and other parameters like pH, temperature, salt concentrations. But several times a specific host with targeted optimization can't be found due to the genetic engineering of specific species are not available and therefore, random mutagenesis or evolutionary optimization used to produce the specific species. One can also start with a known organism for example, *S. cerevisiae* and optimize it for a desired product and conditions used in the process for cultivation. *S. cerevisiae* is always got the priority because a vast range of genetic tools exist and due to extensive range of knowledge about all aspects of yeast biology. Using these tools by the help of metabolic engineering which is the heart of systems biology may give a solution for better optimized process for better productivity. In general, genome scale model (GSM) is exist for almost all yeast species can be used to develop a metabolic model that explain different routes to improve the process for better optimization and can be used with existing tools for better insights and give better solution per requirement. Fig. 1 illustrates a general approach where metabolic engineering under systems biology can play a

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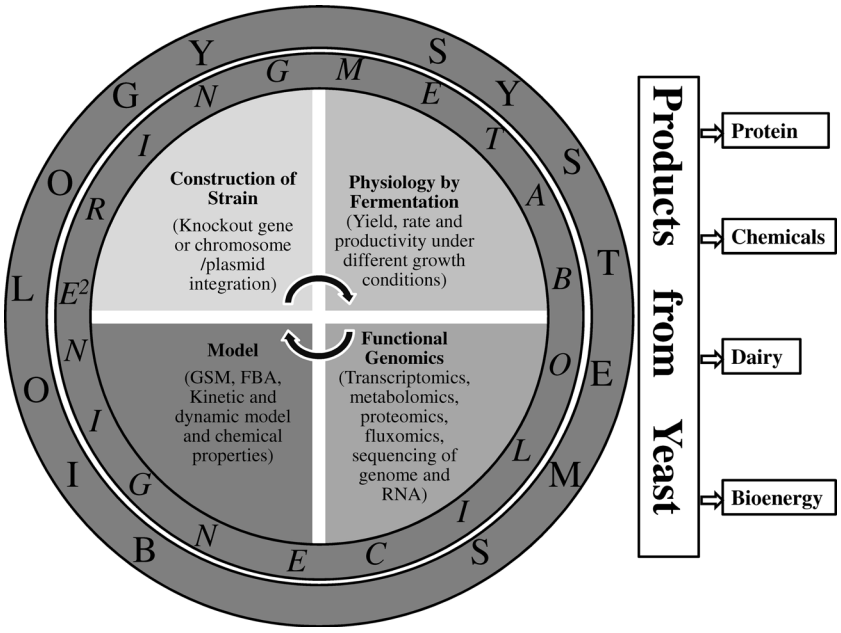

Fig. 1. This schematic diagram illustrates a general metabolic engineering approach where tools of systems biology are used for advanced cell factories for different industrial productions.

vital role by using genetic manipulation for strain construction from the help of metabolic model approach and optimized further by fermentation to get all growth parameters where different omics analysis will help further for better insights to improve further the metabolic model and strain to get more optimized process for better productivity. This is a cyclic process where better improvement will be the key for further success.

In this review, we will underline the developments of *S. cerevisiae* for production of chemicals, protein, enzymes on a same platform such that one can easily find the information easier.

2. Bioprocessing for protein production from yeast specially *S. cerevisiae*

Mainly eukaryotic species are used for protein production where *S. cerevisiae* was applied, but now other microorganisms are also equally used in industry for the same. Yeast is generally regarded as safe (GRAS) status given by FDA and specifically not used as pathogens for humans. *S. cerevisiae* is the most useful species in yeast that has been used industrially for years in production of heterologous proteins and therefore, large scale production is already established for commercial production. “Biopharmaceutical” term was first used in 1980s which is described a class of therapeutic proteins produced by synthetic biology or modern biology techniques such as genetic engineering or using monoclonal antibodies by hybridoma technology. There are several traditional pharmaceutical products are produced from direct chemical synthesis such as for analgesic, acetaminophen and ketamine are used. But here yeast in general discussed for different biopharmaceuticals production (see Table 1).

S. cerevisiae is the most dominated cell factories due to the large volume of products known as Insulin and its analogs where the global market is growing due to the widespread disease all over the world from US$12B in 2011 to more than US$32B in 2018. Engineered yeast with a secretory pathway with the help of metabolic engineering, genetic engineering, systems biology and advanced modelling strategy can help to make different biopharmaceutical products and now-a-days more than 40% of the biopharmaceuticals have been produced by using Chinese Hamster Ovarian cell lines (CHO cells).

More than 10000 pharmaceutical companies are there worldwide where maximum of these companies grow rapidly, reaching an estimated value of US$100B by the mid ‘80 s where around 100 of these companies are considered as international figure. Currently this number is folded several times as both population and also diseases increase. There are several companies in USA and Europe producing approved biopharmaceutical products for general medical uses are as follows, Abbott, Amgen, Bayer, Biogen, Boehringer Manheim, Centocor, Chiron, Cytogen, Eli Lilly, Galenus Manheim, Genentech, Genzyme, GlaxoSmithKline, Hoechst AG, Hoffman-la-Roche, Immunomedics, Isis Pharmaceuticals, Novartis, Novo Nordisk, Organon, Ortho Biotech, Roche, Sanofi-Aventis, Schering Plough, Serono, Wyeth. *S. cerevisiae* is chosen by a number of companies as the most suited organism as a host depending on the known in house knowledge and therefore, a large range of therapeutic proteins are produced as recombinant protein and those are described as follows in the following Table 2. Other examples of recombinant protein from other yeast species are also illustrated in Table 3.

Secretory pathway (SP) in yeast is very complex where more than 550 proteins are involved in the process but around 160 proteins are responsible for different post translational processes (Nielsen, 2013) such as glycosylation and folding. Almost all proteins are targeted to the endoplasmic reticulum (ER), Golgi, Vacuole and cytoplasmic membranes are also processed through the SP. Basically, ER plays a big role for secreting targeted proteins and it depends on if they fold correctly or not. All proteins fold correctly can enter into the secretory pathway else refolding require from stressed ER. Further, these corrected folding proteins are exported to Golgi for further processing and after secreted through the ER-Golgi complex, may be secreted through endosome or enter through vacuole for further storage or degradation. This is a complex process in overall. Therefore, to understand the protein secretion, more rational approach required to build by digging the basics of systems biology and find insights that is much improved and novel applied science. Design such a model can be easily made by engineering of metabolic pathways by using Genome Scale Metabolic Model which is the heart of metabolic engineering in modern era. A mathematical model can also predict the biological system by overexpression or deleting genes using genetic engineering of the cellular system to improve protein secretion. To improve cell factories, strains are characterized by growing them in fermenters for optimizing growth parameters such as biomass growth, substrate consumption and product formation followed by omics analysis to provide new insights into the cellular metabolism and physiology which will also give feedback to improve models further to optimize strain construction (see Fig. 1).