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Yeast toxicogenomics: lessons from a eukaryotic cell model and cell factory

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The yeast *Saccharomyces cerevisiae* remains a highly relevant experimental model in the field of toxicogenomics and is an important microbial cell factory for the production of added-value chemicals and biofuels. Its deep functional characterization coupled with the straightforward exploitation of Omic approaches and metabolic engineering, at the frontline of systems and synthetic biology, is instrumental to obtain mechanistic insights into the response to multiple toxicants and for the development of robust industrial strains. This critical review focuses on the current field, ranging from the identification of toxicological outcomes of exposure to environmental toxicants, with impact in risk assessment, bioremediation and plant biotechnology, to the improvement of biomass-based biorefinery processes, with applications in pharmacology and in the food and beverages industry.

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Introduction

Understanding cellular responses to environmental insults such as the presence of toxic metabolites or components of the production media, pharmacological drugs, agriculturally relevant xenobiotic compounds and other environmental pollutants, has a paramount importance in a range of Biotechnological applications and in the Health and Environmental sectors, and is the focus of intensive scrutiny [1•,2]. Classical toxicological studies have been greatly leveraged by the recent introduction of post-genomic approaches, shifting the focus of toxicological assessment to mechanism-centred analyses at the genome-wide levels [2,3••]. In this context, toxicogenomics has emerged in the past decade as a transdisciplinary new field that integrates genome-wide methodologies, the so-called Omics, with traditional toxicology studies to provide a holistic assessment of the cellular response to different toxicants at the genome, transcriptome, proteome, and metabolome levels, aiming at the characterisation of global molecular mechanisms, at the systems biology level, and the identification of sensitive biomarkers of toxicological responses [2,3••].

The baker's yeast *Saccharomyces cerevisiae* has been at the forefront of post-genomic research and development of high-throughput tools, allowing the easy implementation of global expression analyses and the availability of a wide array of biological material [4•,5•]. Several web database resources provide a wealth of functional and transcription regulation information for the analysis of gene expression datasets, in particular the *Saccharomyces* Genome Database, the major community resource for gene, genomic and protein information in yeast, and YEASTRACT [6]. Furthermore, *S. cerevisiae* itself is a key player in White (Industrial) Biotechnology, where it is a highly useful cell factory in the production of food, alcoholic beverages, and in next generation biorefineries [7•,8]. Yeast also possesses a number of other advantageous characteristics. Most importantly for exploitation as a model in toxicogenomics, its genome has been extensively annotated with functional information, allowing a deeper level of understanding of the molecular mechanisms and functional pathways involved in the cellular response to toxicants [2,3••,9]. Survival and growth of yeast cells under stress conditions is achieved through a series of responses that depend on complex networks of sensing and signaling pathways. The environmental stress response (ESR) program, encompassing a stereotypical genomic expression reprogramming in response to multiple environmental challenges, comprises genetic pathways involved in protein folding and turnover, carbon metabolism, oxidative stress response, synthesis of internal osmolytes, and DNA repair. Multidrug/multixenobiotic resistance (MDR/MXR), mediated by membrane transporters that are presumably able to catalyze the efflux of multiple toxicants out of the cell, is a widespread phenomenon in nature that also plays an important role in the ESR [10].

This review focuses on the use of yeast as a toxicogenomic eukaryotic cell model, more specifically, how over the past two years methodologies such as genomics, chemogenomics, transcriptomics and quantitative proteomics, metabolomics, lipidomics, among others have

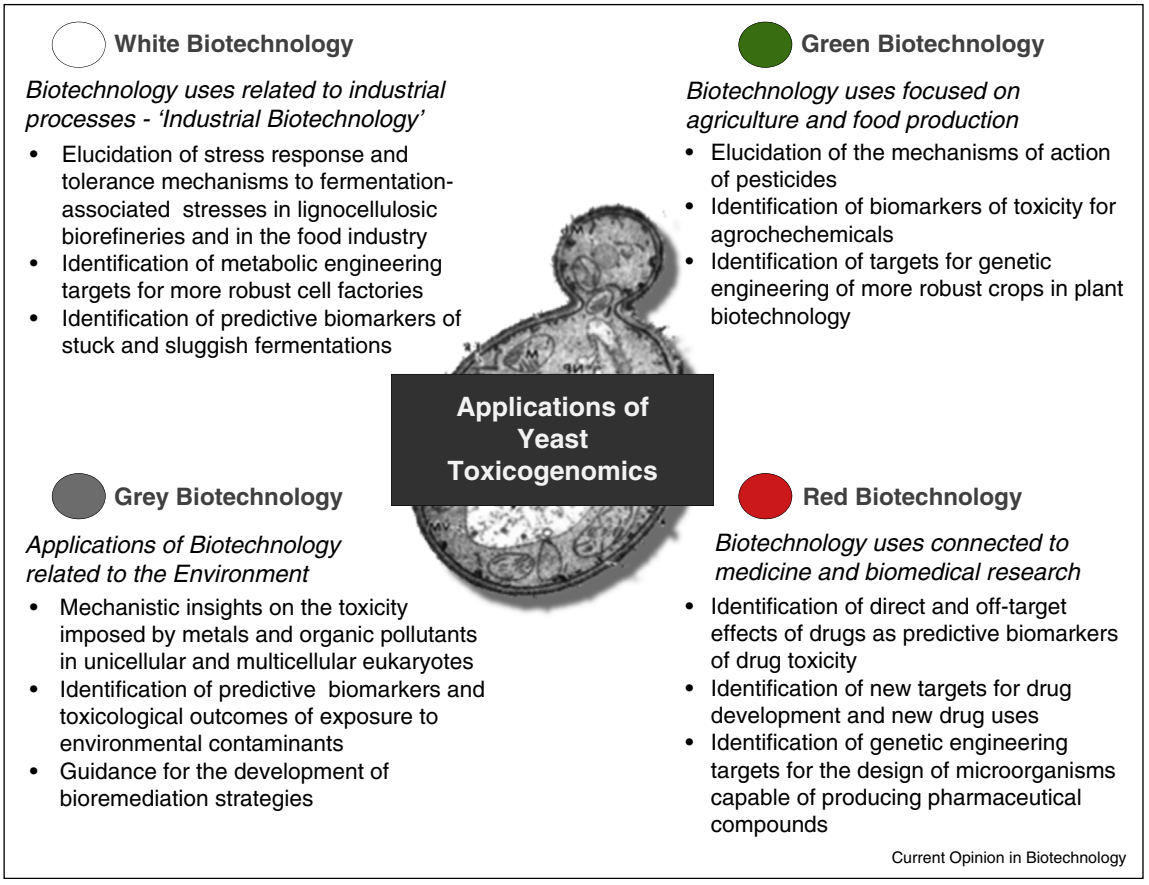
been exploited to obtain mechanistic insights into toxicological responses and resistance to toxicants, and identify biomarkers of toxicant exposure. The application of the same type of knowledge to develop bioprocess conditions and more robust genetically engineered strains for Yeast Biotechnology is also emphasized (Figure 1).

Yeast toxicogenomics applied to environmental and agricultural toxicants

The toxicological outcome of exposure to environmental toxicants, such as metal ions or organic contaminants that can have a profound effect on biological systems and human health is still poorly understood at the cellular and molecular levels. In addition to the previously described advantages of the yeast model [4•,5•], the high-level of functional conservation within the human genome and other more complex eukaryotes makes yeast an invaluable model system for assessing stress mechanisms and gene function in the response to environmental toxicants [3••,9]. The use of yeast, together with other model organisms and cross-species comparison of important genes/proteins, might help elucidate the response to toxic insults at a systems level and allow the prediction of action of similar compounds in other species, contributing to environmental risk assessment and development of detoxification strategies, while limiting the use of animal models for toxicity testing (Figure 1) [2,3••]. A significant body of recent literature describing the use of yeast functional genomic tools in this context can be found, highlighting the current relevance of this model eukaryote in ecotoxicogenomics.

Although there is an important amount of information available regarding yeast exposure to toxic metals [11], the comparison of metal-specific studies is difficult. A recent comparative study based on the transcriptional profiling of the yeast response to acute metal stress, imposed by 10 metals relevant to human health (Ag^{+}, Al^{3+}, As^{3+}, Cd^{2+}, Co^{2+}, Hg^{2+}, Mn^{2+}, Ni^{2+}, V^{3+}, and Zn^{2+}), identified short-term exposure target genes or pathways with some common responses for distinct groups of metals with shared transcriptional regulators, including metal-specific oxidative stress pathways, chelation strategies, and protein degradation [12••]. Evolutionary engineering and transcription analysis have been recently used to evaluate the mechanisms of nickel [13] and cobalt

Figure 1



The colors of biotechnology (see http://www.journals.elsevier.com/journal-of-biotechnology/news/the-colours-of-biotechnology/) and corresponding applications where the exploitation of the yeast model in toxicogenomics is expected to provide mechanistic insights of relevance.