Efficient protein production by yeast requires global tuning of metabolism

The biotech industry relies on cell factories for production of pharmaceutical proteins, of which several are among the top-selling medicines. There is, therefore, considerable interest in improving the efficiency of protein production by cell factories. Protein secretion involves numerous intracellular processes with many underlying mechanisms still remaining unclear. Here, we use RNA-seq to study the genome-wide transcriptional response to protein secretion in mutant yeast strains. We find that many cellular processes have to be attuned to support efficient protein secretion. In particular, altered energy metabolism resulting in reduced respiration and increased fermentation, as well as balancing of amino-acid biosynthesis and reduced thiamine biosynthesis seem to be particularly important. We confirm our findings by inverse engineering and physiological characterization and show that by tuning metabolism cells are able to efficiently secrete recombinant proteins. Our findings provide increased understanding of which cellular regulations and pathways are associated with efficient protein secretion.

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