Flux Control at the Malonyl-CoA Node through Hierarchical Dynamic Pathway Regulation in Saccharomyces cerevisiae - DTU Orbit (09/11/2017)

Flux Control at the Malonyl-CoA Node through Hierarchical Dynamic Pathway Regulation in *Saccharomyces cerevisiae*

The establishment of a heterologous pathway in a microbial host for the production of industrially relevant chemicals at high titers and yields requires efficient adjustment of the central carbon metabolism to ensure that flux is directed toward the product of interest. This can be achieved through regulation at key branch points in the metabolic networks, and here we present a novel approach for dynamic modulation of pathway flux and enzyme expression levels. The approach is based on a hierarchical dynamic control system around the key pathway intermediate malonyl-CoA. The upper level of the control system ensures downregulation of endogenous use of malonyl-CoA for fatty acid biosynthesis, which results in accumulation of this pathway intermediate. The lower level of the control system is based on use of a novel biosensor for malonyl-CoA to activate expression of a heterologous pathway using this metabolite for production of 3-hydroxypropionic acid (3-HP). The malonyl-CoA sensor was developed based on the FapR transcription factor of *Bacillus subtilis*, and it demonstrates one of the first applications of a bacterial metabolite sensor in yeast. Introduction of the dual pathway control increased the production of 3-HP by 10-fold and can also be applied for production of other malonyl-CoA-derived products.

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