SPECIAL LECTURE

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Sensitive cells: enabling tools for static and dynamic control of microbial metabolic pathways

ABSTRACT:

Our research goal it to utilize the richness, versatility but also simplicity of microbial organisms in order to make them ideally suited to convert cheap, renewable resources into either high-value or commodity chemicals.

For the purpose of reprogramming the cellular network in order to achieve optimal phenotypes supporting high-yield production, we have developed *in silico* model of the genome-wide metabolism *Escherichia coli.* Through the application of Metabolic Flux Analysis, we can predict genetic modifications such as deletions and gene expression attenuations that lead to dramatic increases in production levels. Such Systems Biology approaches, in combination with traditional genetic engineering have resulted in robust production levels that can result in the commercially viable processes for the synthesis of important molecules, in particular ones that derive from malonyl-CoA. We also report the engineering of both positive and negative feedback controls for dynamic tuning of metabolic flux in *E. coli*. Specifically, we have identified a dual transcriptional regulator that can act either as an activator or a repressor for two different promoters. The level of activation or repression is dependent on the level of intracellular malonyl-CoA. As a proof of concept, we demonstrated that the expression of two reporter proteins can be exclusively switched between the on and off state. By engineering this synthetic malonyl-CoA controller, both a malonyl-CoA source pathway and a malonyl-CoA sink pathway were dynamically modulated so that carbon flux can be efficiently redirected to synthesize our target compounds, fatty acids. Implementation of this dynamic control resulted in maintaining the intracellular malonyl-CoA at the optimal level and improved both the productivity and yield of value-added metabolites in *E. coli*.