STRUCTURAL SYNTHETIC BIOLOGY STRATEGY FOR THE DESIGN OF A NEW METABOLIC PATHWAY

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To date, notable successes have been made in producing valuable chemicals and fuels from renewable resources by simply modifying and optimizing the metabolic pathways in microorganisms. However, to design a more efficient and desirable pathway with high efficiency from ubiquitously existing multi-branched and multi-level regulated ones, a new approach is needed other than conventional systematic analysis of every bottlenecks embedded in the biosynthetic pathways. Here, we present a strategy combining rational enzyme design and synthetic biology to construct a new metabolic pathway which evades from the highly regulated nature. As a proof-of-concept, we implemented our approach to the design of a new L-methionine biosynthetic pathway. To this end, structure of the MetZ enzyme, which is a key to the construction of new biosynthetic pathway in *Corynebacterium glutamicum*, was modelled, and its substrate specificity was rationally altered toward a substrate required for redirecting the metabolic flux in the pathway. Furthermore, we used mutational approach to relieve feedback inhibition of other enzymes which regulate the metabolic flux in the methionine biosynthetic pathway. As a result, the L-methionine level reached a gram scale in flask culture by recombinant Corynebacterium glutamicum with the methionine biosynthetic pathway. We demonstrate that the “structural synthetic biology” strategy can boost our ability to generate a more efficient metabolic pathway for the production of valuable chemicals.