Establishment of systems metabolic engineering strategies to develop microbial strains

October 12 2015

Although conventional petrochemical processes have generated chemicals and materials which have been useful to mankind, they have also triggered a variety of environmental problems including climate change and relied too much on nonrenewable natural resources. To ameliorate this, researchers have actively pursued the development of industrial microbial strains around the globe in order to overproduce industrially useful chemicals and materials from microbes using renewable biomass. This discipline is called metabolic engineering.

Thanks to advances in genetic engineering and our knowledge of cellular metabolism, conventional metabolic engineering efforts have succeeded to a certain extent in developing microbial strains that overproduce bioproducts at an industrial level. However, many metabolic engineering projects launched in academic labs do not reach commercial markets due to a failure to fully integrate industrial bioprocesses.

In response to this, Distinguished Professor Sang Yup Lee and Dr. Hyun Uk Kim, both from the Department of Chemical and Biomolecular Engineering at the Korea Advanced Institute of Science and Technology (KAIST), have recently suggested ten general strategies of systems metabolic engineering to successfully develop industrial microbial strains. Systems metabolic engineering differs from conventional metabolic engineering by incorporating traditional metabolic engineering approaches along with tools of other fields, such as systems biology,

synthetic biology, and molecular evolution.

The ten strategies of systems metabolic engineering have been featured in *Nature Biotechnology* released online in October 2015, which is entitled "Systems strategies for developing industrial microbial strains."

The strategies cover economic, state-of-the-art biological techniques and traditional bioprocess aspects. Specifically, they consist of: 1) project design including economic evaluation of a target bioproduct; 2) selection of host strains to be used for overproduction of a bioproduct; 3) metabolic pathway reconstruction for bioproducts that are not naturally produced in the selected host strains; 4) increasing tolerance of a host strain against the bioproduct; 5) removing negative regulatory circuits in the microbial host limiting overproduction of a bioproduct; 6) rerouting intracellular fluxes to optimize cofactor and precursor availability necessary for the bioproduct formation; 7) diagnosing and optimizing metabolic fluxes towards product formation; 8) diagnosis and optimization of microbial culture conditions including carbon sources; 9) system-wide gene manipulation to further increase the host strain's production performance using high-throughput genome-scale engineering and computational tools; and 10) scale-up fermentation of the developed strain and diagnosis for the reproducibility of the strain's production performance.

These ten strategies were articulated with successful examples of the production of L-arginine using *Corynebacterium glutamicum*, 1,4-butanediol using *Escherichia coli*, and L-lysine and bio-nylon using *C. glutamicum*.

Professor Sang Yup Lee said, "At the moment, the chance of commercializing microbial strains developed in academic labs is very low. The strategies of systems metabolic engineering outlined in this analysis can serve as guidelines when developing industrial microbial

strains. We hope that these strategies contribute to improving opportunities to commercialize microbial strains developed in academic labs with drastically reduced costs and efforts, and that a large fraction of petroleum-based processes will be replaced with sustainable bioprocesses."

More information: Lee S. Y. & Kim, H. U. Systems Strategies for Developing Industrial Microbial Strains. *Nature Biotechnology* (2015).

Provided by The Korea Advanced Institute of Science and Technology (KAIST)