Researchers develop novel autonomous dynamic regulation system in streptomyces

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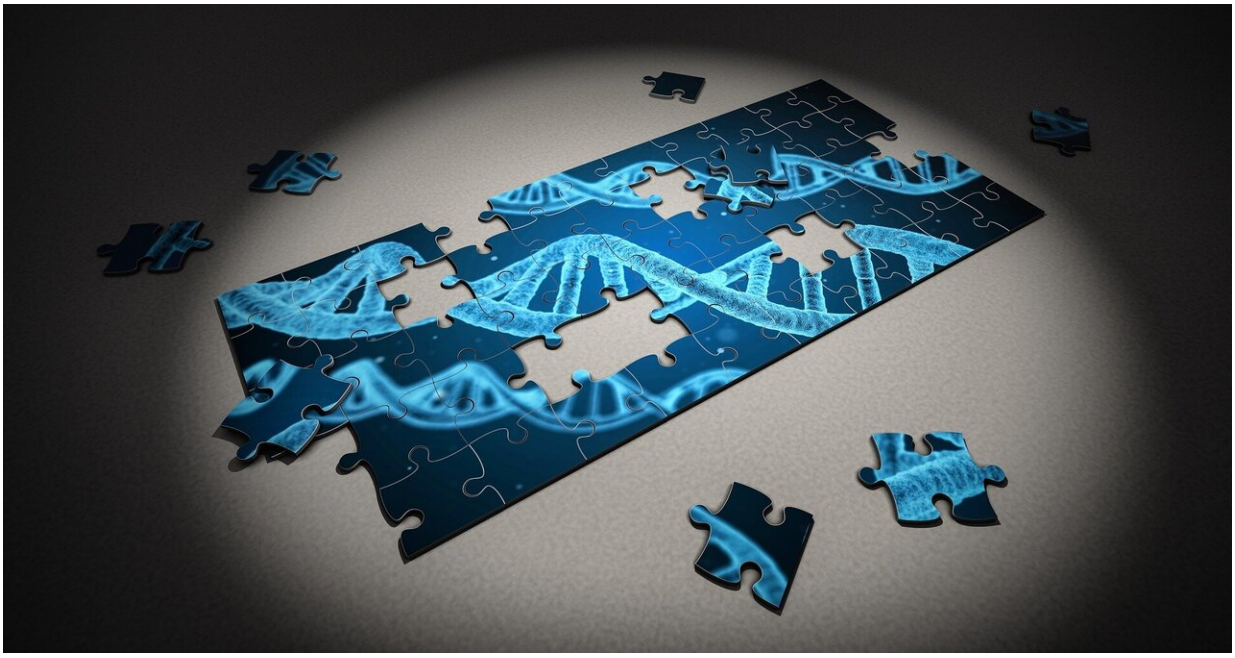

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Microbes have been engineered as renewable cell factories for producing a vast array of products, such as pharmaceuticals, biofuels and bio-chemicals. However, static engineering strategies often result in metabolic imbalance, pathway intermediate accumulation and growth retardation, limiting product titers and yields.

Quorum-sensing (QS) mediated dynamic regulation has emerged as an effective strategy for optimizing product titers in microbes. Nevertheless, these QS-based circuits are often created on heterologous systems and require careful tuning via a tedious testing/optimization process, which hamper their application in industrial microbes.

Now a research team led by Dr. Jiang Weihong Jiang from the Center for Excellence in Molecular Plant Sciences (CEMPS) of the Chinese Academy of Sciences designed a novel QS circuit by directly integrating an endogenous QS system with CRISPRi, named EQCi, in the industrial rapamycin-producing strain Streptomyces rapamycinicus.

The study was published in *Nucleic Acids Research* on July 15.

EQCi combines advantages of both the QS system and CRISPRi to enable tunable, autonomous, and dynamic regulation of multiple targets simultaneously.

Using EQCi, the researchers separately down regulated three key nodes in essential pathways to divert metabolic flux towards rapamycin biosynthesis and significantly increase its titers.

Further application of EQCi to simultaneously regulate these three key nodes with fine-tuned repression strength boosted the rapamycin titer by ~660%, achieving the highest reported titer (1836 ± 191 mg/l).

Compared to static engineering strategies, EQCi-based regulation substantially promotes rapamycin titers without affecting cell growth, indicating that it can achieve a trade-off between essential pathways and product synthesis.

The study provides a convenient and effective strategy for strain improvement and shows potential for application in other industrial

microorganisms. It was supported by the National Key Research and Development Program and the National Natural Science Foundation of China.

More information: Jinzhong Tian et al. Developing an endogenous quorum-sensing based CRISPRi circuit for autonomous and tunable dynamic regulation of multiple targets in Streptomyces, *Nucleic Acids Research* (2020). DOI: 10.1093/nar/gkaa602

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