Bioengineering efficient antibiotic biosynthesis in E. coli

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The pathways underlying the production of antibiotics are now quite well known. For example, the antibacterial activity of erythromycin, an important polyketide antibiotic precursor, requires the transfer of two unusual sugars called mycarose and desosamine (both glycosyl groups) onto the nonsugar part of the glycoside molecule (macrocyclic aglycone).

In a new study published online this week in the open-access journal *PLoS Biology*, Ho Young Lee and Chaitan Khosla demonstrate how they used bioassay-guided evolution of this antibiotic pathway in Escherichia coli (E. coli) to identify more efficient antibiotic-producing mutants.

The authors reconstituted the biosynthetic pathways of both sugars in E. coli to yield the 6-deoxyerythromycin D antibiotic. By engineering a recombinant strain of E. coli that produces the bioactive macrolide 6-deoxyerythromycin D from propionate, they developed a fundamentally new tool for enhancing the efficiency of biosynthetic engineering of this class of antibiotics. Initially, this recombinant strain produced barely enough antibiotic activity to establish an activity-based screening assay.

The authors therefore used the assay to screen for antibiotic overproducers. After three rounds of screening, they were able to identify E. coli cells that overproduced the 6-deoxyerythromycin D antibiotic with significant modifications in the mycarose biosynthetic pathway. They used the same activity-based screening system to evolve E. coli mutants capable of more efficient precursor-directed

biosynthesis. As the first example of bioassay-guided evolution of an antibiotic pathway in E. coli, these results open the door for harnessing the power of genetics for mechanistic investigations into polyketide synthases and also for biosynthetic engineering.

Source: Public Library of Science