E. coli engineered to produce important class of antibiotic, anti-cancer drugs

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Researchers from the UCLA Henry Samueli School of Engineering and Applied Science have taken a major step forward in the field of metabolic engineering, successfully using the bacterium *Escherichia coli* to synthesize a class of natural products known bacterial aromatic polyketides, which include important antibiotic and anticancer drugs.

Natural products are pharmacologically or biologically potent chemical compounds produced by living organisms; many are the active ingredients in pharmaceuticals. Bacterial aromatic polyketides include the antibiotic tetracycline and the compound doxorubicin, used in the treatment of breast and other cancers.

Because many of these natural products are synthesized by organisms that are difficult to collect, grow and maintain, researchers have sought to produce them using simpler organisms like *E. coli*, whose fast growth, variety of genetic tools and well-understood metabolism make it an ideal host for engineering and mass producing these compounds.

While turning *E. coli* into a microbial factory for natural products has been highly successful, resulting in the production of groups of drugs that include antibiotics like erythromycin and vancomycin, as well as terpenes and alkaloids, attempts to synthesize bacterial aromatic polyketides had previously been hindered by the compounds' complicated assembly process.

To achieve the successful synthesis of the aromatic polyketides, the

UCLA research team — which included principal investigator Yi Tang, an associate professor of chemical and biomolecular engineering, and graduate students Wenjun Zhang and Yanran Li — first dissected a polyketide synthase enzyme from a rice plant fungus, then reassembled it and transferred it into the *E. coli* bacterium. The resulting synthetic enzyme is necessary to synthesize the carbon backbone of aromatic polyketides, which was previously inaccessible in *E. coli*.

In addition to the synthetic enzyme, the researchers introduced other enzymes to form a new pathway in *E. coli* that produced a range of bacterial aromatic polyketides from simple nutrients such as glucose.

"This is a key advance in the field of natural product biosynthesis," said Tang of the research, which will be published Dec. 30 in *Proceedings of the National Academy of Sciences* and is currently available on the journal's website. "We have now outfitted *E. coli* with the ability to make this family of compounds that are vital toward treating diseases such as infectious diseases and cancer.

"Furthermore, we can now take advantage of the *E. coli* machinery to engineer the pathways we introduced and synthesize new versions of natural products that may be more potent than the current versions - so-called unnatural natural products."

On a more fundamental level, the UCLA researchers are exploring interactions between the bacterial and fungal components they introduced into *E. coli*, which are from different kingdoms of life.

"There are some beliefs that bacterial and fungal enzymes will not cross-talk to each other," said Zhang, the paper's lead author. "Our work showed that polyketide synthase from the two kingdoms can indeed be functionally combined inside the *E. coli* platform. Therefore, there is much to learn about why these interactions are possible."

Source: University of California - Los Angeles