MedicalXpress

Scientists solve mystery of polyketide drug formation

April 1 2008

Many top-selling drugs used to treat cancer and lower cholesterol are made from organic compounds called polyketides, which are found in nature but historically difficult for chemists to alter and reproduce in large quantities.

For the first time, scientists at UC Irvine have discovered how polyketides form their ringlike shape, making it easier for chemists to manipulate them into new drugs.

The key, they found, is an enzyme called aromatase/cyclase, which forms a C-shape mold in which polyketides can form one molecule at a time. By changing this mold, chemists can control the size and shape of the polyketide, resulting in the formation of new drugs.

“Almost every polyketide has rings in its chemical structure, and if we can control ring formation, we can produce more polyketide drugs,” said Sheryl Tsai, lead author of this study and an assistant professor of molecular biology and biochemistry and chemistry at UCI. “Until now, polyketide ring formation was a mystery that hampered our efforts to produce new drugs.”

The research appears online this week in the *Proceedings of the National Academy of Sciences*.

Polyketide-based drugs and products account for more than $35 billion in sales annually. They include antibiotics that can cure a bacteria

infection (tetracycline and erythromycin); anti-cancer drugs used in chemotherapy (doxorubicin and mithramycin); anti-oxidants that help prevent cancer and promote heart strength (EGCG and resverastrol); and drugs that lower cholesterol levels (Zocor). Green tea and red wine also contain beneficial polyketides.

Polyketides are made naturally by bacteria, fungi, plants and marine animals. Those organisms produce polyketides to kill their predators, be it another bacteria or fungi. They can produce different types of polyketides that kill different types of enemies.

“Because bacteria do not have arthritis or diabetes, they would not evolutionally select polyketides that could be used for arthritis or diabetes treatment,” Tsai said. “But we can coax the bacteria to do precisely that, if we can control the ring formation in the polyketides.”

Prior to this study, it was not known how nature controls the polyketide ring shape, which is essential for antibiotic and anti-cancer properties.

By using molecular cloning and chemical biology techniques, Tsai and her scientific team discovered that the aromatase/cyclase enzyme has a pocket that shapes the polyketide, promoting a unique ring pattern.

Said Tsai: “We hope this will lead to the development of new drugs in such areas as cancer therapeutics, obesity treatment and stem cell research.”

Source: University of California - Irvine

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