BIOCHEMISTRY

COX-3 FOUND

New variant of cyclooxygenase may explain acetaminophen mechanism

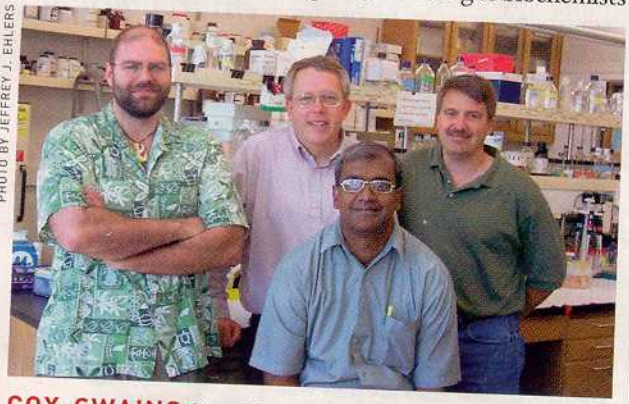
A NEWLY DISCOVERED VARIant of the enzyme cyclooxygenase might be the target of the analgesic acetaminophen, according to biochemists at Brigham Young University.

Daniel L. Simmons and his coworkers have dubbed the enzyme COX-3 [*Proc. Natl. Acad. Sci.*, published online Sept. 19, http://www.pnas.org/cgi/reprint/162468699v1]. Like the other COX enzymes, COX-3 is involved in the synthesis of prostaglandins and plays a role in pain and fever. However, unlike COX-1 and COX-2, COX-3 appears to have no role in inflammation.

The activity of COX-3 is inhibited by the drug acetaminophen, which has little effect on the other two COX enzymes. "If this does turn out to be the target of acetaminophen, the same thing could be done with COX-3 that was done with COX-2—try to develop better inhibitors," Simmons says. COX-2-specific inhibitors include the drugs celecoxib and rofecoxib, marketed as Celebrex and Vioxx, respectively. Simmons was also one of the discoverers of COX-2.

Simmons and his coworkers discovered COX-3 as they were studying cyclooxygenase expression in a number of different dog tissues. Ultimately, they found three previously unknown variants of COX-1: COX-3 and two others not involved in prostaglandin synthesis, which they've called PCOX-1a and -1b (partial COX-1a and -1b). No function is yet known for the two PCOX-1 proteins, but Simmons and his coworkers are trying to identify their role.

Simmons' team is also now turning its attention to cloning the human enzyme. "Even if we find that COX-3 is not expressed at high levels in humans, we now know a way that cyclooxygenases do become sensitive to acetaminophen," Simmons says.—CELIA HENRY



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COX-SWAINS Standing, from left, K. Lamar Turepu Roos, Simmons, and Terry S. Elton. Seated, N. V. Chandrasekharan.