Much ado about a new clue regarding COX-2

A DMS graduate student recently identified one of the reasons why painkillers such as Vioxx, Bextra, and Celebrex can cause heart attacks and strokes. The experiment that led to the discovery began on a whim, but the results were anything but whimsical.

Such drugs, known as COX-2 inhibitors, work by targeting cyclooxygenase-2 (COX-2), an enzyme involved in inflammation. The discovery of COX-2 inhibitors was "really a marvel of modern science," as one DMS epidemiologist has put it. The drugs provided powerful relief from pain and inflammation without harming the digestive track the way aspirin and other painkillers can. But COX-2 inhibitors weren't as safe as they first seemed. In the fall of 2004, the manufacturer of Vioxx withdrew the drug from the market after clinical trials showed that prolonged use could double the risk of heart attack and stroke. (For more on the Dartmouth epidemiologist who was influential in Vioxx's removal from the market, see "DMS's John Baron was at eye of Vioxx storm" in the Winter 2004 Dartmouth Medicine.)

Since then, researchers have been trying to understand why COX-2 inhibitors are so dangerous. The reasons, it turns out, are numerous, and a few of them have to do with COX-2's relationship to vascular smooth-muscle cells.

Clump: One could say that the smooth-muscle cells that line the walls of blood vessels have multiple personalities. Under certain conditions, the cells are spindle-shaped, possess the ability to contract and relax, and stay in one place. Under other conditions, the cells assume a blob-like shape, proliferate, migrate into the main channel of the vessel, clump together, and lose the ability to contract. The contractile state and the proliferative state each have an important role to play—the former in moving blood, and the latter in responding to injury to the vessel wall. The two states are kept in check by the opposing forces of two substances—prostacyclin and thromboxane. That's where COX-2 enters the picture.

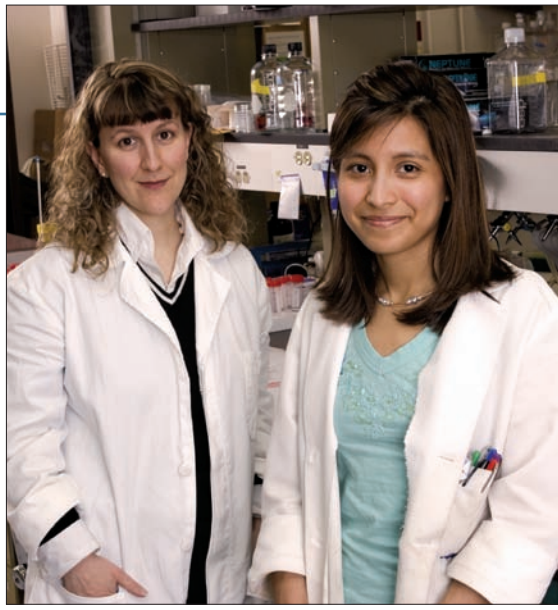
COX-2 synthesizes prostacyclin, a hormone-like fatty acid. Therefore, when COX-2 is inhibited, so is prostacyclin. With prostacyclin out of the picture, thromboxane dominates. As its name indicates, thromboxane promotes thrombotic—blood-clotting—activity, in which the vascular smooth-muscle cells proliferate, migrate, and clump together. Unchecked, this action can lead to blockages in the vessel, strokes, and heart attacks.

Lab: All of this was known when Kristina Fetalvero, a pharmacology and toxicology Ph.D. student, began experimenting with a synthetic form of prostacyclin called iloprost. Fetalvero was encouraged by two DMS mentors: John Hwa, M.B.B.S, Ph.D., whose lab she used to work in, and Kathleen Martin, Ph.D., with whom she's currently working. Martin's lab studies gene expression in vascular smooth-muscle cells, while Hwa's focuses on the prostacyclin receptor.

"I was originally working on one of the major projects in Kathy's lab," explains Fetalvero. Then "John came to us one day and said, 'Why don't we see what happens if we add iloprost?'" Hwa was suggesting that Fetalvero treat vascular smooth-muscle cells in the proliferative state with the synthetic prostacyclin, thinking it might cause them to revert to the contractile state; if the cells did so, it would show that prostacyclin has a larger role than just keeping thromboxane in check. "And it worked!" says Fetalvero, still excited over the finding a year later.

"What Kristina has found," explains Martin, is that "in addition to antagonizing thrombosis, [prostacyclin] actually helps the smooth-muscle cells maintain this contractile, non-proliferative phenotype.

"We think that prostacyclin is able to switch this genetic switch that turns on all the genes for the contractile proteins and the anti-proliferic pathways as well," Martin continues. Martin and Fetalvero believe they've discovered a "master regulatory pathway," and, if so, the consequences of inhibiting COX-2 (and thereby prostacyclin) may prove to be even more widespread.



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Kristina Fetalvero, right, worked in Kathleen Martin's lab studying the side effects of COX-2 inhibitors.

Published in the April 2006 *American Journal of Physiology—Heart and Circulatory Physiology*, the study has drawn a lot of attention. "It turned out that people were really excited about this study," says Martin, thanks in part to its connection to the much-publicized Vioxx story.

Award: Fetalvero, now in her fourth year, recently shared the work at the Experimental Biology conference of the American Society for Pharmacology and Experimental Therapeutics and received a first-place award for her presentation.

Ultimately, the finding may help in the design of a prostacyclin-like drug. Iloprost and prostacyclin break down too quickly to be used themselves. Yet a similar but longer-lasting drug could prove "very useful for treating atherosclerosis," says Martin.

She and Hwa (who are married to each other) plan to continue this line of inquiry, with Martin focusing on genetic factors within vascular smooth-muscle cells and Hwa on receptors on the cells' surface. "We joke that . . . between the two of us," says Martin, "we've got the cell covered, from the outside and the inside."

Jennifer Durgin