Study clarifies action of potential new class of pain relievers that may benefit, not hurt, the heart

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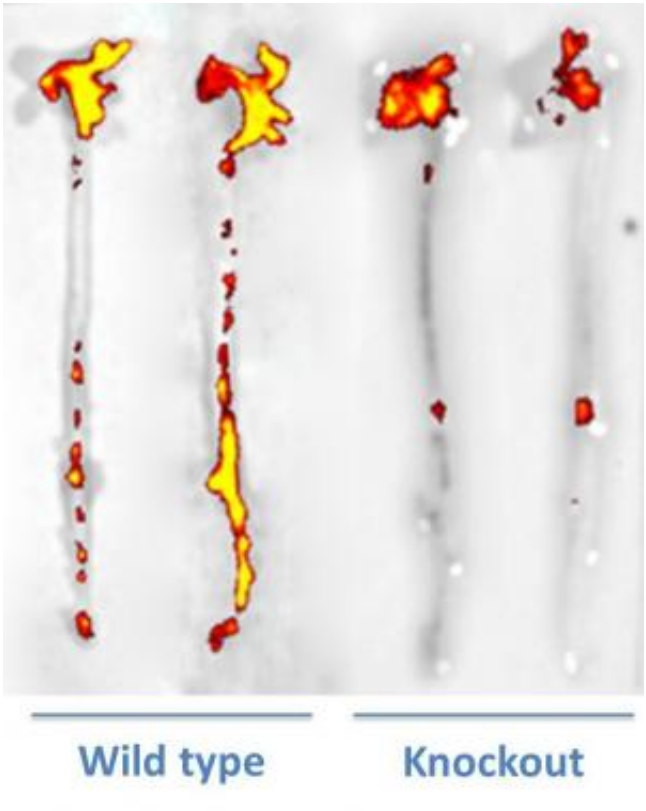

The shows the effects of myeloid cell mPGES-1 deletion on plaque macrophage abundance, less in the myeloid mPGES-1 knockout versus wild type. Credit: Lihong Chen, MD, PhD, Perelman School of Medicine, University of Pennsylvania.

Nonsteroidal antinflamatory drugs (NSAIDs) that block an enzyme called COX-2 relieve pain and inflammation but can cause heart attacks, stroke, heart failure, and even sudden cardiac death. This has prompted a decade-plus search for safer, but still effective, alternatives to these commonly prescribed, pain-relieving drugs.

Building on previous work that showed that deleting an enzyme in the COX-2 pathway in a mouse model of heart disease slowed the development of atherosclerosis, a team from the Perelman School of Medicine at the University of Pennsylvania has now extended this observation by clarifying that the consequence of deleting the enzyme mPEGS-1 differs, depending on the cell type in which it is taken away.

In a report published this week in the online edition of the *Proceedings of the National Academy of Sciences*, Lihong Chen, MD, PhD, a postdoctoral fellow in the lab of senior author Garret FitzGerald, MD, FRS, director of the Institute for Translational Medicine and Therapeutics, found that deleting mPGES-1 in macrophages markedly slows the rate at which arteries harden in mice with high levels of cholesterol. This results from a reduction in the oxidative damage done to the vessel wall due to a shift in the genes expressed because of the suppression of PGE2, a cardioprotective fat. By contrast, deletion of mPGES-1 in vascular cells had no effect.

Chen and FitzGerald are currently working on ways to deliver inhibitors of mPGES-1 selectively to the macrophages, immune system cells that live primarily in connective tissue and blood and ingest foreign particles and infectious microbes.

"While deletion or inhibition of COX-2 in mice elevates their blood pressure and predisposes them to clotting and hardening of the arteries due to suppressing the cardioprotective lipid prostacyclin, deleting mPGES-1 avoids these effects and even restrains the development of

atherosclerosis," explains FitzGerald.

"Taken together these studies add more evidence that targeting the enzyme mPEGS-1 could result in a new class of nonsteroidal anti-inflammatory drugs that steer clear of heart-disease risk and even work to reduce it," says Chen.

In earlier studies, Chen showed a similarly beneficial effect of targeting macrophages in limiting the response to vascular injury of unwanted cell proliferation, such as might complicate angioplasty in humans. "Both sets of studies afford a rationale for targeted inhibition of macrophage mPGES-1 for cardiovascular benefit" says FitzGerald.

Indeed, in other ongoing studies in the FitzGerald lab, Chen has shown that macrophage mPGES-1 plays a dominant role in mediating the pain caused by PGE2. "What is exciting here," says Chen, "is the prospect of retaining the benefit of NSAIDs while substituting cardiovascular benefit for risk."

NSAIDs like ibuprofen (Advil) and naproxen (Naprosyn) relieve pain and inflammation by blocking COX enzymes that help make prostaglandins. COX-2 is the most important source of the two prostaglandins - PGE2 and prostacyclin - that mediate pain and inflammation. However, COX-2-derived prostacyclin particularly may also protect the heart, and loss of this function explains the risk of heart attacks from NSAIDs that inhibit COX-2, such as rofecoxib (Vioxx), valdecoxib (Bextra), and celecoxib (Celebrex).

The problems with COX-2 inhibitors have prompted the search for alternative drug targets that suppress pain and inflammation yet are safe for the cardiovascular system. This is where mPGES-1 comes in – it converts PGH2 (a chemical product of COX-2) into PGE2. In a 2006 study, the FitzGerald lab found that mPGES-1 deletion did not elevate

blood pressure or predispose mice to thrombosis, probably by avoiding suppression of prostacyclin. In the absence of the enzyme, the diseased vessels were depleted of macrophages, which led to the predominance of vascular smooth muscle cells in blood vessel walls.

More information: Myeloid cell microsomal prostaglandin E synthase-1 fosters atherogenesis in mice, *PNAS*, 2014. www.pnas.org/cgi/doi/10.1073/pnas.1401797111

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