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McGill researchers find key to calcification

Discovery could improve treatment of arthritis, bone and cardiovascular diseases

McGill University researchers have proven the existence of a mechanism that controls calcification in bones, teeth and other bodily tissues – a discovery that could lead to new ways of treating defective calcification in skeletal and dental disease, and in a host of other ailments such as cardiovascular disease and arthritis.

The team, led by Dr. Marc McKee, Professor of Dentistry and of Anatomy and Cell Biology, has demonstrated that a small molecule called pyrophosphate (PPi) not only blocks calcification (mineralization) by direct binding to mineral crystals, but also by increasing tissue levels of osteopontin, a protein that performs a similar inhibitory function. PPi also blocks the activity of an enzyme, called alkaline phosphatase, capable of releasing phosphate from organic sources to bind with calcium to harden tissues. Their findings appear in the May 25 issue of the *Journal of Biological Chemistry (JBC) Online*.

“What this tells us is that these two inhibitors, one a protein and the other a small molecule that work together in bones and teeth to control mineralization, in the right balance could be used therapeutically to block unwanted calcification in arteries, joints and other soft tissues. This gives us a new way of looking at how to treat conditions like arthritis and cardiovascular disease, where painful joints and hardening of the arteries is frequently due to calcification,” said Dr. McKee.

“For a long time, it was believed that PPi acted on its own,” said Dr. McKee, noting PPi is used commercially as a food emulsifier and binder, and in products such as toothpaste to stop calcification near the gums that leads to inflammation, then gingivitis and periodontal disease. “But nobody knew that PPi, one of the most potent small molecule inhibitors of calcification, induces a natural defense mechanism of the body, the release of osteopontin protein, one of the most potent calcification inhibitors controlling the development of bones and teeth.”

The two inhibitors work together to build healthy skeletal and dental tissue by controlling the amounts of phosphorous and calcium – primary building block of bones and teeth – added to mineral crystals in these tissues. If the two inhibitors are improperly balanced, the result can either be too much calcification, resulting in the hardening of soft tissue such as in joints or blood vessels, or too little calcification, resulting in soft bones or teeth.

“Understanding the mechanisms that control how calcium and phosphorous combine to harden body tissues opens the door to the development of new drug therapies that could

use the body's own natural inhibitors to regulate calcification," Dr. McKee explained. Derivatives of PPi called bisphosphonates, which likewise bind to bone mineral and are currently used as drugs to treat osteoporosis, are the current focus of the team's work. "We want to see if the bisphosphonates can be similarly used to therapeutically stimulate protein inhibitors in joints and arteries," said Dr. McKee.

This research, conducted by Prof. McKee and Prof. Mari Kaartinen, with PhD student William Addison and research associate Fereshteh Azari, as well as with Prof. Esben Sorensen at the University of Aarhus in Denmark, was funded by the Canadian Institutes of Health Research and in part by the Canadian Arthritis Network.

On the Web: JBC Online

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