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Scientists discovers body's own molecular protection against arthritis

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An international team of scientists from The Scripps Research Institute in California and the National Research Institute for Child Health and Development in Japan has discovered that a natural molecule in the body counters the progression of osteoarthritis. The findings could one day lead to new therapies for some common diseases of aging.

The study was published in an advanced, online issue of the journal Genes *& Development* on May 13, 2010, and will be featured as the cover story of the June 1 print edition of the journal.

The molecule the team studied, microRNA 140 (miR-140), is part of a recently discovered category of genetic molecules—"microRNAs" or "non-coding RNAs" which do not code for proteins, yet often play a vital role in gene expression.

"This is the first report showing the critical role of a specific non-coding RNA in bone development," said Hiroshi Asahara, M.D., Ph.D., associate professor of molecular and experimental medicine at Scripps Research. "Moreover, surprisingly, we observed that microRNA 140 acts against arthritis progression. This is among the first evidence that non-coding RNA plays a key role in age-dependent diseases."

"This finding may lead to a new therapeutic strategy for osteoarthritis," said Shigeru Miyaki, senior research associate in the Asahara lab and first author of the paper with Tempei Sato of the National Research Institute for Child Health and Development, "as well as for conditions

that share a similar mechanism, such as spinal disc degeneration."

Broad Impact

Even in comparison with other diseases of aging, osteoarthritis has a remarkably broad impact. Currently affecting about 15 to 20 million Americans, osteoarthritis is the most common joint disorder and is expected to increase by 50 percent over the next two decades with the aging of the population. With no effective treatments, current management strategies for osteoarthritis focus on reducing pain and inflammation.

Osteoarthritis, also known as degenerative arthritis, is a disease that affects joint cartilage, the major weight-bearing "cushion" in joints. The disease results from a combination of wear and tear on cartilage and underlying age-related changes that causes cartilage to deteriorate. Joint trauma can also play a role. Osteoarthritis commonly affects the hands, spine, hips, and knees.

Asahara and other members his laboratory were interested in the question of why some people's joints age normally, while others' spiral toward disease.

The scientists suspected that microRNA could play a role. Once thought of as mere genetic helpers, microRNAs are now known to prevent proteins from being produced by messenger RNA, thus acting as an important layer of regulation for biological processes.

"Recent research findings indicate that non-coding RNA should be involved in our development and in diseases," said Asahara, "but we know little about the role of the non-coding RNA for age-related adult disorders."

Breaking New Ground

The team's interest in one type of microRNA in particular, miR-140, was piqued by other work ongoing in the lab, which was published last year. In this study, the team made the observation that miR-140—which is only expressed in cartilage—was reduced in cartilage samples from osteoarthritis patients. This led the team to hypothesize that miR-140 is a regulator in osteoarthritis pathology.

To test this idea, the team tried for several years to make targeted "knockout" mouse models that lacked miR-140. They finally succeeded.

With models lacking miR-140, the scientists were able to figure out its effects. Since the animals lacking miR-140 were short in stature, the scientists concluded that miR-140 affected bone formation during development. The mutant mice were also particularly prone to developing osteoarthritis, suggesting that miR-140 retarded the disease. In contrast, the scientists found, transgenic mice that overexpressed miR-140 were resistant to developing the condition.

The team's findings fit in well with other recent research showing that an enzyme called Adamts-5 is necessary for osteoarthritis progression; miR-140 is known to regulate Adamts-5.

The team continues to investigate to learn more about the factors that control miR-140, the proteins it affects, and potential drugs that might influence its action.

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