Scientists home in on cause of osteoarthritis pain

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Researchers at Rush University Medical Center, in collaboration with researchers at Northwestern University, have identified a molecular mechanism central to the development of osteoarthritis (OA) pain, a finding that could have major implications for future treatment of this often-debilitating condition.

"Clinically, scientists have focused on trying to understand how cartilage and joints degenerate in osteoarthritis. But no one knows why it hurts," said Dr. Anne-Marie Malfait, associate professor of biochemistry and of internal medicine at Rush, who led the study. An article describing the research was published in the December 11 print version of the Proceedings of the National Academy of Sciences.

Joint pain associated with OA has unique clinical features that provide insight into the mechanisms that cause it. First, joint pain has a strong mechanical component: It is typically triggered by specific activities (for example, climbing stairs elicits knee pain) and is relieved by rest. As structural joint disease advances, pain may also occur in rest. Heightened sensitivity to pain, including mechanical allodynia (pain caused by a stimulus that does not normally evoke pain, such as lightly brushing the skin with a cotton swab), and reduced pain-pressure thresholds are features of OA.

Malfait and her colleagues took a novel approach to unraveling molecular pathways of OA pain in a surgical mouse model exhibiting the slow, chronically progressive development of the disease. The study was

conducted longitudinally, that is, the researchers were able to monitor development of both pain behaviors and molecular events in the sensory neurons of the knee and correlate the data from repeated observations over an extended period.

"This method essentially provides us with a longitudinal 'read-out' of the development of OA pain and pain-related behaviors, in a mouse model" Malfait said.

The researchers assessed development of pain-related behaviors and concomitant changes in dorsal root ganglia (DRG), nerves that carry signals from sensory organs toward the brain. They found that a chemokine known as monocyte chemoattractant protein (MCP)-1 (CCL2) and its receptor, chemokine receptor 2 (CCR2), are central to the development of pain associated with knee OA.

Monocyte chemoattractant protein-1 regulates migration and infiltration of monocytes into tissues where they replenish infection-fighting macrophages. Previous research has shown that MCP-1/CCR2 are central in pain development following nerve injury.

In the study, following surgery the laboratory mice developed mechanical allodynia that lasted 16 weeks. Levels of MCP-1, CCR2 mRNA and protein were temporarily elevated, and neuronal signaling activity increased in the DRG at eight weeks after surgery. This result correlated with the presentation of movement-provoked pain behaviors (for instance, mice with OA travelled less distance, when monitored overnight, and climbed less often on the lid of their cage – suggesting that they avoid movement that triggers pain) which were maintained up to 16 weeks.

Mice that lack Ccr2 (knockout mice) also developed mechanical allodynia, but this began to resolve from eight weeks onward. Despite

having severe allodynia and structural knee joint damage equal to that in normal mice, Ccr2-knockout mice did not develop movement-provoked pain behaviors at eight weeks.

To confirm the key role of CCR2 signaling in development of the observed movement-provoked pain behavior after surgery, the researchers administered a CCR2 receptor-blocker to normal mice at nine weeks after surgery and found that this reversed the decrease in distance traveled, that is, movement-provoked pain behavior.

Interestingly, levels of MCP-1 and CCR2 returned to baseline or lower by 16 weeks in mice exhibiting movement-provoked pain behaviors. This finding may suggest that the MCP-1/CCR2 pathway is involved only in the initiation of changes in the DRG, but once macrophages are present, the process is no longer dependent on increased MCP-1/CCR2.

"Increased expression of both MCP-1 and its receptor CCR2 may mediate increased pain signaling through direct excitation of DRG neurons, as well as through attracting macrophages to the DRG," the researchers said.

"This is an important contribution to the field of osteoarthritis research. Rather than looking at the cartilage breakdown pathway in osteoarthritis, Dr. Malfait and her colleagues are looking at the pain pathway, and this can take OA research in to a novel direction that can lead to new pain remedies in the future," said Dr. Joshua Jacobs, professor and chairman of orthopedic surgery at Rush University Medical Center.

Treatment of OA in the United States costs almost $200 billion annually. According to the Centers for Disease Control and Prevention, it is expected that by 2030 nearly 70 million adults in the U.S. will have been diagnosed with some form of arthritis.

According to the Arthritis Foundation, an estimated 27 million Americans live with OA, but, despite the frequency of the disease, its cause is still not completely known and there is no cure. In fact, many different factors may play a role in whether or not you get OA, including age, obesity, injury or overuse and genetics.

Osteoarthritis (OA) is one of the oldest and most common forms of arthritis and is a chronic condition characterized by the breakdown of the joint's cartilage. Cartilage is the part of the joint that cushions the ends of the bones and allows easy movement of joints. The breakdown of cartilage causes the bones to rub against each other, causing stiffness, pain and loss of movement in the joint.

Provided by Rush University Medical Center