Osteoarthritis results from inflammatory processes, not just wear and tear, study suggests

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In a study to be published online Nov. 6 in *Nature Medicine*, investigators at the Stanford University School of Medicine have shown that the development of osteoarthritis is in great part driven by low-grade inflammatory processes. This is at odds with the prevailing view attributing the condition to a lifetime of wear and tear on long-suffering joints.

"It's a paradigm change," said William Robinson, MD, PhD, the study's senior author, of the implication of the findings. "People in the field predominantly view osteoarthritis as a matter of simple wear and tear, like tires gradually wearing out on a car." It also is commonly associated with blow-outs, he added, such as a tear in the meniscus - a cartilage-rich, crescent-shaped pad that serves as a shock-absorber in joints - or some other traumatic damage to a joint.

But Robinson's paper suggests a different way of understanding the disease. Its findings offer hope that by targeting the inflammatory processes that occur early on in the development of osteoarthritis - well before it progresses to the point where symptoms appear - the condition might someday be preventable.

Robinson is an associate professor of immunology and rheumatology at Stanford and a staff physician with the Veterans Affairs Palo Alto Health Care System. The first authorship of the study is shared by research associate Qian Wang, MD, PhD, and Andrew Rozelle, MD, a former Stanford rheumatology fellow now at the Palo Alto Medical Foundation.

Osteoarthritis is the most common joint disease, afflicting some 27 million people in the United States alone. It is characterized by breakdown of cartilage, most often in the knees, hips, fingers and spine. Drugs commonly used to treat osteoarthritis, such as acetaminophen and ibuprofen, relieve pain but do not slow the disease's progression.

It has long been known that osteoarthritic joint tissues host a heightened number of migratory inflammatory cells and of some of the substances these cells secrete - "not nearly as much as in the case of rheumatoid arthritis, which is clearly an autoimmune disease, but enough to make us wonder if inflammation is also a major player in osteoarthritis as well," Robinson said. His team's observation of increased numbers of certain specialized inflammatory proteins early in the progress of osteoarthritis, before it becomes symptomatic, suggested that inflammation might be a driver, rather than a secondary consequence, of the disease.

The new study showed that, indeed, initial damage to the joint sets in motion a chain of molecular events that escalates into an attack upon the damaged joint by one of the body's key defense systems against bacterial and viral infections, the so-called complement system. This sequence of events involves activation of a chain reaction called the "complement cascade," and begins early in the development of osteoarthritis.

The complement system consists of an orchestra of proteins present in blood. Upon activation of the complement cascade - typically, in response to the presence of bacterial or viral infection - these proteins engage in a complex interplay, variously enhancing or inhibiting one another's actions at certain points and culminating in the activation of a protein cluster called the MAC (for "membrane attack complex"). By punching holes in the membranes of bacterial or virally infected human cells, the MAC helps to clear the body of infections.

An early clue regarding the complement system's key role in osteoarthritis came when Robinson and his colleagues, employing advanced lab techniques, compared the levels of large numbers of proteins present in the joint fluid taken from osteoarthritis patients with levels present in fluid from healthy individuals. They found that the patients' tissues had a relative overabundance of proteins that act as accelerators in the complement cascade, along with a dearth of proteins that act as brakes.

Robinson's group also examined the activity level of genes (which are recipes for proteins) in joint-lining tissues of osteoarthritic versus healthy subjects, and observed a similar result: more expression of genes encoding complement-activating and related inflammatory proteins, and less expression of genes encoding complement- and inflammation-inhibiting ones, in the osteoarthritic patients' joint tissues.

To further explore the complement system's role in osteoarthritis, the researchers induced the equivalent of meniscal tears or removal in mice who (like humans) are much more prone to getting osteoarthritis in joints that have suffered such damage. The procedure was performed on normal mice and on three separate strains of bioengineered lab mice, each strain missing a different protein component of the complement system. In two cases, the missing protein was one that ordinarily acts as an accelerator within the complement cascade, and in the third case one that acts as a brake.

The normal mice developed osteoarthritis as expected. But in comparison with these mice, the two strains of bioengineered mice lacking a complement-cascade-accelerating protein developed less-severe arthritis, while the mice lacking the complement-inhibiting protein got worse, faster. Thus, mice with impaired complement activation were protected against the development of osteoarthritis in response to meniscal damage.

Next, Robinson's team asked how complement was causing osteoarthritis. Further experiments in mice and with human tissue showed that the MAC, the heavy artillery of the complement system, was damaging joint-tissue cells, but not by punching holes in them. Instead, it was binding to cartilage-producing cells in these tissues and causing them to secrete, on their own, still more complement-component proteins as well as other inflammatory chemicals, and other specialized proteins, or enzymes, that chew up the matrix of cartilage occupying the spaces between cells. They demonstrated that breakdown products of cartilage destruction, including one called fibromodulin, can directly activate the complement system, fostering a continuing cycle of joint-tissue damage.

Finally, the investigators showed that all these insults inflicted by the complement system - measured by microscopic examination of mouse joints - were mirrored by functional impairment. Bioengineered mice lacking a key complement-component protein, without which the complement system fails to activate, maintained their ability to walk normally, while normal mice developed a hindered gait due to severe osteoarthritis following meniscal injury.

"Recent findings suggest that low-grade complement activation contributes to the development of degenerative diseases including Alzheimer's disease and macular degeneration. Our results suggest that osteoarthritis can be added to this list of diseases," said Robinson.

Drugs that target the complement system may someday prove useful in preventing the onset of osteoarthritis in people who have suffered joint injuries, Robinson said, though he cautioned that this system is so crucial to our defense against microbial infection that systemic delivery of complement inhibitors would likely not be safe. But it is possible that a brief period of local administration of a complement inhibitor might provide benefit to patients developing osteoarthritis, while minimizing their risk for the development of infections.

"Right now we don't have anything to offer osteoarthritis patients to treat their underlying disease," Robinson said. "It would be incredible, for the one-third of humans over 60 who have it, to find a way to slow it down."