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New clues to healing arthritis caused by traumatic injury

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A strain of laboratory mice that has "superhealing" powers has been found to resist inflammation after a knee injury, and also to avoid developing arthritis at the injury site in the long term, according to researchers at Duke University Medical Center. Their findings illuminate the mechanisms of post-traumatic arthritis and could point to therapies for this condition, which commonly afflicts younger people who lose productivity during their prime working years.

"After a patient's traumatic injury, orthopaedic surgeons realign the joint surface as anatomically as possible and then hope for the best," said Steven A. Olson, MD, FACS, principal investigator of the post-traumatic arthritis project and chief of the Duke orthopaedic trauma section. "They haven't been thinking about why patients with injuries are subsequently getting arthritis. Our research examines how we could possibly prevent arthritis development with growth factors and anti-inflammatory therapies after a fracture, either before or at the time of the surgery to fix it."

Olson said 10 percent of all arthritis cases - about 4.6 million - are post-traumatic arthritis patients, many of whom suffer for years and are too young for joint replacement surgeries. The economic cost thus is about $12.8 billion annually for this group, according to Arthritis Foundation statistics.

The scientists examined the differences in inflammatory response between two types of mice: one type known as superhealers (or

MRL/MpJ) versus a strain of control mice (C57BL/6).

Previously, scientists discovered that the superhealer mice had such regenerative powers that holes made in their ears for lab identification purposes grew over completely with no sign of scar tissue. Earlier work done at Duke showed no differences between healthy and fractured limbs when the superhealers healed from a fracture of the knee joint.

"The superhealer can almost regenerate tissue," said Bridgette Furman, research analyst and lead scientist of this study. "We thought, 'if they can regenerate cartilage in the ear, what about cartilage in the knee?' This happened in our pilot study, and we now have taken these results further and learned what happens in terms of inflammation. If you can figure out why the animal is a superhealer and apply that to people, then you may help prevent the development of arthritis."

In the latest experiment, the team got very clear results in the genetic response within injured tissue: the control mice showed a greater than 700-fold increase in the expression of one cytokine, interleukin(IL-1β) in the first four hours after a fracture and 37-fold difference in that cytokine level at 7 days after the fracture. Cytokines are signaling molecules produced by cells in response to injury. Interleukin generally promotes inflammation and an increase in temperature. The superhealer mice showed a similar trend, but in much lower amounts: a 70-fold peak in expression at day 0 down to a 3.5-fold increase by day 7.

A second cytokine, TNF-α, was also expressed at a significantly higher rate in the control mice after the fracture (from a 13-fold peak just after fracture to 5-fold at 7 days), while the superhealer mice showed no change in their levels of TNF-α at all over time.

"Current treatments on the market for rheumatoid arthritist include anakinra (Kineret®, an IL-1 receptor antagonist) and etanercept

(Enbrel®, a tumor necrosis factor blocker)," said Farshid Guilak, Ph.D., study scientist and director of the Orthopaedic Bioengineering Laboratory in the Duke Department of Surgery. "In future studies, we plan to use these rheumatoid arthritis drugs right after a fracture to inhibit inflammatory cytokines in the normal mice. If a reduced inflammatory response is what helps the superhealers, we would like to know whether controlling inflammation in fracture patients can prevent arthritis."

The team also studied the mice's joint fluid and blood serum to measure actual levels of the cytokines. Overall, the control mice again showed significantly higher serum levels and synovial (joint) fluid levels of cytokines compared with the superhealers.

The study was presented at the Orthopaedic Research Society meeting, which began on Feb. 22.

Source: Duke University Medical Center