What's been causing your knee to ache? Smurfs!

October 18 2007

A new clinical trial seeks to predict who is most likely to experience osteoarthritis, and to test whether an experimental treatment can prevent it altogether. Physicians are setting their sights on people who sustain a knee injury, seeking to understand why nearly half of them will later go on to develop osteoarthritis, a debilitating condition that causes pain and disability in more than 20 million Americans each year.

The work is funded by a special class of National Institutes of Health grants awarded to research programs that show promise of quickly translating basic science discoveries into patient treatments. In this case, initial research has shown that an enzyme which controls the response of cells to growth factors may in fact be a major cause of osteoarthritis. The enzymes are called "Smad Ubiquitination Regulatory Factors," or, smurfs, but unlike the small, loveable blue cartoon characters, researchers believe that a particular form of these regulatory enzymes, smurf2, might in fact be responsible for America's leading cause of disability.

"We believe that smurf2 controls whether or not a cartilage cell matures and calcifies into hard bone, which is a very good thing when 'turned on' in those areas of the body where we are supposed to have hard bone," said Randy Rosier, M.D., Ph.D., professor of Orthopaedics and director of Research Translation in Orthopaedics at the University of Rochester Medical Center. "But when smurf2 is active in joint cartilage, it may set off a chain reaction that leads to the steady deterioration of the smooth gliding surface tissue, or cartilage, which comprises the joint surface.

When this occurs, the cartilage breaks down and severely damages the weight-bearing surface of a joint. Or, put another way, activation of smurf2 in the joint cartilage appears to significantly contribute to the onset of osteoarthritis."

Frog Embryos and Cartilage Cells

Over the past decade, smurfs have begun to capture the attention of scientists, after a research team led by Gerald H. Thomsen, Ph.D., at Stony Brook University, identified the enzymes' critical role in regulating levels of important molecules that help determine which genes are turned on or off in a variety of cells throughout the body. In fact, Rosier first became intrigued with smurfs after reading about how they helped cell differentiation in frog embryos.

"I got to wondering what, if any, control smurfs might have on cartilage cell development and maturation," he said.

And so, over the course of several years, Rosier and his research team conducted a series of experiments that not only identified the role of smurf2 in bone cell and cartilage signaling, but uncovered its vital link to osteoarthritis.

First, the team compared healthy and diseased cartilage, and discovered that smurf2 was only present in osteoarthritic cartilage. They next demonstrated that smurf2s are stimulated by inflammation, and are expressed in cartilage within a few months following an injury.

Further experiments showed that smurf2 was present in the joints of patients in early-stage arthritis, when patients might begin to experience mild discomfort, but long before other well-known molecular markers of osteoarthritis began to emerge.

“It was at this point that we knew smurf2s are not just a casual bystander in arthritis, but rather, the catalyst that sets off the chain reaction that leads to osteoarthritis,” Rosier said

Rosier is now teaming with sports medicine surgeon Michael Maloney, M.D., to conduct the just underway clinical trial. The team will examine tissue samples from healthy, non-arthritic patients who have sustained an injury to the meniscus to determine the level of smurf2 expression in their cartilage at the beginning of the trial. In addition, a baseline MRI will measure the cartilage at the point of injury, and three years later. If results confirm the team’s earlier findings, the MRIs of patients with high smurf2 expression will show the beginning signs of osteoarthritis as measured by hardening of the cartilage and bone loss.

“Our ultimate goal is to create a simple diagnostic test to determine whether a person with a knee injury has a high level of smurf2s in their cartilage,” Rosier said. “In these cases, physicians can advise the patient to stop high-intensity, wear-and-tear activity, slowing the onset of arthritis and lessening its severity. Eventually, we hope to create an injection that will stop smurf2s’ ability to turn on the calcification and degeneration process in cartilage that leads to osteoarthritis.”

While Rosier admits the development of an injection is a long time off, he believes that physician counseling will do a world of good – and that’s good news for a disease that is estimated to cost the United States about $42 billion a year.

“Think of a 25-year male old who tears his meniscus. Today, after successfully removing the torn meniscus fragment and physical therapy, in most cases, he’s right back to his regular activity level,” Rosier said. “But if his physician can tell him with certainty that he will develop osteoarthritis, he has the opportunity to change his activity level, reducing his risk and severity of osteoarthritis.”

Source: University of Rochester Medical Center