MedicalXpress

Experimental gene therapy 'abolishes' arthritis pain and lessens joint damage

May 25 2007

Work proceeding rapidly toward application for human trials

Early-stage research has found that a new gene therapy can nearly eliminate arthritis pain, and significantly reduce long-term damage to the affected joints, according to a study published today in the journal Arthritis and Rheumatism. While the study was done in mice, they are the first genetically engineered to develop osteoarthritis like humans, with the same genetic predisposition that makes some more likely to develop the disease, the authors said. If all goes well with a follow-up study currently underway, researchers will apply to the U.S. Food and Drug Administration for permission to begin human trials next year.

Nearly everyone aged 65 or older suffers from the pain, swelling and permanent joint damage of osteoarthritis. The most common form of arthritis, it develops over time following initial joint injuries or just as a result of aging. In the current study, researchers found that one injection of a newly designed gene therapy relieved 100 percent of osteoarthritic pain in the study model. In addition, researchers were surprised to find that the therapy also brought about a nearly 35 percent reduction in permanent structural to joints caused by round and after round of osteoarthritic inflammation.

To date, treatment of arthritis is dominated by drug treatments like non-steroidal, anti-inflammatory drugs, COX-2 inhibitors and acetominophen. Morphine and its derivatives are still in common use as well, but can depress breathing and lead to addiction. Taken together, current treatments deliver inconsistent results and new approaches are

needed, researcher said. Gene therapy has been attempted in the past, but older, invasive techniques required that therapeutic genes be injected directly into nerve cells. Strong pain relief resulted, but in some cases the injections caused nerve damage.

"Our publication represents the first proof that gene therapy can work in a way that is clinically applicable," said Stephanos Kyrkanides, D.D.S., Ph.D., associate professor of Dentistry at the University of Rochester Medical Center. "This therapy can simply be injected anywhere in an injured joint, and the treatment will find the nerve endings," said Kyrkanides, whose work on genetics in dentistry led to broader applications. The common ground between arthritis and dentistry: a common site of arthritic pain is the jaw joint.

Study Details

Proteins called receptors are built into the outer surfaces of human cells, enabling them react to the nutrients, toxins and hormones around them. Each receptor is designed to react with a specific signaling molecule, which docks into the receptor like a ship coming into port. The docking changes the shape of the dock to set off chain reactions inside the cell, enabling it to respond to the signal. On nerve cells for instance, certain receptors are shaped to accept naturally occurring painkillers called opioids, which when they dock, prevent the sending of pain messages along nerve pathways.

In the current study, researchers used gene therapy to increase by about one thousand times the number of opioid receptors expressed on the surfaces of nerve cells that carry pain messages back and forth between an osteoarthritic jaw joint and the spinal cord. Thus, nerve cells involved in pain transmission, with so many more receptors on their surfaces, became drastically more responsive to the naturally occurring painkiller, researchers found.

Gene therapy inserts tailor-made genes into cells that can, for instance, direct cells to build more of a needed protein. To deliver the genes into cells, researchers use harmless viruses called vectors, which have evolved to invade human cells and insert their DNA. In designing the new therapy, Kyrkanides' team chose to work first with vectors based on feline immunodeficiency virus (FIV), a lentivirus that attacks the immune system of cats. It resembles HIV in humans, but is incapable of causing human infection.

Despite the strong results, however, the team will seek to deliver the same gene therapy with a different vector in the next phase of experiments. Kyrkanides is partnering with researchers at the National Institute on Drug Abuse, part of the National Institutes of Health, to see whether the same therapeutic gene can be delivered instead by an adeno-associated vector (AAV). AAVs have already been approved as safe for experimental gene therapy by the U.S. Food and Drug Administration, eliminating a tremendous regulatory hurdle. If successful, this next study will provide the proof of principle needed for the team to apply for phase I human clinical trials, perhaps within 18 months, Kyrkanides said. Early results, while not yet published, suggest that one serotype of the AAV vector they are working with will provide results comparable to FIV.

Beyond the current study, Kyrkanides' work has contributed to the emerging theory that pain is not a symptom of osteoarthritis, but is instead part of the disease. According to this new paradigm, pain is composed of nerve messages that over time cause permanent chemical changes in the pathways they travel along, making them more sensitive to pain and encouraging inflammation. This two-way "crosstalk" may mean that arthritis in one joint can spread, through the central nervous system (CNS), to other joints. Worse yet, joint arthritis may export inflammation to the brain, where it plays a role in neurological conditions (e.g. Alzheimer's disease, dementia and multiple sclerosis).

While the just published study involved a technique that delivers gene therapy by injection at the joint, other promising approaches may involve interrupting crosstalk in the brain instead. Based on that promise, the Medical Center is in the process of founding a private biotech company to develop the technology. It would search for new drugs that interfere with key inflammatory receptors on sensory nerve cells within the CNS.

Joining Kyrkanides in the publication from the University of Rochester School of Medicine and Dentistry were co-authors J. Edward Puzas, Ph.D., Donald & Mary Clark Professor of Orthopaedics, M. Kerry O'Banion, M.D., Ph.D., associate professor of Neurobiology and Anatomy and Ross Tallents, D.D.S., professor of Dentistry and director of the Orofacial Pain Program within the University of Rochester's Eastman Dental Center. Student contributors were Paolo Fiorentino, Yanjun Gan, Yu-Ching Lai and Solomon Shaftel. Jennie Miller was involved as Kyrkanides' technical associate. Maria Piancino, of the University of Torino, Italy, was also an author based on an alliance between the two institutions. The study was funded in part by the National Institute of Dental and Craniofacial Research.

"Near future applications of the work may include amplifying the body's response to morphine, drastically reducing the amount needed for powerful pain relief," Tallents said. "A little further out, the new idea that peripheral inflammatory diseases like arthritis can lead to brain inflammation may provide an entirely new way to treat inflammatory neurological conditions that affect millions."

Source: University of Rochester Medical Center