SPOTLIGHT ON RESEARCH
Osteoarthritis
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WINTER 2011

Getting Closer to the Clinic

Three researchers talk about how their findings in gene identification, imaging biomarkers and stem cell-based therapies are leading to more effective treatments for osteoarthritis.

BY JO CAVALLO

Arthritis is the leading cause of disability in the United States, affecting more than 46 million people and costing the economy more than $128 billion a year in lost productivity and direct medical costs. Osteoarthritis, a degenerative joint disease, is the most common form of arthritis, affecting more than 27 million in the U.S.—more than any other joint disease—and costing the economy a staggering sum of over $60 billion a year.

Over the Arthritis Foundation's 61-year-long history, it has supported the training of more than 1,300 postdoctoral fellows in arthritis research, including many who have gone on to devote their careers to the study of osteoarthritis. In addition to training grants, the Arthritis Foundation has funded over $400 million dollars in research—$150 million in osteoarthritis research alone.

While the Foundation is dedicated to funding arthritis research, it is also committed to educating government agencies such as the Department of Defense (DOD) about the impact a debilitating disease like osteoarthritis has on national security. Those efforts are now paying off.

"We made a case to the Department of Defense about how osteoarthritis is a significant defense matter since soldiers carry heavy loads and work under harsh physical conditions, both of which contribute to joint injuries, one of the leading medical issues that sideline soldiers," says John Hardin, MD, Vice President for Research for the Arthritis Foundation. "Through our initiatives, in 2009 the DOD named osteoarthritis as a principle area for its research investment and earmarked $2.5 million to investigate this disease. Now we're requesting that it consider investing $8 million a year."

In addition to the DOD, the Arthritis Foundation is also working with the National Institutes of Health (NIH) on its Osteoarthritis Initiative (OAI), a public-private partnership that is building a database of magnetic resonance (MR) images and clinical outcome information to facilitate the discovery of the biomarkers that will make it possible for clinicians to detect the presence and progression of osteoarthritis. So far the Initiative has gathered blood and urine samples and MR images of nearly 6,000 individuals, some of whom are at high risk for developing the disease but do not yet have OA, as well as others with mild to moderate osteoarthritis.

"To date, the OAI has cost over $100 million to acquire the patients and the clinical information needed for this study. This is the largest and most powerful study of OA ever conducted. The final analysis phase will cost an additional $3 million, so the Arthritis Foundation is taking the strategy that the best approach for learning about the development of OA is to help fund the final phase of this very large research initiative," says Dr. Hardin. "In 2011 we will find the funding that will permit us to have a central role in the ultimate payoff of this very ambitious and most important project. It will also permit us to initiate some new research projects designed to develop new drugs, new drug delivery systems and find ways to identify people most vulnerable to develop OA before they ever become clinically symptomatic."

Although the exact causes of OA are unknown, advancing age—about half of those over age 65 have osteoarthritis—obesity and joint injury are all contributing risk factors for disease onset. But why some people at high risk for the disease develop OA while others do not is still a question researchers are trying to answer. Two of those researchers, Steven B. Abramson and Lawrence V. Gulotta, are profiled on the following pages. Their research findings are shedding light on the possible genetic factors involved in OA onset as well as the potential role stem cell-based therapy may play in hastening joint repair.

Research findings are shedding light on the possible genetic factors involved in OA.

A third researcher, Ravinder Reddy, is developing new magnetic resonance imaging technology that can detect the early onset of disease, before there is joint degradation. All of their research investigations promise to spur drug development to, if not cure OA altogether, stop it from progressing.

According to Dr. Hardin, new therapies to treat osteoarthritis could be in clinical trials within the next five to eight years.

Steven B. Abramson, MD

Director, Division of Rheumatology and Senior Vice President and Vice Dean for Education, Faculty and Academic Affairs, New York University Langone Medical Center, New York City

There were two factors, says Steven B. Abramson, MD, that were involved in helping him decide to dedicate his medical career to rheumatology. One was an intellectual fascination with the unknowns of the immune and inflammatory processes at work in the development of arthritis and, two, his mentor during his residency at New York University (NYU) Langone Medical Center in New York City, Gerald Weissmann, MD, Professor of Medicine in Rheumatology and Director of the Biotechnology Study Center at NYU Langone Medical Center.

Today, Dr. Abramson is the principal investigator in the Abramson Lab at NYU where he and his colleagues are focused on both basic science and clinical research in the field of inflammation and arthritis. Their work has led to a better understanding of the causes of osteoarthritis (OA) onset and its severity, including the role genetics may play in the disease.

"It used to be thought that osteoarthritis was just the degeneration of tissues, as the skin wrinkles, the joints degenerate," says Dr. Abramson. "But it turns out that there are many active processes that go on within the cartilage synovium and bone of people with OA that may determine how rapidly they get worse and why some people get [the disease] and others don't."

While aging does contribute to OA onset due to the molecular changes taking place in joint cartilage, causing the cartilage to stiffen and to lose its ability to act as a "shock absorber," the majority of the elderly do not develop clinically significant, symptomatic OA. "Although we talk about OA as a disease of the aging, in fact, at the age of 70 or 80, only 20 percent to 30 percent of people have significant knee or hip OA, so there must be some metabolic processes independent from age that are different in the joints between people," says Dr. Abramson.

Those metabolic processes may be triggered, according to Dr. Abramson, by oxidation products produced by OA chondrocytes, which release pro inflammatory cytokines, including Interleuken 1, prostaglandin E2 and nitric oxide, causing an aging accelerating process within the cartilage.

"A chondrocyte may "age" prematurely if it produces more free radicals or oxidation products and that may lead to what Thomas Aigner, PhD [program director, Division of Basic Neuroscience and Behavioral Research at the NIH] has termed Alzheimer's disease of the cartilage," says Dr. Abramson. A genetic predisposition to making more of these oxidation products, explains Dr. Abramson, may be why some older people get OA and others don't.

Obesity and OA

Biochemical abnormalities within the joints, says Dr. Abramson, often driven by altered biomechanics, are believed to be the driving force behind joint degeneration leading to OA. Obesity may contribute to osteoarthritis onset by some biomechanical abnormality that takes place as the result of too much weight placed on leg and knee joints, causing a malalignment of those joints to occur.

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Another possibility, says Dr. Abramson, is that adipokine molecules produced by the fat cells may cause an accelerated production of inflammatory mediators, such as Interleuken 1 and nitric oxide, hastening OA onset and progression. Traumatic injury to a joint, such as a torn meniscus, may also trigger a biomechanical abnormality to occur, resulting in the production of destructive enzymes and inflammatory mediators.

Dr. Abramson's research has led to the discovery of certain genes related to Interleuken 1, which may worsen OA, as well as a group of Interleuken 1 antagonist genes, which may slow disease progression. That discovery, if confirmed, could be of clinical importance in enabling drug development and in the future treatment of patients.

"We'll know more about which genes are involved in the progression of OA within a few years. [Gene studies] are the focus not only of our lab but of many investigators worldwide in the field of OA. The field is moving forward and one hopes that effective treatments that slow progression of OA are on the horizon," says Dr. Abramson.

Lawrence V. Gulotta, MD

Department of Orthopaedic Surgery, Hospital for Special Surgery, New York City, New York

Already contemplating a career in medicine while still in high school, a sports injury to his knee during a football game convinced Lawrence V. Gulotta, MD, to specialize in orthopedic surgery. "I was a sports enthusiast and the realization that I could combine my two interests—sports and medicine—was a revelation to me," says Dr. Gulotta.

Today, Dr. Gulotta works with athletes at all levels, as well as with other patients, to improve their mobility and reduce the pain associated with osteoarthritis. With a one-year $50,000 grant from the Arthritis Foundation awarded in 2006, Dr. Gulotta began laboratory investigations into ways mesenchymal stem cells harvested from the bone marrow of rats can be manipulated to improve rotator cuff healing after surgery to repair an injury.

"Despite being one of the most common surgeries we perform, the rotator cuff does not always heal following surgical repair," says Dr. Gulotta. "The tendon heals to the bone through an interposed layer of scar tissue. This scar tissue is weaker than normal tissue and we think that the formation of this scar tissue is what makes surgical repairs prone to failure."

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Although the stem cells alone failed to improve rotator cuff healing in the rats, Dr. Gulotta found that when he genetically altered the stem cells with the transcription factors membrane-type metalloproteinase (MTI-MMP) and scleraxis, the rats' injured rotator cuffs began healing as soon as two weeks following the experimental surgery. That finding, says Dr. Gulotta, has led him to investigate the effects of MTI-MMP and scleraxis have on healing.

"Since very little is known about exactly how scleraxis works, we are currently performing more studies to determine its mechanism of action and how we can optimize these technologies for clinical use," says Dr. Gulotta. Although, admits Dr. Gulotta, effective stem cell-based therapy in the treatment of osteoarthritis may be years away from becoming a reality for patient care, his research is furthering the understanding of the pathologic processes involved in the onset of osteoarthritis and how those processes can be blunted.

"Research to develop new therapies to prevent osteoarthritis takes time, but I'm confident that we will get there eventually," says Dr. Gulotta.

Ravinder Reddy, PhD

Professor of Radiology and Director,
Center for Magnetic Resonance and Optical Imaging,
University of Pennsylvania School of Medicine,
Philadelphia, Pennsylvania

Ravinder Reddy, PhD, choose the field of magnetic resonance imaging (MRI) and diagnostic radiology as his area of research because he was interested in utilizing advances in MRI physics to directly impact patient care. Over the last several years, Dr. Reddy has been developing novel MRI diagnostic methods for several diseases, including osteoarthritis (OA). The new MRI technology is able to spot not just the structural damage to cartilage caused by osteoarthritis, but to detect molecular changes taking place before the disease becomes symptomatic.

"One of the shortcomings of diagnostic imaging in arthritis is in the insensitive and qualitative imaging of the articular cartilage involved in osteoarthritis," says Dr. Reddy. "Current radiographic methods only detect very late-stage disease, which may be fine to look at OA patients over a long period of time, but it doesn't give us the opportunity to treat patients in an early stage when it might be possible to stop or reverse the disease. Because of the long natural history of the disease, the lack of adequate sensitive diagnostic tools has also hampered the development of therapies targeting OA."

With grants from the Arthritis Foundation and the National Institutes of Health, Dr. Reddy has been able to continue his research to develop multinuclear MRI methods, including a 3D T1p MRI and a sodium MRI system, which, unlike traditional MRI technology, doesn't need contrast agents to improve visibility of internal organs and tissue structure. Instead these MRI systems are able to detect the molecular changes leading to OA caused by an imbalance in the turnover of proteoglycan (PG) and collagen, two major macromolecules of cartilage. It's the loss of PG that starts the OA process. The 3D T1p MRI is sensitive to changes in both PG and collagen content, while the sodium MRI is a specific biomarker of only PG. As a result, both methods exploit tissue molecules to create images with improved visibility of tissue biochemistry and structure.

Dr. Reddy is currently evaluating the sensitivity and specificity of these noninvasive MRI methods on patients with early onset OA. Although these new magnetic resonance methods have shown great promise in research studies, they have to undergo the rigors of clinical trials before they can be approved for routine diagnostic use. But getting to that next important step may be challenging since it requires funding for the recruitment of large pools of OA patients with early onset disease.

"One of the issues is being able to recruit people with very early stage osteoarthritis when the cartilage still looks pretty much intact on a conventional MRI, but where there are molecular-level changes taking place," says Dr. Reddy. However, these challenges are not insurmountable, he says.

If approved for clinical use, these MRI technologies are expected to both improve the diagnosis of early onset OA and management of the disease. Although at present there are no treatments to halt OA progression, "development of powerful diagnostic techniques, such as the new MRIs, will expedite the development of disease-modifying drugs and enable us to evaluate their efficacy at the early stages of the disease. And that's the goal," says Dr. Reddy.

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