SPOTLIGHT ON RESEARCH
Rheumatoid Arthritis
ARTHRITIS FOUNDATION®
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SPRING 2012

Making Personalized Medicine a Reality

Sequencing of the human genome and a better understanding of the role of cytokines in the pathogenesis of rheumatoid arthritis (RA) are helping researchers isolate both the genes involved in disease onset and the molecules that promote joint destruction. The findings are paving the way for better diagnostic tests to determine who is at risk for developing RA and personalized treatment to halt RA progression—and even cure it.

BY JO CAVALLO

Rheumatoid arthritis (RA), the most crippling form of arthritis, affects about 2.1 million Americans, most of whom—1.5 million—are women. An autoimmune disease in which the body's own immune system mistakenly attacks healthy tissue, RA causes pain and inflammation in the joints and surrounding tissues, it can also affect other organs, including the heart, lungs and skin.

While average age of disease onset is between 30 and 50, RA can strike people in their 20s and younger, jeopardizing college plans and careers and hindering long-term quality of life. Without effective treatment, it is estimated that within ten years of being diagnosed with RA, half of all working patients become disabled, costing society in lost productivity and healthcare spending a staggering $58.5 billion each year, according to research from Analysis Group.

For more than 63 years, the Arthritis Foundation has led the effort to uncover the causes of the three major types of arthritis—osteoarthritis, rheumatoid arthritis and juvenile arthritis—and to find more effective treatments for the 50 million people suffering from these diseases. Currently, the Foundation nationwide is supporting 24 research grants in RA totaling over $4.5 million. Three of those grants are focusing on how and why RA is associated with increased cardiac disease; indentifying new techniques for measuring white blood cells (the agents of the immune system) that are directly driving joint inflammation; and identifying chemokines (a group of proteins that attract white blood cells) that are important in the pathogenesis of RA and that may be regulating how inflammatory cells find their way to the affected joint. In addition to funding individual research projects, the Foundation has also partnered with the American College of Rheumatology Research and Education Foundation, contributing $1 million to its Within Our Reach program, a $24-million dollar research initiative aimed at accelerating medical breakthroughs in RA.

The Arthritis Foundation is also supporting the Treatment Efficacy and Toxicity in Rheumatoid Arthritis Database (TETRAD), a patient registry established to help identify clinical and genetic features of the disease and predict which patients will benefit from specific treatment, with the goal of delivering personalized medicine to patients. "What makes personalized medicine a near-reality is the fact that being able to decode each individual's whole genome is within reach," says John Hardin, MD, Vice President for Research for the Arthritis Foundation.

To date, genomic research has led to the isolation of 32 genes that correlate to RA onset, but those genes only account for about 20 percent of the cases of RA, so additional research is needed to learn what other genes are involved. One of the leading investigators in genomics, Peter K. Gregersen, MD, Head of the Robert S. Boas Center for Genomics and Human Genetics at North-Shore-Long Island Jewish Health System, says that the next five years promise to bring a greater understanding of the combination of genes that contribute to each person's risk for developing RA. His research is profiled on page 2 of this newsletter.

Also featured in this issue is the work George D. Kalliolias, MD, PhD, Instructor in Medicine at the Hospital for Special Surgery in New York City, is doing in the molecular mechanisms that lead to inflammation and joint destruction in RA. And on page 4, we profile the experience of patient Karen Ager and how advances in new biologics for RA are giving her hope for the future.

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Peter K. Gregersen, MD

Head, Robert S. Boas Center for Genomics and Human Genetics, Feinstein Institute for Medical Research, North Shore-Long Island Jewish Health System, Manhasset, New York; and Principal Investigator for the North American Rheumatoid Arthritis Consortium

A lack of understanding of the causes of rheumatic diseases, the limited therapies available to treat them and the desire to help patients suffering from these ailments were the determinant factors in Peter K. Gregersen's decision to specialize in rheumatology after completing his medical residency in the late 1970s. After taking a couple of years off from medicine to train as a classical guitarist, Dr. Gregersen became a rheumatology fellow at the Hospital for Joint Diseases, NYU Langone Medical Center in New York City, where he began his research into the genetics of rheumatoid arthritis (RA) and other rheumatic diseases.

"In the early 1980s, pretty much the only genetic study going on in RA and other autoimmune disorders were relatively crude studies of human leukocyte antigens (HLA). I started in the field just when it was possible to apply recombinant DNA techniques to this problem, and so we cloned and sequenced the HLA molecules. By 1987 we had figured out the likely structures in the HLA molecules that are involved in risk for developing RA," says Dr. Gregersen.

But it would be more than a decade-and-a-half later and the advent of single-nucleotide polymorphism (SNP) microarray technology for Dr. Gregersen and his colleagues to find three more susceptibility genes involved in RA onset, STAT4, TRAF1-C5 and the protein tyrosine phosphatase PTPN22. Having two copies of the risk variant of STAT4 is associated with a 60 percent increased risk of developing RA compared with people who do not have the gene. Having the TRAF1-C5 variant, located on chromosome 9, increases RA risk by 35 percent. The PTPN22 genetic variant has been linked to the development of a host of autoimmune diseases, including RA, nearly doubling a person's risk for contracting the disease.

An Arthritis Foundation grant recipient, Dr. Gregersen's latest research is extending this work to sequencing whole genomes of RA patients to define the entire set of genetic risk variants in these patients. There are now 32 genes identified as conferring risk for RA. Combined with other advances, this information can be used to develop and evaluate biomarker-screening tests. For example, Dr. Gregersen is co-principal investigator of a study called BATTER-UP (Biomarkers of Anti-TNF-Alpha Therapy Efficacy in Rheumatoid Arthritis to Define Unresponsive Patients), which aims to help predict who is likely to benefit from antitumor necrosis factor-alpha (anti-TNF) medications, such as Remicade (infliximab), Enbrel (etanercept) and Humira (adalimumab). The multicenter clinical study is currently enrolling 1,000 patients diagnosed with moderate to severe RA who have been prescribed anti-TNF therapy. (For additional information, go to www.clinicaltrials.gov; and type in BATTER-UP in the search field.)

"TNF inhibitors work very well for about 30 percent of RA patients and not at all for about 30 percent of patients, with 40 percent of patients falling somewhere in-between and the question is, 'Can genetics tell us who is going to respond to treatment and who is not?' The answer so far is 'no.' However, I am optimistic that we are going to get a better understanding of the diversity of the biology of RA and that understanding will ultimately enable us to more precisely match patients with effective therapies."

Progress over the next five years, says Dr. Gregersen, promises to usher in a new era in investigations in the pathogenesis of RA based in part on understanding the particular combinations of genes that contribute to each person's risk for developing the disease.

"We are still in the early stages of studying the gene variation involved in disease and there is a huge effort going on to understand how these gene variants impact the biology of autoimmune disorders like RA," says Dr. Gregersen. "For the person suffering from RA, progress is never fast enough. But this is an extraordinary time for biomedical science, with many new biologically targeted therapies being developed and coming onto the market, some of which have produced dramatic results in some patients. We need to understand why these drugs work when they do. This is the key to extending these benefits to everyone suffering from rheumatic diseases."

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George D. Kalliolias MD, PhD

Instructor in Medicine, Hospital for Special Surgery, Weill Cornell Medical College, New York City, New York

The surge in the discovery of biologic therapies in the treatment of rheumatic diseases during the early 1990s was the catalyst that propelled George D. Kalliolias, MD, PhD, to devote his medical career to researching more effective treatments for his patients suffering from these diseases, especially rheumatoid arthritis (RA). A native of Patras, Greece, in 2006, with support from a postdoctoral fellowship from the Arthritis Foundation, Dr. Kalliolias became a research fellow in rheumatology at the Hospital for Special Surgery (HSS) in New York City and is now working with his mentor Lionel Ivashkiv, MD, Associate Chief Scientific Officer at HSS, investigating the molecular mechanisms leading to inflammation and joint destruction in RA.

"When I was a medial student in Greece, I was fascinated by the advent of molecular medicine in rheumatology that led to the first biologic therapies for rheumatic diseases. In the early 1990s, the development of antibodies that specifically targeted tumor necrosis factor-alpha (TNF-α) revolutionized the way we treat RA. I was impressed by the idea that you could generate targeted and individualized therapies," says Dr. Kalliolias. "That was my primary reason for becoming a rheumatologist. The second reason was my desire to solve the mystery of how the immune system, which defends us from microbial pathogens, is reprogrammed in rheumatic diseases and harms our bodies. It is still a puzzling question."

In three studies funded by the Arthritis Foundation, Dr. Kalliolias discovered that the cytokine (a protein produced by cells) interleukin-27 (IL-27) may help control inflammation and joint destruction in RA. Macrophage-derived cytokines, especially TNF-α cytokines, play a significant role in the development of RA. In addition, osteoclasts (cells that break down bone) are increased and hyperactive in RA patients, leading to bone erosion and joint destruction. Dr. Kalliolias' findings suggest that IL-27 inhibits the TNF-α pro-inflammatory function in macrophages and suppresses the number of osteoclasts.

"We know that RA is characterized by chronic inflammation and joint destruction. Inflammation is mediated by a cytokine cascade, with TNF-α being the most important in at least 50 percent of RA patients. Joint destruction includes both cartilage and bone destruction in which bone destruction is mediated by osteoclasts. A rational strategy to treat RA is to block pathogenic cytokines and control osteoclast function. IL-27 is a very interesting molecule that can suppress both TNF-α effects and the potent inhibition of osteoclastogenesis. The beneficial effects of IL-27 in arthritis may also come from a suppressive effect on T-lymphocyte functions," says Dr. Kalliolias.

While his research findings look promising for the potential development of new treatments in RA, Dr. Kallilolias cautions that more work needs to be done. "In animal models, IL-27 was proven beneficial in treating arthritis. However, there are some safety and efficacy issues that must be resolved before we can move forward with human clinical trials," says Dr. Kallilolias.

Another area of Dr. Kallilolias' research is the role of synovial fibroblasts in the pathogenesis of RA. Synovial fibroblasts are resident cells in normal joints, but in RA they become activated and participate in the development of disease. Dr. Kallilolias' work aims to understand how fibroblasts become activated by the inflammatory stimuli found in RA joints and how they interact with the immune cells that infiltrate the inflamed joints.

"We're studying the pathogenic properties of synovial fibroblasts obtained from patients with RA who have undergone joint replacement. Activated synovial fibroblasts produce mediators that perpetuate joint inflammation and induce cartilage and bone destruction. While there are a number of therapeutic options targeting immune cells or their products, there is no treatment that specifically targets synovial fibroblasts in RA. I'm hopeful that in the next five to ten years, new therapies that effectively target the joint fibroblasts will be available in clinical trials for patients with RA," says Dr. Kalliolias.

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A PATIENT'S STORY
Karen Ager

Karen Ager, 47, remembers being awakened in the middle of the night when she was just seven years old from pain in her legs so severe she had to call out to her mother for help. Thinking that what Karen was suffering from was nothing more serious than childhood growing pains, Karen's mother comforted her by rubbing her legs and giving her aspirin, which eased the pain. Although the sporadic pain in Karen's legs, and eventually her right shoulder and hip, intensified throughout her adolescence, it wasn't until Karen was 17 that a diagnosis of rheumatoid arthritis (RA) was made. A native of Australia, Karen says the chronic nature of the disease and its long-term effects weren't well known in 1981 and effective treatments were limited. As her RA progressed, Karen feared for her future.

"Once I got the diagnosis of RA and my pain became more severe and I needed frequent cortisone injections in my shoulders and knees, I thought there was no hope for a good future for me. My mother started to prepare for my financial well-being because it was felt that by the time I was 40 I would be wheelchair-bound and unable to work," says Karen.

Over the next 15 years, Karen was given a variety of treatments, including the antimetabolite drug methotrexate, which reduced her joint inflammation and pain but caused bilateral pneumonia, a rare side effect of the drug, which nearly took her life when she was 27. A series of treatments followed, including massive doses of corticosteroids, which necessitated the replacement of Karen's right hip because of vascular necrosis caused by the heavy steroid doses. Karen's prospects for a productive life seemed so remote, the Australian government offered to put her on permanent disability.

"When you hit rock bottom sometimes you learn who you are and at that moment I remember looking at my mother and saying, 'I'm not going on permanent disability. There's got to be another way and that's when I tried gold injections and different medications like Plaquenil (hydroxychloroquine). They got me well enough to start working again teaching elementary-grade school students," says Karen.

Although struggling through bouts of depression and poor body image caused by joint disfigurement from the disease, in 2000, Karen made the bold decision to move to New York City and start a new life.

"I had reached the stage in my psychological battle with RA where I decided that I wouldn't let the disease define me anymore and I was determined to live the life I thought I deserved, so I moved to New York and got a job teaching at the United Nations International School. It takes sheer will to get up every morning and go to work when you have a chronic disease like RA but I'm proud that I can do it," says Karen.

Treatments with some of the newer biologics, including Remicade (infliximab), Enbrel (etanercept) and Humira (adalimumab), have reduced Karen's RA symptoms so much she no longer fears the future and is now happily married. To help other patients cope with the effects of RA, Karen wrote about her experience with the disease in the *Enemy Within: A Memoir of Strength, Determination and Acceptance* (New Holland Publishers; 2010) and speaks at fund-raising events to raise public awareness of RA and money for research.

Her interest in supporting research to advance a better understanding of RA and discover more effective treatments for the disease prompted her to join the Board of Governors for the New York Chapter of the Arthritis Foundation seven years ago.

"Knowing that there are other drugs being developed takes the fear out of having this disease and gives me hope," says Karen.

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