RHEUMATOLOGY RESEARCH
UPDATE

FALL 2019

DIVISION OF RHEUMATOLOGY AND CLINICAL IMMUNOLOGY

Inside This Edition

Illuminating the Role of IL-17 in Enabling T Cells to Talk to Their Environment

Interleukin 17 (IL-17) supports protective immunity and helps to maintain healthy skin and gut. It also promotes chronic inflammation in autoimmune diseases. A University of Pittsburgh research team led by **Mandy McGeachy, PhD**, has found that IL-17 produced by Th17 cells promotes autoimmunity by changing the environment in the inflamed lymph node. Specifically, IL-17 signaling changes the metabolism of nonimmune stromal cells, activating them and leading them to proliferate. This ultimately supports autoantibody production.

"This is a new role for IL-17," says Dr. McGeachy, who is an associate professor in the Division of Rheumatology and Clinical Immunology. "Most of the diseases that rheumatologists see involve a component of autoantibody as well as inflammatory T cell responses. What this study shows is that IL-17 is linking T cell response and autoantibody production by acting on nonimmune cells in the lymph nodes," says Dr. McGeachy. The study was published in *Nature Immunology* in May 2019.

Dr. McGeachy received her undergraduate degree from the University of Glasgow, Scotland, in 2001 and her doctorate from the University of Edinburgh in 2005. She completed her postdoctoral training at Schering-Plough Biopharma/Merck, formerly DNAX Research, in Palo Alto, California, where Th17 cells were first discovered. During her training, she became an expert in experimental autoimmune encephalomyelitis (EAE), a mouse model of autoimmunity. Since she joined the University of Pittsburgh in 2012, Dr. McGeachy and her colleagues have studied Th17 cells in this model and in humans to understand the biological mechanisms underlying autoimmune inflammation.

Elucidating the Behavior of Th17 Cells

Dr. McGeachy's laboratory has identified clues that can explain difficulties in generating human Th17 cells in vitro, defined pathogenic and regulatory Th17 cell phenotypes in autoimmune disease, and described a role for IL-23 in effector Th17 cells and autoimmune Th17 memory cells that cause disease in the brain. Now they are looking at the lymph node and spleen.

"In autoimmunity, we tend to think about blood and peripheral and target tissues, but not so much about the actual lymph node, which is where T cells are first activated," says Dr. McGeachy.

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Toward Patient-Specific Therapies for Advanced Cutaneous T Cell Lymphoma

Cutaneous T cell lymphomas (CTCL) are a group of T lymphocyte malignancies that mainly affect the skin. Early diagnosis of CTCL is difficult due to a lack of highly specific markers for malignant lymphocytes. In its early stages, CTCL progresses slowly, is treatable, and has a good prognosis. However, patients with advanced-stage CTCL have few treatment options available, reflecting continued poor understanding of the disease's origins and development. Due to the absence of markers for CTCL, diagnosis typically occurs about seven years after symptom onset, preventing timely treatment and resulting in poorer clinical outcomes.

In the spring of 2019, pharmaceutical chemist **Patrizia Fuschiotti, PhD**, published new findings in *Clinical Cancer Research* on single-cell analysis of CTCL skin-tumor samples using droplet-based single-cell CTCL skin biopsies. The study describes patient-specific lymphocyte heterogeneity and identifies specific markers that pave the way for early diagnosis of and development of patient-specific therapies for CTCL.

Dr. Fuschiotti completed her doctoral work in pharmaceutical chemistry at the University of Perugia, Italy, before joining the Division of Rheumatology and Clinical Immunology at the University of Pittsburgh School of Medicine as an assistant professor in 2009. Her research interests focus on the cellular and molecular mechanisms of pathogenesis by T cell and T cell-derived cytokines in chronic inflammatory conditions.

In particular, she has examined the roles played by the cytokine interleukin-13 (IL-13) and its receptors (IL-13Ra1 and IL-13Ra2) in fibrosis, autoimmunity, and cancer in the context of human diseases that affect the skin. Dr. Fuschiotti has shown that IL-13 and its molecular pathways are involved in both systemic sclerosis, an autoimmune connective tissue disease whose main clinical feature is fibrosis, and CTCL. In addition to understanding the underlying mechanisms of pathogenesis, Dr. Fuschiotti has been developing strategies for targeting IL-13 and its molecular pathways to provide therapeutic relief.

Laying the Groundwork for Personalized Medicine

Dr. Fuschiotti's current work investigates CTCL skin-tumor heterogeneity with the aim of developing therapeutic strategies tailored to specific patients, aided by the use of novel single-cell RNA sequencing technology applied to a 3 mm screen biopsy. Explaining the technology's value for physicians, she says, "It gives a more patient-specific feature of the disease, for developing patient-specific therapy." This lays the groundwork for personalized medicine and is therefore very topical.

The *Clinical Cancer Research* study found patterns of gene expression that were unique for each patient, as well as a common gene-expression signature for the disease itself — findings that are important for the future development of both CTCL-specific and patient-specific drug therapies, says Dr. Fuschiotti.

The 3 mm screen biopsy yielded a huge amount of information on all the cell types present within the biopsied tissue, providing a general picture of lymphocytes — both malignant and nonmalignant — as well as of other cell types present within the microenvironment that are important because they produce proteins that enhance tumor growth and suppress the immune response against the tumor.

The study found vast heterogeneity not only among tumors but also within each tumor. This diversity may ultimately point the way to the development of patient-specific therapies for CTCL.

"For example, we have identified that in one patient there was activation partly associated with the tumor invasion. In another patient there was a strong inflammatory component that was similar to psoriasis. These activated patient-specific pathways suggest that therapies need to be tailored to individual patients," says Dr. Fuschiotti.

Identifying Markers of Tumor Proliferation

An additional very important finding from the study was that some signatures were common to most patients with advanced-stage CTCL and were markers of tumor proliferation. A critical problem in diagnosing and treating CTCL is that it is difficult to identify malignant cells from healthy reactive T cells because no marker has been identified for this. In its early stages, CTCL tumors are indolent and difficult to find — a key reason for delayed diagnosis of CTCL. Validated markers of tumor proliferation could potentially be used to diagnose CTCL earlier in the disease course.

Another finding addresses the character of the reactive lymphocytes that are often found infiltrating CTCL skin tumors. These lymphocytes differ in their ability to respond to and reject tumors.

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Illuminating the Role of IL-17 *(Continued from Page 1)*

Th17 cells start out as naïve T cells. They are activated and differentiate into Th17 cells in the lymph nodes, and they produce IL-17 as they differentiate. They also interact with nonimmune stromal cells in the lymph node. Among these cells are fibroblastic reticular cells (FRCs). Immunization or pathogen invasion trigger a series of events leading to lymphocyte retention and swelling of local lymph nodes. Activated FRCs undergo changes to support T cells, dendritic cells, and lymph transport, and they proliferate to support the expanded lymphoid tissue. Depleted or dysfunctional FRCs have been associated with secondary lymphoid fibrosis, reduced T- and B-cell viability, and impaired antiviral immunity.

Relevant to Autoimmune Diseases

By examining the EAE model and a colitis model in wild-type mice and mice deficient in IL-17 signaling, Dr. McGeachy and her colleagues found that FRC proliferation and global antibody production both depend on a functional IL-17 receptor signaling pathway within the FRCs. When they analyzed gene expression patterns in FRCs isolated from mice deficient in IL-17 signaling, they found changes in expression for genes associated with the cell cycle, glucose uptake, aerobic glycolysis, and oxidative phosphorylation. Consistent with these findings, FRCs underwent cell cycle arrest and apoptosis, and showed signs of nutrient distress in the absence of IL-17 receptor signaling.

Other experiments showed that IL-17 itself increased glucose uptake and mitochondrial *Cpt1a* expression through the transcription co-activator IκBξ, which was previously known to work with NFκB to induce inflammatory cytokines. Dr. McGeachy and her colleagues concluded that IL-17 produced by differentiating Th17 cells drives FRC activation in inflamed lymph nodes by reprogramming FRC metabolism. They will explore these effects further in tissues where disease occurs, both in mouse models and in humans.

"Understanding how the immune system metabolically activates stromal cells is a fairly new area within immunology," says Dr. McGeachy. "This is relevant to most autoimmune diseases because in any tissue site you have resident cells and immune cells speaking to each other. IL-17 always acts on nonimmune cells. In rheumatoid arthritis, it activates synovial stromal cells to drive inflammation in the joint. In the skin, it activates keratin to drive inflammation during psoriasis or psoriatic arthritis. Now we've found that IL-17 is acting on nonimmune cells in the lymph nodes."

A Collaborative Environment

The U.S. Food and Drug Administration has approved several biologic therapies targeting IL-17 or its receptor for psoriasis, psoriatic arthritis, and ankylosing spondylitis. These therapies have become the new gold standard in psoriasis treatment, and they work just as well in psoriatic arthritis and ankylosing spondylitis. The results of clinical trials in other inflammatory diseases, however, have been more disappointing.

"Some rheumatologists might think IL-17 is not important or that it's only important in mouse studies," says Dr. McGeachy. "They assume it doesn't work for these diseases. But there is pretty good evidence for IL-17 in rheumatoid arthritis and other rheumatology-related diseases that hasn't been tested yet. When you examine the data, it appears to work in a subset of patients."

Dr. McGeachy credits a collaborative environment at UPMC and the University of Pittsburgh for bringing this and other studies in her lab to fruition. While her laboratory focuses primarily on the interactions between Th17 cells and nonimmune cells, Dr. McGeachy and her team explored IL-17 signaling and metabolic changes in collaboration with Sarah Gaffen, PhD, the Gerald P. Rodnan Endowed Professor of Medicine in the Division of Rheumatology and Clinical Immunology, and Greg M. Delgoffe, PhD, assistant professor in the Department of Immunology at the University of Pittsburgh. Dr. McGeachy and Dr. Gaffen also have published several studies on IL-17 signaling in autoimmunity and infections.

Incorporating a Translational Focus

Through interactions with clinicians at UPMC, and with access to patient samples, Dr. McGeachy's laboratory has incorporated a translational focus into its work. This translational aspect is bidirectional, says Dr. McGeachy. Collaboration enables her laboratory not only to translate mouse findings into human studies but also to use findings from human studies to validate and optimize mouse models. The laboratory is now exploring FRCs from human tonsils and expanding its focus into other diseases.

"The next arm of this work is considering the extent to which the change in metabolism and the ramping up of the energy capability of the stromal cells are happening in the connective tissues where disease is occurring," says Dr. McGeachy. "Is IL-17 driving the pathways that promote increased metabolism that in turn allow inflammation and pathologic proliferation? Because in a lot of rheumatic diseases, what's happening is overextension of populations of cells that are not helpful and that then cause more inflammation and contribute to the disease. This is one of the areas where I think this work will lead that will have more direct translational relevance."

Dr. McGeachy and her study collaborators were supported by grants from the National Institutes of Health, the Richard King Mellon Institute for Pediatric Research, and the American Association for Cancer Research, as well as by resources from the University of Pittsburgh Center for Research Computing.

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Division News and Awards

Amr H. Sawalha, MD, was awarded the 2019 Henry Kunkel Young Investigator Award from the American College of Rheumatology. The Henry Kunkel Young Investigator Award is awarded to a young physician scientist, age 45 or younger by October 1 of the year in which they are nominated, who has made outstanding and promising independent contributions to basic or clinical research in the field of rheumatology.

Dr. Sawalha joined UPMC in April as director of the Division of Pediatric Rheumatology at UPMC Children's Hospital of Pittsburgh. He previously served as professor of medicine and the Marvin and Betty Danto Research Professor of Connective Tissue Research at the University of Michigan. At UPMC Children's, Dr. Sawalha is working to establish and lead a new Autoimmune Genomics Research Center. Additionally, Dr. Sawalha serves as the director of the comprehensive Lupus Center of Excellence that spans the clinical and research enterprises of UPMC and the University of Pittsburgh. His research focuses on elucidating genetic and epigenetic contributions to the pathogenesis of systemic autoimmune and inflammatory diseases. His research applies state-of-the-art genomic, epigenomic, and bioinformatics methodologies, and subsequent functional studies using in vitro and in vivo systems to identify and characterize genetic loci and pathways involved in the pathogenesis of immune-mediated diseases. Using clinical phenotyping and extensive national and international collaborations, Dr. Sawalha seeks to discover genomic and epigenomic markers of disease progression, specific organ involvement, and responses to therapies.

Chester V. Oddis, MD, professor of Medicine in the Division and director of the Myositis Center was recognized as a Master of the American College of Rheumatology at the 2019 annual American College of Rheumatology (ACR) conference. The Master of the American College of Rheumatology is one of the highest honors the College bestows. The designation of Master is conferred on ACR members, age 65 or older by October 1 of the year in which they are nominated, who have made outstanding contributions to the ACR and the field of rheumatology through scholarly achievement and/or service to their patients, students, and profession.

Mehret Birru Talabi, MD, PhD, is a 2020 recipient of a Robert Wood Johnson Foundation Harold Amos Faculty Development Award for her work advancing family planning care for individuals with rheumatic diseases. In this competitive four-year career development award, Dr. Birru Talabi will create and test a clinical intervention to help rheumatologists engage patients in family planning conversations.

According to Dr. Birru Talabi, "Our work and that of others suggests that family planning conversations rarely occur in the context of their rheumatologic care, although many rheumatic diseases and antirheumatic drugs have the potential to affect the reproductive health of patients. We are excited to develop an intervention to help patients receive the family planning care they have strongly indicated that they need."

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Presented by Larry W. Moreland, MD

Dr. Moreland presents on rheumatoid and psoriatic arthritis, and focuses on the names of biologics and targets in the immune system. Dr. Moreland reviews the guidelines for monitoring and prevention of side effects associated with therapies for treating rheumatoid and psoriatic arthritis.

Spondyloarthropathies

Presented by Thaddeus Osial, MD

Dr. Osial presents on spondyloarthropathies and reviews the history, spectrum of diseases, distinguishing characteristics, pathogenesis, and treatment. This course teaches the varied manifestations as they relate to peripheral arthritis and inflammatory back disease, which extra-articular findings are associated with the spondyloarthropathies, and symptomatology.

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Therapies for Advanced Cutaneous T Cell Lymphoma *(Continued from Page 2)*

"We saw that within different patients the reactive lymphocytes express different types of checkpoint inhibitory receptors. Not all of the patients expressed these receptors, and some patients may express more than one. So, we have demonstrated an important tumor cell heterogeneity that may affect how patients respond to cancer immunotherapy, requiring personalized approaches to be developed," says Dr. Fuschiotti.

Another current direction of work in Dr. Fuschiotti's lab is focused on potential CTCL prevention strategies. In 2015, in a paper published in *Blood,* Dr. Fuschiotti and her colleagues uncovered how IL-13 modulates tumor proliferation or growth.

Following up on that work, Dr. Fuschiotti is now working on interfering with IL-13's signaling pathways and collaborating with a pharmaceutical company, Regeneron, to determine whether a novel antibody targeting the IL-13 receptor can block cell proliferation that leads to the development of CTCL.

In a related project, supported by a CLARIONS Research Grant from the Cutaneous Lymphoma Foundation, the team is following up on an observation that malignant T lymphocytes in CTCL express the IL-13 alpha 1 and alpha 2 receptor subunits and is examining whether targeting a molecule located downstream from IL-13 activation can block lymphocyte proliferation.

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The Division of Rheumatology and Clinical Immunology has had a tradition of excellence in patient care, education, and research for more than 50 years. Our clinical activities emphasize care of both common and rare rheumatic diseases. We have outpatient clinics devoted to all types of autoimmune diseases and musculoskeletal disorders. Our faculty have a clinical and research interest in rheumatoid arthritis, systemic lupus erythematosus, myositis, vasculitis, and scleroderma.

We are committed to a mission of providing the highest quality care for patients with arthritis and autoimmune diseases, and mentoring and training medical students, residents, fellows, and young faculty. Our research mission is to better understand arthritis, autoimmune, and other connective tissue diseases in order to improve diagnosis and therapies, with the ultimate goal of finding a cure or preventing these disorders. Faculty members are involved in both clinical and laboratory research. Our research programs are centered in the clinical areas noted above and include the disciplines of clinical epidemiology, health services, and laboratory research. Our research includes collaborative efforts with other programs in the University of Pittsburgh School of Medicine and the Graduate School of Public Health.

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USNW513100 AS/MP 11/19