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Basic Science Session 2. Recent Advances in Our Understanding of Psoriatic Arthritis Pathogenesis

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ABSTRACT. The second basic science session at the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) annual meeting focused on 2 recent publications that have increased our understanding of the pathogenesis of psoriatic arthritis (PsA). Data from the first publication, presented by Prof. Erik Lubberts, showed that interleukin (IL)-17A is produced by CD4+ and not CD8+ T cells in PsA synovial fluid following T cell receptor activation. These findings contrast with previously published data, which had suggested that CD8+ T cells are a prominent source of IL-17A. In further experiments, they showed that when CD8+ T cells were stimulated with paramethoxyamphetamine/ionomycin, relatively high levels of IL-17A were detected. Prof. Jose Scher presented work on the role of the microbiome in PsA and more specifically, on pharmacomicrobiomics. He demonstrated the baseline collection of genomes and genes from the microbiota community (the metagenome) can be used as predictor for future treatment response in early rheumatoid arthritis and also likely in PsA.

Key Indexing Terms: GRAPPA, psoriasis, psoriatic arthritis

Introduction

Significant advances have been made in recent years to our understanding of the pathogenesis of psoriatic arthritis (PsA). Studies have suggested an important role for CD8+ T cells, which produce interleukin (IL)-17A, with a population of such cells identified in PsA synovial fluid.[1] This observation is consistent with other known PsA findings including the association of PsA with HLA class 1 antigens, which present antigen to CD8+ T cells. The work of Prof. Erik Lubberts and his colleagues, presented below, casts some doubt on the importance of CD8+ T cells, as CD4+ and not CD8+ T cells produced IL-17A following T cell receptor (TCR) activation. However, the relative roles of CD4+ and CD8+ T cells in PsA pathogenesis require further elucidation.

As part of the supplement series GRAPPA 2021, this report was reviewed internally and approved by the Guest Editors for integrity, accuracy, and consistency with scientific and ethical standards.

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Potentially connecting the gut with stimulating the expansion of IL-17A–producing T cells are changes in the gut microbiome. Prof. Jose Scher recently published several important papers on this topic, which he included in his review of the current understanding of changes in gut microbiome, both in disease pathogenesis and also in determining treatment responses. This is an exciting area of research that deserves much greater attention.

Basic research presentations

Basic research presentation by Prof. Lubberts on the role of CD4+ cells. IL-17A was found to be produced by CD4+ but not CD8+ T cells in synovial fluid following TCR activation and to regulate different inflammatory mediators compared to tumor necrosis factor (TNF) in a model of PsA synovitis. This research was discussed by Prof. Lubberts on behalf of his colleagues at Erasmus University Medical Center (Erasmus MC): X. Xu, N. Davelaar, A.M.C. Otten-Mus, P.S. Asmawidjaja, J.M.W. Hazes, D.L.P. Baeten, M. Vis, R. Bisoendial and E.P. Prens.

An increased percentage of IL-17A–producing T cells, including CD4+ and CD8+ T cells, have been found in patients with PsA and correlates with PsA disease activity.[1,2] Tissue-resident memory CD8+ T cells derived from the skin are enhanced in the circulation of patients with PsA compared with patients with psoriasis (PsO) alone.[3] However, whether the synovial fluid–derived CD8+ T cells also excrete IL-17A is not clear. In their work, Prof. Lubberts and his team presented and confirmed enriched percentage of IL-17A+CD8+ T cells in PsA synovial fluid compared to peripheral blood using flow cytometry techniques.[1] Using this technique, the cells are stimulated for 4–6 hours with paramethoxyamphetamine (PMA)/ionomycin. Interestingly, when FACS-sorted synovial fluid–derived CD4+ or CD8+ T cells were cultured and stimulated with anti-CD3/anti-CD28 for 72 hours, CD4+ (but not CD8+)

T cells excreted IL-17A. Similar results were found when anti-CD3/anti-CD28–stimulated CD4+ or CD8+ T cells were cocultured with autologous PsA monocytes or allogenic PsA synovial fibroblasts. However, when the fluorescence-activated cell sorting (FACS)-sorted synovial fluid–derived CD8+ T cells were stimulated with PMA/ionomycin for 72 hours, relatively high levels of IL-17A were found in the supernatant. Even after 4 hours of stimulation with PMA/ionomycin, detectable IL-17A secretion was noted by these PsA synovial fluid–derived CD8+ T cells.[4] These data suggest IL-17A is secreted by TCR-stimulated PsA synovial fluid–derived CD4+ (but not CD8+) T cells and further indicate that the role and mechanism of CD8+ T cells in producing IL-17A locally in PsA joints needs further examination.

In addition to IL-17A, TNF-α is also a key cytokine in PsA, and neutralizing agents against these cytokines have been approved as therapy. However, further understanding of the potential overlapping and distinct effects of anti–IL-17A and anti-TNF treatment is still needed and may be relevant to achieve a more sustainable therapeutic effect for individuals with PsA. For this reason, the research team from the Netherlands developed a PsA synovitis model system ex vivo where PsA synovial fibroblasts were cocultured with sorted memory CD4+ T cells and anti–IL-17 and/or anti-TNF antibodies were added. Neutralizing IL-17A strongly inhibited IL-6 and IL-1β, whereas anti-TNF treatment was more potent in reducing matrix metalloprotease (MMP)-3 and MMP-13.[4]

In conclusion, PsA synovial fluid specimen–derived CD8+ T cells, in contrast to CD4+ T cells, did not secrete IL-17A when stimulated through the T cell receptor. In addition, there is overlap but also clear distinction at the level of inflammatory cytokines and MMPs when IL-17A is neutralized compared to TNF inhibition.[4]

Basic research presentation by Prof. Scher on the role of the gut microbiome and PsA. Prof. Scher discussed how the gut microbiome may act as a potential triggering factor in PsA and how changes in microbiome may determine how patients respond to PsA treatments. This work was done by Prof. Scher on behalf and his teams at New York University (NYU) Langone Health, USA (Julia Manasson); the Foundation for the Promotion of Health and Biomedical Research of Valencia Region (FISABIO), Spain (Carles Ubeda, Alejandro Artacho); and the University of California San Francisco, USA (Renuka Nayak, Peter Turnbaugh).

The last decade has witnessed significant progress in the understanding of the how the human microbiome can affect the pathogenesis of inflammatory conditions, including psoriatic diseases (PsD), rheumatoid arthritis (RA), and other immune-mediated and oncologic conditions.[5] Most recently, the field of pharmacomicrobiomics (which studies the interface between the gut microbiome and efficacy and toxicity of drugs) has provided novel potential tools for precision medicine application in the clinic.[6,7]

PsA represents a unique disease model by which to study triggering factors for inflammatory arthritis in immune-mediated disease, as it has now been established that cutaneous PsO precedes PsA by several years in most patients and a quarter of people with skin inflammation will develop a form of synovio-entheseal disease.[8] This creates a unique window of opportunity to study environmental exposures (obesity, mental or biomechanical stress, and/or infections) and the downstream immune activation features in at-risk individuals with the right genetic substrate.[9]

One such environmental factor is the microbiome, the collection of microorganisms and their genes that shares our body cavities and surfaces. The microbiome are also known to exert significant contributions to the human host, most notably contributions to xenobiotic chemical modifications and the shaping of local and systemic immune responses.[10]

The notion that the microbiome should be considered among the most prominent potential determinants of disease progression derives from murine models and anecdotal human evidence. Classic examples include streptococcal infections causing guttate PsO and some evidence suggesting amelioration of lesions posttonsillectomy.[11]

For spondyloarthritis (SpA)-like disease, multiple animal models have shown that the presence of specific microbiota can trigger arthritis, sacroiliitis, inflammatory bowel disease (IBD) and psoriasiform lesions, whereas mice raised under germ-free conditions do not develop the phenotype. Two valuable models include the SKG model[12] and the HLA-B27 transgenic rat.[13]

In humans, a number of groups have shown that both gut and skin dysbiosis are involved in nearly every autoimmune and rheumatic process. In particular, patients with PsO and PsA had decreased gut microbiota diversity, which was characterized by a significant decrease in Clostridia, *Ruminoccoci*, and other beneficial commensals, as well as protective metabolites, including medium-chain fatty acids.[14] The challenge for this and similar observations, however, has been to better understand the directionality of this microbial perturbation and whether this constant finding has any mechanistic implications.

There are many different ways to exploit the gut microbiome to potentially modulate infection and autoimmunity. The most studied of them all is fecal microbial transplantation (FMT), which is based on the administration of a donor stool solution into the intestinal tract of a recipient. This can be achieved through many different routes and procedures, including upper/lower endoscopy, enema, and most recently, frozen capsules. FMT is approved by the U.S. Food and Drug Administration for the treatment of refractory *Clostridia difficile colitis*[15] and has proven quite effective in IBD.[16]

Based on the accumulated animal and human data in PsD, the first results of the FLORA study have now been published.[17] This was a double-blind, randomized, placebo-controlled trial comparing 1 FMT procedure by upper endoscopy vs a sham solution (placebo). Despite lower-than-expected enrollment, the use of nonconventional outcomes, and lack of microbiome analysis, this study provides scientific value to the field. First, the procedure was accepted and well tolerated by patients overall. Although we are currently not at liberty to discuss this, we will certainly learn a significant amount from this study. Second, and perhaps more importantly, the fact that patients in the FMT

group fared significantly worse (60% on FMT failed treatment compared to 19% of those given the sham control) adds to the notion that there is a biological connection between the gut microbiome and the downstream inflammatory response in PsA that needs further research. Multiple aspects of this line of work need to be elucidated, including the rigorous study of microbial colonization after FMT, a better understanding of who constitutes an adequate donor, and whether other microbiome-based therapeutics can be tailored to therapeutics in a more targeted fashion.

As discussed, another nascent and potentially clinically relevant field is pharmacomicrobiomics, a discipline that investigates the effects of variations within the human microbiome on drug efficacy, toxicity, and tolerance. Pharmacomicrobiomics has already proven highly significant in predicting response to multiple oncologic treatments (including, most notably, checkpoint inhibitors)[18,19] and FMT utilizing responder-derived microbiome has proven to enhance therapeutic outcomes.

In patients with SpA, Prof. Scher and others have demonstrated that the gut microbiome may predict response to treatments. IL-17 blockade leads to an increase in intestinal *Candida* concentrations in one-third of patients, suggesting that biologic disease-modifying antirheumatic drugs (DMARDs) can perturb both the microbiome as well as the mycobiome. This potentially explains why a small proportion of patients develop intestinal inflammation after being exposed to these medications.

This concept is not foreign to rheumatology, as the pharmacokinetics of some DMARDs (ie, sulfasalazine) were established over 50 years ago and have been shown to be dependent on the chemical modification exerted by gut microbes.[20,21] This is also the case with methotrexate (MTX), which was shown to be effectively metabolized by intestinal bacteria in mice in studies published in the 1970s.[22]

Most recently, MTX was shown to be metabolized by the human gut bacteria and the baseline metagenome (ie, the collection of genomes and genes from the microbiota community) may be used as predictor for future treatment responses in new-onset RA, surpassing the performance of previously proposed clinical/pharmacogenetic models.[23,24]

Taken together, emerging data suggest that the gut microbiome merits further investigation as a potential triggering factor in PsD, and that it can also potentially be used for precision medicine treatment approaches in inflammatory arthritis and related conditions.

Conclusions

Taken together, both the work from Erasmus MC, presented by Prof. Lubberts, and the work from NYU, presented by Prof. Scher, provide us with novel insights into the role of T cells and of perturbations in the microbiome in the pathogenesis of PsA. Additional work needs to focus on reconciling the findings on T cells with other published literature. A number of explanations are possible, including the heterogeneity of PsA or differences in methodology. It is also possible that classical TCR activation pathway may not be as applicable in CD8+ T cells as alternate, more relevant activation pathways. Either way, more work is required to further elucidate the role of the T cell in PsA pathogenesis.

The observations presented by Prof. Scher provide us with early insights into how changes in the gut microbiome may trigger PsA in patients who are genetically susceptible. Linking these observations to the downstream pathways, which ultimately result in inflamed skin or joint tissue, requires a focused research effort over the years ahead. Finally, that the microbiome composition might also determine treatment response is an intriguing observation that is also worthy of further research. Such research may be possible in the context of new, significant funding being provided in Europe by the Innovative Medicines Initiative to the HIPPOCRATES consortium (www.hippocrates-imi.eu) and by the Accelerated Medicines Partnership (AMP)-2 program in the USA, both targeting areas of unmet need in PsO and PsA.

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