Basic and Translational Science: A Report from the GRAPPA 2016 Annual Meeting

James G. Krueger, Bruce Kirkham, and Christopher T. Ritchlin

ABSTRACT. Rapid advances in effective treatments for psoriasis and psoriatic arthritis (PsA) have emerged from improved understanding of cell subsets and critical mediators that promote tissue inflammation and destruction. More specifically, increased knowledge of innate immunity and the important involvement of cytokines in the interleukin (IL)-23–IL-17 axis as key mediators of psoriatic plaque and joint inflammation in both psoriasis and PsA have led to new theories of immunopathogenesis. Herein we summarize recent discussions on IL-17–related pathways and their relationship to psoriasis and PsA. (J Rheumatol 2017;44:679–83; doi:10.3899/jrheum.170143)

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At the 2016 annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), Drs. James Krueger (New York, New York, USA), Bruce Kirkham (London, UK), and Christopher Ritchlin (Rochester, New York, USA) updated the membership on the effects of interleukin 17 (IL-17)-related pathways on the skin and joints in patients with psoriasis and psoriatic arthritis (PsA). Summaries of their presentations are below.

IL-17–related pathways and psoriasis (Dr. James Krueger)

The common form of psoriasis is characterized by red, raised, scaly skin lesions (psoriasis plaques), usually symmetrical, that occur on virtually any area of the skin. Mild disease is defined somewhat arbitrarily as involvement of < 10% of the skin surface area, while moderate to severe disease involves > 10%. Tremendous progress has been made in defining the cellular and molecular basis of cutaneous disease pathogenesis across the spectrum of mild to severe disease and many new biologic therapies have been developed based on evolving science. This translational success now provides the ability to treat skin disease extremely well (as measured by a Psoriasis Area and Severity 75 response) in ~90% of moderate-to-severe patients with single agent therapeutics that are targeted to 2 central cytokines in disease pathogenesis, IL-23 and IL-17[1].

Psoriasis is a disease of T cell autoreactivity to cutaneous antigens that include cathelicidin and the melanocyte-related protein ADAMTSL5. Psoriasis is also a "polar" immune disease with specific activation of Type 17 T cells of both CD4+ (Th17) and CD8+ (Tc17) subsets that produce IL-17A and IL-17F, the defining cytokines of this T cell subset. However, Type 17 T cells also produce additional cytokines: IL-26 and IL-29, cytokines with interferon (IFN)-like actions. Psoriasis lesions also contain other activated T cell subsets including Th22 (producing IL-22) and Th1 (producing IFN-γ), but these additional T cell subsets have a less certain pathogenic involvement than Type 17 T cells in psoriasis. It is likely that all T cells in skin lesions have activation controlled by cutaneous dendritic cells (DC), which include highly abundant myeloid (CD11c+) DC in both the dermis and epidermis of the skin. These myeloid DC are the main producers of the "p40" cytokines, IL-12 and IL-23, which are heterodimeric cytokines that contain the p40-subunit. IL-23, which also contains a p19-subunit, is a key differentiation and survival factor for Type 17 T cells. Thus, both IL-23–producing DC and Type IL-17 T cells are key elements of the pathogenic immune axis in this disease[1].

Psoriasis plaques are produced by complex changes in the growth and differentiation of resident skin cells, but the features of raised and scaly lesions result largely from epidermal hyperplasia and altered differentiation, while redness results from vascular proliferation and dilation. These cellular changes are caused, in turn, by the response of skin cells to immune-derived cytokines, with an especially critical role for IL-17 and its ability to act synergistically with other cytokines such as tumor necrosis factor (TNF) and IL-22. The

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epidermis is composed mainly of keratinocytes, cells that undergo proliferation and differentiate to form a stratified epithelium. Keratinocytes have highly abundant IL-17 receptors and respond to this cytokine by producing many products that have key roles in controlling innate immunity and inflammation, e.g., numerous antimicrobial proteins (cathelicidin, β defensins, S100A7, A8, A9, and A12), chemokines that attract neutrophils (CXCL1, 2, 3, 8), CCL20 that attracts myeloid DC and Type 17 T cells, and cytokines that stimulate keratinocyte hyperplasia (IL-19 and IL-36). The resulting reaction, which is reinforced by synergistic responders to TNF and IL-22, creates "feed forward" inflammation and production of autoantigens that lead to chronic T cell activation in skin lesions and high-level production of IL-23 from cutaneous DC[1]. The vascular reaction is produced by increased production of several angiogenic cytokines from epidermal keratinocytes. Cytokines and other inflammatory molecules that are produced at high levels in psoriasis plaques may "spill over" into the systemic circulation, so increases in circulating IL-17, TNF, and other products are commonly measured in the blood of patients with moderate to severe disease; it has been proposed that these factors may underlie initiation or progression of systemic inflammation and comorbid conditions such as vascular inflammation, dyslipidemia, cardiovascular disease, and obesity/metabolic deregulation[2].

The treatment of psoriasis vulgaris now depends on antagonizing key immune cytokines that create cutaneous inflammation. TNF antagonists are commonly used to treat both cutaneous disease and PsA. Regarding skin inflammation, the primary therapeutic action of the TNF blockade is to reduce IL-23 production and the resulting Type 17 T cell response. Ustekinumab is a monoclonal antibody to the common "p40" subunit of IL-12 and IL-23, so it reduces activation of Type 17 T cells in psoriasis lesions. Two direct IL-17 antagonists, secukinumab and ixekizumab, are recently approved drugs to treat psoriasis, and an antibody to the IL-17 receptor (brodalumab) is currently pending approval by the US Food and Drug Administration. Antibodies to the p19-subunit of IL-23 (tildrakizumab, guselkumab, and risankizumab) have shown high-level activity in phase II and phase III trials, and these agents are likely to emerge as new treatment options for patients with moderate to severe cutaneous disease and perhaps also for PsA[1].

Mild psoriasis involves a lower extent of skin involvement, but at the level of T cell activation, cytokine production, and resulting alterations of skin structure and function, these lesions are very similar overall to more extensive moderate to severe disease. Given that even mild disease is a risk for comorbid disease development and that skin is highly dysfunctional in affected areas, some patients with mild disease might be more appropriately treated with targeted cytokine antagonists that have proven to be safe and effective in patients with more extensive skin lesions[3].

IL-17–related pathways and PsA (Dr. Bruce Kirkham)

New concepts are now proposed for the pathogenesis of PsA, previously considered a T lymphocyte–driven autoimmune condition[4]. In addition to Class I genes such as *HLA-B38*, *-B39*, and *-B27*, genome-wide association (GWA) studies in PsA have identified genes involved in IL-17 signaling and CD8+ T cell development as risk factors[5]. The involvement of entheseal mechanical stress and inflammation is also being unraveled[6]. These concepts are supported by new information of the cells producing IL-17 and related IL-23 cytokines[7].

In the IL-17 cytokine family, IL-17A to IL-17F are structurally related members with differing properties, interacting with 6 receptors, IL-17RA to IL-17RE homo- or heterodimers[8]. IL-17A, followed by IL-17F, are the primary products at sites of immune-mediated disease, with IL-17A being the most studied. IL-17A shows significant synergy with TNF-α in most proinflammatory and joint-damaging activities, which may be a critical function in immunopathogenesis.

Targeted anticytokine therapies provide critical information about the importance of cytokines in disease. To date, TNF-α has been the key therapeutic cytokine in PsA, with others, such as IL-6 receptor blockers, having little effect. However, IL-17A inhibition has shown similar efficacy to TNF inhibition in PsA[9], emphasizing the importance of this pathway.

Cells of the innate immune system respond immediately to signals from pathogens or cellular damage, with cytokine and cell-to-cell responses providing early defense and triggering the acquired immune system[10]. Lymphoid innate cells including natural killer (NK) cells, γδ T cells, and innate lymphoid cells (ILC; which lack T and B cell markers) can produce cytokines, including IL-17A, and kill cellular targets[11]. The ILC3 subset can produce IL-17A and IL-22[12]. Gamma delta (γδ) CD3+ T cells using a T cell receptor consisting of γ and δ chains are enriched in epithelial and mucosal tissues[11]. An animal model in spondyloarthritis with high levels of exogenous IL-23 showed enthesitis was an early lesion[7]. The IL-23 responsive entheseal cells were CD3+CD4–CD8–IL-23R+T lymphoid cells, producing IL-17A and IL-22, suggesting the involvement of innate immune cells in early enthesitis[7]. In psoriasis, a substantial proportion of IL-17A– and IL-22–producing cells in skin and blood are ILC[13]. In PsA synovial fluid (SF), ILC were 4-fold more abundant than in PsA peripheral blood (PB), and enriched for CCR6+ ILC compared with PsA PB and rheumatoid arthritis (RA) SF[14].

Immunohistochemical studies of IL-17A in psoriasis skin showed that neutrophils and mast cells were frequently identified, with similar findings in PsA[15], and in the spinal joints in ankylosing spondylitis[16]. However, when skin from psoriasis plaques was digested to collect mononuclear cells, followed by short *in vitro* stimulation and flow cytometry, CD4+ and CD8+IL-17+ lymphocytes were detected[17].

CD8+IL-17+ cells, previously detected in bacterial infections, are called "Tc17" cells, differentiating them from Th17 cells[18]. CD8+ T cells are enriched in PsA SF compared with CD4+ T cells. Tc17 and Th17 cells were increased in PsA SF compared with PB[19]. Only Tc17 SF cells correlated with multiple disease activity measures and erosive disease, suggesting a pathogenic involvement. Interestingly, SF in RA only had elevated Th17 cells, clearly different from PsA and psoriasis.

Increased knowledge of innate immunity and the important role of IL-17–IL-23 biology in both psoriasis and PsA have led to new theories of immunopathogenesis. Adaptive (CD8 and CD4) and innate immune cells producing IL-17 (Type 17 cells) could directly translate environmental signals into a chronic adaptive immune response.

Pathogenesis (Dr. Christopher T. Ritchlin)

As outlined above, psoriasis and PsA share common disease pathogenesis pathways. Most importantly, data from animal models and analysis of human blood, skin, and synovium implicate cytokines in the IL-23–IL-17 axis and TNF as key mediators of psoriatic plaque and joint inflammation[20]. An array of innate immune cells along with the acquired T cell subsets CD4+ (Th17) and CD8+ (Tc17) release IL-17, including mucosal-associated invariant T cells, ILC3, γδ T lymphocytes, invariant T cells, and KIR3DL2þ killer cell immunoglobulin-like receptor 3DL2þ T cells. Perhaps the most striking divergence between psoriasis and PsA is the lower therapeutic response in the joints compared with the skin in patients treated with agents that target molecules in the IL-23–IL-17 axis[21]. Indeed, single-agent therapeutics are remarkably effective for psoriasis; unfortunately, that is not the case for PsA. Thus, a major challenge is the identification of barriers that limit treatment response in PsA.

Potential factors accountable for the lower response of arthritis compared with psoriasis to targeted biologic agents are listed in Table 1. The peripheral and axial skeleton consists of synovium, cartilage, bone, and fibrocartilage. The osteoimmunologic interactions in these tissues are complex, and both homeostasis and pathologic responses are dependent on pathways specific to the joint. A transcriptome analysis of skin and synovial tissue from patients with psoriasis and PsA showed a dominant Th17 signature in the skin and not the joints, while TNF, angiogenic factors, and IL-6 pathways were more dominant in the joint[22]. These findings support the presence of discrete disease pathways in the plaque and joint that may account for the lower response in arthritis. It is also entirely plausible that unidentified pathways promote immune-mediated inflammation in connective tissues. Involvement of multiple musculoskeletal domains (dactylitis, enthesitis, axial disease, peripheral arthritis) in a single patient, a common clinical scenario, may involve a number of distinct disease mechanisms unresponsive to a single agent.

Table 1. Potential factors accountable for the lower response to targeted biologic agents of arthritis compared with psoriasis.

Potential Factors
Complex cell and tissue interactions
Unidentified pathogenetic pathways
Involvement of multiple domains
Loss of suppression
Drug bioavailability
Comorbidities
Altered microbiome

Much emphasis has centered on targeting effector inflammatory pathways, but a loss of suppression is another consideration. It remains unknown why only 12%–30% of patients with psoriasis develop PsA. Efforts to identify genetic and environmental factors capable of promoting this transition have not been revealing. Five PsA-specific genetic variants have been identified in GWA studies and multiple environmental factors (smoking, trauma, rubella vaccination) have been linked to arthritis, but these genetic and environmental factors explain only a small amount of the risk[23]. Loss of suppression may be operative in this transition and the finding that knockdown of A20, an inhibitor of the nuclear factor-κB signaling pathways, is associated with enthesitis development in an animal model and that transcriptome analysis of PsA PB showed inhibition of suppressive immune pathways not observed in RA provide support for this model[24,25].

Additional factors that may contribute to drug resistance in PsA are comorbidities, altered drug bioavailability, and dysbiosis related to microbial communities in the gut and skin. Patients with PsA have a higher prevalence of metabolic syndrome than patients with psoriasis; they are often obese and fatty liver disease is prevalent[26]. Indeed, obesity is associated with a lower treatment response to anti-TNF agents that can be restored with weight loss[27]. High levels of anxiety and depression observed in PsA may limit the magnitude of treatment response; the presence of fibromyalgia (FM) may also influence study outcomes. It is also conceivable that drug bioavailablity is significantly lower in patients with multiple sites of musculoskeletal inflammation compared with patients with only skin disease. Last, several studies have implicated microbiomal interactions in disease pathogenesis, and the presence of a "gut-joint axis" has been proposed[28]. If this proves to be the case, therapeutic interventions will also need to be directed toward dysbiosis in the skin and/or gut.

Given all these potential variables that contribute to nonresponse in PsA, what is the best path moving forward? Efforts can be divided between translational studies to identify new targets and alteration of clinical trial designs to test new treatment strategies. Detailed analysis of variants identified by GWA studies with RNA profiling and epigenetic studies of immune and resident cell populations revealed that

most disease-associated variants are in the noncoding dark matter located in the promotor and enhancer regions of the genome. Focused analyses with these methods of cells from patients with psoriasis and PsA will undoubtedly yield new targets[29]. These studies should be combined with analysis of blood, synovium, and skin samples with RNA sequence analysis, serum cytokine immunoassays, and flow cytometry studies to reveal new pathologic cell subsets and molecules. Last, next generation and new methods of metagenomic sequencing of the skin and gut microbiome may also lead to new discoveries linking dysbiosis with skin and joint disease.

Additional clinical studies are required to better understand the relationship between obesity, metabolic syndrome, and impaired treatment response. Other approaches to consider are studies with combinations of biologic agents given at lower doses together or sequentially, a strategy used successfully in cancer. Dual variable domain antibodies such as ABT-22, a platform that combines anti-TNF and IL-17 activity, showed numerical but not statistical superiority in a recent PsA trial, but additional studies are necessary[30]. To address bioavailability challenges, altered dosing regimens should be tested. Treatment intervals with a specific biologic may be effective for the skin, but not the joint, for example. Identification of how specific comorbidities affect treatment response and developing strategies to address them with weight loss programs (obesity), counseling (anxiety/depression) or cognitive behavioral therapy, and exercise (FM) may greatly improve outcomes.

Rapid advances in effective treatments for psoriasis and PsA emerged from improved understanding of cell subsets and critical mediators that promote tissue inflammation and destruction. These therapies are proving to be transformational in the treatment of psoriasis; however, identification of single or combined drug regimens that provide therapeutic responses in musculoskeletal tissues awaits further study. Focused analysis of cells and tissues from well-phenotyped patients coupled with incorporation of novel clinical study designs will likely yield new treatment targets and strategies that will improve outcomes for patients with psoriatic joint inflammation.

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