Interleukin-17 alters the biology of many cell types involved in the genesis of psoriasis, systemic inflammation and associated comorbidities

James G. Krueger | Patrick M. Brunner

Abstract
Psoriasis is a chronic, immune-mediated, systemic inflammatory disease that is defined by a characteristic skin reaction produced when elevated levels of inflammatory cytokines such as interleukin (IL)-17 alter the growth and differentiation of skin cells. The pathogenesis of comorbid conditions associated with psoriasis, including psoriatic arthritis, cardiovascular disease, obesity, metabolic syndrome, liver disorders, renal disease and depression, is also largely affected by inflammation. In this review, we examine the effect of IL-17 on the inflammatory pathways in a variety of different cell types, including keratinocytes, as well as epithelial cells of the colon, kidney, gut and liver. Additionally, we investigate the role of IL-17 in mediating the psoriasis-associated comorbidities detailed above.

KEYWORDS
cardiovascular disease, keratinocyte, metabolic syndrome, obesity, review

1 | INTRODUCTION

Psoriasis is a chronic, immune-mediated, systemic inflammatory disease affecting approximately 3% of adults (~7 million people) in the United States.[1,2] In genetically susceptible individuals, psoriasis onset and progression are triggered by a combination of epigenetic and environmental factors.[3] Psoriasis is defined by a characteristic skin reaction in which inflammatory cytokines, produced by activated leukocytes, alter growth and differentiation of resident skin cells; this reaction is especially evident in keratinocytes and epidermal alterations.[4] This review focuses on potential pathogenic links between interleukin (IL)-17-centred inflammation driving cutaneous psoriasis lesions and more distant alterations in many different cell types that collectively produce systemic inflammation and psoriasis-associated comorbidities such as psoriatic arthritis, cardiovascular disease, obesity, metabolic dysregulation, liver disorders, renal disease, hypertension and depression.

Activation of mature and inflammatory dendritic cells (DC) is a major driver of psoriasis pathogenesis in skin. These DCs, along with T cells and keratinocytes, secrete scores of different proinflammatory molecules, including cytokines, chemokines and antimicrobial peptides (AMPs).[4,5] The IL-23/T helper (Th)17 axis is particularly important in the immunopathogenesis of psoriasis. Through this pathway, DCs produce high levels of IL-23, which stimulates differentiation and activation of Th17 cells to produce high levels of IL-17A, IL-17F and other cytokines (e.g., IL-26 and IL-29) that have direct effects on epidermal keratinocytes and other resident skin cells. Immune cytokines, including IL-17, IL-26, IL-29 and tumor necrosis factor (TNF)-α, have strong effects as transcriptional activators of many keratinocyte gene products. These effects, along with autoantigen stimulation of T-cell responses, create feed-forward inflammatory cycles perpetuating T-cell activation and the psoriasis disease phenotype.[4–6]

IL-17, along with TNF-α and type I interferons (IFNs), plays an important role in psoriasis pathogenesis,[7] and monoclonal antibodies targeting IL-17A can dramatically reduce psoriasis.[8–10] While IL-17 is the prototypic Th17 cytokine, it is also produced by cytotoxic T cells, γδ T cells and innate lymphoid cells,[11] which might all contribute to IL-17 burden. In moderate-to-severe psoriasis, IL-17 and other...
cytokines are released into systemic circulation.\textsuperscript{[12,13]} Consequently, plasma levels of IL-17 are elevated in psoriasis, especially severe psoriasis.\textsuperscript{[14–16]} Once in circulation, these cytokines can trigger inflammatory responses in perfused tissues that varies based on cell type and differentiation status.\textsuperscript{[17]} It is now recognized that inflammation is a key contributor to the pathogenesis of many distinct comorbidities associated with psoriasis.\textsuperscript{[17]} While cytokines besides IL-17 and genetic factors are also involved in the development of psoriasis comorbidities, we hypothesize that IL-17, alone and in additive/synergistic combinations with cytokines such as TNF-\(\alpha\) and IL-22, is a key factor for altering responses of many different cell types that contribute to development of comorbidities. Despite the complexity of interactions of different pathways that we are currently only beginning to understand, we focus here on evaluating evidence showing how IL-17-mediated inflammation can potentially impact pathways that are known risk factors for psoriasis comorbidities.

2 | CELLULAR EFFECTS OF IL-17

IL-17 activates inflammatory responses in many different cells across a variety of organs.\textsuperscript{[18]} In studies of the global effects of IL-17 on endothelial dysfunction, Hot and colleagues\textsuperscript{[19]} treated human umbilical vein endothelial cells with IL-17 alone and combined with TNF-\(\alpha\), and found that IL-17 alone induced 245 proinflammatory genes, TNF-\(\alpha\) alone induced 1036 genes and the combination of IL-17 plus TNF-\(\alpha\) induced 10 873 proinflammatory genes. These cytokines also synergistically induced endothelial cell migration and invasion.\textsuperscript{[19]}

Responses to IL-17 in different cell types vary based on the unique tissue distribution of IL-17 receptors in different organs and the specific cytokine milieu provided by immune cell sources.\textsuperscript{[20]} When IL-17 levels are elevated in different tissues, this cytokine can induce granulopoiesis factors, neutrophil-specific chemokines, acute-phase response mediators, other proinflammatory cytokines, bone-resorptive cytokines and matrix metalloproteinases (MMPs) to promote inflammation and antimicrobial functions (Figure 1).\textsuperscript{[20]}

However, elevated levels of IL-17 alone are usually insufficient to produce a significant inflammatory response; rather, IL-17 acts cooperatively or synergistically with other cytokines (eg TNF-\(\alpha\), IL-23, IL-1\(\beta\), IL-6, transforming growth factor-\(\beta\) [TGF-\(\beta\)], resulting in a proinflammatory cascade.\textsuperscript{[20]}

Keratinocyte hyperproliferation and abnormal differentiation are a hallmark of psoriasis.\textsuperscript{[5,21]} In humans, when Th17/Th22 cells are stimulated by IL-23, they produce IL-17 and IL-22, respectively, which modulate distinct keratinocyte responses.\textsuperscript{[22,23]} IL-22 promotes keratinocyte hyperplasia by disrupting normal differentiation, regulating motility and retarding terminal differentiation.\textsuperscript{[23]}

Exposure of keratinocytes to IL-17 results in induction of IL-19, acting as an autocrine mitogen through induction of epidermal hyperplasia, and IL-17 can also stimulate production of IL-36 isoforms, which are potent proinflammatory cytokines.\textsuperscript{[5,24]}

Positive gene expression loops between IL-36, IL-17, IL-23, TNF-\(\alpha\) and IFN-\(\gamma\) in psoriatic lesions result in persistent inflammation.\textsuperscript{[24]} Combination of IL-17 and TNF-\(\alpha\) results in synergistic expression of IL-19 in keratinocytes. IL-17 alone promotes IL-19 expression by approximately twofold, and TNF-\(\alpha\) alone reduces IL-19 expression, whereas the combination of IL-17 and TNF-\(\alpha\) promotes expression by \(>50\)-fold.\textsuperscript{[25]}

When tested on monolayer keratinocytes in vitro, the molecular response to IL-17 leads to upregulation of approximately 50 genes that include AMPs, S100 proteins and chemokines that regulate neutrophil, DC and Th17 cell chemotaxis into skin lesions.\textsuperscript{[23,25]} The response to IL-17 is strongly boosted by synergy with IL-22, especially for S100 proteins, and by additive and synergistic gene induction in combination with TNF-\(\alpha\). The combined set of genes induced by IL-17 and TNF-\(\alpha\) includes several hundred products that are highly expressed in psoriatic lesions. The likely reason for this synergistic interaction is that gene responses to IL-17 are regulated by two sets of transcription factors: the nuclear factor kappa-light-chain-enhancer of activated B cells (NF\(\kappa\)B) and the C/CAA2T-enhancer-binding

![FIGURE 1](image129x742 to 228x756)

**FIGURE 1** Biologic functions of IL-17 in different cell types during the development of psoriasis. AMPs, antimicrobial peptides; CCL20, C-C motif ligand 20; GI, gastrointestinal; IL, interleukin; ILIC3, type 3 innate lymphoid cells; MMP, matrix metalloproteinases; MSC, mesenchymal stem cell; RANK(L), receptor activator of nuclear factor kappa-B (ligand); Tc17, a subset of CD8(+) T cells characterized by the production of IL-17; T cell, thymus cell; Th, T helper; TNF, tumor necrosis factor; S100, a family of proteins that function as calcium sensors and extracellular factors.
proteins (C/EBP), C/EBPβ or C/EBPδ. TNF-α is a strong inducer of active NFκB, while IL-17 is a stronger inducer of C/EBPβ or C/EBPδ activation.\textsuperscript{[6,26]} Notably, inhibition of IL-17 with an anti-IL-17A monoclonal antibody reduces expression of these genes to a greater extent than TNF-α inhibition.\textsuperscript{[27]}

IL-17 can also induce expression of AMPs and some chemokines in colonic epithelial cells,\textsuperscript{[28–31]} but the range of regulated genes is smaller than in skin keratinocytes. This is partly due to selective expression of S100 genes by epidermal keratocytes.\textsuperscript{[6,28]} Another factor is that C/EBPβ are expressed at much higher basal levels in epidermal keratocytes that are highly differentiated in the granular layer of the epidermis. Some of the most characteristic psoriasis gene products are synthesized at high levels in the upper spinous and granular layers of the epidermis, and this association is likely driven by high concentrations of C/EBP family transcription factors in these epidermal layers and the activation of these factors by IL-17. When IL-17 activity is tested in keratinocyte models with stratified cell interactions,\textsuperscript{[32–34]} the set of genes induced by IL-17 alone increases to several hundred products that are highly aligned with psoriasis disease-defining genes.\textsuperscript{[6]}

Studies in human renal proximal tubule epithelial cells and models of renal inflammation show that IL-17 stimulates production of chemokines, cytokines, angiogenic factors and granulopoietic growth factors through upregulation of numerous proinflammatory and profibrotic genes and alteration of gene associated with extracellular matrix remodelling and cell-cell interactions.\textsuperscript{[32–34]} In Th17-mediated kidney injury, infiltrating Th17 cells secrete IL-17, which stimulates resident renal proximal tubular epithelial cells to produce IL-6, C-X-C motif ligand (CXCL) 8, C-C motif ligand (CCL) 2 and other chemokines and inflammatory mediators. The pattern of chemokine expression leads to recruitment of neutrophils and induction of monocyte- and Th1 cell-attracting chemokines that promote immune-mediated kidney damage.\textsuperscript{[33]} Interestingly, acute kidney injury promotes subsequent damage to the liver and small intestine, which is linked to increases in plasma levels of IL-17, IL-6 and TNF-α, and especially to increased production of IL-17 in the portal circulation of the small intestine, highlighting the systemic inflammatory effects of IL-17-mediated organ damage.\textsuperscript{[35]}

Studies of liver and gut injury and inflammation show that high concentrations of IL-6 and TGF-β promote differentiation and activation of Th17 cells.\textsuperscript{[26,37]} The chemokine receptor 6 (CCR6) and CCR4 drive recruitment and infiltration of Th17 cells into liver and intestines.\textsuperscript{[36,38]} However, Th17 function may differ in different tissues. In liver, Th17 cells produce IL-17, which induces other proinflammatory mediators and recruits neutrophils to sites of inflammation. Specifically, in biliary epithelial cells, IL-17 acts directly to mobilize and activate neutrophils and stimulates expression of neutrophil-attracting chemokines, such as CXCL1, CXCL2, CXCL8 and CCL20. Increased IL-17R expression to enhance the integrity of the intestinal barrier and protect against pathogens.\textsuperscript{[37]}

### 3 | THE “INFLAMMATORY MARCH” MODEL

The "inflammatory march" hypothesis postulates that systemic inflammation associated with obesity and/or related dysregulation of metabolic axes (eg metabolic syndrome) drives the progression of cardiovascular disease.\textsuperscript{[39]} In psoriasis, the proximal event triggering this march was considered to be the release of cytokines from keratinocytes or immune cells in skin lesions, driving systemic inflammation followed by insulin resistance, endothelial dysfunction, dyslipidaemia, arteriosclerosis and cardiovascular disease.\textsuperscript{[39,40]} However, other data provide evidence that obesity may be the driving process. Several studies have shown that obesity is a risk factor for psoriasis, whereby underlying systemic inflammation associated with obesity may cause dysregulation of immune function and cytokines involved in psoriasis pathogenesis.\textsuperscript{[39]} In this case, both obesity and psoriasis may initiate processes leading to metabolic syndrome and cardiovascular disease (eg endothelial dysfunction, oxidative stress, dyslipidaemia and associated vascular stiffness and atherosclerosis; Figure 2).\textsuperscript{[39,41,42]}

However, it has also been posited that the increased incidences of obesity, diabetes, dyslipidaemia and hypertension associated with psoriasis do not fully account for the increased risk of cardiovascular disease in this population.\textsuperscript{[43]} Rather, evidence from animal models strongly suggests that skin inflammation alone is the primary driver...
of cardiovascular disease pathology in psoriasis through its effects on endothelial cells and blood leucocytes. The hypothesis that obesity is not required to drive this process is also supported by studies in rheumatoid arthritis (RA) showing that there is not a strong correlation between obesity and RA, but that patients with RA and associated chronic, systemic inflammation are at increased risk for cardiovascular events due to systemic inflammation and other traditional risk factors, such as diabetes, renal dysfunction and hypertension.

4. THE INFLAMMATORY ROLE OF IL-17 IN PSORIASIS COMORBIDITIES

4.1. Psoriatic arthritis

Up to 30% of patients with psoriasis develop psoriatic arthritis (PsA), characterized by asymmetric inflammatory arthritis, inflammation at tendon or ligament insertion sites into bone (enthesitis), dactylitis and sacroiliitis. Additionally, joint pain is reported in 52% of patients with psoriasis not diagnosed with PsA. The pathogenesis of PsA is not fully understood; however, findings from several studies suggest that IL-17 plays a role in disease development and progression, including genomewide association studies showing a link to IL-23/Th17 mediated pathogenesis. IL-17 plays a role in disease development and progression, including genomewide association studies showing a link to IL-23/Th17 mediators such as IL-12B and IL-23R. Using flow cytometry and Western blot analyses, Raychaudhuri and colleagues found that PsA-isolated synoviocytes have higher IL-17A receptor (IL-17RA) levels than synoviocytes from patients with osteoarthritis and that the synovial fluid of patients with PsA has significantly higher levels of Th17 cells that produce functionally active IL-17 and that, in turn, induces upregulation of IL-6, IL-8 and MMP-3. Furthermore, in animal models of collagen-induced arthritis, disruption of IL-17 signalling (IL-17-deficient mice and an anti-IL-17 antibody) protects against bone resorption.

In PsA, IL-17 and IL-23 upregulate expression of the receptor activator of NFκB (RANK). RANK binds to its ligand (RANKL), which induces NFκB and mitogen-activated kinases (eg Jun N-terminal kinase) triggering secretion of bone-matrix-degrading enzymes. IL-17 can induce osteoclastogenesis as a downstream effector of IL-23 and through mechanisms involving TNF-α and RANKL. IL-17 can also stimulate osteoblast secretion of RANKL and modulate expression of the osteoclast fusion protein, DC-specific transmembrane protein (DC-STAMP), a biomarker for PsA prognosis.

Findings from clinical studies of monoclonal antibodies that target IL-17 in PsA support the role of this cytokine in disease pathogenesis. The IL-17A inhibitor secukinumab significantly improves American College of Rheumatology response rates compared with placebo and slow radiographic progression of joint damage. Additionally, ixekizumab, another IL-17A inhibitor, and brodalumab, an anti-IL17RA monoclonal antibody, were superior to placebo in improving American College of Rheumatology response rates.

4.2. Cardiovascular disease

The chronic inflammatory state that occurs in psoriasis is associated with increased risk for cardiovascular disease. In a series of seminal studies, Gelfand and colleagues showed that psoriasis is associated with a significantly increased risk of cardiovascular events (eg stroke and myocardial infarction) and that the increased incidence of cardiovascular disease and other comorbidities shortens the average lifespan of patients with psoriasis.

In psoriasis, conventional biomarkers for inflammation and cardiovascular disease (eg C-reactive protein [CRP] and human soluble CD40 ligand) are elevated, and high-sensitivity CRP levels are predictive of coronary artery disease risk. Cardiovascular disease is a complex condition yet to be fully elucidated. However, numerous studies have also shown that elevated serum levels of Th17 cells and associated proinflammatory cytokines (ie IL-17, IL-6, and IL-8) are present in psoriasis. These three cytokines and CRP have been shown to drive inflammation in unstable coronary artery disease, including unstable angina and acute myocardial infarction, and IL-17 and IL-6, along with IL-1β and TNF-α, are preferentially expressed in animal models of ageing coronary arteries that are susceptible to ischaemia. Elevated levels of IL-17, TNF-α, IL-6, IL-8 and CRP have also been observed in atherosclerotic plaques. In a recent controlled trial, the IL-1β blocker canakinumab significantly reduced cardiovascular events. IL-1β and IL-17 could interact in promoting cardiovascular risk in two ways: (i) IL-17 in psoriasis increases expression of IL-1β by >10-fold and (ii) IL-1β can act synergistically with IL-17 to increase transcription of IL-17 and regulated autocrine inflammation.

In animal models of psoriasis, Wang and colleagues showed that sustained elevations in IL-17, CCL-2 and TNF-α associated with skin-specific inflammation were sufficient to promote aortic inflammation and thrombosis, supporting the hypothesis that skin inflammation in psoriasis can produce systemic changes in the cytokine milieu that promote vascular inflammation and increase the risk of adverse cardiovascular events.

In addition to its proinflammatory role, IL-17 stimulates production of vascular endothelial growth factor (VEGF) in keratinocytes, which promotes angiogenesis in patients with psoriasis and atherosclerosis. The Th17 pathway also regulates immune responses against oxidized low-density lipoprotein and collagen V, and associated increases in IL-17 production can exacerbate hyperlipidaemia and atherosclerosis in severe psoriasis. Reactive oxygen species generated in atherosclerosis can also induce cyclic adenosine monophosphate response element-binding protein, which enhances IL-17 production and promotes vascular inflammation via a feed-forward circuit, resulting in sustained atherogenic inflammation.
many of the suppressed products have been shown to be directly regulated by IL-17 in blood monocytes. The ongoing vascular inflammation in psoriasis with secukinumab (VIP-S) trial is evaluating the effects of IL-17A inhibition with secukinumab on aortic vascular inflammation (measured using (18)F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT)) in moderate-to-severe plaque psoriasis. Results will provide insight on the anti-inflammatory and potential cardioprotective role of therapies targeting IL-17A.

### 4.3 | Obesity

Similar to psoriasis, obesity is associated with chronic subclinical inflammation. When adipose tissue becomes inflamed, adipokine production is altered (eg leptin is upregulated and adiponectin is downregulated). This dysregulation promotes thrombosis and contributes to an ongoing inflammatory cascade by stimulating TNF-α, CRP, IL-6, fibrinogen and plasminogen activator inhibitor-1. Adipose tissue also expresses high levels of VEGF, and circulating IL-17A that reaches adipose tissue in psoriasis may further promote VEGF production and act synergistically with adipokines to promote a cycle of inflammation, angiogenesis and endothelial dysfunction. Models exploring the relationship between psoriasis and obesity have shown that obese animals develop an immunologic phenotype in which Th17 cell populations expand in adipose tissue, promoting inflammation and production of IL-17.

Treatments for psoriasis can affect adipokine levels and body weight. For example, methotrexate treatment is associated with reductions in high-sensitivity CRP and the adipokines omentin and chemerin. Biologic therapies targeting TNF-α have been shown to promote modest weight gain, possibly due to changes in glucose-dependent insulinoctropic polypeptide, leptin and ghrelin levels and reduction in metabolism. In contrast, biologic therapies directly targeting IL-12/23 and IL-17 are weight neutral. An ongoing study (ObEps-S) will evaluate the effects of IL-17A inhibition on adipose tissue in moderate-to-severe psoriasis.

### 4.4 | Metabolic syndrome

Psoriasis is associated with an increased risk of metabolic syndrome, which consists of a constellation of comorbidities including insulin resistance, visceral obesity, dyslipidaemia and hypertension. Patients’ risk of developing metabolic syndrome increases with increasing psoriasis severity.

It is hypothesized that the association between psoriasis and metabolic syndrome is a result of adipocyte dysfunction, chronically elevated free fatty acid levels and increased levels of inflammatory Th cell cytokines (eg TNF-α and IL-6) that exert systemic effects on insulin regulation and lipid metabolism in both skin and blood. Hyperinsulinemia associated with metabolic dysfunction also increases adipocyte production of VEGF. As VEGF promotes inflammation in keratinocytes via interactions with IL-17, it is possible that metabolic syndrome may increase psoriasis severity or susceptibility. This association between psoriasis and metabolic syndrome provides another possible pathway for the inflammatory march model (Figure 2).

### 4.5 | Liver disorders

Alcoholism, liver cirrhosis and non-alcoholic fatty liver disease are more common in psoriasis than in the general population, and high alcohol intake is associated with reduced treatment efficacy in psoriasis. These hepatic comorbidities are associated with chronic inflammation that is mediated, in part, by activation of the Th17 axis. Serum IL-17 levels are elevated in inflammatory liver diseases, and the number of IL-17-positive cells correlates with severity of hepatocellular damage. IL-17 receptors are expressed on virtually all types of liver cells (eg hepatocytes, Kupffer cells, stellate cells and biliary and sinusoidal epithelial cells). In these cells, binding of IL-17 to its receptor activates NFκB and mitogen-activated protein kinase signalling pathways that stimulate secretion of proinflammatory cytokines and chemokines. Other effects of IL-17 in inflammatory liver disorders include stimulation of endothelial tissue factor, p38, and reactive oxygen species, which contribute to coagulation dysfunction in cirrhosis, and recruitment of lymphocytes and neutrophils to infiltrate fibrotic septa and inflammatory foci in hepatitis. As in other types of tissue inflammation, there is a high level of synergism of IL-17 with TNF-α to stimulate inflammatory cytokines and chemokines in hepatic tissue.

An animal model of cholestatic liver fibrosis suggests that anti-IL-17 monoclonal antibodies may reduce inflammation and target organ damage in hepatitis or other liver disorders. In these experiments, IL-17 blockade was associated with significant improvements in liver function, along with decreases in hepatocellular necrosis and levels of proinflammatory cytokines, neutrophils and macrophages.

### 4.6 | Renal disease and hypertension

Elevated levels of IL-17 have been observed in hypertension, vascular dysfunction and lupus nephritis, and renin and angiotensin II levels are elevated in psoriasis. In fact, renin is produced at increased levels in psoriatic skin lesions, and it may be a direct link between IL-17-centred inflammation and hypertension leading to cardiovascular risk and renal dysfunction. Additionally, adipose tissue contains all components of the renin-angiotensin system. Findings from experimental models of hypertension and nephritis support this hypothesis, as IL-17 (alone or synergistically with TNF-α) has been shown to promote inflammation by stimulating production of neutrophil chemoattractants (eg IL-6, CXCL2, CXCL8, CCL2, CCL7, CCL8 and CCL20), many of which are also implicated in development of psoriatic plaque. Another notable similarity between psoriasis and renal disease is that in response to angiotensin II stimulation, effector T-cell formation is upregulated. These T cells infiltrate the kidney and perivascular regions of large arteries and arterioles and produce high levels of IL-17, IFN-γ, TNF-α and IL-6, which promote inflammation that causes renal and vascular damage,
resulting in increased sodium reabsorption and increased renal fibrosis. In the kidneys, IL-17 also promotes aortic stiffening, possibly through upregulation of type I collagen deposition in the coronary and renal arteries.

Therapeutic interventions targeting proinflammatory cytokines improve cardioenal outcomes. Blockade of the renin-angiotensin-aldosterone system with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers downregulates Th17-mediated production of IL-17 and IFN-γ in animal models of autoimmune inflammation. TNF-α inhibition with etanercept prevents hypertension in animal models. Conversely, in an animal model of severe psoriasis, upregulation of IL-17A in keratinocytes was associated with increased blood levels of reactive oxygen species, inflammatory leukocytes, endothelial dysfunction, elevated blood pressure and left ventricular hypertrophy, suggesting that elevations in plasma IL-17A associated with severe psoriasis can increase risks for arterial hypertension and vascular disease.

4.7 | Depression

In psoriasis, depression is associated with increased systemic and vascular inflammation and coronary plaque burden. However, the role of IL-17 in depression has not been well characterized. While one study found elevated levels of IL-17 in patients with RA and comorbid anxiety or depression, it has been speculated that the increase in IL-17 was simply a result of inflammatory arthritis and was not directly related to depression. Of note, a recent study using mouse models of depression showed that administration of Th17 cells was directly correlated with depression sensitivity, suggesting that the Th17 axis may play a role in neuro-immune interactions. However, the role of IL-17 in such interactions is not known.

5 | DISCUSSION

The high level of synergism between IL-17 and other cytokines and adipokines across various organ systems suggests that if plasma levels of IL-17 become elevated in psoriasis, circulating IL-17 could interact with other cytokines and adipokines in different types of tissue to trigger both local and systemic inflammation. We favour the concept that increased circulatory IL-17 levels are the most consistent drivers of inflammation at local sites as opposed to circulating IL-17-producing cells triggering inflammation at tissue distal from psoriatic lesions. This idea is supported by data indicating that IL-17 is elevated in the blood of patients with psoriasis, and in non-involved skin, there is elevation of IL-17-induced gene products but not all patients have elevated IL-17 in non-involved skin. Studies are warranted to investigate the hypothesis of whether blocking IL-17 signalling pathways might improve symptoms of common comorbidities associated with psoriasis. Notably, targeting IL-17A may be more effective for reducing systemic inflammation than targeting IL-17RA because the receptor is localized to tissue, whereas IL-17 can be targeted systemically by circulating antibodies. Results from ongoing studies, such as VIP-S evaluating cardiovascular outcomes in patients with psoriasis treated with secukinumab, ObePso-S evaluating changes in adipose tissue in patients with psoriasis treated with secukinumab and real-world data from sources such as the Corrona psoriasis registry, will test the hypothesis of whether IL-17A inhibition has long-term effects on systemic inflammation and psoriasis comorbidities. These studies will potentially help establish what the independent contribution of IL-17A is to systemic inflammation and associated pathology.

Based on evidence of increased activity of IL-17 and other chemokines and cytokines in the Th17 axis and increases in both tissue-specific and systemic inflammation, it has been suggested that antibodies against IL-17 could have therapeutic potential for treatment of liver and kidney diseases, hypertension, atherosclerosis and other inflammatory disorders. The Th17 cytokine signatures are remarkably similar between psoriasis and comorbidities such as atherosclerosis, suggesting common treatment strategies could result in similar responses. To this end, data on the effect of IL-17 antagonism on vascular inflammation will provide valuable insight on the management of cardiovascular disease in psoriasis.

ACKNOWLEDGEMENTS

Both authors contributed to analysis and interpretation of the data presented, wrote the manuscript and approved the final version. Technical assistance with editing and styling of the manuscript for submission was provided by Oxford PharmaGenesis Inc., funded by Novartis Pharmaceuticals Corporation. Authors were fully responsible for all content and editorial decisions and received no financial support or other form of compensation related to the manuscript.

CONFLICT OF INTEREST

J.G.K. reports grants paid to The Rockefeller University from: Novartis, Pfizer, Janssen, Lilly, Kadmon, Dermira, Boehringer, BMS, Pararel, Kineta, Leo Pharma, Regeneron, Amgen, Innovaderm, Vitae, Provectus and Kyowa; personal fees from: Novartis, Pfizer, Janssen, Lilly, Kadmon, Dermira, Boehringer, BMS, Kineta, Merck, Serono, Biogen Idec, Delenex, AbbVie, Sanofi, Baxter and Xenopon. P.M.B. reports personal fees from: LEO Pharma and Sanofi.

REFERENCES

[1] C. G. Helmick, H. Lee-Han, S. C. Hirsch, T. L. Baird, C. Bartlett, Am. J. Prev. Med. 2014, 47, 37.
[2] T. D. Rachakonda, C. W. Schupp, A. W. Armstrong, J. Am. Acad. Dermatol. 2014, 70, 512.
[3] D. O’Rielly, P. Rahman, Rheum. Dis. Clin. North Am. 2015, 41, 623.
[4] J. Kim, J. G. Krueger, Annu. Rev. Med. 2017, 68, 255.
[5] A. Chiricozzi, M. Suarez-Fiaynas, J. Fuentes-Duculan, I. Cueto, K. Li, S. Tian, C. Brodmerkel, J. G. Krueger, Br. J. Dermatol. 2016, 174, 136.
with moderate to severe plaque psoriasis: results from the FIXTURE study. Presented at the 23rd World Congress of Dermatology, June 8–13, 2015; Vancouver, Canada.

[92] ClinicalTrials.gov. Study to Explore the Effect of Secukinumab, Compared to Placebo, on Fat Tissue and Skin in Plaque Psoriasis Patients (ObePso-S). https://clinicaltrials.gov/ct2/show/NCT03055494. Accessed June 9, 2017.

[93] A. W. Armstrong, C. T. Harskamp, E. J. Armstrong, J. Am. Acad. Dermatol. 2013, 68, 654.

[94] S. M. Langan, N. M. Seminara, D. B. Shin, A. B. Troxel, S. E. Kimmel, N. N. Mehta, D. J. Margolis, J. M. Gelfand, J. Invest. Dermatol. 2012, 132, 556.

[95] D. M. Sommer, S. Jenisch, M. Suchan, E. Christophers, M. Weichenthal, Arch. Dermatol. Res. 2006, 298, 321.

[96] P. Gisondi, G. Targher, G. Girolomoni, Br. J. Dermatol. 2007, 157, 68.

[97] T. Suzuki, S. Hirakawa, T. Shimatsu, T. Ito, J. Sakabe, M. Detmar, Y. Tokura, J. Dermatol. Sci. 2014, 74, 116.

[98] A. B. Kimball, D. Gladman, J. M. Gelfand, K. Gordon, E. J. Horn, N. J. Korman, G. Korver, G. G. Krueger, B. E. Strober, M. G. Lebwohl, National Psoriasis Foundation, J. Am. Acad. Dermatol. 2008, 58, 1031.

[99] P. Gisondi, G. Targher, G. Zoppini, G. Girolomoni, J. Hepatol. 2009, 51, 758.

[100] F. Lafiﬁ, A. M. Miller, S. H. Hi, B. Gao, Cell. Mol. Immunol. 2010, 7, 250.

[101] Y. Pu, S. Zhang, R. Zhou, N. Huang, H. Li, W. Wei, L. Li, C. Huang, J. Yang, Z. Li, Biochem. Biophys. Res. Commun. 2016, 470, 41.

[102] A. Lemmers, C. Moreno, T. Gustot, R. Maréchal, D. Degré, P. Demetter, P. de Nadai, A. Geerts, E. Quertinmont, V. Vercruysses, O. Le Moine, J. Devière, Hypertension 2009, 49, 646.

[103] S. Zhang, D. Huang, J. Weng, Y. Huang, S. Liu, Q. Zhang, N. Li, M. Wen, G. Zhu, F. Lin, W. Gu, Scand. J. Immunol. 2016, 83, 102.

[104] M. S. Madhur, H. E. Lob, L. A. McCann, Y. Iwakura, Y. Blinder, T. J. Guzik, D. G. Harrison, Hypertension 2010, 55, 500.

[105] M. Suárez-Fariñas, K. Li, J. Fuentes-Duculan, K. Hayden, C. Brodmerkel, J. G. Krueger, J. Invest. Dermatol. 2012, 132, 2552.

[106] S. Kagami, Clin. Exp. Nephrol. 2012, 16, 214.

[107] A. R. Kitching, S. R. Holdsworth, J. Am. Soc. Nephrol. 2011, 22, 235.

[108] H. J. Paust, J. E. Turner, O. M. Steinmetz, A. Peters, F. Heymann, C. Hölscher, G. Wolf, C. Kurts, H. W. Mittrücker, R. A. Stahl, U. Panzer, J. Am. Soc. Nephrol. 2009, 20, 969.

[109] A. Chiricozzi, R. Saraceno, M. S. Chimenti, E. Guttmann-Yassky, J. G. Krueger, Expert Opin. Ther. Targets. 2014, 18, 513.

[110] W. G. McMaster, A. Kirabo, M. S. Madhur, D. G. Harrison, Circ. Res. 2015, 116, 1022.

[111] M. Platten, S. Youssef, E. M. Hur, P. P. Ho, M. H. Han, T. V. Lanz, L. K. Phillips, M. J. Goldstein, R. Bhat, C. S. Raine, R. A. Sobel, L. Steinman, Proc. Natl Acad. Sci. USA 2009, 106, 14948.

[112] L. T. Tran, K. M. MacLeod, J. H. McNeill, Mol. Cell. Biochem. 2009, 310, 219.

[113] M. Venegas-Pont, M. B. Manigrasso, S. C. Grifoni, B. B. LaMarca, C. Maric, L. C. Racusen, P. H. Glover, A. V. Jones, H. A. Drummmond, M. J. Ryan, Hypertension 2010, 56, 643.

[114] S. Karbach, A. L. Croxford, M. Oelze, R. Schüler, D. Minwegen, J. Shimauchi, T. Ito, J. Sakabe, M. Detmar, Y. Tokura, J. Dermatol. Sci. 2010, 61, 137.

[115] T. M. Aberra, A. A. Joshi, J. B. Lerman, J. A. Rodante, A. K. Dahiyi, H. L. Teague, Q. Ng, J. I. Silverman, A. V. Sorokin, F. Sallahuddin, B. N. Lockshin, M. A. Ahlman, M. P. Playford, M. Y. Chen, J. M. Gelfand, N. N. Mehta, Atherosclerosis 2016, 251, 219.

[116] C. J. Connor, V. Liu, J. G. Fiedorowicz, Dermatol. Res. Pract. 2015, 2015, 409637.
[117] Y. Liu, R. C. Ho, A. Mak, Int. J. Rheum. Dis. 2012, 15, 183.
[118] A. Waisman, J. Hauptmann, T. Regen, Acta Neuropathol. 2015, 129, 625.
[119] E. Beurel, L. E. Harrington, R. S. Jope, Biol. Psychiatry 2013, 73, 622.
[120] L. Grine, L. Dejager, C. Libert, R. E. Vandenbroucke, Cytokine Growth Factor Rev. 2015, 26, 25.
[121] ClinicalTrials.gov. The Corrona Psoriasis Registry. https://clinicaltrials.gov/ct2/show/NCT02707341. Accessed February 1, 2017.

How to cite this article: Krueger JG, Brunner PM. Interleukin-17 alters the biology of many cell types involved in the genesis of psoriasis, systemic inflammation and associated comorbidities. Exp Dermatol. 2018;27:115-123. https://doi.org/10.1111/exd.13467