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IL-17 in psoriasis: Implications for therapy and cardiovascular co-morbidities

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Abstract

Psoriasis is a prevalent, chronic inflammatory disease of the skin mediated by cross-talk occurring between epidermal keratinocytes, dermal vascular cells and immunocytes, including activated antigen presenting cells (APCs), monocytes/macrophages, and Th1 and Th17 cells. Increased proliferation of keratinocytes and endothelial cells in conjunction with immune cell infiltration leads to the distinct epidermal and vascular hyperplasia that is characteristic of lesional psoriatic skin. Interaction of activated T cells with monocytes/macrophages occurs via the Th17/IL-23 axis and is crucial for maintaining the chronic inflammation. Recent epidemiological evidence has demonstrated that psoriasis patients have an increased risk of developing and dying of cardiovascular disease. Similar pathology between psoriasis and cardiovascular disease, including involvement of key immunologic cell populations together with release of common inflammatory mediators such as IL-17A suggest a mechanistic link between the two diseases. This review will focus on concepts critical to psoriasis pathogenesis, systemic manifestations of psoriasis, the role of IL-17 in psoriasis and cardiovascular disease and the potential role for IL-17 in mediating cardiovascular co-morbidities in psoriasis patients.

Keywords

IL-17A; IL-17F; Th17; Psoriasis; Skin; Atherosclerosis; Cardiovascular Disease

1. Introduction

Psoriasis is a chronic inflammatory skin disease; its cause remains unknown as a strict mitigating signal or a single antigenic target has yet to be identified. A combination of human and animal studies has led to the understanding that in patients with a susceptible genetic background, some stimulus, perhaps an infection, leads to a coordinated series of

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signaling events involving release and signaling of cytokines that occurs between keratinocytes, endothelial cells, T cells, monocytes and macrophages, and dendritic cells (DCs) that once initiated results in a vicious pro-inflammatory proliferative cycle that perpetuates a sustained cutaneous inflammatory response. Intervention at several key points in this cycle results in clinical resolution; however durable remission and/or permanent clearance have not been achievable.

Psoriasis as an immune-centric disease stems from clinical observations associated with the disease clearance following immunosuppressive therapies [1]. Further evidence has demonstrated a strong T cell component to disease maintenance via Th1, Th17, and Th22 cells and their derived cytokines [2–5]. Release of cytokines from these T cells including IFN-γ, IL-17A, IL-17F, and IL-22 following cutaneous DC activation induces keratinocyte hyperproliferation and further proinflammatory immune responses. Although psoriasis primarily affects the skin and joints (psoriatic arthritis), several co-morbidities, including inflammatory bowel disease (IBD), lymphoma, obesity, and metabolic syndrome are associated with psoriasis [6, 7]. Most recently, growing epidemiologic evidence has shown that psoriasis patients have a significantly increased risk of developing and dying of cardiovascular disease (CVD) [8–13]. Because vascular inflammation and atherosclerosis share common mechanisms of pathogenesis with lesional psoriasis including similar inflammatory cytokine profiles and proinflammatory cell types including T cells, monocytes/macrophages, and neutrophils (Table 1), the hypothesis that aggressive treatment of the primary disease (psoriasis) may decrease the risk of developing the other co-morbidities (CVD) is now currently being investigated.

1.1 Psoriasis pathogenesis and treatment

Psoriasis is a chronic inflammatory skin disease affecting 2–3% of the US population [14] and the most common variant of psoriasis, psoriasis vulgaris, affects approximately 85 to 90% of all patients [15]. Psoriasis is clinically characterized by erythematous, raised, well-demarcated scaly patches of skin. Skin lesions form as a result of epidermal hyperplasia, premature keratinocyte maturation, parakeratosis due to retention of nuclei in the stratum corneum [16], and the formation of epidermal rete ridges: elongated, thin, downward projections of keratinocytes into the dermis [17]. In addition to the epidermal changes, changes to the skin microvasculature occur, including increased expression of vascular endothelial growth factor (VEGF) leading to the formation of leaky vessels [18], and increases in skin infiltrating leukocytes. The disease can be exacerbated by stress, infections, and medications such as beta blockers [19–21].

Treatments for psoriasis include topicals such as corticosteroids, as well as agents such as anthralin, synthetic Vitamin D3, and Vitamin A; phototherapy including broad and narrowband-UVB, laser UVB, and psoralen UVA (PUVA); systemics such as cyclosporine, methotrexate, and retinoid receptor inhibitors (Acitretin); and biological therapeutics including TNF-α inhibitors and cytokine inhibitors such as anti-IL23p40 and IL-17 inhibitors. Historically, psoriasis was believed to originate due to keratinocyte dysfunction until the discovery that cyclosporine A (CsA), a calcineurin inhibitor that blocks cytokine production and interleukin release resulting in reduced function of effector T-cells and ultimately immuno-suppression, was found to be highly effective [1]. Since this time, the focus has shifted toward immune-mediated mechanisms to explain the keratinocyte hyperproliferation and subsequent therapeutics have targeted immune cells present in psoriatic tissue.

Additional support for the importance of T cells as pathogenic in psoriasis is derived from the efficacy of biologic agents used in the treatment of psoriasis, including therapies which target T cells/T cell activation directly and those which target pro-inflammatory cytokine

pathways present in lesional psoriasis skin. T cell-specific interventions, such as FK506 (tacrolimus, another calcineurin inhibitor that blocks T cell signal transduction and IL-2 transcription), DAB-IL-2 (denileukin diftitox, a fusion protein of interleukin-2 (IL-2) and the enzymatically active and translocating domains of diphtheria toxin which induces apoptosis in IL-2 receptor bearing cells that take up the drug), anti-CD4 (Hu-Max, targeting helper T cells, regulatory T cells, DC subtypes and monocytes and therefore highly immunosuppressive), CTLA4-Ig (abatacept, a fusion protein of the Fc region of immunoglobulin IgG1 with the extracellular domain of CTLA-4 which prevents antigen-presenting cells (APCs) from delivering the co-stimulatory signal to T cells), and anti-CD3 (ala-ala, a humanized non-FcR binding derivative of the anti-human CD3 monoclonal antibody OKT3 (huOKT3y1), which has been proposed to lead to a preferential depletion of pathogenic effector T cells via apoptosis and concomitant stabilized expression of Helios positive regulatory T cells) [22] as systemic therapy, proved that T cell activation is critical for sustaining psoriatic lesions (reviewed in [23–28]). Effector memory T cells persist in the skin in order to provide a rapid response to infection [29] and resident T cells in normal skin express the skin-homing receptors cutaneous lymphocyte antigen (CLA), CCR4, and CCR6 [30]. Non-lesional skin from psoriasis patients develops psoriatic lesions in the absence of infiltration of blood lymphocytes [31], highlighting the importance of skin-resident memory T cells in perpetuation of the disease. While memory effector T cells play a role in psoriasis, it should be noted that the first FDA-approved biological therapy for psoriasis LFA3-Ig (alefacept), which binds $CD2^{high}$ activated Tmem/eff cells and selectively depletes these cells [32], has been voluntarily discontinued in the U.S. for the treatment of psoriasis due to, among many factors, minimal response rates.

Clinical improvement is also accompanied by a reduction in T cells and Th17-related mediators following treatment by several biological therapies including TNF inhibitors (e.g., infliximab, etanercept, adalimumab) [33, 34], the IL-12/IL-23p40 inhibitor ustekinumab [35], and the new IL-23p19 antibody (MK-3222) [36] which indirectly inhibit T cell activation/differentiation and maintenance, as well as recently reported anti-IL-17 therapeutics (e.g. ixekizumab, broadalumab) [37, 38] which directly target IL-17 and IL-17 receptors.

Taken together, the efficacy of agents described above demonstrates that depleting T cells or their cytokines directly, or targeting their signaling pathways, can be an effective strategy in the treatment of psoriasis. TNF-α inhibitors produce psoriasis remission by blocking the cytokine itself or its receptor and preventing the activation and expansion of T cells, leading to a decrease in overall inflammation and allowing the lesion time for repair [39, 40]. Ustekinumab's effects appear to result in potentially better durable remission [41, 42], perhaps reflecting a direct effect on reducing the circulating numbers of DCs, and decreases in IL-23p19 and IL-12p40 levels in psoriasis lesions [25, 43, 44] which in turn leads not only to the marked decrease in IFN-γ production (IL-12 effect), but also to a decrease in Th17 activation (IL-23 effect) [45]. Evaluation of MK-3222 efficacy is still in early clinical trials; however preliminary reports of initial results appear promising [36]. Two new humanized antibodies that target IL-17 through either neutralization of IL-17 or blocking the IL-17 receptor, ixekizumab and broadalumab respectively, are effective in the treatment of moderate-to-severe-psoriasis and will be discussed in more detail below [37, 38].

2. Psoriasis immunology and the role of IL-17

2.1 T-helper subtypes important in psoriasis pathogenesis

Psoriasis is now defined as a Th1/Th17/Th22-biased inflammatory disease [46–51]. Lesions and peripheral blood of psoriasis patients contain Th1 cells that produce high levels of IFN-γ and low levels of IL-4 and IL-10 [52–54], Th17 cells that produce IL-17 and IL-22, Th22

cells which produce IL-22, and cytotoxic epithelial CD8 T cells. A large scale gene expression analysis confirmed the contribution of the Th1 population as it demonstrated IFN-related genes were differentially expressed in involved psoriatic skin than in noninvolved and control skin [55]. While historically the Th1 cell population has been well established to play a role in psoriasis, Th17 cells have been recently identified as distinct from the Th1 subset in the psoriatic dermis [47]. Increases in circulating Th1 and Th22 cells are also observed in psoriasis patients, but to a lesser extent than the Th17 population [4].

Interest in the Th17 population in relationship to psoriasis advanced when patients were shown to have increased numbers of circulating Th17 cells [4, 56] as well as cutaneous Th17 cells in lesional compared to non-lesional skin [47]. The Th17 class of T cells exhibits a unique cytokine and transcription factor profile which is neither Th1- nor Th2-specific [57, 58]. Th17 cells are controlled by the transcription factors STAT3 and RORγt; in humans they primarily produce IL-17A and IL-17F, and are associated with initiation of autoimmune and inflammatory conditions [3, 59, 60]. Immunohistochemistry has confirmed the increases in IL-17F [61] and IL-17A protein in lesional psoriasis tissue. Serum levels of IL-17 protein have been found to correlate with psoriasis severity [34, 56].

Th22 cells exhibit epidermal homing and express the chemokine receptor CCR6 and the skin homing receptors CCR4 and CCR10, and consequently have been implicated in psoriasis and psoriatic arthritis [4, 62–64]. IL-22 mRNA and protein are increased in psoriatic plaques when compared to normal skin while levels in peripheral blood do not vary significantly [65]. Increased lesional mRNA levels of IFN-γ, IL-17 and IL-22 in psoriasis lesions normalize to non-lesional levels following cyclosporine treatment [47], further highlighting the role these cytokines play in potentiating inflammation in the plaque. Interestingly, IL-22 has very little autocrine effect, as neither T cells nor NK cells possess the IL-22 receptor yet keratinocytes in psoriatic skin demonstrate increased levels of IL-22R [66]. Expression of IL-22R can also be up-regulated by other pro-inflammatory cytokines elevated in psoriasis such as IFN-γ [67]. Murine psoriasis models have demonstrated epidermal hyperplasia mediated in part by IL-22/22R signaling [48], but the IL-22 dependency is not observed in human disease.

The Th17/IL-23 axis is crucial for maintaining the chronic inflammation characteristic of psoriasis [68]. IL-23 is a key cytokine involved in autoimmunity that promotes the expansion and maintenance of Th17 cells, providing a link between innate and adaptive immunity in psoriasis [69, 70]. TGF-β in combination with IL-6 and IL-21 signals through STAT-3 to direct Th17 differentiation from naïve cells *in vitro*, while IL-23 is required *in vivo* [71]. TGF-β and IL-1, in addition to IL-6 or IL-21, act as differentiation factors for Th17 cells while IL-23 promotes growth and stabilization of Th17 cells. Although IL-23 promotes release of IL-17A, it does not appear to effect IL-22 production [72]. Th17 cells express the receptor for IL-23 [3, 73, 74] and over-expression of IL-23 in psoriatic lesions promotes Th17 cell cytokine production, potentiating a cycle of inflammation between IL-23-producing DCs and IL-17-producing Th17 cells present in lesional psoriatic dermis [75, 76].

2.2 IL-17A in human psoriasis

As described above, involved psoriatic plaques contain increased numbers of Th17 cells [56, 77]. Th17 cells are localized to the dermis of psoriasis patients and IL-17mRNA expression increases with disease development and severity [47]. RT-PCR shows a relative increase in IL-17A mRNA in psoriatic lesions when compared to controls [73]. While Th17 cells are the best characterized producers of IL-17A in psoriatic skin [3, 60, 61], other investigators have suggested that the major sources of IL-17 in human psoriatic skin may not be the classic Th17 cell, but other cells present in the inflammatory cell milieu [78]. These

investigators show, in a small cohort of 8 psoriasis patients, that the majority of IL-17A producing cells in active plaques were neutrophils and mast cells while less than 10% of the dermal T cell population expressed IL-17A by immuno fluorescence microscopy [78]. A second study also identified mast cells as major producers of IL-17A in healthy skin as well as psoriasis tissue as well as an enrichment of IL-17A producing neutrophils compared to control subjects [79]. Flow sorted neutrophils from these patients produced IL-17A but not IL-17F as determined by Western blot.

Another potential source of IL-17A in the dermis of psoriatic skin may be γδ-T cells, although in human psoriasis patients, a clear pathogenic role for γδ-T cells has not been demonstrated. The frequency of γδ-T cells present in lesional skin of psoriasis patients has been suggested to be between 1 [80] and 42 percent [81] of the $CD3^+$ T cell population in the skin. Moreover, of the γδ-T cells in the psoriatic dermis of the latter study, only 15% of these cells produced IL-17A after stimulation with IL-23 [81]. An overall reduction in circulating numbers of γδ-T cells was seen in the blood of psoriasis patients (2.16%) when compared to normal controls (4.21%) and atopic dermatitis patients (5.18%) [80] suggesting that it is unlikely for γδ-T cells to be the sole sources of pathogenic IL-17.

Finally, $CD8^+$ cells isolated from psoriatic lesions produce both IL-22 and IL-17 [82, 83]. An *in vitro* analysis of isolated T cells that spontaneously migrated from cultured dermal skin fragments demonstrated that $CD8^+$ T cells were capable of producing IL-17A. The $CD8^+$ population from psoriasis skin contained a significantly higher percentage of IL-17A producing cells when compared to normal skin (3.39 and 0.35%, respectively) [78] suggesting a possible role for this additional T cell population in contributing to overall IL-17A production in psoriasis. These observations may provide a mechanistic explanation for the pathogenesis ascribed to $CD8^+$ T cells in psoriasis.

2.3 IL-17 targeted human therapeutics

Recently, two clinical trials have demonstrated the importance of IL-17 and the IL-17 receptor (IL-17RA) as therapeutic targets for psoriasis. In the first clinical trial, ixekizumab (previously known as LY2439821), a humanized monoclonal antibody that binds to and neutralizes IL-17A was evaluated in 142 psoriasis patients treated with either ixekizumab (10, 25, 75, or 150 mg at 0, 2, 4, 8, 12, and 16 weeks) or placebo [37]. In patients with chronic moderate-to-severe plaque psoriasis, significant reductions in Psoriasis Area-and-Severity Index (PASI) scores, an assessment tool used to measure the severity of psoriasis based on the erythema, scaling, and induration of the lesions weighted by the overall area of involvement [84], occurred within the first week of treatment in the two highest dose groups when compared to placebo. As early as two weeks a 75% reduction in PASI was seen in the 150mg group. After 12 weeks, a reduction in PASI score by at least 75% over baseline in the 150mg, 75mg, and 25mg treatment groups was observed and sustained for ≥ 20 weeks. In both the 150mg and 75mg groups, a 100% reduction in PASI score (defined as complete clearance of plaque) was achieved in 40% of patients when compared to the placebo group after 12 weeks.

A second clinical trial assessed the efficacy of brodalumab (previously known as AMG827), a monoclonal antibody that specifically blocks the IL-17 receptor A, thereby neutralizing the effects of IL-17A, -17C, -17F, and 17E [38, 85, 86]. In this trial, 198 psoriasis patients were treated with either placebo or brodalumab (70, 140, or 210 mg at day 1 and weeks 1, 2, 4, 6, 8, and 10 or 280 mg monthly). At the conclusion of the 12 week trial, the percentage improvement in PASI from baseline was above a mean percentage increase of 75% in the three highest dose groups, 45% in the 70 mg group, and 16% in placebo. After 12 weeks, at least 90% improvement in PASI was seen in 72% of patients in the 140 mg group and 75% in the 210 mg group.

3. Psoriasis and cardiovascular co-morbidities

A growing body of evidence suggests that psoriasis is associated with an increased risk of adverse cardiovascular events. Several studies have demonstrated that patients with psoriasis have an increased risk of numerous factors all associated with CVD [10, 87–90]. More recently, it has been reported that patients with severe psoriasis have an increased risk of developing and dying of CVD independent of these risk factors [11, 91]. Psoriasis patients have a higher prevalence of metabolic syndrome than the normal population [92] and this association increases with increased psoriasis disease severity [93, 94]. Patients with mild to severe psoriasis have an increased risk of venous thromboembolism [95], hypertension [96], dyslipidaemia, myocardial infarction [13], and stroke [97, 98], while patients with psoriasis >8 years have a higher prevalence of coronary artery disease (CAD) than patients without psoriasis [99].

A mechanism linking psoriasis pathogenesis and onset of CVD has not yet been elucidated, but a recent genome-wide association study (GWAS) found common genetic variants in psoriatic individuals that predispose them to increased risk of dyslipidemia, hypertension, and CAD, revealing an association between cardiovascular and metabolic disease genes with psoriasis [100]. Additionally, the concept of a “psoriatic march” has been proposed where cardiovascular comorbidities and psoriasis are linked via a mechanism driven by the systemic inflammation observed in psoriasis [101, 102]. This systemic inflammation is hypothesized to contribute to a state of insulin resistance, leading to endothelial cell dysfunction and resulting in atherosclerosis. Although epidemiological data has demonstrated that psoriasis patients are at risk of developing and dying of CVD [8–13], the idea of causality cannot be definitively explored in humans as confounding factors are difficult to control for in the patient population.

We have recently shown using the skin-specific transgenic KC-Tie2 murine model of psoriasiform skin inflammation [103] that long term skin-specific inflammation may in fact have the capacity to cause systemic levels of inflammation sufficient to drive atherogenesis [104]. KC-Tie2 psoriasiform mice develop skin lesions that are similar to human psoriasis, including areas of uninvolved and involved skin, increases in epidermal thickness (acanthosis), erythema, dermal angiogenesis, and increases in infiltrating T cells skewed towards the Th1/Th17 profile along with increases in DCs and macrophages and their derived cytokines, in particular IL-12/23 and TNF-α [103]. These cutaneous characteristics of psoriasis were improved or reversed following gene repression, CsA administration [103], APC depletion using clodronate liposomes, TNF-α inhibition [105] and following chemical or surgical denervation [106, 107]. Of particular relevance to cardiovascular comorbidities observed in the epidemiological human studies were our observations of elevated systemic inflammation, including increases in biomarkers associated with cardiovascular disease/risk including serum TNF-α, vascular endothelial growth factor (VEGF), IL-12, monocyte chemotactic protein-1 (MCP-1), S100A8/A9 and importantly systemic levels of circulating IL-17A [104]. These increases occurred in the absence of hyperlipidemia or metabolic syndrome and preceded the spontaneous development of aortic root vascular lesions in 33% of the KC-Tie2 mice by one year of age. Moreover, KC-Tie2 mice were pro-thrombotic evidenced by arterial thrombosis clotting times being significantly shortened compared to controls. Of particular relevance to treating psoriasis patients, reversal of the skin disease in KC-Tie2 mice eliminated aortic root vascular lesions and returned thrombus formation to control mouse levels. This suggests that chronic sustained skin inflammation may be sufficient on its own, independent of hyperlipidemia or metabolic syndrome, to elicit levels of systemic inflammation sufficient to induce atherothrombosis. As a corollary to this observation, aggressive treatment of inflammatory skin disease may prevent cardiovascular

disease co-morbidities. Recent results support this corollary in psoriasis patients [108], yet the specific mechanisms mediating this interaction have not yet been defined.

3.1 Th17 cytokines link psoriasis and CVD

The idea that Th17 cytokines may provide a link between psoriasis and CVD stems from independent literature reporting a pathogenic role of IL-17 in psoriasis (see above) and from murine and human studies examining the contribution of Th17 cells and their derived cytokines to atherosclerosis. Psoriasis patients with moderate to severe disease have significantly elevated serum IL-17A levels [34, 56]. Patients with elevated IL-17A appear to be at the highest risk for developing and dying from cardiovascular complications including stroke and MI. With the advent of IL-17 biologics and their known efficacy in significantly improving psoriasis disease severity, time will tell whether this targeted inhibition of IL-17 will also lead to improved CVD outcomes in psoriasis patients.

In human atherosclerotic lesions, IL-17A/IL-17F are elevated at each stage of plaque development [109], are thought to be derived from mast cells and neutrophils, and increase in the late stage, more advanced plaque. $CD4^+$ T cells also infiltrate athero-susceptible arteries and express both IFN-γ and IL-17 concomitantly [110]; this combination of cytokines has been demonstrated to produce a synergistic effect on cultured human vascular smooth muscle cells (VSMC), leading to the secretion of IL-6, CXCL8, and CXCL10 which are pro-inflammatory cytokines and chemo kines elevated in atherosclerosis. Moreover, patients with acute coronary syndrome (defined as acute myocardial infarction or unstable angina) show increased levels of Th17-related mediators such as circulating RORγt, plasma IL-17, IL-6, and IL-23 along with decreased levels of circulating Foxp3, plasma IL-10 and TGF-β, all associated with regulatory T cells (Treg) [111], demonstrating a cytokine and cellular milieu reminiscent of psoriasis (Table 1). The profile of a proinflammatory cytokine milieu, increased monocyte/macrophage levels, and decreased Foxp3 in acute coronary syndrome is also reflected in psoriasis [112].

T cells have also been demonstrated to play a critical role in atherosclerotic plaque formation in murine models. $ApoE^{-/-}$ mice fed a high fat diet express higher levels of IL-17 and IFN-γ in $CD4^+$ T cells and macrophages that infiltrate the atherosclerotic plaque in the carotid vascular wall during early (16wk) and late (24wk) atherosclerosis [113] and demonstrate increases in circulating IL-17A levels [114]. Splenic RORγt and IL-17A levels are also increased in $apoE^{-/-}$ mice with the greatest differences observed early in the onset of athero genesis suggesting a pathogenic role for the increase [115]. Aortic $CD4^+$ T cells and $\gamma\delta^+$ T cells from $apoE^{-/-}$ mice produce increased amounts of IL-17A when fed a high-fat diet [114]. The strongest evidence for a role for IL-17A in athero genesis is the observation that functional inhibition of IL-17A using monoclonal antibodies [106] or adenovirus delivered fusion blocking protein [116] in apoe−/− mice fed a high fat high cholesterol diet leads to reduced atherosclerotic lesional area, as well as a decrease in the number of aortic root plaque infiltrating $CD3^+$ T cells [117] and decreases in serum IL-6, G-CSF, CXCL1 and infiltrating aortic macrophages [108]. Moreover, apoE−/− animals back crossed to IL-17−/− mice develop significantly less atherosclerotic plaque, containing less macrophage infiltrate and have reduced levels of MCP-1, IL-1β, IL-6, IFN-γ, and IL-12p40 [116].

4. Conclusion

Psoriasis presents the opportunity to examine and isolate various pathologic cell subsets including IL-17-producing Th17 cells. The ability to obtain these cells makes psoriasis a unique disease that is amenable to isolation of primary cells that are rarely available from other diseases such as atherosclerosis. Because many key immunologic mechanisms are

shared between psoriasis and atherosclerosis, lessons learned from Th17 cells isolated from psoriatic tissue regarding Th17 cell development and activity, Th1–Th17 interplay, monocyte/macrophage interaction with pathogenic T helper cell subsets, etc, may provide key insight into pathological processes occurring in atherogenesis as well. Indeed, it is possible that patients with co-morbid diseases such as psoriasis and atherosclerosis may be at risk for cellular mediators from one disease site exacerbating the co-morbid condition. For instance, skin inflammation associated with increased levels of Th17 cells and their derived cytokines may release pro-inflammatory mediators or even cells themselves that may initiate or participate in other co-morbid conditions such as atherosclerosis, metabolic syndrome or inflammatory bowel disease. If the development of co-morbid conditions is precipitated by inflammatory mediators that initiate with skin disease (in the case of psoriasis) then it is logical to predict that aggressive treatment of the initiating factor may also mediate resolution of the co-morbidities associated with disease. Thus it will be of great interest to follow psoriasis patients treated with current therapeutic regimens, especially the new class of IL-17 inhibitors to determine if a concurrent decrease in co-morbid pathologies is also decreased.

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Highlights

IL-17 plays a critical role in psoriasis pathogenesis.

Targeting IL-17 or IL-17RA significantly improves psoriasis disease severity.

IL-17 may provide a mechanistic link between CVD and psoriasis.

Table 1

Common cell Types and Mediators in Psoriasis and Atherosclerosis

Cytokines	**Psoriasis**	**Atherosclerosis**	**Leukocytes**	**Psoriasis**	**Atherosclerosis**
IL-2	+	+	Th1/Th17 upregulation	+	+
IL-6	+	+	Treg misregulation	+	+
IL-15	+	+	CD4	+	+
IL-17	+	+	CD8	+	+
IL-18	+	+	CLA+ T cells	+	(no)
IL-20	+	+	CD103+ T cells	+	(no)
IL-21	+	(no)	NK cells	+	+
IL-22	+	(no)	NK T cells	+	+
IL-23	+	+	Myeloid dendritic cells	+	+
IFN-α	+	+	Plasmacytoid dendritic cells	+	+
IFN-γ	+	+	Monocytes/macrophages	+	+
Oncostatin M	+	+	Mast cells	+	+
TNF-α	+	+	Neutrophils	+	+
TGF-β	+	+			
VEGF	+	+	Other Cellular Participants		
			Keratinocytes	+	(no)
Chemokines			Endothelial cells	+	+
Fractalkine	+	+	Vascular Smooth Muscle cells	(no)	+
GRO-α	+	+			
IP-10	+	+	Other important molecules		
IL-8	+	+	LL-37	+	+
MCP-1	+	+	CRP	+	+
MIG	+	+	Endothelin-1	+	+
			iNOS	+	+
Adipokines			HSP60	+	+
Resistin	+	+	HSP65	+	+
Leptin	+	+	HSP70	+	+
PAI-1	+	+	MMP-2	+	+
			MMP-9	+	+

Cytokines	Psoriasis	Atherosclerosis
Adhesion and co-stimulatory molecules		
CD80, CD28	+	+
CD40/CD40L	+	+
ICAM/LFA-1	+	+
OX40/OX40L		
(CD134/CD134L)	+	+
VCAM-1/VLA-4	+	+

Leukocytes	Psoriasis	Atherosclerosis
Oxidized LDL	+	+
S100A7	+	(no)
S100A8/A9	+	+
TLR2	+	+
TLR4	+	+
TLR9	+	+
EDA-Fibronectin	+	+