Identifying a Potential Therapeutic Host Target in Cutaneous Leishmaniasis

David O. Croitoru and Vincent Piguet

Intracellular cutaneous infectious agents can trigger autoreactive immune responses, exacerbating or leading to new acute and chronic systemic illness. Cutaneous leishmaniasis (CL) causes vigorous immunopathologic responses that contribute to mucosal disease and ulceration. In this issue of the Journal of Investigative Dermatology, Novais et al. (2020) expand on their previous work demonstrating that a cytotoxic CD8⁺ response is associated with therapeutic failure. In this study, they show that inhibition of granzyme B with the Jak1/3 inhibitor, tofacitinib, is associated with decreased severity of cutaneous lesions without the attenuation of T helper type 1 signaling or parasite control. Their findings, including the utility of topical delivery, suggest an attractive role for Jak inhibition alongside antiparasitic agents in the treatment of CL in patients.

"Blocking CD8 cytolyis with tofacitinib lessens the severity of cutaneous leishmania in mouse models where CD8 T cells are known to kill Leishmania-infected cells."

Clinical importance
Cutaneous leishmaniasis (CL) is a poverty-associated protozoan disease that manifests in mucocutaneous and visceral forms and is transmitted by the sand flies Lutzomyia and Phlebotomus (Reithinger et al., 2007). There are more than 20 species (spp.) of Leishmania that are endemic in Central and/or South America, Africa, and Asia, with an estimated 0.7–1 million new cases annually (Reithinger et al., 2007; Scott and Novais, 2016). Certain spp. of both Old World (L. aethiopica) and New World CL (L. mexicana, L. amazonensis, L. viannia) can lead to disseminated cutaneous or mucosal disease with debilitating sequelae. To mitigate the risk of mucosal spread, higher risk spp. such as L. viannia spp. are often treated with systemic therapies including pentavalent antimony, amphotericin B, paromomycin, and miltefosine (Reithinger et al., 2007; Scott and Novais, 2016; Soto et al., 2004).

Transcriptional cytokine profiling of CL
The inflammatory signaling cascades in CL lesions and the subsequent polarization of immune responses are dependent on host factors as well as Leishmania spp. Early murine models suggested that a CD4⁺ T helper type (Th) 2–driven response predicted CL disease severity (Scott and Novais, 2016). However, more recent studies have demonstrated that increased IL-10 leading to reduced dendritic cell (DC) activation and CD8⁺ cytolysis is also associated with poor prognosis (Scott and Novais, 2016; Soong, 2008). Novais et al. (2015) have expanded their previous work, which demonstrated an immunopathogenic role for CD8⁺ cytolytic T cells in cases of treatment failure, by reanalyzing their previously published mRNA dataset for CD132 family cytokines (n = 10 normal skin biopsies, n = 25 L. [viannia] braziliensis infected). In these transcriptional profiles, they found that IL-15 was the only differentially expressed cytokine in the infected lesions compared with that in normal skin (Novais et al., 2020).

The role of Jak3 signaling in CD8⁺ granzyme B expression
There is precedent for IL-15 inducing CD8⁺ T-cell cycling and granzyme B production in both murine and human ex vivo models (Younes et al., 2016). Granzyme B, rather than perforin, has been implicated in the pathogenesis of CD8⁺ cytolytic responses in ulcerated and mucosal CL (Scott and Novais, 2016). Novais et al. demonstrate increased granzyme B production in CD8⁺ T cells of murine splenocytes after incubation with IL-15. They also show that granzyme B production is completely inhibited by the addition of the Jak1/3 inhibitor, tofacitinib (Novais et al., 2020). Notably, the authors detected a modest decrease (20%) in IFN-γ production by CD8⁺ cells without significant impairment of CD4⁺ Th1 IFN-γ production (Novais et al., 2020).

Systemic tofacitinib does not attenuate Th1 response
To functionally interrogate the effect of Jak inhibition on the Th1 response, which is suspected to help control Leishmania through IFN-γ, activation of macrophages, and eventual long-term immunity (Scott and Novais, 2016), Novais et al. (2020) assessed delayed hypersensitivity (Gell-Coombs type 4) in vivo. They sensitized immunocompetent mice to L. major in one ear and rechallenged in the contralateral ear at >10 weeks after infection. Delayed...
Clinical Implications

- Transcriptional data from human biopsies demonstrate an upregulation of IL-15 and granzyme B in CD8+ cells in lesions of cutaneous leishmaniasis.
- In murine models, tofacitinib (Jak1/3 inhibition) attenuates granzyme B expression but not IFN-γ, and it does not impair T helper type 1 responses.
- In RAG+CD8 mice, tofacitinib decreases the number and severity of ulcers during Leishmania (viannia) braziliensis infection.

Systemic tofacitinib mitigates CD8+ mediated disease
To explore the potential therapeutic benefit of inhibiting the activity of pathogenic cytolytic CD8+ T cells with systemic Jak inhibitors, Novais et al. (2020) used a RAG-deficient murine model reconstituted with CD8+ T cells. This model has been demonstrated to develop severe CL with increased granzyme B expression and lesional neutrophil recruitment (Novais et al., 2013). In this study, RAG+CD8 mice infected with L. (viannia) braziliensis treated with tofacitinib from 2 weeks after infection developed fewer and smaller lesions of CL. Interestingly, despite decreased neutrophil recruitment and granzyme B-expressing CD8+ cells, parasite numbers remained equal between the groups (Novais et al., 2020).

Recruitment of bystander CD8+ T cells to lesions of CL during viral co-infection has also been shown to contribute to keratinocyte lysis in an IL-15-dependent manner, and this is associated with worsened disease (Crosby et al., 2015). In murine models of leishmaniasis, coinfection with lymphocytic choriomeningitis virus (LCMV) has been shown to increase lesional populations of NKG2D+CD8+ T cells and worsen disease burden (Crosby et al., 2015). To study Jak inhibition in this model, Novais et al. (2020) coinfeated L. (viannia) braziliensis+RAG+CD8 mice at 2 weeks with LCMV and then treated them with tofacitinib injections. They again saw decreases in the severity of CL ulcers with no significant changes in parasite numbers (Younes et al., 2016).

Topical tofacitinib reduces cutaneous severity in murine models
Given that topical tofacitinib is effective in selected dermatologic disorders (eczema, alopecia areata) without causing systemic toxicity (Schwartz et al., 2017), this approach was also explored using the RAG+CD8 model. The authors again found significant reductions in lesion counts, neutrophil recruitment, and granzyme B production by CD8+ T cells after tofacitinib treatment (Younes et al., 2016).

Expanding model complexity to investigate mucocutaneous control and prognosis
Through three mouse models, Novais et al. (2020) have additionally defined the role of pathogenic cytolytic CD8+ in CL and highlighted Jak1/3 as a possible host target (summary, Figure 1). As the authors describe in their discussion, the interplay of host immunity and virulent factors in CL is complex. It has been demonstrated that even the saliva of the sand fly vector contributes to blunted neutrophil responses to promastigotes before macrophage infiltration (Scott and Novais, 2016). Future studies of tofacitinib’s utility in additional murine and human models may serve to define the role of Jak inhibition in nonlymphoid cells, given the role of neutrophil infiltration, as well as DCs in IL-12 production and the protective role of monocytes (Scott and Novais, 2016). The work of Novais et al. (2020), discussed in this paper, suggests the rational combination of host-directed Jak inhibition and antiparasitic therapy as a possible strategy for the treatment of CL.

Figure 1. CD8+ -reconstituted RAG mice injected with Leishmania spp. and treated with tofacitinib have decreased lesional CD8+ T cells and granzyme B production, with reduced disease severity and no change in Leishmania parasite number, spp., species; Th1, T helper type 1.
Psoriasis is a common chronic immune-mediated inflammatory disease (IMID) characterized by varying severity and clinical presentations. Data from the Global Psoriasis Atlas indicate that its prevalence in adults varies from 0.17% in East Asia to 2.50% in Western Europe and also reveals that an estimated 60 million people suffer from psoriasis worldwide (https://globalpsoriasisatlas.org). The pathophysiology of psoriasis is complex and involves an interplay between cells of the innate (dendritic cells, macrophages, neutrophils, keratinocytes [KCs]) and adaptive (T cells) arms of the immune system as well as multiple cytokines with predominantly regulatory (IL-1, IL-6, IL-8, TGF-β, IL-23) or effector (IL-22, IL-17, TNF, IFN-γ, and IL-12) functions.

Psoriasis is increasingly considered as a systemic IMID. In addition to the characteristic cutaneous manifestations, psoriasis is often associated with other inflammatory conditions, including psoriatic arthritis (PsA), inflammatory bowel disease (IBD), and metabolic syndrome, a constellation of cardiovascular risk factors that includes obesity, hypertension, hyperlipemia, and insulin resistance. Whether or not psoriasis is a contributing factor or an independent risk factor for the development of metabolic syndrome remains unclear, as does the identity of cytokines that may act as drivers of metabolic syndrome. However, the presence of comorbidities and the severity of psoriasis are of great clinical relevance and may guide the clinician’s therapeutic strategy. Cardiovascular disease and the often-associated metabolic syndrome are of concern to the clinician and the patient because they may have a considerable impact on patient life expectancy, especially in the case of severe psoriasis. It is therefore important to detect comorbidities early and to identify optimal therapeutic strategies aimed at reducing skin manifestations of psoriasis and also associated systemic inflammation with its potentially severe consequences.

Verma et al. (2021) provide circumstantial evidence that patients with psoriasis exhibit higher circulating levels of the proinflammatory cytokines IL-1β and IL-18 and that patients treated with TNF antagonists had