Toxic Memories in Systemic Sclerosis

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Systemic sclerosis is an autoimmune disease characterized by T-cell infiltration in the skin that leads to fibrosis, which can be life-limiting. Although T cells are important, it is not known which types mediate the fibrosis. The work presented by Li et al shows that memory CD8⁺ cytotoxic T cells mediate fibrosis via the secretion of IL-13. IL-13 is profibrotic, and it is released in a higher amount in patients with systemic sclerosis. This suggests that targeting IL-13 may be therapeutically beneficial.


Neuralization of IL-13 reduced T cell-derived dermal fibrosis.

In this issue, Li et al. (2017) have shown that CD8⁺/CD28⁻ T cells have a profibrotic phenotype in SSc (Li et al., 2017). Their study found increased percentages of circulating CD8⁺/CD28⁻ T cells in patients with SSc compared with age-matched control subjects. Patients with diffuse cutaneous SSc had a higher median percentage of circulating CD8⁺/CD28⁻ T cells than patients with limited cutaneous SSc. This suggests a role for this particular subset of T cells in diffuse cutaneous SSc, where they may exacerbate fibrosis through aberrant cytokine production. Moreover, after adjusting for age, the modified Rodnan skin score correlated highly with CD8⁺/CD28⁻ T-cell frequency ($r = 0.72$; $P < 0.001$).

The study (Li et al., 2017) then compares the cytokine production of skin and blood CD8⁺/CD28⁻ T cells, finding a substantial increase in IL-13—positive and IFN-γ—positive CD8⁺/CD28⁻ T cells in the skin. Furthermore, supernatants from CD8⁺/CD28⁻ T cells were added to both normal dermal fibroblasts and SSC fibroblasts, showing a significant increase in COL1A1 production. This could be attenuated with an IL-13—neutralizing antibody in both normal and SSC dermal fibroblasts. Li et al. conclude that this is a critical role for CD8⁺/CD28⁻ T cells produce IL-13, thereby sustaining the accumulation of extracellular matrix proteins, as well as fibrosis. The evidence presented indicates that CD8⁺/CD28⁻ T cells are involved in the pathogenesis of SSc, with a direct implication that they mediate dermal fibrosis. We had also shown previously the role of IL-13 in mediating fibrosis released from SSC T cells; however, we did not identify the T-cell subset that was responsible (Hüggle et al., 2013). Li et al. not only identify the T-cell subset responsible for the high IL-13 production but also report that the CD8⁺CD28⁻IL-13⁺ subset may be found in much higher numbers in the skin of patients than in matched donors, suggesting an important early event.

SSC has few effective therapies; however, the work presented by Li et al. (2017) allow new insight into the complex mechanisms that underlie the disease and suggest that IL-13 may be a therapeutic target. IL-13 signals through IL-13Rα1 and a shared receptor, IL-4R, to elicit downstream signaling via STAT6 in dermal fibrosis (O’Reilly et al., 2016). Lebrikizumab is a monoclonal antibody from Roche (Basel, Switzerland) that targets and neutralizes IL-13. Studies with it are now taking place for patients with asthma and idiopathic pulmonary fibrosis, and we suggest it may be a therapeutic option for SSC, which to date has no accepted treatment. Because of the heterogeneity

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of the disease, using CD8^+ CD28− IL-13^+ T cells as a biomarker to guide treatment may also be useful.

CONFLICT OF INTEREST
The authors state no conflict of interest.

REFERENCES


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Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Associations, Outcomes, and Pathobiology Thirty Years of Progress but Still Much to Be Done
Robert S. Stern and Sherrie J. Divito

Although rare, Stevens-Johnson syndrome and toxic epidermal necrolysis remain among the most devastating of acute conditions involving the skin. In the past 30 years, tremendous progress has been made in understanding the causes and pathobiology of this often life-threatening condition. Su et al demonstrate associations between IL-15 serum levels and the outcome of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. Their findings provide ideas for further investigations that may help us better understand the role of cytokines in this T-cell mediated disease and provides clues to possible new therapies.

The clinical spectrum of SJS/TEN
For any prognostic test to be useful, the disease to which it is applied must be defined precisely, that is, there should be a close to as possible gold standard definition of that condition. More than 40 years ago, clinical, bacteriologic,