VASCULITIS SYNDROMES

T cells turned killer by IL-15 attack the endothelium in GPA

A subpopulation of CD4⁺ T cells in patients with granulomatosis with polyangiitis (GPA, formerly Wegener's vasculitis) expresses a receptor usually found on natural killer (NK) cells, clonally expands in response to IL-15, and acquires an NK-like phenotype. Cytotoxic to vascular endothelial cells, this T-cell subset might be responsible for the vascular injury that occurs in the patients with GPA in whom localized granulomatous inflammation progresses into diffuse vasculitis, report Sophie Caillat-Zucman *et al.* The pathogenesis of GPA, and why it sometimes progresses to diffuse disease, are largely unknown.

Caillat-Zucman and colleagues study dysregulated signaling involving NKG2-D type II integral membrane protein in human disease, and the relationship between activation of NKG2-D (which itself activates NK cells) and aberrant expression of IL-15. They turned their focus to GPA after data from other groups showed the presence of autoreactive

NKG2-D⁺ CD28⁻ CD4⁺ T cells in rheumatoid arthritis, and the presence of CD28⁻ CD4⁺ T cells in the granulomatous lesions of GPA.

With phenotypic and functional analysis of CD4⁺ T cells from 90 patients with GPA (some with localized and others with generalized inflammation) and 39 age-matched controls, the researchers found not only that the proportion of NKG2-D⁺ CD4⁺ T cells was increased in the people with GPA, but also, in quantifying the expansion, that a cutoff value of 3% NKG2-D⁺ CD4⁺ T cells gave 100% specificity (and 45.3% sensitivity) for those with generalized vasculitis.

"We thus raised the hypothesis that these cells might be deleterious to the vascular endothelium", says Caillat-Zucman. Supporting this theory, other activating NK cell receptors and their signaling partners were also found to be expressed by the cells. "Indeed," continues Caillat-Zucman, "we observed that NKG2-D⁺ CD4⁺ T cells behave as NK-like cells, with

MHC-independent lytic capacity toward vascular endothelial cells. Finally, we found that these cells were expanded and activated by IL-15."

Macrophages (a major cellular component of the granuloma in GPA) express IL-15, and the researchers propose that generalized GPA develops in two steps: granuloma formation triggered by an unknown antigen involves clonal expansion of antigen-specific CD4⁺ T cells, which then become NK-like in some patients as a consequence of excessive IL-15 trans-presentation within the granuloma. Thus, the IL-15 pathway might provide new therapeutic targets for the treatment of generalized GPA.

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Original article de Menthon, M. *et al.* Excessive IL-15 transpresentation endows NKG2D⁺ CD4⁺ T cells with innate-like lytic capacity to vascular endothelium in Wegener's vasculitis. *Arthritis Rheum.* doi:10.1002/art.30355