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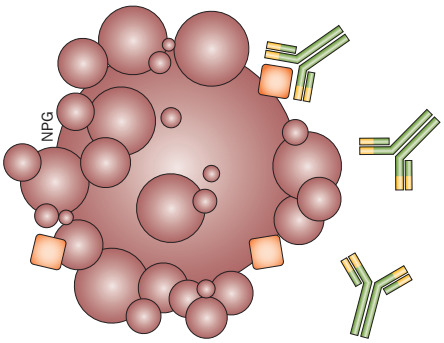
VASCULITIS SYNDROMES

PR3 on apoptotic cells promotes inflammation in GPA

New research provides insights into the involvement of leukocyte proteinase 3 (PR3, also known as myeloblastin), and of anti-neutrophil cytoplasmic antibodies directed against this serine protease (PR3-ANCAs), in the pathophysiology of granulomatosis with polyangiitis (GPA). Building on previous work showing that PR3 expressed on apoptotic neutrophils impairs resolution of inflammation by interfering with phagocytosis of these cells by macrophages (efferocytosis),



Millet *et al.* now suggest that this membrane-bound PR3 also perpetuates inflammation through macrophage polarization and effects on plasmacytoid dendritic cell (pDC)–T-cell interactions.

In mice, intraperitoneal injection of apoptotic cells expressing enzymatically active PR3 on the cell membrane, but not control apoptotic cells, led to increased expression of proinflammatory cytokines and chemokines, and decreased expression of the M2 macrophage marker CD206. Experiments using macrophages isolated from *Il1r1*$^{-/-}$, *Myd88*$^{-/-}$ and *Nos2*$^{-/-}$ mice demonstrated that the inflammatory response induced by efferocytosis of PR3-expressing apoptotic cells depended on the IL-1 receptor–MyD88 signalling pathway and on nitric oxide production.

In cell-injection mouse models, pDCs exposed *in vivo* to PR3-expressing apoptotic cells induced T helper (T_H)2 cell and T_H9 cell production. Notably, the addition of PR3-ANCAs induced T_H17 cell polarization. Highlighting the clinical relevance of the findings, CD4 T cells from patients with active GPA had skewed T_H9:T_H2:T_H17 cell ratios, and granulomatous lung tissue showed pDCs in close proximity to macrophages and PR3-expressing apoptotic neutrophils.

Together, the results suggest PR3 expressed on the membrane of apoptotic cells acts as a 'danger' signal, and that PR3-ANCA-associated vasculitis might be considered not only as an autoimmune disease, but also as a typical nonresolving autoinflammatory disease. The authors contend that these insights into the role of PR3 and PR3-ANCAs in GPA could inform the development of new therapies.

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Original article Millet, A. *et al.* Proteinase 3 on apoptotic cells disrupts immune silencing in autoimmune vasculitis. *J. Clin. Invest.* doi:10.1172/JCI78182