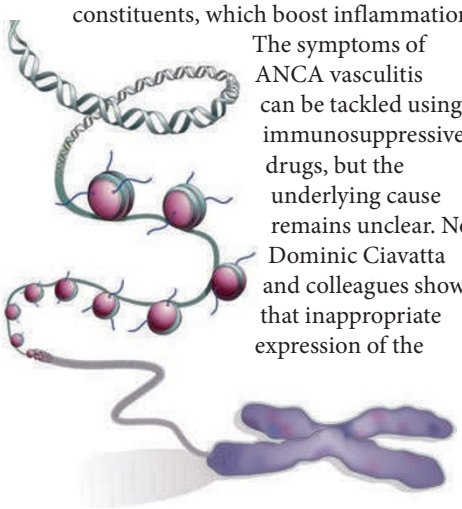
VASCULITIS SYNDROMES

Silence is golden as epigenetic mechanisms are blamed for autoantigen expression in ANCA vasculitis

In patients with systemic small-vessel vasculitis, microvascular inflammation and damage are caused by aberrant activation of neutrophils, induced by circulating antineutrophil cytoplasmic autoantibodies (ANCAs). Activated neutrophils release pre-formed granule constituents, which boost inflammation.



The symptoms of ANCA vasculitis can be tackled using immunosuppressive drugs, but the underlying cause remains unclear. Now Dominic Ciavatta and colleagues show that inappropriate expression of the principle autoantigen targets of ANCAs, proteinase 3 (PR3) and myeloperoxidase (MPO), stems from a failure of transcriptional silencing mechanisms in neutrophils.

PR3 and MPO are granule proteins whose genes are normally only expressed during neutrophil development; they are silent in healthy mature neutrophils. However, *PR3* and *MPO* messenger RNAs are present in mature neutrophils from patients with ANCA vasculitis; if these transcripts are translated into protein, the availability of these autoantigens could increase. Are the *PR3* and *MPO* genes actively transcribed in ANCA neutrophils, and could their overexpression result from failed epigenetic silencing? Ciavatta *et al.* set out to investigate.

The researchers examined whether histone modifications associated with epigenetic silencing were depleted in *PR3* and *MPO* from ANCA neutrophils compared to those from healthy controls. A CpG island in *MPO* from ANCA cells was unmethylated. Furthermore, levels of trimethylation at lysine 27 of histone H3 were reduced at the two loci in ANCA cells. The group discovered that this deficiency stemmed from both failed methylation and aberrant demethylation mechanisms, which potentially underpin the etiology of ANCA vasculitis.

"Our work highlights the importance of the epigenetic status of neutrophils," says Ciavatta. "This research implies that therapies against factors that determine the epigenetic state should be tested for efficacy in patients with ANCA disease."

Emma Leah

Original article Ciavatta, D. J. *et al.* Epigenetic basis for aberrant upregulation of autoantigen genes in humans with ANCA vasculitis. *J. Clin. Invest.* **120**, 3209–3219 (2010)
Further reading Chen, M. & Kallenberg, C. G. M. ANCA-associated vasculitides—advances in pathogenesis and treatment. *Nat. Rev. Rheumatol.* **6**, 653–664 (2010)