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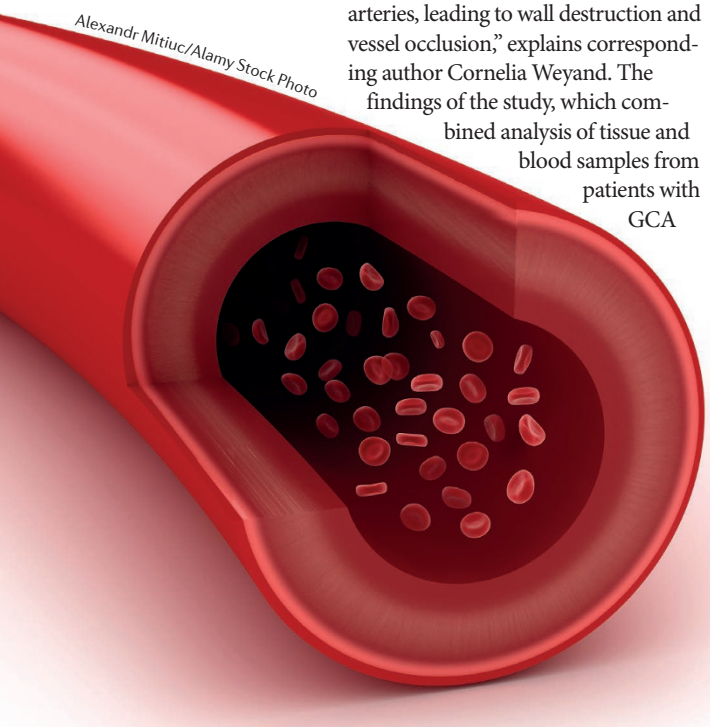
VASCULITIS SYNDROMES

Loss of immunoinhibitory checkpoint implicated in GCA

> PD1$^+$ T cells in the inflamed vessel wall produced effector cytokines...

Therapeutic blockade of immunoinhibitory checkpoints has proved phenomenally successful in the treatment of many cancers: by hindering the function of inhibitory receptors such as programmed cell death protein 1 (PD1), checkpoint blockers 'unleash' anti-tumour immune responses. However, the effects of immune checkpoint deficiency on susceptibility to spontaneous autoimmune disease is unclear. New research published in *Proceedings of the National Academy of Sciences USA* implicates deficiency in the PD1–programmed cell death protein 1 ligand 1 (PDL1) pathway in the pathogenesis of giant cell arteritis (GCA), a form of autoimmune vasculitis.

"In [GCA], granulomatous infiltrates (CD4$^+$ T cells, dendritic cells, macrophages) attack the walls of arteries, leading to wall destruction and vessel occlusion," explains corresponding author Cornelia Weyand. The findings of the study, which combined analysis of tissue and blood samples from patients with GCA and experiments in a humanized mouse model of vasculitis, suggest that a breakdown in the inhibitory PD1–PDL1 pathway promotes ischaemic organ damage, and that activation of this checkpoint could be a novel strategy for the treatment of autoimmune vasculitis. "We need to develop means to reconstitute that negative signalling," Weyand suggests.



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Transcriptome analysis revealed PD1 was present at high concentrations in GCA-affected arteries, whereas expression of the inhibitory ligand PDL1 was low. "We localized PDL1 expression to dendritic cells in the tissue," recounts Weyand. "The PDL1^{lo} phenotype was also present in *ex vivo* generated dendritic cells from patients (compared to age-matched controls). Indeed, the intensity of PDL1 expression correlated inversely with the intensity of inflammation measured by acute phase reactants," she continues. Analysis of the tissue-infiltrating T cells in granulomatous lesions revealed that the majority expressed PD1. "We concluded that the lack of PDL1 signalling (which provides a negative signal) enabled PD1$^+$ T cells to infiltrate the tissue, survive, and remain activated," says Weyand.

The investigators next turned to a model system of vasculitis induction in human artery–severe combined immunodeficiency (SCID) mouse chimeras. "We create this model by engrafting human medium-sized and large arteries into immune-deficient mice and then we reconstitute[d] the mice with the patient's immune system," Weyand explains. "We [could] then measure the vasculitis-inducing potential of the patient's immune system by harvesting the engrafted human arteries and analyse the infiltrates in the vessel wall." In this model, inhibition of PD1–PDL1 interaction by use of an anti-PD1 antibody enhanced T cell recruitment and retention in the engrafted human arteries and exacerbated vascular inflammation.

PD1$^+$ T cells in the inflamed vessel wall produced effector cytokines including IFNγ, IL-17 and IL-21. "To our surprise, the frequency of PD1$^+$ T cells in the vasculitic infiltrates correlated tightly with the intensity of microvessel formation and with the thickening of the intimal layer," Weyand reveals. "Neoangiogenesis and intimal hyperplasia are the two major mechanisms that cause the pathologic complications of GCA — the occlusion of the vascular lumen and the subsequent ischaemia of the tissue. Thus, PD1–PDL1 signalling has a direct impact on the remodelling of the vascular wall," she concludes.

Together, the results of the study shed light on the disease process of GCA and suggest new avenues for immunomodulatory treatment. Another consideration is that patients treated with checkpoint inhibitors can develop drug-induced autoimmunity. "We should be prepared to see cases of drug-induced vasculitis as the use of checkpoint inhibitors increases in [patients with cancer]," Weyand notes.

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ORIGINAL ARTICLE Zhang, H. *et al.* Immunoinhibitory checkpoint deficiency in medium and large vessel vasculitis. *Proc. Natl Acad. Sci. USA* http://dx.doi.org/10.1073/pnas.1616848114 (2017)
FURTHER READING van der Vlist, M. *et al.* Immune checkpoints and rheumatic diseases: what can cancer immunotherapy teach us? *Nat. Rev. Rheumatol.* **12**, 593–604 (2016)