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Autoantibodies with a silver lining?

Autoantibodies are typically associated with immunopathology, but a recent study in *Cell* has identified a tissue-protective role for such antibodies. Meyer *et al.* report that patients with autoimmune polyendocrine syndrome type 1 (APS1; also known as APECED) produce type I interferon (IFN)-specific neutralizing autoantibodies that protect against the development of type 1 diabetes (T1D).

Patients with APS1 have defects in autoimmune regulator (AIRE), a transcription factor that regulates the expression of tissue-specific antigens and promotes T cell central tolerance. These patients are known to develop autoantibodies against self-proteins, including type I IFNs and interleukin-17 (IL-17); however, no large-scale analysis of their autoantibody repertoire had ever been undertaken. Meyer *et al.* used a ProtoArray displaying ~9,000 human proteins to assess the self-reactivity shown by sera from 81 patients with APS1. Collectively, patients showed strong reactivity against more than 40% of the proteins tested. The specific repertoires of proteins recognized by individual patients were highly variable, but cytokines were commonly targeted. Furthermore, 12 proteins were targeted by more than 60% of the patients, and these 'public' specificities included several type I IFNs and T helper 17 (T_H17)-type cytokines.

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Additional analyses showed that all 13 IFNα subtypes and IFNω were common targets of the autoantibodies of patients with APS1, but IFNβ was rarely targeted. To better understand the nature of the autoantibodies, the authors characterized nine IFNα-specific monoclonal antibodies derived from four patients with APS1. These IFNα-specific antibodies had highly mutated variable regions, appeared to bind epitopes shared by several IFN subtypes and showed extremely high affinity for their targets. Reporter assays showed that two of the patient-derived antibodies (19D11 and 26B9) could neutralize IFN-dependent responses at lower doses than sifalimumab and rontalizumab, which are anti-IFN monoclonal antibodies that have been used in clinical trials. Interestingly, although 26B9, sifalimumab and rontalizumab varied in their ability to neutralize different IFNα subtypes, 19D11 neutralized all IFNα subtypes tested.

Patient-derived antibodies targeting IL-17F, IL-22, IL-32γ and IL-20 also showed neutralizing activity *in vitro*, so the authors assessed whether these autoantibodies could neutralize their targets *in vivo*. Indeed, intraperitoneal delivery of patient-derived monoclonal antibodies to mice protected against ear swelling induced by intradermal injection of the target cytokine. Furthermore, a patient-derived autoantibody targeting IL-22 significantly reduced pathology in a mouse model of psoriasis.

Given these findings, the authors were interested in determining how the autoantibodies produced by patients with APS1 affect the patients themselves. Type I IFNs have been linked to the development of T1D, and many patients with APS1 have GAD65-reactive autoantibodies (which are also associated with T1D) but do not present with this disease. To assess whether IFN-neutralizing autoantibodies may protect against T1D development, the authors compared 8 patients with APS1 who had presented with T1D with a cohort of 13 patients with APS1 who had not developed T1D but showed strong GAD65 reactivity. All of the patients had autoantibodies to IFNα and IFNω; however, although the autoantibodies from the patients without T1D effectively neutralized IFNs, the autoantibodies from patients with T1D showed low or negligible neutralizing activity.

These data not only show that the production of autoantibodies can be protective in certain instances but also indicate that targeting type I IFNs may be effective against T1D. The authors suggest that further study of patients with APS1 could identify other protective autoantibodies with clinical applications. In support of this, only two of the patients involved in this study developed psoriasis, and both of these individuals lacked autoantibodies for T_H17-type cytokines.

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ORIGINAL ARTICLE Meyer, S. *et al.* AIRE-deficient patients harbor unique high-affinity disease-ameliorating autoantibodies. *Cell* http://dx.doi.org/10.1016/j.cell.2016.06.024 (2016)