

Journal Club

PREPRINT WATCH


**TARGETING AUTOANTIBODIES
IN COVID-19**

Autoantibodies to host proteins can trigger or exacerbate disease by perturbing target-dependent biological pathways, directing cell lysis and/or triggering inflammation. Although the generation of these antibodies is constrained by tolerance mechanisms, some autoantibody production is detectable in healthy individuals. An increased prevalence of more diverse autoantibodies has been reported in several inflammatory settings, including chronic viral infections. However, the breadth of antigens that are targeted and the ensuing pathophysiological effects are poorly understood.

In this preprint (non-peer-reviewed), Wang et al. used a novel high-throughput assay to quantitate circulating antibodies reactive with 2,770 secreted and cell surface-expressed human proteins in individuals infected with SARS-CoV-2 and control subjects. This work provided unprecedented insight into pre-existing and COVID-19-associated autoantibody reactivities and their contribution to pathogenesis. More proteins were targeted in infected individuals, with patients with severe COVID-19 exhibiting higher-level reactivity to the greatest number of antigens.

Notably, autoantibody reactivities found in patients with COVID-19 included many that targeted immune-relevant proteins such as cytokines (for example, type I interferons), chemokines or their receptors, as well as particular leukocyte subsets (B cells, T cells, natural killer cells and monocytes). These antibodies had immunomodulatory effects in vitro and were associated with virological and immune parameters in vivo. Blockade of key innate cytokine pathways exacerbated disease in a murine model of SARS-CoV-2 infection. Other autoantibodies in individuals infected with SARS-CoV-2 recognized tissue-associated antigens from sites including blood vessels and the brain and correlated with clinical markers of inflammation and disease severity.

The findings reported suggest pivotal immune-modulatory and effector roles for diverse autoantibodies in COVID-19 pathogenesis and prompt future work to investigate the persistence of tissue-targeted autoantibodies and their putative contribution to the long-term effects of COVID-19. It is unclear whether the remarkable breadth of autoantibody reactivities in patients with COVID-19 highlighted by this study reflects enrichment for individuals with rare pre-existing autoantibodies and/or perturbation of humoral immunoregulation in the inflammatory environment induced during infection. Understanding the mechanisms that drive these autoantibody responses could inform strategies to ameliorate severe COVID-19 and to treat 'long COVID'.

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ORIGINAL ARTICLE Wang, E. Y. et al. Diverse functional autoantibodies in patients with COVID-19. Preprint at medRxiv <https://doi.org/10.1101/2020.12.10.20247205> (2021)

RELATED ARTICLE Pedroza-Pacheco, I. Oxford–Mount Sinai (OxMS) Preprint Journal Club. OxMS <https://www.preprintclub.com/2021-jan-wang> (2021)

MAIT cells boost adenovirus-induced CD8⁺ T cells

Mucosal-associated invariant T (MAIT) cells are unconventional T cells that can act as innate sensors for viruses in mucosal tissues. Provine et al. now demonstrate that the ChAdOx1 virus, of recent fame as a vector for one of the first approved vaccines against SARS-CoV-2, robustly activates MAIT cells and that these cells play a central role in activating CD8⁺ T cell responses to vaccine-encoded antigens.

MAIT cells specifically recognize microbially derived metabolites of vitamin B₂ synthesis but can also be activated via cytokines produced by virus-infected antigen-presenting cells. For example, they are known to amplify the early local immune responses to influenza infection. The authors hypothesized that these cells may also play a role in the immunogenicity of vaccines based on replication-incompetent adenoviral vectors like ChAdOx1.

Indeed, they found that stimulation of human peripheral blood mononuclear cells (PBMCs) with ChAdOx1 induced a dose-dependent upregulation of CD69, granzyme B and IFN γ in MAIT cells, indicating activation. Significant MAIT cell activation was detected after immunization of human volunteers with ChAdOx1, which correlated with an increase in plasma levels of IFN γ . RNA sequencing of human MAIT cells after ChAdOx1 stimulation revealed a strong induction of type I interferons and the IL-1, IL-12 and IL-2 family signalling pathways.

Next, the authors sought to investigate how these MAIT cells are activated. They found that ChAdOx1 mainly infects monocytes, conventional dendritic cells and CD123⁺ plasmacytoid dendritic cells (pDCs). Using in vitro analysis and various knockout mice,

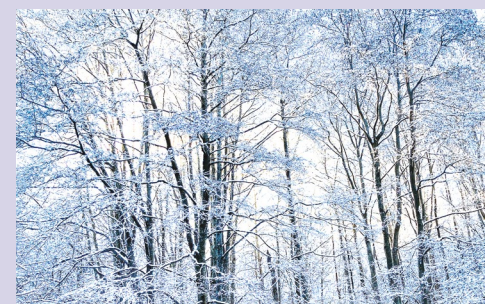
Mutant p53 chills tumours by turning off cGAS

The tumour microenvironment can be referred to as 'hot' or 'cold' depending on whether it contains immune cells with anti-tumour or pro-tumour functions. A recent study in *Cancer Cell* has found that mutant p53 (mtp53) proteins can promote tumorigenesis by inhibiting the cGAS–STING signalling pathway and rendering tumours immunologically cold.

Cancer cells have aberrantly high levels of cytoplasmic DNA and these can be detected by cGAS; this leads to downstream formation of STING–TBK1–IRF3 complexes, in which IRF3 is phosphorylated and activated by TBK1. Activated IRF3 enters the nucleus to upregulate type I interferons or can translocate to the mitochondria to induce apoptosis, and these IRF3-driven responses protect against tumorigenesis.

However, in some cancer cells the cGAS–STING pathway cannot activate IRF3 (despite high levels of cytoplasmic DNA) and instead promotes metastasis.

Ghosh et al. assessed whether mtp53 proteins with mutations affecting the DNA-binding domain (which typically inactivate the tumour suppressor function of p53 and cause gain-of-function oncogenic activity) interfere with the cGAS–STING



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