ing it harder to achieve the requisite multilog reductions. Even if a way can be found to safely induce all replication-competent proviruses, it will be necessary to ensure that all of the infected cells are killed, a problem confounded by immune exhaustion and viral escape mutations. Other strategies that focus on the excision of latent proviruses or permanently silencing them face similar problems related to the scale of the effect needed to produce a cure.

An alternative approach to reservoir reduction, which is known as "functional cure," involves the induction of immune responses that will keep viral replication in check so that viremia remains undetectable with clinical assays. In this situation, disease progression and virus transmission are unlikely even though the reservoir persists. Precedent for immune control comes from the rare individuals (1/300) who spontaneously control HIV-1 replication without ART (*13*). Extensive studies indicate that control is most likely mediated by HIV-1–specific cytolytic T lymphocytes. Unfortunately, it has not yet been possible to induce this degree of control in most people with HIV-1 using therapeutic vaccines. Broadly neutralizing antibodies (bNAbs) to the HIV-1 envelope protein can delay rebound and contribute to lower levels of postrebound viremia in recipients with sensitive virus, although some of the observed effects may be related to direct neutralization by trace residual levels of the bNAbs (*14*). It is also important to note that the autologous neutralizing antibody response can prevent outgrowth of a substantial but variable fraction of HIV-1 variants in the latent reservoir (*15*). Together, these results suggest that preventing viral rebound and thus achieving a functional cure may depend on enhancing virus-specific humoral immunity to cover all reservoir variants. Although shock-and-kill strategies are unlikely to produce the degree of reservoir reduction required for cure, reservoir reduction will facilitate immune control, and thus these strategies may be a useful adjunct to immune-based cure efforts. ■

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IMMUNOLOGY

Decoding the autoantibody reactome

Autoantibodies influence a wide range of conditions beyond autoimmune diseases

By **Jillian R. Jaycox[1,2], Yile Dai[1], Aaron M. Ring[2]**

Investigating the causes of individual variation in health outcomes has led to transformative insights into human biology and advances in nearly every branch of medicine. Historically, emphasis has been placed on how genetic factors contribute to phenotypic variation within populations. However, an emerging concept is that self-reactive antibodies (autoantibodies) represent a critical yet largely underexplored factor that influences human health and disease. Investigating autoantibodies and their protective as well as pathological roles in disease may unlock new treatment paradigms, much like the prior study of genetics.

Generated by the humoral immune system, antibodies are capable of specifically binding to virtually any biomolecule target (broadly termed "antigens") (*1*). Although the primary function of antibodies is to provide adaptive immunity against pathogens, invariably some antibodies arise that bind to self-antigens. These autoantibodies elicit a wide range of biological effects, including altering the activity of their targets and immunomodulation (see the figure). Every person carries a distinct array of autoantibodies—an "autoantibody reactome"—offering a potential avenue for trait diversity that mirrors the way genetic differences influence phenotypes.

Autoantibodies are usually known for their etiologic role in mediating autoimmune diseases. Canonically, autoantibodies can drive pathological inflammation within nearly any tissue, notably affecting the skin, joints, muscles, and central nervous system as well as organs such as the thyroid and pancreas (*2*). Similarly, autoantibodies can trigger distinctive syndromes marked by highly specific biological effects, akin to the distinct impact observed with Mendelian single-gene mutations, because they interfere with essential pathways in the body. Notable examples include myasthenia gravis, a neuromuscular disease caused by autoantibodies that inhibit the acetylcholine receptor, and the hyperthyroidism in Grave's disease that is driven by autoantibodies that activate the thyrotropin receptor.

Less appreciated are the more subtle phenotypic effects of autoantibodies that are disease-modifying or even clinically silent until their activity is unmasked in states of stress. A key example of this phenomenon was revealed during the COVID-19 pandemic in which type I interferon (IFN-I)–neutralizing autoantibodies were found to confer up to 200-fold increased risk of death from COVID-19 (*3*). Although they are apparently clinically silent in most circumstances, the prevalence of IFN-I autoantibodies sharply increases with age, peaking at ~4% of individuals over 70 years old (*4*). Consistent with their substantial clinical influence and overall frequency, it is estimated that 20% of all COVID-19 deaths are associated with the presence of IFN-I autoantibodies (*4*). These findings underscore the ability of autoantibodies to reveal both key biological insights [for example, the critical importance of IFN-I in host immunity to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)] and the profound impact that autoantibodies may exert at a population level.

However, autoantibodies are not uniformly deleterious, and in some instances, they may provide protective effects that ameliorate or prevent disease. IFN-I autoantibodies are again instructive. Systemic lupus erythematosus (SLE) is an autoimmune disease that is characterized by elevated IFN-I signaling in >50% of patients. Intriguingly, ~5% of SLE patients have autoantibodies that neutralize IFN-I signaling (*5*). In contrast to COVID-19, these autoantibodies are associated with substantially lower disease activity, presumably by attenuating pathological IFN-I pathway function (*5*). This counterintuitive observation emphasizes the dualistic nature of autoantibodies, demonstrating their ability to confer protective benefits in the very diseases they are typically implicated in causing.

The protective effects of autoantibodies are apparent across numerous diseases. For

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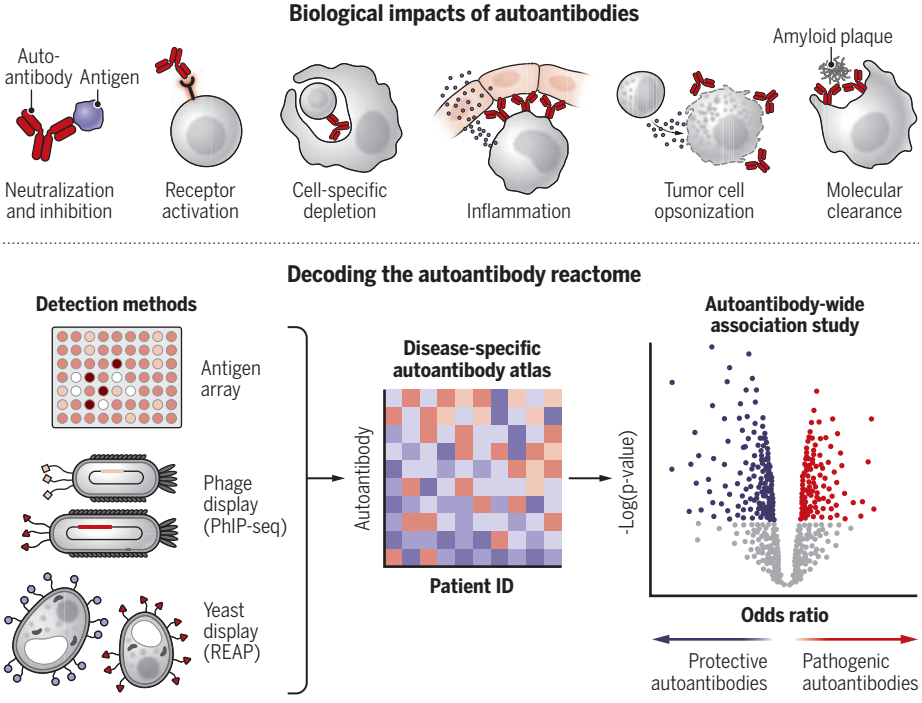
The influence of autoantibodies on health and disease

Autoantibodies elicit a diverse array of biological effects that result in disparate health outcomes, with both pathogenic and protective clinical effects. Emerging autoantibody discovery technologies such as antigen microarrays, phage immunoprecipitation sequencing (PhIP-seq), and rapid extracellular antigen profiling (REAP) now enable "autoantibody-wide association studies" to identify putatively causal autoantibodies present within the autoantibody reactome, analogous to genome-wide association studies. Disease-modifying autoantibodies identified in this way can elucidate new drug targets and provide a template for therapeutic development.



example, the presence of autoantibodies against tumor-associated antigens (TAAs) has long been appreciated to represent a positive prognostic factor for patients with a variety of cancers. Multiple studies have linked TAA-reactive autoantibodies—such as anti–mucin 1 (MUC1) in various epithelial cancers and anti–human epidermal growth factor receptor 2 (HER2) in breast cancer—with better survival and recurrence outcomes in patients (*6*, *7*). These autoantibodies have been hypothesized to elicit immune-directed tumor cell killing, contributing to improved tumor control. In other cases, determining the specific molecular targets of tumor-reactive autoantibodies led to the identification of new TAAs, including NY-ESO, MAGE, BAGE, GAGE, and HOM-MEL-40 (*8*). Cancer autoantibodies have thus provided a key line of evidence to support a role for the immune system in tumor surveillance and revealed previously unidentified targets for cancer therapy. Autoantibodies may have other effects on tumors, such as modulating therapeutic responses, but this requires further research.

Autoantibodies in neurodegenerative diseases provide another example of beneficial autoreactivity. Autoantibodies that recognize amyloidogenic peptides—short fragments of amyloid-β that are prone to form plaques that are implicated in neurodegeneration—are found in healthy individuals and decrease with aging, particularly in patients with Alzheimer's disease (AD) (*9*). This observation suggests that such antibodies may provide protection from AD and could provide therapeutic benefit. Building on these findings, monoclonal antibodies that target amyloid-β peptides have been developed and found to promote plaque clearance within the brain and to slow cognitive decline in preclinical AD models and clinical trials of AD patients (*10*). Indeed, an amyloid-β antibody recently approved by the US Food and Drug Administration (FDA), aducanumab, was developed from an autoantibody obtained from a cohort of older individuals who exhibited no indications of cognitive deterioration or displayed unusually gradual cognitive decline (*10*). This demonstrates that autoantibodies not only highlight potential therapeutic paradigms but, in some cases, can also be advanced as therapeutic drugs themselves.

As a general theme, autoantibody associations with health outcomes can provide crucial information about what to drug (what gene product) and when to drug it (which disease indication). For example, protective IFN-I–blocking autoantibodies in SLE appear to mimic the therapeutic benefits of anifrolumab (a therapeutic monoclonal antibody used in SLE that targets the IFN-I receptor IFNAR1), and HER2 autoantibodies in breast cancer mirror the pharmacology of trastuzumab (a HER2 monoclonal antibody used in the treatment of $HER2^{+}$ malignancies) (*5*, *6*). However, potential therapeutic targets can be identified not only from protective autoantibodies, which should be therapeutically mimicked, but also from deleterious autoantibodies. Deleterious autoantibodies highlight pathways whose unperturbed functions are necessary for optimal health outcomes, implying that an ideal therapeutic agent would exert the opposite effect. For example, although autoantibodies that neutralize IFN-I exacerbate COVID-19 severity, administration of recombinant type-III interferon, which has similar biological properties to those of IFN-I, has shown promise as a COVID-19 therapeutic (*11*).

Notably, the function of autoantibodies can inform how a particular target should be drugged (what pharmacologic mechanism of action). Autoantibodies can be conceptualized as natural biologic drugs with an extraordinary array of potential impacts on human physiology. Examples include directly activating or inhibiting signaling receptors, stabilizing and extending the circulating half-life of ligands, or promoting their clearance (*2*). Additionally, autoantibodies can exert immunomodulatory functions by interacting with Fc receptors expressed on immune effector cells to drive antibody-directed cell-mediated cytotoxicity (ADCC), phagocytosis (ADCP), or complement-directed killing (CDC), depleting cells that express the target antigen on their surface (*1*). Integrating knowledge of autoantibody-clinical associations with an understanding of their functions can thus enable the development of comprehensive therapeutic hypotheses that link drug targets to specific therapeutic indications and potential mechanisms of action.

Although autoantibodies can exert large clinical effects and offer insights into therapeutic development, their impact on physiology has probably been underestimated. This is likely because there have been no comprehensive surveys to determine how common autoantibodies are throughout the human population at a proteome-wide scale. Central to this challenge has been a lack of experimental tools for unbiased, high-throughput autoantibody detection. Consequently, disease-modifying autoantibodies have largely been discovered through hypothesis-driven approaches informed by known biology or through challenging experimental techniques with limited throughput and scalability. Nevertheless, the emergence of next-generation autoantibody detection methodol-

ogies represents a substantial breakthrough, enabling in-depth and high-throughput studies of the full landscape of human autoantibodies across diverse populations.

Pioneering work toward comprehensive detection of autoantibodies has been inspired by advances in genomic technologies. Building on the success of DNA arrays, autoantigen microarrays enabled highly multiplexed assays for autoantibodies that are capable of screening thousands of antigens (*12*). The advent of next-generation sequencing (NGS) technology facilitated new approaches such as phage immunoprecipitation sequencing (PhIP-seq), which uses genetically encoded bacteriophage display libraries to present diverse peptide "tiles" ~50 amino acids in length (*13*). These self-propagating phage libraries can be screened for binding to autoantibodies present in patient samples, effectively converting autoantibody-antigen binding into a high-throughput sequencing readout with proteome-scale depth. However, PhIP-seq and related peptide-display technologies do not capture properly folded "conformational" antigens that are the targets of many autoantibodies. Other technologies have been developed to address this gap. One example is rapid extracellular antigen profiling (REAP), which is analogous to PhIP-seq but leverages the capacity of the yeast *Saccharomyces cerevisiae* to express and display full-length ectodomains of extracellular and secreted proteins (*14*). Ultimately, no current technique can sample all autoantigens, but in aggregate, they can detect a substantial fraction of the autoantibody reactome.

PhIP-seq and REAP have been used to collectively reveal thousands of autoreactivities across numerous disease indications as well as in healthy individuals. Just as the human genome has been sequenced to annotate mutations across the genome, it is tantalizing to consider that a similar principle may apply to the human proteome and autoantibodies: For every protein, there could potentially be individuals with functional autoantibodies that influence the activity and/or behavior of that protein. The emergence of highly scalable autoantibody detection technologies now permits "autoantibody-wide association studies" to be conducted in the same way that DNA-sequencing technologies enabled genome-wide association studies. These efforts promise to pinpoint autoantibodies with putatively causal effects on health, essentially decoding "clinical trials of nature" in which endogenous medicines (autoantibodies) that meaningfully affect disease can be identified.

Realizing the promise of autoantibody-wide association studies requires challenges that are inherent to autoantibody biology to be addressed. One major challenge is autoantibody diversity itself. Although thousands of distinct autoantibody classes have been observed, individual autoreactivities seen in PhIP-seq and REAP datasets are usually rare, often present in <1% of the population (*15*). Obtaining statistical power to detect significant autoantibody clinical associations may thus require large cohorts of thousands of patients per indication. Another challenge is autoantibody dynamics. Autoantibodies are not present throughout an individual's entire lifetime and generally emerge in adulthood. Longitudinal studies show that some autoantibody responses can persist for years, as was observed for IFN-I autoantibodies in SLE patients (*5*). By contrast, other autoantibody responses are transient, as was seen for some autoreactivities that arose during the course of SARS-CoV-2 infection and resolved on a timescale of weeks (*15*). The disparate temporal variance of autoantibodies thus introduces complexity in establishing their causal relationship to disease. Moreover, autoantibody responses typically consist of polyclonal mixtures of antibody lineages, which may have divergent functions that evolve over time (*2*). Autoantibody effector functions can also undergo dynamic alterations, owing to changing antibody isotypes, subclasses, and posttranslational Fc modifications (*1*).

These challenges also pose compelling opportunities for future study toward understanding the distinctive aspects of autoantibodies and their wide-ranging functions. Ultimately, the evolving landscape of autoantibody research promises to open new horizons in biomedical innovation, enabling discoveries that draw inspiration from our own immune system. ■

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PLANT SCIENCE

Mixed-organism enzyme in plant defense

Plants commandeer a pathogen's virulence factor to bolster immunity

By **Elisha Thynne**[1,2] *and* **Bostjan Kobe**[3]

All pathogens and their hosts engage in an arms race to gain the upper hand. Understanding how plants defend themselves could play a key role in the world's food security. One of the first lines of defense in plants is the cell wall. Pathogens, therefore, use enzymes called polygalacturonases (PGs) to degrade it, and at the same time, to suppress the plant's immune response. Plants, in turn, counteract by inhibiting PGs with inhibitory proteins (PGIPs). On page 732 of this issue, Xiao *et al.* (*1*) report the molecular details of how plant PGIPs do not just inhibit PGs, but also convert this virulence factor into an enzyme that triggers defense responses instead.

PGs are one of many virulence factors (or in the case of plant pathogens, effectors) that pathogens use to support infection. They secrete these molecules and deliver some of them into host cells. Hosts have evolved strategies not only to counteract these virulence factors, but also to use them as triggers of broader immune responses to eliminate pathogens. In plants, there are two interconnected tiers of immune responses (see the figure). Pattern-triggered immunity involves pattern-recognition receptors located in the plant cell plasma membrane that recognize conserved pathogen molecules and provide resistance to a broad range of pathogens. Intracellular immune receptors from the nucleotide binding leucine-rich repeat family recognize pathogen effectors delivered into the plant cell and initiate effector-triggered immunity. This often leads

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