COMMENTARY

Autoimmune imprinting in the post-COVID-19 era

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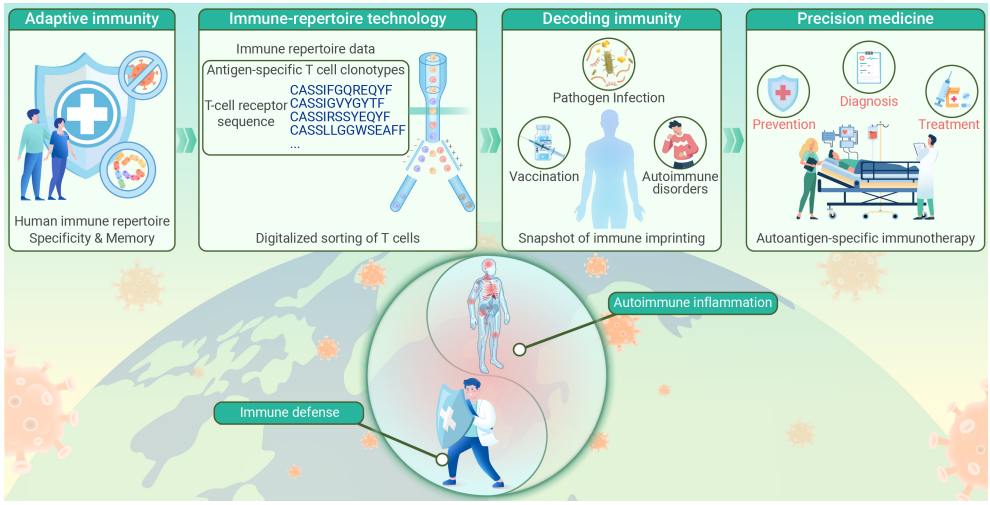

Figure 1. Navigating the entanglement of immune defense and autoimmune inflammation: precision medicine on the horizon.

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has substantially increased the risk of new-onset autoimmune disorders. In the post-COVID-19 era, this calls for a mechanism-based strategy to analyze disease-predisposing factors using auto-reactive T cells—a key driver of autoimmune inflammation,[1] which requires an additional term: "autoimmune imprinting."[2]

IMMUNE DEFENSE AND AUTOIMMUNE IMPRINTING

Pathogen infection is one of the most potent environmental stimuli that disrupt the homeostasis of human health, akin to the pathogen hypothesis that infection-triggered inflammatory immune response may subsequently lead to autoimmune disorders. However, most infection-triggered autoimmune disorders remain enigmatic. Until recently, the COVID-19 pandemic has revealed SARS-CoV-2 as a novel etiological agent driving a wide spectrum of autoimmune disorders, providing a unique opportunity to study in more detail how autoimmunity arises as a result of immune adaptation to pathogen infection.

As a recent evolutionary innovation of defense mechanism against pathogens, adaptive immunity exhibits antigen recognition and response properties, conferring protection against non-self pathogens but producing a side effect of autoimmune inflammation against self. Adaptive immunity actually memorizes the recognition of non-self and self-antigens through the immune repertoire, making it the primary carrier of immune imprinting. Based on this mechanism, the U.S. Food and Drug Administration has approved the T-Detect™ COVID—the first immune-repertoire-based assay—to determine the immune imprinting of COVID-19 by detecting SARS-CoV-2-specific T cells. Characterization of the precise mechanisms underpinning the immune repertoire revealed that COVID-19 infection resulted in profound differential patterns of antiviral immunity, while concurrently imprinted with significantly correlated magnitudes of auto-reactive T cells —termed autoimmune imprinting.[2] This infection-triggered autoimmune imprinting suggests a pathogenesis of antigenic cross-reactivity between immune defense and autoimmune inflammation, thereby increasing the likelihood of developing autoimmune disorders. Autoimmune imprinting reflects how microbial infection shapes the immune repertoire and whether this perturbation leads to the susceptibility to autoimmunity, advancing our understanding of pathogen hypothesis.

Adaptive immunity, encompasses a complex immune repertoire of quadrillions of T-cell clonotypes, each defined by a different T cell receptor (TCR) responsible for recognizing antigens. This complex system operates in a flexible manner through antigen-specific T-cell clonotypes that may also be cross-reactive with autoantigens, encompassing autoimmune imprinting.[2] Autoimmune imprinting reflects the double-edged effects of adaptive immunity in the light of Chinese Yin-Yang philosophy. The *Yang* (阳; bright) side of adaptive immunity confers immune defense, whereas the *Yin* (阴 ; dark) side produces autoimmune inflammation. Since the *Yang* side is indispensable for protecting the host from lethal infection, its interconnected *Yin* side (autoimmunity) is inevitable due to the necessary immune adaptation to environmental threats. In summary, immune defense against non-self carries the risk of autoimmunity against self. From this perspective, autoimmune disease can be broadly defined as arising from different but intertwined aspects of immune defense, representing different ends in the spectrum of the adaptive immune response (Figure 1). Given the urgency of the pandemic, the activation of adaptive immune defense is unavoidable but comes at the cost of autoimmunity, a price to be paid in the future.

TRANSLATIONAL PERSPECTIVE ON AUTOIMMUNE IMPRINTING

COVID-19 pandemic has become less deadly and more mild endemic waves, heralding the post-COVID-19 era of long-COVID syndrome. Going forward, can we propose autoimmune imprinting as a potential indicator of post-COVID-19 autoimmune risk? To address the needs of comprehensive immunophenotyping, case surveillance and definitions, autoimmune imprinting should be detected by immune-repertoire technology to track the clonal emergence of auto-reactive lymphocytes, particularly in the face of emerging SARS-CoV-2 subvariants.

Although autoimmune imprinting is of concern, it is unlikely to negate the public health value of COVID-19 vaccination. Vaccination confers protection against severe disease, often attributed to primed antiviral T cells—for the same reason that protective immunity exists after natural infection. This accentuates the need for long-term follow-up of populations with heterogeneous immune histories due to natural infection, reinfection, vaccination, or some combination thereof. The safety of COVID-19 vaccination may not be achieved through a one-size-fits-all policy. Given that prior antigen exposure imprints subsequent cross-reactive immunity to autoantigen, additional epidemiological studies are required to evaluate the vaccination-related autoimmune imprinting in vaccination programs such as "vaccines-plus" action, especially for those vaccines obtained emergency use authorization without rigorous clinical trials.

AUTOANTIGEN-SPECIFIC IMMUNOTHERAPY

Patients with autoimmune disorders, often receive systemic immunosuppressive therapy. However, this broad-acting therapy is not antigen- or disease-specific, thereby is not curative, and thus provides only low-to-moderate clinical benefit. Moreover, it carries debilitating and life-threatening

side effects, such as malignancies and severe infections. Indeed, autoimmune disorders are primarily caused by auto-reactive lymphocytes that specifically target autoantigens. There is currently an unmet need to develop autoantigen-specific immunotherapy targeting auto-reactive lymphocytes —the root cause of autoimmune disorders —for the curative treatment of autoimmune disorders.

Since adaptive immunity bears the risk of unleashing autoimmunity, evolution has endowed a natural mechanism of immune tolerance: suppression and deletion of auto-reactive lymphocytes. This natural strategy of immune tolerance can be employed to design autoantigen-specific immunotherapy. This therapy requires a priori knowledge of cognate antigen-specific autoimmune imprinting. Based on state-of-the-art antigen-specific immunotherapy, it is now possible to restore immune tolerance by comprehensively, yet selectively, suppressing and/or depleting auto-reactive lymphocytes without systemic immunosuppression, with the aim of purging the immune system of pathogenic autoimmunity without impairing normal immunity.

Intriguingly, previous studies have demonstrated the feasibility, safety, tolerability, and efficacy of immunotherapeutics that preferentially target auto-reactive T cells.[3] This kind of immunotherapeutics includes indirect approaches via antigen-presenting cells and direct approaches via major histocompatibility complex molecules or cytotoxic anti-TCR-motif antibodies, in ways designed to trigger clonal anergy and clonal deletion of disease-associated T cells. These disease-associated T cells encompass only a small fraction of the total T-cell repertoire, so the remaining T-cell repertoire covers sufficient antigenic specificities required for immune defense. Additionally, this therapy is not intended to systemically suppress any T-cell subsets of Th1, Th2, Th17, Treg, etc., and, therefore, should not cause systemic immunosuppression risks.

Autoantigen-specific immunotherapy represents an individualized treatment of autoimmune disorders via selectively attenuating autoimmune inflammation, while not disrupting normal immune function. Unlike systemic immunosuppressive therapies, autoantigen-specific therapies preferentially target disease-specific lymphocytes, thus requiring detailed analysis of differential autoimmune imprintings involved in disease initiation, progression, and maintenance for each patient, in order to determine the choice of personalized therapeutic options. Additionally, autoantigen-specific immunotherapies could be used as preventive treatments to ameliorate or block the initial onset of autoimmunity in at-risk individuals. This precision-medicine-based strategy centered on autoimmune imprinting represents the next-generation prevention, diagnosis, early intervention, and personalized treatment of autoimmune disorders. We can utilize autoantigen-specific immunotherapy to selectively ameliorate and abrogate autoimmune imprinting, with minimal impact on the protective function of immune defense.

THEORY OF PATHOGEN-IMPRINTED AUTOIMMUNITY IN HUMAN

The recent decades have witnessed a remarkable increase in the prevalence of autoimmune disorders. After cardiovascular disease and cancer, autoimmune disorder has now become the most common disease category in modern humans, with a global prevalence estimated at approximately 4.5%. For eighty autoimmune disorders identified, the worldwide incidence and prevalence have rapidly increased at rates of 19.1 and 12.5% annually.[4] This raises the question of why these fitness-reducing diseases maintain such an increasing trend in modern humans.

One plausible mechanism driving the trend is that, through the lens of Yin-Yang philosophy, a *Yang* side of retaining advantageous immune defense can inevitably create a *Yin* side of boosted autoimmune imprinting. Pathogen infections leave immunological scars in adaptive immunity. In addition to its canonical function of protection against infections that would otherwise be lethal, adaptive immunity can become detrimental when inappropriately launched against autoantigen. As such, adaptive immunity intrinsically incorporates risk-benefit trade-offs, reflecting the strategic prioritization of immune defense over the potential risks of autoimmune disorders. The risk-benefit trade-off may contribute to the increasing prevalence of autoimmune disorders in modern humans —a highly connected society that is particularly vulnerable to epidemics and pandemics.

This theory is also supported by evolutionary genetics during historical pandemics. Pathogen infection is among the strongest selective pressures driving human evolution, causing the greatest number of deaths and leaving protective genomic variants in the descendants of survivors. During the historical pandemic of Black Death, the genomic variants in immune genes underwent intense natural selection, leaving protective variants against the pathogenic bacterium *Yersinia pestis*, and some of these protective variants overlap with alleles associated with autoimmune disorders in modern humans.[5] The selective forces exerted by historical pandemics have imprinted the present-day human genome with genetic predisposition to infections, which has to be counterbalanced against the cost of autoimmune disorders, thus arising as a result of balancing selection on immune genes. Therefore, modern humans have enhanced immune defense against infectious diseases but increased susceptibility to autoimmune disorders.

In conclusion, genetic predisposition, combined with environmental triggers and autoimmune imprinting, can contribute to the development of autoimmune disorders. Adaptations to past and present pandemics underlie the interface of host-environment interactions, leading to evolutionary imprinting at the genomic level and autoimmune imprinting at the immune-repertoire level. Immune repertoire, a major determinant of pathogen sensing and adaptation, is more receptive to environmental perturbations. Autoimmune imprinting, a name coined to denote the permissiveness of adaptive immunity to be shaped or "programmed" by environmental triggers, reflects a shared fundamental mechanism that also protectively adapts the hosts to real environmental threats. In the post-COVID-19 era, autoimmune imprinting serves as a synchronizing signal of pathogen-imprinted autoimmunity, supporting the pathogen hypothesis. From this perspective, autoimmune disorders are not separate disease entities but exist along the same disease continuum following microbial infection, implying the "transmissible" potential of autoimmune disease.

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DECLARATION OF INTERESTS

The author declares no competing interests.