Journal of Mosaic of Autoimmunity
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Comments

Pathogen-Induced Autoimmune Imprinting: Immune-Repertoire Alteration Syndrome

Ming Zheng [1,2]

[1] Beijing Institute of Basic Medical Sciences, 27 Taiping Road, Beijing 100850, China; mmzheng@fmmu.edu.cn or zhengming_china@163.com
[2] Academy of Military Medical Sciences, 27 Taiping Road, Beijing 100850, China

How To Cite: Zheng, M. Pathogen-Induced Autoimmune Imprinting: Immune-Repertoire Alteration Syndrome. *Journal of Mosaic of Autoimmunity* **2025**, *1*(1), 6. https://doi.org/10.53941/jmai.2025.100006.

Received: 10 April 2025
Accepted: 19 May 2025
Published: 23 May 2025

Abstract: The COVID-19 pandemic has not only reshaped human health through its acute effects but has also induced long-term consequences, particularly in emerging autoimmune diseases. This introduces the concept of Immune-Repertoire Alteration Syndrome (IRAS), a post-infectious autoimmune phenotype, which describes how pathogen-induced changes in the immune system lead to lasting predispositions for autoimmune disorders. The immune system's adaptive response to infection, including modifying T-cell repertoires, may inadvertently result in autoimmunity due to cross-reactivity with self-antigens. This phenomenon, referred to as pathogen-induced autoimmune imprinting, leaves a persistent "scar" on the immune system, predisposing individuals to autoimmune diseases long after the initial infection has resolved. This highlights how SARS-CoV-2 and similar pathogens can initiate this process, altering immune responses in a way that may trigger conditions such as autoimmune thyroid disease, lupus, and vasculitis. Additionally, the concept of antigenic imprinting explains how infections and vaccinations influence the immune system's future responses, often leading to mistaken recognition of self. Finally, the Human Disease Continuum Project (HDCP) is introduced as a research initiative that aims to decode the links between pathogen exposure and autoimmune disease susceptibility. Through comprehensive immune profiling and longitudinal studies, the HDCP seeks to unravel the molecular and immunological mechanisms that underlie these diseases, paving the way for early detection, prevention, and personalized treatment strategies in the post-COVID-19 era. Understanding autoimmune imprinting will unravel new avenues for precision medicine and provides critical insights into the long-term impact of global pandemics on human health.

Keywords: COVID-19; pathogen-induced autoimmune imprinting; Immune-Repertoire Alteration Syndrome; Human Disease Continuum Project

1. Introduction

In the post-pandemic world, COVID-19 has undoubtedly reshaped the trajectory of human health [1,2], not only in terms of its immediate effects but also through long-term consequences that are beginning to surface more prominently in the clinic. One such consequence is the phenomenon of autoimmune diseases that seem to have emerged or become more pronounced following infection with SARS-CoV-2 [3,4]. This article explores the concept of "Immune-repertoire Alteration Syndrome" (IRAS), also referred to as the post-infectious autoimmune phenotype, and the crucial role of pathogen-induced autoimmune imprinting in the pathogenesis of these diseases [5].

2. Immune-Repertoire Alteration Syndrome (IRAS)

The immune system is constantly adapting and evolving to fight off infections, and adaptive immunity plays a critical role in this process. Adaptive immunity, specifically the T-cell repertoire, can recognize and respond to an almost infinite variety of pathogens. However, this intricate defense mechanism is not infallible, and infections, including SARS-CoV-2, can leave lasting imprints on the immune system that predispose individuals to autoimmune diseases [5].

Immune-repertoire Alteration Syndrome refers to the phenomenon whereby the immune repertoire—the vast collection of T-cell clonotypes that can recognize a multitude of foreign antigens—is fundamentally altered following infection. In the case of COVID-19, a viral pathogen that elicits a robust immune response, the T-cell repertoire is modified to target the virus and, inadvertently, to cross-react with self-antigens, leading to autoimmune inflammation. This alteration, which results in an imbalance favoring autoimmunity, represents a clinical syndrome in which autoimmune responses are triggered long after the initial infection.

The persistent imprint of SARS-CoV-2 infection, or even vaccination against it, on the immune repertoire can lead to the development of autoimmune diseases [6,7]. For example, studies have shown that after a COVID-19 infection, patients may present with new-onset autoimmune conditions, such as autoimmune thyroid disease, lupus, and vasculitis [4,5,8]. These diseases are a direct manifestation of the immune-repertoire changes that have occurred, where the adaptive immune system, originally designed to protect the host, begins to erroneously attack self-tissues. The autoimmune imprinting created by these infections results in T-cell clonotypes that are cross-reactive with self-antigens, fostering the emergence of autoimmune symptoms [5,9].

3. Pathogen-Induced Autoimmune Imprinting

Pathogen-Induced Autoimmune Imprinting builds on the idea of immunological scarification, where exposure to a pathogen or its components leaves an enduring mark on the immune system. This “scar” is created by pathogen-driven alterations to the immune repertoire that can increase the likelihood of autoimmune disease development later on. When the immune system is exposed to a pathogen like SARS-CoV-2, it generates immune memory, including T-cells that are primed to recognize and neutralize the pathogen in future encounters. However, this same immune memory can be detrimental if the T-cells become cross-reactive with self-antigens, ultimately leading to autoimmune responses [3].

The enduring effects of pathogen exposure, or vaccination, on the immune system’s ability to recognize self versus non-self can also be referred to as antigenic imprinting. This term describes the phenomenon where the initial immune exposure—whether through infection or vaccination—can shape subsequent immune responses, rendering them more likely to mistakenly target self-antigens [10]. In the context of COVID-19, the immune system’s adaptation to the virus creates a situation where T-cells may retain memory of the pathogen’s structure. These T-cells, in turn, may cross-react with similar molecular structures on the body’s tissues, triggering autoimmune disease.

One of the critical features of this imprinting is that it is not transient; it persists long after the infection has cleared. For instance, SARS-CoV-2 infection has been shown to leave a “footprint” on the immune system, with altered T-cell responses that last for months, and in some cases, even years. These long-lasting immune changes are an adaptive response to the pathogen and a potential risk factor for the development of autoimmune diseases.

4. Cross-Reactive Immune Memory and Evolutionary Trade-Offs

The phenomenon of cross-reactivity between pathogen-derived antigens and self-antigens is central to understanding how autoimmune diseases emerge post-infection. During an infection like COVID-19, the immune system is presented with a vast array of viral antigens, and the adaptive immune response selects T-cells that recognize these antigens. However, the immune system’s mechanisms are imperfect, and some T-cells may also recognize similar structures on the body’s tissues, leading to autoimmune attacks. This is an example of cross-reactive immune memory, where the immune system’s memory of the pathogen mistakenly targets the host’s own cells, setting the stage for autoimmune disease development [5].

The concept of pathogen-induced autoimmune imprinting must also be understood within the context of evolutionary trade-offs. Adaptive immunity evolved to provide protection against pathogens, but this immune system strategy carries an inherent risk: the more the immune system learns to protect against infectious threats, the more susceptible it may become to autoimmune reactions. This trade-off is a result of the same immune mechanisms that enable the body to recognize and eliminate pathogens. When these immune responses are inappropriately triggered by self-antigens, autoimmune diseases can arise.

This risk-benefit trade-off is not merely theoretical but supported by evolutionary genetics. Past pandemics, such as the Black Death, exerted intense selective pressure on human populations, favoring genetic variations that protected against pathogens. However, these same genetic variants that provided an advantage against deadly infections also predisposed individuals to autoimmune disorders [11]. In modern humans, the consequences of these evolutionary pressures continue to be observed as autoimmune diseases have risen in prevalence, likely exacerbated by the increased frequency and diversity of pathogen exposures.

5. Human Disease Continuum Project (HDCP): Decoding Predisposition Links between Diseases, from Pathogen Infection to Autoimmune Diseases

The HDCP aims to bridge the gap between pathogen exposure and the development of chronic diseases, such as autoimmune disorders, through a comprehensive understanding of immune system alterations over time (Figure 1). This project is particularly relevant in the post-COVID-19 era, where the interplay between viral infections and subsequent immune responses has become a critical area of research. COVID-19, like other infections, provides a unique lens to explore how initial pathogen encounters—whether through infection or vaccination—imprint lasting changes on the immune repertoire, predisposing individuals to autoimmune diseases.

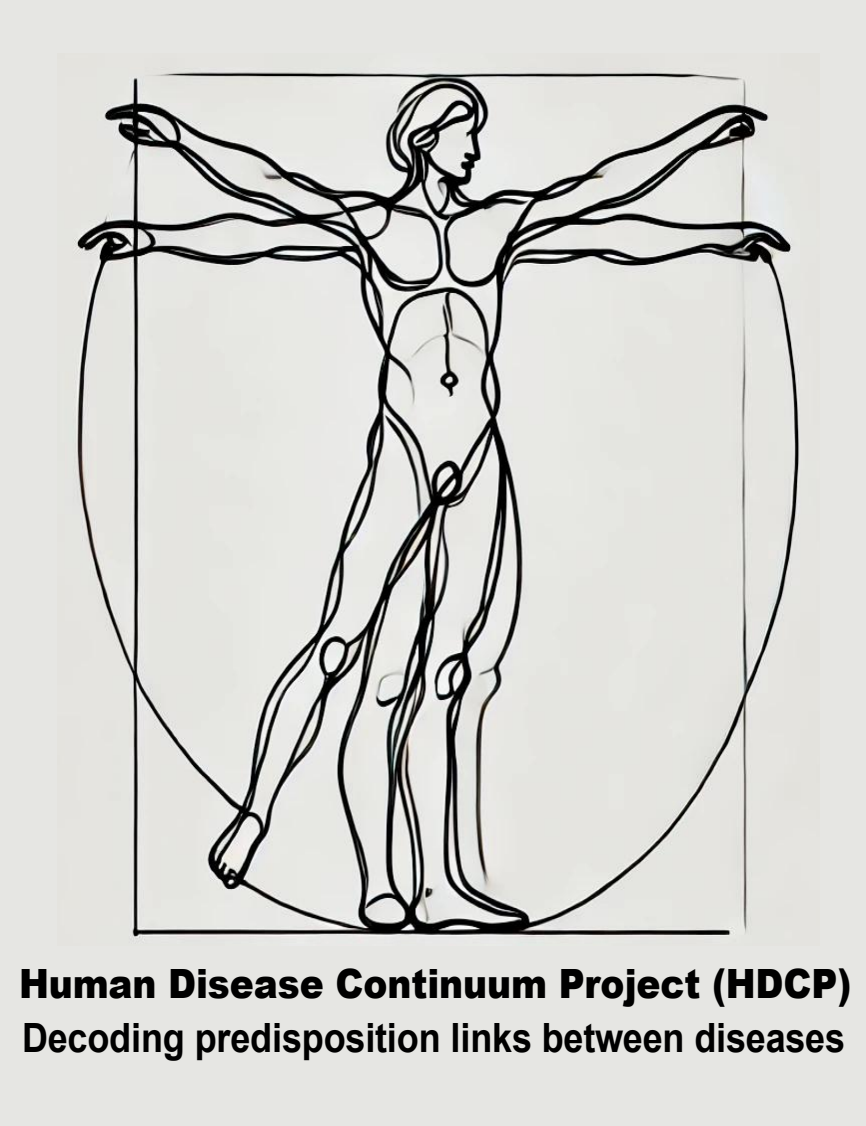

Figure 1. Human Disease Continuum Project (HDCP): Decoding predisposition links between diseases.

The HDCP focuses on decoding the molecular and immunological mechanisms linking pathogen exposure to autoimmune disease susceptibility. By leveraging cutting-edge technologies, such as immune-repertoire profiling and antigenic mapping, the project aims to identify biomarkers and immune signatures that predict the development of autoimmune disorders after an infection. This approach could revolutionize how we understand

the transition from pathogen infection to autoimmune diseases, offering new opportunities for early detection, prevention, and personalized treatments.

Moreover, the HDCP project emphasizes the importance of studying these immune alterations across diverse populations, considering genetic factors, environmental triggers, and previous pathogen exposures. By exploring these connections, the HDCP seeks to provide valuable insights into the long-term health implications of global pandemics and epidemics. In the case of COVID-19, this research could contribute to developing strategies for managing the risk of autoimmune diseases in the aftermath of the pandemic and future infectious disease outbreaks.

Ultimately, the HDCP will advance our understanding of the pathogen-autoimmunity link, uncovering critical disease predisposition pathways that could lead to novel therapeutic interventions and public health strategies to mitigate the autoimmune burden following viral infections.

6. The Price of Immune Defense

In conclusion, Immune-repertoire Alteration Syndrome and Pathogen-Induced Autoimmune Imprinting represent crucial concepts in understanding the post-infectious landscape of autoimmune disease. SARS-CoV-2, along with other pathogens, triggers profound alterations in the immune repertoire that create lasting consequences [12]. The imprint left by such infections can be protective and pathological—protecting the host against future infections while fostering autoimmunity. These phenomena underscore the dual role of immune defense: protecting against non-self threats but, when dysregulated, leading to autoimmune diseases that target the self.

As we continue to navigate the post-COVID-19 era, it is imperative to recognize the long-term implications of pathogen exposure on immune system function. Understanding autoimmune imprinting opens new avenues for precision medicine, where interventions can be tailored to restore immune tolerance and mitigate autoimmune diseases triggered by past infections. This knowledge will be key in managing not only the lingering effects of COVID-19 but also in the broader context of immune-mediated diseases that continue to challenge human health.

Funding

This project was supported by the National Natural Science Foundation of China (32100739) to Ming Zheng. All funding sources have been identified, and no additional funding was received for this study.

Conflicts of Interest

The author declares no conflict of interest.

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