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Cross-reactivity in Adaptive Immunity: An Overview

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ABSTRACT

Cross-reactivity in adaptive immunity refers to the ability of immune cells to recognize and respond to similar but distinct antigens. This phenomenon, while aiding in the recognition and defense against diverse pathogens, can also lead to unintended immune responses, including autoimmune reactions. The review explores key mechanisms underlying cross-reactivity, including molecular mimicry, T cell receptor degeneracy, and antibody cross-recognition. It discusses the dual role of cross-reactivity in infectious diseases, where it contributes to both protective immunity and potential disease enhancement, as seen in infections like dengue and Zika. Cross-reactivity is also implicated in autoimmunity, where immune responses to microbial antigens can mistakenly target self-tissues, potentially triggering conditions such as type 1 diabetes and multiple sclerosis. Additionally, the review addresses the implications of cross-reactivity in vaccine design, emphasizing the need to balance broad immune protection with safety, as well as challenges in immunotherapy where cross-reactivity may lead to off-target effects. Understanding cross-reactivity is essential to leveraging adaptive immunity effectively while minimizing potential adverse effects, with applications spanning infection control, vaccine development, and therapeutic interventions in immune-mediated diseases.

Keywords: Adaptive immunity, Cross-reactivity, Molecular mimicry, Autoimmunity, Vaccine development, Immunotherapy

INTRODUCTION

Chronic viral infections, including HIV, hepatitis B (HBV), hepatitis C (HCV), and herpesviruses, remain significant global health challenges, leading to long-term complications such as liver disease, immune dysfunction, and cancer [1]. Unlike acute infections, which are generally cleared by the immune system, these viruses evade immune defenses and establish persistent infections that are difficult to eradicate. The adaptive immune system, responsible for pathogen-specific responses and long-term immunity, plays a crucial role in attempting to control these infections [2]. However, chronic viral infections present unique challenges to the immune system, which must adapt to ongoing antigen exposure and the viruses' sophisticated evasion mechanisms.

The adaptive immune response is largely mediated by T cells and B cells [3]. CD8+ cytotoxic T cells (CTLs) target and kill infected cells, while CD4+ helper T cells support CTL and B cell functions by producing cytokines and co-stimulatory signals [4]. B cells produce antibodies specific to viral antigens, aiming to neutralize the virus and prevent its spread.[5] In chronic infections, however, continuous antigen exposure can lead to immune exhaustion, characterized by a gradual loss of T cell function [6]. Immune checkpoints like PD-1 and CTLA-4 become upregulated in this state, further suppressing T cell activity and allowing viral persistence.

In response, viruses use evasion strategies such as antigenic variation, latency, and manipulation of host cell machinery to persist within the host (7,8). HIV and HCV, for instance, mutate rapidly to escape immune recognition, while HBV and herpesviruses establish latent reservoirs that avoid immune detection [9]. This review examines the complex interactions between chronic viruses and the adaptive immune system, focusing on the mechanisms of immune response, viral evasion tactics, and therapeutic approaches to restore immune function and target these infections more effectively.

2. Overview of Adaptive Immunity

Adaptive immunity is a highly specialized immune response that targets specific pathogens through the coordinated actions of B and T lymphocytes [10]. These cells are essential for recognizing unique viral antigens, mounting targeted immune responses, and establishing immunological memory, which enables a faster and

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stronger response upon re-infection. B cells are responsible for producing antibodies proteins that bind specifically to antigens on pathogens. When B cells encounter their target antigen, they differentiate into plasma cells, which secrete large quantities of antibodies [11]. These antibodies can neutralize pathogens directly by blocking their entry into host cells or tagging them for destruction by other immune cells, such as macrophages. Additionally, some B cells become memory cells, remaining in the body long-term to provide rapid antibody production upon subsequent exposures. T cells are activated when they encounter antigens presented by major histocompatibility complex (MHC) molecules on infected or specialized immune cells [12]. There are two primary types of T cells involved in adaptive immunity namely Cytotoxic T cells (CD8+ T cells) identify and destroy cells displaying viral antigens bound to MHC-I molecules, directly killing infected cells to limit viral replication [13], and Helper T cells (CD4+ T cells) recognize antigens on MHC-II molecules and produce cytokines to coordinate the immune response [14]. By activating and enhancing the functions of both B cells and cytotoxic T cells, helper T cells play a crucial role in shaping and sustaining an effective immune response. Together, B and T cells form the basis of adaptive immunity, allowing the body to respond more effectively to repeated exposures and enhancing its ability to combat chronic viral infections. This adaptability, however, is challenged by the prolonged antigen exposure and immune evasion strategies typical of chronic infections, which can lead to immune exhaustion and impaired responses.

3. Mechanisms of Cross-reactivity in Adaptive Immunity

Cross-reactivity in adaptive immunity refers to the ability of immune cells, particularly T and B lymphocytes, to recognize and respond to epitopes from different antigens that share similar structural or biochemical characteristics [15]. This phenomenon can have significant implications for both immune responses and potential autoimmune reactions, and several mechanisms contribute to its occurrence.

3.1. Molecular Mimicry

Molecular mimicry arises when a pathogen presents epitopes that resemble those found in host tissues. In such cases, the immune system may inadvertently target host cells while responding to the pathogen [16]. A notable example is rheumatic fever, where antibodies generated against *Streptococcus pyogenes* cross-react with cardiac myosin, leading to damage to heart tissue [17]. This highlights the delicate balance the immune system must maintain to distinguish between self and non-self.

3.2. Degenerate T Cell Receptors

T cell receptors (TCRs) exhibit degeneracy, allowing them to recognize multiple peptides that share structural similarities [18] This flexibility is advantageous for the immune system, especially in rapidly evolving pathogens, as it facilitates a broader recognition of diverse viral or bacterial strains. However, this can also lead to cross-reactivity with self-antigens, potentially resulting in autoimmune disorders when the immune response is directed against the body's own tissues [19].

3.3. Polyclonal Activation

Certain pathogens can induce polyclonal activation, stimulating multiple clones of T and B cells simultaneously [20]. This broad immune response can encompass cross-reactive clones that may target both foreign and self-antigens. Superantigens, for instance, can activate a vast number of T cells in a non-specific manner, increasing the risk of cross-reactivity and subsequent autoimmune complications [21].

3.4. B Cell Cross-reactivity and Antibody Specificity

B cell cross-reactivity occurs when antibodies recognize structurally similar epitopes across different pathogens [22]. This can be advantageous in responding to closely related strains, such as various influenza virus subtypes, facilitating quicker immune responses. However, it can also pose risks, particularly if antibodies inadvertently target host tissues due to structural similarities, potentially leading to autoimmune reactions [23]. Understanding these mechanisms is crucial for developing effective vaccines and therapeutic strategies that minimize unintended cross-reactive responses.

4. Cross-reactivity in Infectious Diseases

Cross-reactivity plays a crucial role in infectious disease immunology, influencing infection outcomes, vaccination strategies, and the development of immunity against emerging pathogens [24]. This phenomenon can have both beneficial and detrimental effects, depending on the context and pathogens involved.

4.1. Viral Infections

In the case of viral infections, cross-reactivity is often observed. For instance, influenza viruses exhibit considerable genetic diversity. Antibodies generated against one strain may demonstrate partial efficacy against others due to shared epitopes [25]. However, the frequent mutations of the influenza virus can lead to immune escape, complicating effective long-term immunity and vaccine design. Another significant example involves dengue and Zika viruses, both members of the flavivirus family. Extensive studies have shown that antibodies formed during a prior infection with one of these viruses can inadvertently enhance subsequent infection with the other, a phenomenon known as antibody-dependent enhancement (ADE)[26]. This can result in more severe disease outcomes, complicating public health efforts to control these infections.

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4.2. Bacterial Infections

In bacterial infections, cross-reactivity can provoke autoimmune responses that harm the host. A classic example is rheumatic fever, where antibodies produced in response to Streptococcus pyogenes infections exhibit cross-reactivity with cardiac tissue [17]. This similarity between streptococcal antigens and proteins in the heart can lead to inflammation and damage, highlighting the risks associated with cross-reactive immune responses.

4.3. Parasitic Infections

Cross-reactive immune responses are also significant in parasitic infections. In malaria, for instance, antibodies targeting surface proteins of the Plasmodium parasite can cross-react with human red blood cells, contributing to disease severity and complications such as hemolysis and anemia [27]. This interaction underscores the complex dynamics of immune recognition and its potential implications for disease pathology. Understanding cross-reactivity in various infectious diseases is essential for developing effective vaccines and therapeutic interventions, ensuring better management of infectious diseases while minimizing adverse effects.

5. Cross-reactivity in Autoimmunity

Cross-reactivity plays a significant role in various autoimmune disorders by causing the immune system to mistakenly target self-antigens. When cross-reactive T cells or antibodies generated in response to pathogens inadvertently attack the body's own tissues, they can trigger or worsen autoimmune conditions [28]. Type 1 Diabetes is one example, where cross-reactive T cells have been implicated in the destruction of insulin-producing beta cells in the pancreas. Certain viral infections may provoke an immune response that inadvertently targets these cells, contributing to disease onset [29]. In Multiple Sclerosis (MS), molecular mimicry is believed to be a key mechanism. Immune responses to microbial antigens can cross-react with myelin, the protective sheath surrounding nerve fibers [30]. This misdirected immune attack leads to inflammation and nerve damage, further exacerbating the condition. Understanding these mechanisms is crucial for developing strategies to prevent or mitigate autoimmune responses triggered by cross-reactivity.

6. Cross-reactivity and Vaccine Development

Understanding cross-reactivity is crucial in vaccine development, as it can influence both the efficacy and safety of vaccines. By leveraging the principles of cross-reactivity, researchers can design vaccines that provide broader protection while minimizing the risk of adverse effects [31]. One key aspect is the breadth of immunity. Some vaccines are formulated to elicit antibodies capable of targeting multiple strains of a pathogen by utilizing cross-reactive epitopes. For example, influenza vaccines are designed to generate a wide-ranging immune response that can protect against various circulating strains [32]. This approach aims to account for the virus's frequent mutations and helps ensure that the immune system can recognize and respond to diverse variants. Another critical consideration is the need to avoid antibody-dependent enhancement (ADE), particularly in vaccine development against viruses such as dengue and COVID-19. ADE occurs when antibodies generated by a previous infection or vaccination facilitate, rather than inhibit, viral entry into host cells [33]. This phenomenon can lead to more severe disease upon subsequent exposure to the virus. Consequently, ensuring that the antibodies produced by vaccines do not enhance infection is paramount in designing safe and effective vaccines. Additionally, targeting conserved epitopes is a strategy employed in vaccine design to promote cross-protection [34]. By focusing on regions of the pathogen that remain relatively unchanged across different strains and species, vaccines can potentially elicit immune responses that provide broader protection. This approach is particularly beneficial for rapidly mutating viruses, such as HIV and influenza, where constant antigenic variation poses challenges for traditional vaccine strategies. In summary, a thorough understanding of cross-reactivity in vaccine development is essential for creating effective vaccines that not only enhance immunity but also minimize the risk of adverse effects, thereby improving public health outcomes.

7. Therapeutic Implications and Challenges

Cross-reactivity presents significant implications and challenges in immunotherapy, particularly in the fields of cancer treatment and transplant medicine. In cancer immunotherapy, T cell receptor (TCR)-based therapies and chimeric antigen receptor (CAR) T cell therapies aim to target tumor-specific antigens [35]. However, these therapies must be designed with precision to avoid cross-reactivity with normal tissues. Off-target effects can lead to serious toxicities, limiting the therapeutic potential and safety of these treatments. In transplant immunology, alloreactivity occurs when T cells recognize foreign major histocompatibility complex (MHC) molecules present in transplanted tissues [36]. This form of cross-reactivity poses challenges for graft acceptance, as the recipient's immune system may mount an attack against the transplanted organ. Ensuring immune compatibility and minimizing alloreactive responses are crucial for successful transplant outcomes. Addressing these challenges is essential for advancing immunotherapy and improving patient safety and efficacy.

CONCLUSION

Cross-reactivity in adaptive immunity represents a complex interplay between pathogen defense and self-tolerance. While it allows the immune system to effectively combat a broad range of pathogens, it can also result in adverse effects, such as autoimmunity and immune-enhanced disease severity. The phenomenon has wide-

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ranging implications in fields from vaccine development to immunotherapy. Understanding and managing cross-reactivity is key to harnessing the benefits of the adaptive immune system while minimizing potential risks.

REFERENCES

1. Ren M, Lu C, Zhou M, Jiang X, Li X, Liu N. The intersection of virus infection and liver disease: A comprehensive review of pathogenesis, diagnosis, and treatment. WIREs Mechanisms of Disease. 2024 May;16(3):e1640.
2. Vaillant AA, Sabir S, Jan A. Physiology, immune response. InStatPearls [Internet] 2022 Sep 26. StatPearls Publishing.
3. Sun L, Wang X, Saredy J, Yuan Z, Yang X, Wang H. Innate-adaptive immunity interplay and redox regulation in immune response. Redox biology. 2020 Oct 1; 37:101759.
4. Li T, Wu B, Yang T, Zhang L, Jin K. The outstanding antitumor capacity of CD4+ T helper lymphocytes. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2020 Dec 1;1874(2):188439.
5. Ali MG, Zhang Z, Gao Q, Pan M, Rowan EG, Zhang J. Recent advances in therapeutic applications of neutralizing antibodies for virus infections: an overview. Immunologic Research. 2020 Dec; 68:325-39.
6. Chow A, Perica K, Klebanoff CA, Wolchok JD. Clinical implications of T cell exhaustion for cancer immunotherapy. Nature reviews Clinical oncology. 2022 Dec;19(12):775-90.
7. Zhu H, Zheng C. The race between host antiviral innate immunity and the immune evasion strategies of herpes simplex virus 1. Microbiology and Molecular Biology Reviews. 2020 Nov 18;84(4):10-128.
8. Sausen DG, Reed KM, Bhutta MS, Gallo ES, Borenstein R. Evasion of the host immune response by beta herpes viruses. International Journal of Molecular Sciences. 2021 Jul 13;22(14):7503.
9. Tsai K, Cullen BR. Epigenetic and epitranscriptomic regulation of viral replication. Nature Reviews Microbiology. 2020 Oct;18(10):559-70
10. Wang R, Lan C, Benlagha K, Camara NO, Miller H, Kubo M, Heegaard S, Lee P, Yang L, Forsman H, Li X. The interaction of innate immune and adaptive immune system. MedComm. 2024 Oct;5(10):e714.
11. Sharma SK. B Cells. In Basics of Hematopoietic Stem Cell Transplant 2023 Jul 21 (pp. 87-120). Singapore: Springer Nature Singapore.
12. Pishesha N, Harmand TJ, Ploegh HL. A guide to antigen processing and presentation. Nature Reviews Immunology. 2022 Dec;22(12):751-64.
13. Kervevan J, Chakrabarti LA. Role of CD4+ T cells in the control of viral infections: recent advances and open questions. International Journal of Molecular Sciences. 2021 Jan 7;22(2):523.
14. Krovi SH, Kuchroo VK. Activation pathways that drive CD4+ T cells to break tolerance in autoimmune diseases. Immunological reviews. 2022 May;307(1):161-90.
15. Wallace R, Bliss CM, Parker AL. The Immune System–Friend or Foe for Adenovirus Based Therapies?. Preprints. May 27tjh, 2024.
16. Suliman BA. Potential clinical implications of molecular mimicry-induced autoimmunity. Immunity, Inflammation and Disease. 2024 Feb;12(2):e1178.
17. Cunningham MW, Kirvan CA. Post-Streptococcal Autoimmune Sequelae, Rheumatic Fever and Beyond: A New Perspective. Streptococcus pyogenes: Basic Biology to Clinical Manifestations [Internet]. 2nd edition. 2024 Mar 12.
18. Mayer A, Callan Jr CG. Measures of epitope binding degeneracy from T cell receptor repertoires. Proceedings of the National Academy of Sciences. 2023 Jan 24;120(4): e2213264120.
19. Gouttefangeas C, Klein R, Maia A. The good and the bad of T cell cross-reactivity: challenges and opportunities for novel therapeutics in autoimmunity and cancer. Frontiers in Immunology. 2023 Jun 19; 14:1212546.
20. Reed JH. Transforming mutations in the development of pathogenic B cell clones and autoantibodies. Immunological Reviews. 2022 May;307(1):101-15.
21. Olanrewaju EO. *Effect of Superantigen on Detecting Group A Streptococcus Specific T Cell Responses* (Doctoral dissertation, University of Bristol).2023.
22. Trier NH, Houen G. Antibody cross-reactivity in auto-immune diseases. International Journal of Molecular Sciences. 2023 Sep 2;24(17):13609.
23. Chavda VP, Gogoi NR, Shah Y, Shah D, Mazumder B. New approaches to vaccines for autoimmunity. In Advanced Vaccination Technologies for Infectious and Chronic Diseases 2024 Jan 1 (pp. 391-414). Academic Press.
24. Alturaiki W. The role of cross-reactive immunity to emerging coronaviruses: Implications for novel universal mucosal vaccine design. Saudi Medical Journal. 2023 Oct;44(10):965.
25. Rajão DS, Pérez DR. Universal vaccines and vaccine platforms to protect against influenza viruses in humans and agriculture. Frontiers in microbiology. 2018 Feb 6;9:123.

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ONLINE ISSN: 2992-5797
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26. Gartlan C, Tipton T, Salguero FJ, Sattentau Q, Gorringe A, Carroll MW. Vaccine-associated enhanced disease and pathogenic human coronaviruses. Frontiers in immunology. 2022 Apr 4;13:882972.
27. Zekar L, Sharman T. Plasmodium falciparum malaria. In Stat Pearls [Internet] 2023 Aug 8. Stat Pearls Publishing.
28. Kataki C. Overview of Autoimmune Diseases and the Role of Diet. In Nutrition Controversies and Advances in Autoimmune Disease 2024 (pp. 51-73). IGI Global.
29. Lemos JR, Hirani K, von Herrath M. Immunological and virological triggers of type 1 diabetes: insights and implications. Frontiers in Immunology. 2024 Jan 4;14:1326711.
30. Dejbakht M, Akhzari M, Jalili S, Faraji F, Barazesh M. Multiple Sclerosis: New Insights into Molecular Pathogenesis and Novel Platforms for Disease Treatment. Current Drug Research Reviews Formerly: Current Drug Abuse Reviews. 2024 Jul 1;16(2):175-97.
31. Jang YH, Seong BL. Cross-protective immune responses elicited by live attenuated influenza vaccines. Yonsei medical journal. 2013 Mar 1;54(2):271-82.
32. Wiggins KB, Smith MA, Schultz-Cherry S. The nature of immune responses to influenza vaccination in high-risk populations. Viruses. 2021 Jun 9;13(6):1109.
33. Xu L, Ma Z, Li Y, Pang Z, Xiao S. Antibody dependent enhancement: Unavoidable problems in vaccine development. Advances in immunology. 2021 Jan 1;151:99-133.
34. Abdulla F, Nain Z, Hossain MM, Syed SB, Khan MS, Adhikari UK. A comprehensive screening of the whole proteome of hantavirus and designing a multi-epitope subunit vaccine for cross-protection against hantavirus: Structural vaccinology and immunoinformatics study. Microbial Pathogenesis. 2021 Jan 1;150:104705.
35. Sun Y, Li F, Sonnemann H, Jackson KR, Talukder AH, Katailiha AS, Lizee G. Evolution of CD8+ T cell receptor (TCR) engineered therapies for the treatment of cancer. Cells. 2021 Sep 10;10(9):2379.
36. Duneton C, Winterberg PD, Ford ML. Activation and regulation of alloreactive T cell immunity in solid organ transplantation. Nature Reviews Nephrology. 2022 Oct;18(10):663-76.

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