Classification of Immune Adjuvants and Progress in the Study of Their Mechanisms of Action

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Abstract: Immunological adjuvants are indispensable in vaccine development and immunotherapy, serving as pivotal elements that amplify the immune system's response to antigens. These substances are extensively employed to bolster the immunogenicity and longevity of diverse vaccines. In immunotherapy, adjuvants treat numerous diseases, modulating and enhancing the body's defense mechanisms. This paper collates recent research on immune adjuvants' categorization and modes of action, meticulously examining the distinct attributes of various adjuvant types. It encapsulates their mechanisms of action and the potential for their utilization in vaccine formulation and immunotherapeutic strategies. It provides a robust theoretical foundation for crafting future vaccines and enhancing immunotherapeutic approaches. In conclusion, exploring immunological adjuvants is critical in advancing vaccine science and immunotherapy. By understanding the mechanisms and classifications of these substances, researchers can optimize vaccine efficacy and tailor immunotherapeutic interventions to combat a range of diseases more effectively. The insights gained from this research enhance our theoretical grasp and pave the way for practical applications that could significantly improve public health outcomes. As we continue to unravel the complexities of the immune system, the role of adjuvants will undoubtedly remain central to developing innovative solutions in the fight against infectious diseases and beyond.

1 INTRODUCTION

The immune system's efficiency, as the core barrier of the body's defense against pathogens, directly impacts the protective effect of vaccines. Many antigens (e.g., recombinant proteins, synthetic peptides, etc.) have difficulty triggering a sufficiently strong immune response due to their simple molecular structure or weak immunogenicity (Janeway et al.1992). The emergence of immune adjuvants has provided a key breakthrough to solve this problem. By synergizing with antigens, adjuvants can significantly enhance specific antibodies and cellular immune responses, making the development of immune adjuvants one of the core technologies in modern vaccine development (Gupta et al.1995). According to the World Health Organisation (WHO), about 30% of the world's vaccines rely on adjuvants to enhance the immune effect, especially in new types of vaccines, such as cancer and genetically engineered vaccines. The role of adjuvants is even more critical.

Historically, the study of immune adjuvants can be traced back to the early 1900s. 1926 saw the first discovery by Ramon that alum enhanced antibody production to diphtheria toxin, initiating the study of adjuvants, and the introduction of Freund's adjuvant in the 1950s led to the rapid development of experimental immunology (Pardi et al. 2018). Still, its clinical use was severely limited by its limitation of a vigorous inflammatory response. This was strictly limited due to the restriction of a strong inflammatory response and the clinical application of Freund's adjuvants. In the last decade, with the breakthroughs in immunological theories and advances in nanotechnology, significant progress has been made in the research and development of novel adjuvants, such as lipid nanoparticles (LNP) and CpG oligonucleotides, which provide new ideas to address the safety and efficacy of traditional adjuvants (Oleszycka et al. 2018).

However, current adjuvant research still faces multiple challenges. Some adjuvants (e.g., aluminum salts) only induce Th2 type immune response and have limited effect on pathogens that require Th1 type

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response (e.g., viruses, intracellular bacteria) (Kool et al. 2008). In addition, the mechanism of action of adjuvants has not been fully elucidated, and in particular, the mechanism of interaction between nano-adjuvants and the immune system remains controversial. The lack of systematic theoretical guidance for personalised adjuvant design limits the development of disease-specific vaccines (McKernan et al. 2020). Therefore, an in-depth analysis of the classification and mechanism of action of adjuvants is of great scientific significance and clinical value for optimizing the performance of existing vaccines and developing new vaccines (Takeuchi et al.2010).

2 CLASSIFICATION OF ADJUVANTS

According to the composition of immune adjuvants, adjuvants can be classified into chemical inorganic adjuvants, chemical organic adjuvants, synthetic adjuvants, and biological cytokine adjuvants. Their composition, characteristics, mechanism of action, scope of application, and disadvantages are shown in Table 1.

Table 1. Their composition, characteristics, action mechanism, application scope, and disadvantages.

Adjuvant Category	Ingredient	Specificities	Mechanism of action	Scope of application	Drawbacks
Chemical inorganic adjuvant	Aluminium salt adjuvants e.g. $Al(OH)_3$, $AlPO_4$, calcium salts (Lin et al. 2018)	Highly safe and easy to prepare Calcium salt adjuvants are less commonly used and gradually replace aluminium salts due to their high biocompatibility (Jinsu et al.2024).	Formation of antigen-adjuvant complexes and enhancement of the immune response.	Hepatitis B vaccine, HPV vaccine, etc.	Th2 bias and localized side effects limit applications
Chemical, organic adjuvant	Oil emulsion, liposome adjuvant (c, polysaccharide adjuvant (Ganoderma lucidum, Angelica sinensis), soap base (QS-21), etc. (Jiangsu et al. 2024).	Chemical and organic adjuvants are commonly added to vaccines to reduce antigen use and improve vaccine immune persistence.	May optimise the balance and efficiency of the immune response by regulating interactions between immune cells (Li jet al. 2024; Li 2023).	Immunological effects at mucosal sites include the intestine and oral cavity with machines, zosters, coronavirus, etc.	Although well-expressed short-term trials are safe, issues such as long-term toxicity that arise need to be evaluated in more long-term follow-up studies (Li jet al. 2024; Li 2023).
Synthetic adjuvant	CPG oligonucleotide POLY L :C, etc.	Sequences can be designed to optimize their immune activation effect and target specific diseases according to different needs (Kayraklioglu et al. 2021).	For example, the ability of CpG ODN to stimulate innate and adaptive immune responses in humans and various animal species	Hepatitis B vaccine, influenza vaccine, HPV vaccine, HIV vaccine, etc.	In some cases, non-specific activation of other immune cells or signaling pathways may lead to a lack of precision in immunomodulation and potentially increase the risk of side effects (Chen et al. 2021)
Cytokine adjuvant	Interleukins: e.g. IL-2, IL-4, IL-12, GM-CSF, IFN-γ, etc.	One cytokine can act on multiple target cells and produce various regulatory effects; different cytokines can also act on the same target cells and produce the same or similar biological activities (Firdaus et al. 2022).	Inducing multiple cytokines to form a complex cytokine network that finely regulates immune cells' proliferation, differentiation and functioning (Michalak et al. 2022).	HIV, influenza, rabies, hepatitis B virus (HBV), hepatitis C virus (HCV), etc.	Cytokine interactions are complex and require precise design and optimal combinations when applied in combination. Otherwise, the desired immune-enhancing effects may not be achieved, or even antagonism or increased risk of side effects may occur.

3 MECHANISMS OF ACTION OF IMMUNE ADJUVANTS

Different immune adjuvants play other roles, and cells broadly, their mechanisms of action can be divided into three categories.

Antigen Delivery Enhancement Adjuvants enhance antigen delivery by forming antigen reservoirs and slowly releasing antigenic liposomes and nanoparticles (Ding et al.2023).

Immune cell activation Adjuvants enhance immune cell response by activating pattern recognition receptors such as TLR. Cytokine adjuvants can regulate the function of immune cells, such as promoting the proliferation and differentiation of T cells and enhancing the phagocytosis of macrophages. By controlling the cytokine network, cytokine adjuvants can synergize with other immune adjuvants to enhance the immune effect of the vaccine. In addition, cytokine adjuvants can also regulate the migration and localization of immune cells so that they can reach the site of an infection more effectively and play an immune role (Tao et al., 2023).

Immune Response Modulation Adjuvants enhance the immune response by regulating the Th1/Th2 balance. Novel adjuvants enhance antiviral immune response by activating the STING pathway (Duan et al. 2025).

4 PROSPECTS FOR THE APPLICATION OF IMMUNE ADJUVANTS

4.1 Vaccine Development—The Use of Adjuvants in Novel Vaccines

Adjuvants, as an essential component of vaccines, can significantly enhance the immune response to a vaccine, thereby improving the protective efficacy of the vaccine. The use of adjuvants is becoming increasingly common in developing novel vaccines, especially in vaccines that are difficult to elicit an adequate immune response, and the role of adjuvants is particularly critical. Complex adjuvants further optimize the immune effect of vaccines by combining multiple immune-enhancing mechanisms and offer new possibilities for vaccine development (Ben-Akiva et al. 2025).

For instance, the adjuvant MF59, used in the influenza vaccine, has been shown to boost the immune response in the elderly, a population group that often has a weaker response to vaccines (Ko et al. 2018). Similarly, AS03, another oil-in-water emulsion adjuvant, has been utilized in the H1N1 influenza vaccine to enhance the immune response and provide broader protection against various strains (Cohet et al. 2019). In addition, the adjuvant system AS01 has been successfully applied in the shingles vaccine, demonstrating its ability to elicit a strong and durable immune response. As research continues (Didierlaurent et al. 2017), developing new adjuvants with improved safety profiles and enhanced efficacy will be crucial for the future of vaccine innovation, particularly in the fight against emerging infectious diseases.

4.2 Immunotherapy—The Use of Adjuvants in Tumor Immunotherapy

Adjuvants play an essential role in vaccine development and show excellent application prospects in immunotherapy. In tumor immunotherapy, adjuvants can activate and enhance the body's immune response to tumor cells, thus contributing to tumor clearance. Meanwhile, the potential of adjuvants in treating autoimmune diseases should not be overlooked. By modulating the immune system's response, adjuvants have the potential to become a new strategy for treating autoimmune diseases. These applications demonstrate the diverse potential and future direction of adjuvants in immunotherapy. In conclusion, adjuvants are pivotal in enhancing the efficacy of immunotherapies, whether in combating cancer or managing autoimmune conditions. Their ability to fine-tune the immune response highlights their significance in advancing personalized medicine. As research progresses, optimizing adjuvant use could lead to breakthroughs in treating various diseases, offering hope for improved patient outcomes (Dredge et al. 2002; Jeon 2023).

5 CONCLUSION

Immunological adjuvants are key components in enhancing the effectiveness and durability of vaccine immunity. Adjuvants are classified as chemically inorganic, chemically organic, synthetic and cytokine adjuvants, each with their characteristics and scope of application. Still, challenges, such as safety and mechanisms of action, are not entirely clear.

They play an essential role in vaccine development and immunotherapy. They enhance antigen presentation, activate immune cells and modulate the immune response in their respective roles in three pathways. They can improve the effectiveness of vaccines by activating specific immune cells and modulating the type and strength of the immune response. As molecular biology and immunology continue to advance, the study of immune adjuvants is also seeing new development opportunities. Scientists are now trying to design more precise and efficient adjuvants using cutting-edge technologies such as nanotechnology and gene editing. For example, the synthetic adjuvant CPG oligonucleotide can be sequence-designed to optimize its immune-activating effect and target specific diseases according to different needs. In addition, the concept of vaccines is emerging, whereby an individual's immune genotype is analyzed to other populations, personalized tailor adjuvants and vaccines that are best suited. These innovations will advance the development of vaccinology and the treatment of various infectious and specific diseases, bringing new hope for chronic diseases. Through these studies, scientists can provide new ideas and methods for vaccine design and immunotherapy, which will lead to the development of safer, more effective and more targeted vaccines and treatments and ultimately make more significant contributions to human health.

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