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Review

On vaccine's adjuvants and autoimmunity: Current evidence and future perspectives

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ABSTRACT

Adjuvants are compounds incorporated into vaccines to enhance immunogenicity and the development of these molecules has become an expanding field of research in the last decades. Adding an adjuvant to a vaccine antigen leads to several advantages, including dose sparing and the induction of a more rapid, broader and strong immune response. Several of these molecules have been approved, including aluminium salts, oil-in-water emulsions (MF59, AS03 and AF03), virosomes and AS04.

Adjuvants have recently been implicated in the new syndrome named "ASIA—Autoimmune/inflammatory Syndrome Induced by Adjuvants", which describes an umbrella of clinical conditions including post-vaccination adverse reactions.

Recent studies implicate a web of mechanisms in the development of vaccine adjuvant-induced autoimmune diseases, in particular, in those associated with aluminium-based compounds. Fewer and unsystematised data are instead available about other adjuvants, despite recent evidence indicating that vaccines with different adjuvants may also cause specific autoimmune adverse reactions possible towards different pathogenic mechanisms.

This topic is of importance as the specific mechanism of action of each single adjuvant may have different effects on the course of different diseases. Herein, we review the current evidence about the mechanism of action of currently employed adjuvants and discuss the mechanisms by which such components may trigger autoimmunity.

Contents

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1. Introduction

One of the brightest chapters of medical history is the development and the introduction of immunisation programmes [1]. The results generated by these interventions on human health and longevity changed profoundly the historical relationship between infectious diseases and human race [2–4]. The eradication of smallpox and the large reduction of cases of poliomyelitis and measles are some examples of the beneficial impact of immunisation programmes [2,3].

Classical vaccines rely on the use of whole killed or attenuated pathogens and many currently licenced vaccines are formulated with this technology [5]. Newer and current in-development vaccines are instead based on rationally designed and highly purified recombinant antigens characterised by an excellent safety profiles [5]. Because of their well-defined structure, such antigens may be less immunogenic than live attenuated or inactivated pathogen preparations, which intrinsically contain components capable of enhancing immunogenicity [6,7].

Vaccination with highly purified antigens typically results in the induction of a modest antibody and T cell response and requires multiple vaccinations to elicit sufficient antibody responses [6,7]. For this reason, a significant amount of efforts has been invested to identify components capable of ameliorating immune responses to be added to vaccines. These components are defined adjuvants and consist in well-defined molecules and/or formulations [6,8]. Adding an adjuvant to a vaccine antigen leads to practical advantages, including dose sparing and the induction of a more rapid, broader and strong immune response [8–10].

A general and over-simplified classification for vaccine adjuvants includes two broad groups, called delivery systems and immune potentiators [10]. Immune potentiators are often used in combination with the delivery systems and are thought to be able to shift the immune response towards a more Th1 (CD4+) cellular immune response [10]. Approved adjuvants include aluminium salts, oil-in-water emulsions (MF59, AS03 and AF03), virosomes and AS04 [8–10].

The development and the increasing diffusion of new vaccination and immunisation programmes have also raised concerns about the safety of adjuvants and their immunogenicity-enhancing effect in vaccines [11–18]. The term "ASIA—Autoimmune/inflammatory Syndrome Induced by Adjuvants" was coined in 2011 to describe the spectrum of immune-mediated diseases triggered by an adjuvant stimulus [11,13,15,16,19–22]. This syndrome comprehends an "umbrella" of clinical including post-vaccination phenomena caused by vaccine adjuvants [23–26].

The pathogenesis of the ASIA syndrome is founded on the hypothesis that an early exposure to an adjuvant may set in motion a chain of biological and immunological events that, in susceptible individuals, may ultimately lead to the development of autoimmune diseases [13,15,16,20,21,27].

Recent studies implicate a web of mechanisms in the development of vaccine adjuvant-induced autoimmune diseases, in particular, in those associated with aluminium-based compounds (Alum), which comprise a major bulk of contemporary adjuvants. Fewer and unsystematised data are instead available about other adjuvants, despite recent evidence indicating that vaccines with adjuvants different from alum may also cause specific autoimmune adverse reactions [28–32].

2. The rationale for this review

While adjuvants have been employed for over 80 years, the mechanism by which these components ameliorate immune responses has been generally under-studied and its importance has been underappreciated for a long time [10]. The knowledge at the molecular and cellular levels of adjuvant-induced immune responses is a critical step in the developing of a more efficacious and safer generation of vaccines. This topic is of importance as the specific mechanism of action of each single adjuvant may have different effects on the course of different diseases. As an example, some preclinical models highlighted the importance of Toll like receptor 4 (TLR4) activation in rheumatoid arthritis and systemic lupus erythematosus [33]. This datum may be of importance for adjuvants that interact directly with the TLR4 receptor, while it is unlikely to be of concern for adjuvants acting with different mechanism.

Herein we review the current evidence about the mechanism of action of currently employed adjuvants and discuss the mechanisms by which such compounds may trigger autoimmunity.

3. Mechanism of action of adjuvants

3.1. Alum

Aluminium hydroxide and other aluminium salts (Aluminium hydroxyl-phosphate sulphate, Aluminium potassium phosphate, and others), typically referred to as "Alum", are the most widely used adjuvants in human and animal vaccines [34]. Alum elicits strong humoural immune responses primarily mediated by secreted antigen-specific antibodies [35,36], which are effective against diseases such as diphtheria, tetanus and hepatitis B, where neutralising antibodies to bacterial and viral antigens are required for protection [37]. In contrast, alum is a poor inducer of cell-mediated immune responses and is unsuitable for vaccines that require a strong cellular immune response [38].

The first evidence about the effect of alum as adjuvant was reported in 1926 by Glenny et al., who observed that the injection of diphtheria toxoid precipitated with potassium aluminium sulphate induced an antibody response in guinea pigs stronger than the one obtained with the toxin alone [39]. Authors also observed the formation of nodules at injection site [39], which were suspected to act as depot site for the antigens. This hypothesis was confirmed further by the observations of Harrison [40], who found that immune response could be transferred surgically, by extracting and injecting these nodules in a naïve animal. These observations suggested that the mechanism by which alum act as adjuvant was the formation of nodules.

These were the basis of the "depot theory", which states that alum acts by forming nodules that slowly release antigen, thus providing both a priming and a boosting effect with the same inoculation [40].

Further analysis on alum nodule's structure questioned the depot theory: alum nodules were found to be composed of fibrinogen, but fibrinogen-deficient mice were found to develop a normal immune response to alum vaccines, thus indicating that nodules are not required for alum salts to act as adjuvants [41]. Hutchison et al., who found that the removal of alum depot has no effect on antigen-specific T- and B-cell responses, questioned the depot theory further [42].

Notwithstanding the claims against the depot theory, it remains to be understood whether the long term response (i.e. after 35 days from immunisation) is still due to a depot effect or if the depot mechanism may be of importance for driving local immune responses in draining lymph nodes following transport from the injection site [43].

A possible role for the NACHT, LRR and PYD domains—containing protein-3 (NLRP3) inflammasome was also proposed [44–46], as it had been reported that alum-induced immune responses were abrogated in NLRP3-deficient mice. Specifically, NLRP3-deficient mice were found to have an impaired cell recruitment, a reduced secretion of IL-1β, expression of MHC class II and of the co-stimulatory molecule CD86. Additionally, these mice showed a decreased number of inflammatory monocytes carrying antigen into the draining lymph nodes and a reduced alum-driven antigen-specific IgG1 [44,47,48]. These data, however, were not further confirmed as Franchi et al. reported that the inflammasome is not required for the alum-dependent increase of antibody titres following intraperitoneal injection of human serum albumin [46].

Along with the "depot theory" and the inflammasome hypothesis, other theories have been put forward to explain the adjuvant effect of alum [43]. It has been shown that alum vaccination may lead to an