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Review

Efficacy and safety of immunological adjuvants. Where is the cut-off?

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ABSTRACT

Research over the past several decades has provided insight into the mode of action of adjuvants. However, the main focus of attention has been the efficacy in the induction of protective immunogenicity, while less effort has been devoted to the study of toxicity mechanisms. Evidences suggest that several mechanisms that are responsible for the immunostimulating effects are, at the same time, responsible of the adverse effects. In this context, it is often very difficult to establish the boundaries between immunostimulation and immunotoxicity to reach the ideal balance of efficacy/safety. During decades, hundreds of adjuvants and adjuvant formulations have been proposed as immunostimulants for vaccines but very few have been used in human vaccines due to toxicity concerns. In this review, relevant aspects about immunotoxicology of adjuvants, based on clinical and experimental studies are discussed. Some effects are only observed under hyperstimulating regimens using non-approved adjuvants for human use, but these are nonetheless useful to understanding basic principles of adjuvant toxicity. The acute local and systemic reactions, during the first hours and those that can be observed after the third day of vaccination in the inoculation site and systemically are discussed.

1. Introduction

Adjuvants are essential for efficacy of most vaccines [1]. Historically, the focus of attention in adjuvant research has been the efficacy in the induction of protective immunogenicity, while less effort has been devoted to the study of toxicity mechanisms [2]. However, vaccine safety is currently a key concern of regulatory agencies and health institutions. Regrettably, the vast majority of toxicity studies with adjuvants were performed in combination with a wide variety of antigens. Thus, information about the toxicity of adjuvants alone is scarce, hampering the understanding of the mechanisms involved in several adverse events [3].

The physicochemical properties of adjuvants, the antigenic structure, the doses, the frequency and route of administration, as well as the genetic characteristics of the organism, are determinant conditions that influence the quality of the immune response [4,5]. In the same way, these factors influence the toxicity reactions of the adjuvanted vaccines. Nowadays, it is accepted that many adverse reactions induced by immunological adjuvants occurs through an immunological-based mechanism (Table 1). The immunostimulatory effects that are necessary to increase the effectiveness of the vaccine can lead to undesirable effects if exceeding certain limits (Fig. 1). However, for immunological adjuvants, the limits between the desired pharmacological effects and toxicity are often imprecise [2,3,6].

Currently, one of the greatest challenges in vaccine design is the use of highly effective antigen-adjuvant combinations while causing minimal adverse effects. Increasing insight into immunological mechanisms and how to manipulate them using molecules with well-defined mechanisms of action, has replaced empirical with rational design of adjuvants and targeted molecular modulation [1,7,8].

In the following sections, the acute local and systemic immunotoxic reactions occurring during the first hours post-administration are analyzed. Following, those reactions that can be observed after the third day of vaccination in the inoculation site and systemically are also discussed (Fig. 2).

Several of the adverse effects mentioned here have been observed only under experimental conditions in laboratory animals, in veterinary vaccines or during different phases of clinical trials. Others have been reported in human prophylactic and therapeutic vaccines.

2. Acute immunotoxic reactions induced by adjuvants

After vaccination, the early innate immune responses that is stimulated in the inoculation site by the adjuvant, define the characteristics and magnitude of the adaptive responses as well as the vaccine efficacy and toxicity [9,10]. The acute immunotoxic reactions are those

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Table 1
Some relevant mechanisms involved in vaccine adjuvant immunotoxicity.

Mechanisms	Consequence	Clinical manifestations	Adjuvant examples	Selected References
Associated with local reactions				
Direct cytolytic	Direct lytic effects on cells in the inoculation site. Damage-associated molecular patterns (DAMPs) release from injured cells.	Local irritation and inflammation	Alum Saponins	[11,14,15,16]
Depot effect and slow degradation	Excessive recruitment of immune cells and Th1-biased response	Long lasting local inflammation, granuloma (delayed-type hypersensitivity)	Gels Emulsions	[17,96,63,64]
Inflammation-associated oncogenesis	Tumorigenesis	Tumors in the inoculation site	Alum	[68,69,70,71,72,73,74]
Associated with local and (or) systemic reactions				
Profuse release of inflammatory cytokine/chemokines	Excessive stimulation and/or suboptimal downregulation of innate immune system	Local inflammation, acute phase response Vascular leak syndrome Aplastic-like bone marrow	Multiple Cytokines pATRex	[44,45] [57,58,59,60] [109,110]
Disturbs in hepatic cytochrome P450 expression/activity mediated. Changes in drug transporters	Changes in pharmacokinetics (including metabolism) and pharmacodynamics of drugs mediated by cytokines	Toxicity of some drugs administered during or shortly after vaccination	Freund´s adjuvants Alum LPS	[46,47,48,49,50,51,52,53,54]
Off-target effect	Expression of innate immune receptors by cell types not involved in the immune response	Inflammation in non-immune tissues. Autoimmune/inflammatory symdrome associated to adjuvants?	Alum	[9,79]
Failure in the contraction of adaptive immune response	Homeostatic disturbances in several immune mechanisms	Hypersensibility reactions and autoimmune disorders	Freund´s adjuvants, Alum. Regulatory T cells modulators	[75,76,77,78,79,80] [8]
Loss of peripheral immunotolerance	Immune response against own tissues	Autoimmune process	Freund´s adjuvants Alum	[75,76,77,78,79,80]
Excessive Th2-biased response	Excessive stimulation of IgE response and allergy mediators	Immediate-type hypersensitivity reactions	Alum	[27,30,32]
Formation and deposition of immune complex (IC)	Local or systemic inflammatory reactions mediated by IC	Arthus reactions, vasculitis	Alum	[26,27,28,29,30]

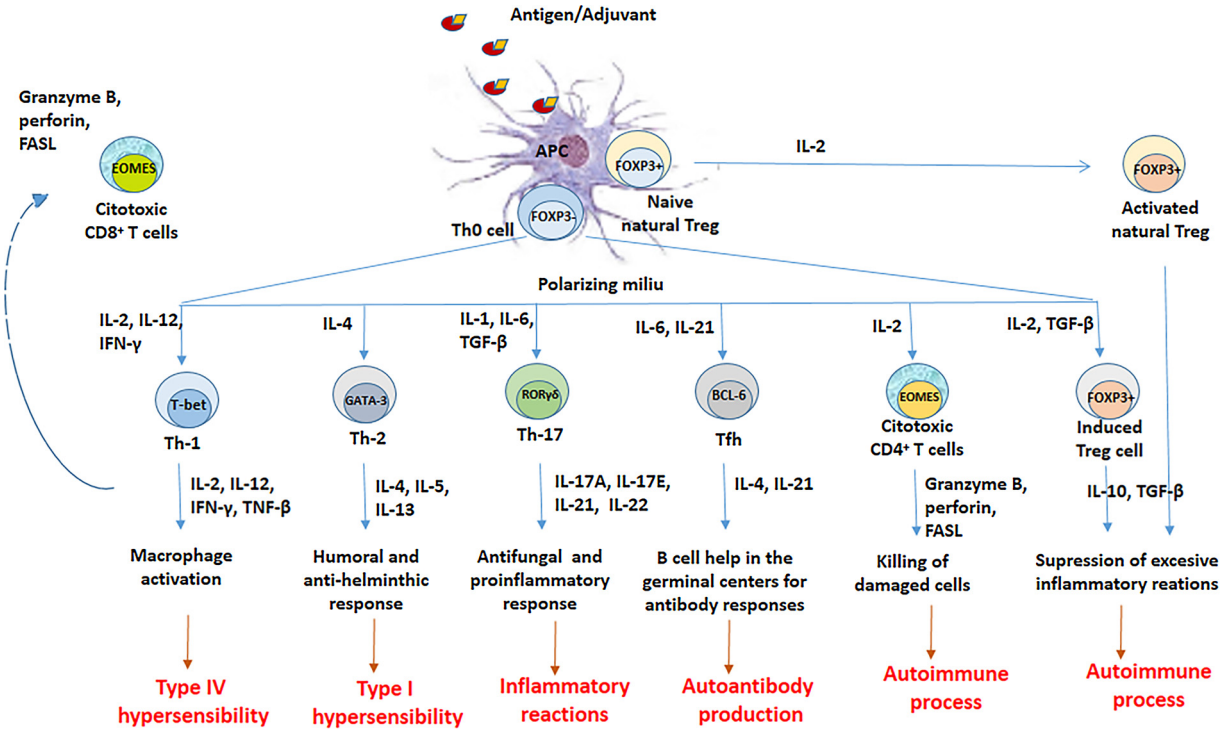

Fig. 1. CD4 + T cell polarization into functionally distinct cell lines after antigen/adjuvant stimulation and associated immunotoxicity reactions. After antigen/adjuvant interaction with antigen presentating cells (APCs) and presentation to naive T cells, natural Treg are activated while Th0 cells can be polarized to different Th subsets cells. The CD4 + T cell polarization is driven by the nature of the antigen and the adjuvant, the way of administration and the genetic background. Immune polarization optimize the immune response but under misregulated conditions, different immunotoxic responses (highlighted in red words) can be induced.