Adjuvants

Description

To complete this overview on vaccine design, it is noteworthy at least mentioning the wide role of adjuvants : immune-enhancing additives employed since the earliest attempts to raise significant immune responses. All adjuvant systems are basically focused on two mechanisms : (i) specific immune activation, and/or (ii) delivery-depot effect. Despite the abundance of adjuvant systems employed in preclinical models, only a few resulted compatible with human vaccines, being the primary limitation for this diversified class of immunomodulators their safety issues.Ott & Van Nest, 2007

Aluminum salts adjuvants, generally referred as alums, represent early, successful examples employed in anti-diphtheria vaccines. They are composed of a co-precipitate of aluminum hydroxide and diphtheria toxoid in carbonate buffer. Only occasional and moderate toxicities were reported with these vaccine settings.White & Schlageter, 1934The next step in adjuvant research was made by Freund, whose water-in-oil emulsion, formed by the mixture of one volume 10% Arlacel A and 90% mineral oil with one volume of antigen (heat-killed *Mycobacterium tuberculosis*, cf. Complete Freund's Adjuvant : CFA) in solution represented the standard for adjuvant activity from the 1930s to the 1970s.Freund, 1947 Mechanistic studies on oil-based adjuvants revealed a correlation between maintenance of antibody titers and presence of adjuvant depot for a period of months after injection.McKinney & Davenport, 1961 Nevertheless, documentation of intense inflammations, pieces of evidence that the emulsion was not entirely retained at the injection site, and the suspected role of the poorly metabolized mineral oils as carcinogens made Freund's adjuvant acceptation controversial.

Advances in immunology allowed the characterization of APC's receptors and cytokine expression profiles, posing the basis for next generations of adjuvants based on a receptor-driven rational. The families of pattern recognition receptors (PRRs) implicated in bridging innate-adaptive responses, such as TLRs and NOD (nucleotide-binding oligomerization domain), are continuously growing and offering new possibilities in adjuvant's design. Lipid A-related adjuvants, CpG oligonucleotides, alone or in combination with liposome- or particulate-based delivery systems represent just a few examples of the contemporary state-of-art in adjuvant settings.

The fate and functions of activated TH cells depend in large part on the microenvironment present at the time of the initial antigen encounter. The cytokine milieu composition biases the development of naïve CD4+ cells towards one or several differentiation pathways, leading to effector TH cell subsets with different functional profiles.Kennedy & Celis, 2008 Likewise, the nature of the antigen acquired by APCs will affect the expression of different sets of costimulatory molecules (e.g. CD80, CD86), which will also influence the developmental path of antigen-stimulated TH cells.de Jong, Smits & Kapsenberg, 2005

In the vaccine set, (i) dendritic cells maturation, (ii) migration to the lymph nodes, and (iii) their cytokine expression can be stimulated, for example by the co-administration of delivery-depot adjuvants and ligands for DC's toll-like receptors (TLRs).Duthie et al., 2011Seya et al., 2015

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