25

Adjuvants for the Future

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INTRODUCTION

The past decade has seen dramatic progress in our understanding of immune mechanisms and host defense. Along with the ability that vertebrates have to acquire immunity to pathogenic antigens by expanding specific populations of T and B cells and making cytokines and antibodies, scientists have discovered that like invertebrates, we have multiple innate pathways to activate more generic host responses through a whole new family of receptors. Over 80 years ago, Ramon demonstrated that it was possible to artificially increase antigen-specific levels of diphtheria or tetanus antitoxin by the addition of bread crumbs, agar, tapioca, starch oil, lecithin, or saponin to the vaccines (1). Since then, aluminum salts have been the dominant substance used and are still the only adjuvant currently used in licensed vaccines in the United States. The field has become much more sophisticated recently with the introduction of numerous new adjuvants and new concepts regarding the mechanisms of action. In this brief chapter, we review the modern adjuvants used in a variety of current and experimental human vaccines. After a more general discussion of adjuvants, including their definition, mechanisms of action, and safety, we will discuss recent clinical trials of investigational adjuvants. For additional study of this complex subject, including a historical perspective, the reader is referred to published reviews of vaccine adjuvants (see Refs. 2–4).

DEFINITIONS

The term ''adjuvant'' (from the Latin *adjuvare*, meaning *to help*) was coined in 1926 by Ramon for a substance used in combination with a specific antigen that produces a stronger immune response than the antigen could if used alone (5). The enormous diversity of compounds, which increase specific immune responses to an antigen and thus function as vaccine adjuvants, makes any classification system somewhat arbitrary. Adjuvants can be loosely categorized in terms of their source or their physical nature as (*i*) mineral salts; (*ii*) mycobacterial, bacterial, and plant derivatives; (*iii*) surface-active agents and microparticles; (*iv*) polymers, cytokines, vitamins, and hormones; and (*v*) synthetic constructs. Those listed in Table 1 are examples of immunopotentiators used during the past 25 years. They are grouped according to origin rather than mechanism of action, because the latter are incompletely understood for most adjuvants. All agents in Table 1 have immunomodulating capabilities and are reported to augment the immune response to specific antigens; nonspecific enhancers of the immune response that principally stimulate innate immunity are largely excluded. A comprehensive list of adjuvants, beyond the scope of this chapter, is available and updated by the NIAID (National Institutes of Health/National Institute of Allergy and Infectious Diseases, U.S.A.) (6).

A ''carrier'' is an immunogenic protein to which a hapten or a weakly immunogenic antigen is bound (7). It may also be a living organism (or vector) bearing genes for expression of the foreign hapten or antigen on its surface. A naked DNA vaccine is a carrier in the sense that it entails injection into the host of a plasmid-based DNA vector that encodes the production of the protein antigen (8). Carriers increase the immune response by providing T cell help to the hapten or antigen.

A ''vehicle'' provides the substrate for the adjuvant, the antigen, or the antigen-carrier complex. Unlike the carriers listed in Table 1, vehicles are not themselves immunogenic. Like carriers, most vehicles can enhance the immune response to antigens alone and are sometimes considered to be another class of adjuvants. Scientists have also investigated the result of combining adjuvants with different sources/mechanisms of action to increase their immunostimulatory effect. These ''adjuvant formulations'' can, in some cases, combine delivery improvement and immune modulation. Thus, in most cases, an adjuvant formulation is composed of two or more adjuvants with complementary immunomodulating effects, such as the adjuvant systems (ASs) being developed by GlaxoSmithKline (GSK). Many examples of such adjuvant formulations have been tested in humans.

MECHANISMS OF ACTION

The effects of adjuvants can be strongly impacted by (*i*) the nature and dose of the immunogen; (*ii*) the nature and dose of the adjuvant(s) or carrier in the formulation; (*iii*) the stability of the formulation; (*iv*) the immunization schedule; (*v*) the route of administration; (*vi*) the species of animal; and (*vii*) the genetic and other biologic variations within species, including their immune status. The discovery of a class of receptors similar to Toll, an essential receptor for innate defense against fungal infection in *Drosophila*, changed the approach to understanding