Chapter 27

Cytokines as Vaccine Adjuvants

Current Status and Potential Applications

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1. INTRODUCTION

Since Jenner's discovery that cowpox vaccinations protect humans against smallpox, vaccines have been used effectively to protect humans and livestock from contagious and deadly diseases. Most of the marketed vaccines are made from either inactivated or attenuated pathogens (i.e., viruses or bacteria). Although vaccines prepared with inactivated pathogens are often effective, their use may be limited because a small but measurable chance of infection exists, a result of the incomplete inactivation of pathogens in these preparations. The incomplete inactivation of pathogens is particularly a concern for vaccines against viruses that may produce a latent infection (i.e., herpes and retroviruses). Similarly, vaccines constructed with attenuated pathogens may invoke the very disease they are designed to prevent if they are insufficiently attenuated. Therefore, subunit vaccines composed of antigenic components (usually proteins) free of pathogenic components are likely to offer improved safety.

With the advent of recombinant DNA technology, it is possible to manufacture proteins on a large scale for use as subunit vaccines. However, most subunit proteins are weak immunogens compared with inactivated or attenuated vaccines. Therefore, immunogenicity of subunit vaccines must be enhanced with adjuvants to provide antigen-specific protective immunity. Alum (aluminum hydroxide) is the only vaccine adjuvant in products approved by the Food and Drug Administration for human use, despite its weak adjuvanticity. Potent vaccine adjuvants such as Freund's adjuvant, bacillus Calmette–Guérin (BCG), and others are effective in eliciting antigen-specific immune responses; however, their clinical use may be limited because of potential toxicity. In fact, these potent vaccine adjuvants mediate their immune enhancement through nonspecific induction of

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several cytokines that regulate immune interactions. Based on this, the selective use of cytokines should effectively and directly improve the immunogenicity of the weak subunit vaccines while minimizing the side effects of nonspecific cytokine inducers, e.g., Freund’s adjuvant. Recent advances in our knowledge of cytokine functions and the large availability of recombinant cytokines permit us to systematically test the use of cytokines as adjuvants.

Cytokines are protein factors that produce multiple, pleiotropic effects on many immune cells. In general, they are small (10–50 kDa) proteins that exhibit short biologic half lives and function as autocrines and/or paracrines. The biologic actions of cytokines are often mediated by multiple receptors expressed on the cell surface. The high affinity ($K_a = 10^{10}$ to $10^{12}$) and specificity of cytokines for their receptors and their short biologic half-life ensure localized and specific actions on the target cells. It is not a single cytokine but rather the network of cytokines that modulates the immune response. Cytokines generally can be categorized into (1) colony-stimulating factors [e.g., monocyte colony-stimulating factor (M-CSF) and granulocyte CSF (G-CSF)] that are produced primarily in antigen-presenting cells (APCs) and promote the growth of immune progenitor cells and (2) lymphokines such as interleukins that are produced by and stimulate leukocytes and interferons (IFNs).

This chapter focuses on the use of cytokines to enhance the immunogenicity of protein antigens. To systematically develop strategies for using cytokines as vaccine adjuvants, it is essential to understand the roles of cytokines involved in mediating natural immune interactions leading to protective immune responses (i.e., humoral or cellular responses against pathogens). Therefore, we discuss the role of cytokines in antigen presentation and T- and B-cell growth and differentiation. Subsequently, we discuss the application of selected cytokines that have been tested in vivo for vaccine immune enhancement. Finally, we will discuss strategies for optimizing the use of cytokines as vaccine adjuvants.

Because this chapter focuses on the use of cytokines as vaccine adjuvants, the reader should refer to recent reviews on molecular and cellular aspects of cytokine functions for additional details (Kroemer et al., 1993; St. Georgiev and Albright, 1993).

1.1. The Role of Cytokines in Antigen Presentation

When foreign antigen is introduced into the host, the antigen, either in its native form or processed, is presented by APCs at the first step in immune recognition that leads to T- and B-cell responses. The antigen presentation process determines the magnitude and the nature of the immune response. The APCs include monocytes, endothelial cells, fibroblasts, Langerhans cells, dendritic cells, and B cells. With the exception of B cells, antigens taken up by APCs are processed into short peptides either in endosomes or in other proteolytic compartments. The peptide fragments associate with the class II MHC (major histocompatibility complex), or in the cytoplasm with the class I MHC. The efficiency of antigen presentation will depend on the number of surface MHC molecules, the efficiency of antigen uptake, internalization, and processing, and the expression of costimulators for T-cell activation such as IFN and IL-1 (Harding et al., 1988). Cytokines may modulate the antigen presentation process in two ways: (1) increase the number of activated APCs that can present antigen and (2) activate APCs. For example, M-CSF and