result in lymphocyte activation and proliferation. For details on the intracellular signaling pathways and their critical role in the generation of effective adaptive immunity, the reader is referred to a number of excellent reviews (16,94,129,134).

Use of Epitopes in Vaccine Development

The use of defined epitopes that bind to class I and II MHC molecules (59,135,136) is an attractive vaccine strategy, the advantages of which include (*i*) the selection of epitopes from conserved regions of various proteins from the microorganism, that is, avoiding variable antigenic epitopes, which can lead to immune evasion, (*ii*) increased safety, (*iii*) the ability to select only epitopes likely to play key roles in host defense or tilt the immune response toward desired effector mechanism(s), and (*iv*) the fact that multiple epitopes can be incorporated in a single vaccine. Moreover, the availability of fluorochrome-labeled epitope multimers could greatly aid in the monitoring of immunogenicity in vaccine trials. However, it is unlikely that a vaccine consisting solely of CTL epitopes will be successful. Accumulating evidence indicates that successful subunit peptide vaccines might require the use of the appropriate CTL epitopes in combination with ''universal Th epitopes'' (i.e., able to bind to a large number of MHC class II molecules) and powerful adjuvants (59,135–137). Moreover, significant efforts are being directed toward enhancing the immunogenicity of subunit vaccines by rationally modifying antigenic determinants (i.e., creating ''agonistic peptides'') to enhance the host's immune response through upregulation of Ag recognition (59,135–137).

Activation of T Cells by Superantigens

Superantigens consist of certain bacterial and viral proteins that, without processing, trigger activation of up to 20% of T cells, including $CD4^+$ and $CD8^+$ cells (138,139). This activation is triggered by high-affinity binding of these superantigens to the lateral sides of class II MHC molecules on APC and to the β chain (Vβ) of α/β TCR T cells (138,139). The recognition between T cells and superantigens is specific and clonally variable, since superantigens activate T cells bearing particular Vβ regions. Triggering of T cells by superantigens requires the complete TCR-CD3 complex and accessory molecules, including CD4, CD8, CD2, and LFA-1 (αLβ2 integrin). Instead of priming an adaptive immune response to the pathogen, T-cell activation by superantigens causes a massive cytokine production and release, mainly by $CD4^+$ T cells. The cytokine response not only causes systemic toxicity but also downregulates the host's adaptive immunity and might be involved in the triggering of autoimmune diseases. In addition, superantigens result in the activation of APC, leading to the production of proinflammatory cytokines such as IL-1β and TNF-α. The high levels of T-cell and APC cell activation and the ensuing release of cytokines triggered by superantigens play a significant role in the generation of toxic shock syndrome and food poisoning associated with some bacterial infections. Superantigens include products of bacterial and viral origins. Bacterial superantigens include staphylococcal enterotoxins (SE)-A, SE-B, SE-C, SC-D, SC-E, the toxic shock syndrome toxin-1 (TSST-1), and those produced by *Streptococcus*, *Yersinia*, and *Mycoplasma arthritidis* (138,139). Viral superantigens include retroviral glycoproteins, such as the minor lymphocyte stimulating Ag (Mls) produced by the mouse mammary tumor viruses, and products of rabies and moloney leukemia viruses (138,140).

Cytokines, Chemokines, and T-cell Subpopulations: Linking Adaptive and Innate Immunities

These immunoregulatory molecules, secreted by immune as well as other cells, play key roles in the clonal expansion of lymphocytes, in mediating the action of effector cells, and in regulating innate immunity (110,141–146). Despite their diversity, most cytokines and chemokines share a number of characteristics, including that (*i*) they are produced by more than one cell type and act on many different cells (pleiotropism), sometimes exerting more than one effect on a single target cell; (*ii*) their production follows cell activation, requires de novo RNA and protein synthesis, and is transient; (*iii*) similar activities are typically performed by more than one cytokine (redundancy); (*iv*) production of individual cytokines follows the release of other cytokines producing a ''cascading effect;'' (*v*) they regulate each other, either positively or negatively, sometimes synergizing or exhibiting additive effects; (*vi*) they exert their functions by interacting with high-affinity specific receptors on the target cells (10^{-9} to 10^{-12} dissociation constant) that they help regulate; (*vii*) they can exert their activities locally, systemically, or both, by acting in an autocrine (i.e., on the cells that produce them), paracrine (i.e., on adjacent cells), or endocrine (i.e., on distant cells) fashion; and (*viii*) their actions on the target cells usually involve regulation of proliferation and state of differentiation (110,141–146).

The Th1/Th2/Th17 Paradigm

Distinct Th cell populations exhibit discrete or overlapping patterns of cytokine production that designate them as Th1, Th2, and Th17 $CD4^+$ T cells (110,141,142,144–150). The predominance of these polarized patterns of cytokine and chemokine production, as well as the temporal sequence of their production, plays a pivotal role in determining the type and characteristics of the effector immune responses generated upon antigenic stimulation, for example, whether the predominant responses will be Ab production (and of which isotypes), enhanced intracellular killing by macrophages, generation of effector CTL, etc., (109,110,144,147). For detailed descriptions of individual cytokines and chemokines, the reader is referred to excellent recent reviews (110,141,142,144–146,149,150). Instead, we will briefly describe how the coordinated induction of chemokines and polarized cytokine patterns plays a role in resistance to disease by invading pathogens and their role in downregulating immune responses. We will also provide some examples on the intricate interactions among these potent mediators in cross-regulating innate and adaptive immunity.

Th1 cells are characterized by the production of IFN-γ and IL-2, while Th2 cells are characterized by the production of IL-4, IL-13, and IL-33, among others (144,145). Cells producing a combination of these cytokines were named Th0. Moreover, a relatively new subset, named Th17, which appears to play a significant role in autoimmunity and infectious diseases, is characterized by a polarization in the production of IFN-γ driven by IL-17 via the intermediate production of IL-23 (143,144,151). Similarly, the function of regulatory T cells (Treg, see below) is characterized by the production of defined cytokines (e.g., IL-10 and TGF-β) (9,144,152,153). $CD8^+$ cells also exhibit type 1 (Tc1) and type 2 (Tc2) cytokine profiles and have been shown to produce IL-17 family cytokines (142,145). Many Th cells exhibit ''mixed'' cytokine production (e.g., IL-2, IL-4, IL-5, and IFN-γ) that does not allow them to be classified into Th1 or Th2 cells, even within populations that are