*T-Independent B-Cell Responses*

Production of Ab to most nonprotein Ag, such as glycolipids, nucleic acids, and polymeric polysaccharides, does not require help by cognate T cells and is therefore referred to as thymus-independent (TI) Ag (87–90). In contrast to T-dependent Ag, TI Ag induce mostly IgM Ab of low affinity and, in the majority of cases, do not show significant heavy-chain class switching, affinity maturation, or memory (88). TI Ag have been further subdivided into types 1 and 2 depending on whether they are able (type 1) or not (type 2) to induce immune responses in neonates (88,90). An example of TI-1 Ag is LPS, while most bacterial capsular polysaccharides and carbohydrates are TI-2 Ag. The fact that Ab responses to TI-2 Ag develop later in life is evidenced by the limited responses observed in small infants immunized with, for example, polysaccharide vaccines. In contrast, it is now well established that immunization with conjugate vaccines composed of polysaccharides from, for example, *Haemophilus influenzae* type B or *Salmonella enterica* serovar Typhi coupled to T cell–dependent protein Ag elicit strong antipolysaccharide Ab responses that can be increased with repeated immunization and that are very effective in protecting small infants from invasive *H. influenzae* type B or preschool children from *S. enterica* serovar Typhi infection (87,91,92). It is unclear what mechanisms underlie these responses and to what extent cytokines derived from APC or small numbers of nonspecific T cells are required to provide a second signal for B-cell triggering after exposure to TI-2 Ag. Because of its importance in vaccine development, particularly for neonates and small infants, this remains an area of intense investigation.

*T Lymphocytes, Memory and Cell-Mediated Immunity to Vaccines*

T lymphocytes, in contrast to B cells, recognize peptides (short continuous aa sequences) derived from protein Ag that are presented on the surface of APC in conjunction with class I or class II major histocompatibility complex molecules (pMHC) in the presence of costimulatory molecules (93–98). These Ag may originate from bacteria, viruses, or parasites that have infected host cells and reside intracellularly or from the extracellular environment following internalization by endocytosis (99). Spectacular advances in the ability to track in vivo T cells of known specificity have led to the widely accepted view that naive T cells expressing TCR of the appropriate specificity are activated, almost exclusively, by pMHC complexes presented by DC that have acquired the Ag at the site it entered the host and that, in the presence of the appropriate inflammatory stimuli, migrated to the T-cell areas of secondary lymphoid tissues (e.g., LN, spleen, and Peyer's Patches [PP]) (98–105). Following Ag presentation and activation in the presence of inflammatory stimuli (e.g., IL-12, IFN-α, IFN-β), T cells undergo an explosive clonal expansion (later to be followed by a contraction phase), mature into effector cells, and migrate to effector sites (98–105). Some Ag-specific T-cell clones remain for long periods of time as memory T cells (Tm) that, upon subsequent exposures to Ag, provide a stronger, rapid, and sometimes qualitatively different specific immune response. Induction of effective Tm cells is critical for successful vaccination. Recent evidence from several laboratories indicates that there are at least two pools of Tm cells: (*i*) central memory T cells (Tcm) that recirculate through LN and quickly acquire the capacity to produce effector cytokines upon Ag stimulation and (*ii*) effector memory T cells (Tem) that recirculate through nonlymphoid tissues and are capable of immediate effector function (101,106–108).

There are two main populations of T cells, those expressing CD4 molecules and those expressing CD8 molecules. CD4 and CD8 molecules are T-cell surface glycoproteins that serve as important accessory molecules (coreceptors) during Ag presentation by binding to class II and class I MHC molecules, respectively (93,95,101,106–108). Consequently, CD4 and CD8 molecules, originally used primarily as markers to identify T-cell populations with different functional characteristics, play a major role in class II and I MHC-restricted T-cell activation. $CD4^+$ cells (Th) are mainly involved in inflammatory responses and in providing help for Ab production by B cells, while $CD8^+$ cells, in addition to secreting cytokines, compose the majority of CTLs primarily involved in class I MHC-restricted killing of target cells infected by pathogenic organisms, including bacteria, viruses, and parasites (93,98,99,109,110). Of note, cytotoxic $CD4^+$ T cells have also been described in both animals and humans (111). Cell activation triggered by cross-linking of TCR by pMHC complexes, aided by costimulatory molecules, results in the production of a multitude of molecules with strong immunoregulatory properties collectively known as cytokines and chemokines (discussed below). Acting in concert, cytokines not only modulate the growth, maturation, and differentiation of all cells involved in the generation of adaptive immunity (93,98–100,110) but also strongly regulate innate immunity.

*Antigen Processing and Presentation to T Cells by Antigen-Presenting Cells*

An in-depth understanding of the mechanisms involved in these early stages of immune activation is helpful for the development of successful vaccines. Because of space limitations, we will not review here in detail the various pathways of Ag processing and presentation (16). Instead, we will summarize the field and refer the readers to some excellent reviews on this subject. Presentation of Ag to T cells involves a series of intracellular events within the APC, including the generation of antigenic peptide fragments, binding of these peptides to MHC molecules to form stable peptide-MHC complexes, and transport of these complexes to the cell surface where they can be recognized by TCR on the surface of T cells. Two main pathways of Ag processing and presentation (''classical pathways''), that is, cytosolic and endosomic, have been described (16,112). The ''cytosolic pathway'' is predominantly used for presentation of peptides produced endogenously in the APC, such as viral proteins, tumor Ag, and self-peptides, associated with class I MHC molecules (59,113–116). The presentation of large numbers of self-peptides complexed to class I MHC molecules results from the inability of APC to differentiate between self and nonself. Under normal conditions, most T cells selected to recognize self-peptides were eliminated during T-cell differentiation or are actively downregulated and, consequently, cannot be activated by self-peptide class I MHC complexes. The second ''classical pathway'' of Ag processing and presentation, ''endosomal pathway,'' which is predominantly used for presentation of soluble exogenous Ag bound to class II MHC molecules, involves the capture of Ag by APC, either by binding to a specific receptor or by uptake in the fluid phase by macropinocytosis (117–120).

*Cross-Presentation and Alternative Pathways for Antigen Processing and Presentation by MHC Molecules*

Cross-presentation is a process by which Ag is transferred from cells expressing the Ag to host APC (114,115,121,122).