correlate with high IL-2 and IL-4 production, and good responsiveness to vaccinations (20,21). Furthermore, $CD28^{-}CD4^{+}$ T cells display decreased expression of CD154 (CD40L), which reduces their capacity to provide help for B-cell proliferation and antibody production. Although aging confers a major risk of morbidity and mortality from infectious diseases, chronic infections with cytomegalovirus (CMV), hepatitis C, human immunodeficiency virus (HIV), and Epstein-Barr virus may accelerate the aging process of the immune system and lead to premature immune senescence. Experimental evidence for this hypothesis comes from the identification of expanded, dysfunctional HIV- and CMV-specific $CD28^{-}$ T-cell clones in chronically infected persons (22,23). In longitudinal studies, CMV-seropositivity has been included in a set of immunological parameters (immune risk phenotype), which predict a two-year mortality in the very elderly (24).

B Lymphocytes

Similar to T cells, the number of peripheral B cells is maintained during aging, but each B-cell subset undergoes severe perturbations in size, dynamics, and repertoire. The changes that affect the B-cell subsets are due to a decreased generation of B-cell precursors, such as early lymphoid precursors and pro–B cells. Cell-intrinsic as well as microenvironmental disturbances are both likely to contribute to the decreased output of pro–B cells. Environmental factors also impair overall V(D)J recombinase activity among pro–B cells which, together with a decline in peripheral naive $CD27^{+}$ B cells, accounts for the limited peripheral B-cell repertoire frequently detected in elderly persons (25). Of particular importance, impaired T-cell-mediated immunity as well as impaired stimulation by APCs also contribute to the decline in B-cell-specific function (26). For example, B cells from elderly individuals are stimulated 70% less efficiently by follicular dendritic cells (DCs) than B cells from young subjects. Additionally, germinal center reactions in lymph nodes, which are crucial for isotype switching and affinity maturation of antibodies, are impaired in old age because of the decline in $CD4^{+}$ T-cell-mediated B-cell help. The molecular mechanisms of the dysregulated T-cell/B-cell interactions involve the loss of the costimulatory molecules CD27 and CD40L as well as the reduced production of IL-2 and IL-4 by $CD28^{-}CD4^{+}$ T cells. As a consequence, primary antibody responses in elderly persons are frequently weak and short-lived and the produced antibodies bind with lower affinity (27).

Innate Immunity

Innate immunity is dependent on a variety of cell types and mechanisms that provide the basis for an adequate response to pathogens. With increasing age, however, inflammatory processes occur ubiquitously and are referred to as ''inflammaging'' (28). This chronic inflammation can support the development and progression of age-related diseases, such as atherosclerosis, rheumatoid arthritis, osteoporosis, and neurodegeneration. The severity of chronic inflammatory processes in elderly people also depends on genetic factors, such as polymorphisms within genes encoding for cytokines like IL-6, IL-10, and IFN-γ, and have been associated with changes in life span (29). Functional deficits of innate immune system components may lead to the inability to eliminate pathogens and may consequently trigger the chronic activation of nonspecific responses. For example, neutrophils produce reduced amounts of superoxide anion and exhibit changes in membrane fluidity and chemotaxis. Of great relevance for vaccine efficacy is the question of how aging affects professional APCs. The recognition and uptake of antigen initializes a maturation program within DCs and leads to the upregulation of major histocompatibility complex (MHC) and costimulatory molecules. Adequate stimulation of DCs is therefore a prerequisite for proper T-and B-cell responses. However, the impact of aging on DC function has not been fully elucidated yet. Experiments in mice suggest that the density of DCs in the skin, the expression of MHC class II and other cell-surface molecules, and the capacity of DCs to present antigen can all be altered with increasing age (30). Though, only few studies have been carried out to analyze these effects in humans (31).

STRATEGIES TO ENHANCE THE IMMUNOGENICITY OF VACCINES

Because of the reduced protective effect of vaccinations and the high morbidity and mortality from infectious diseases in old age, there is a tremendous need to improve vaccine efficacy. Vaccines that target an old immune system need to stimulate $CD4^{+}$ T-helper cells and B cells more efficiently to enhance antibody responses and ensure the formation of long-lasting memory. Furthermore, cell-mediated immunity has been shown to play a key role in protection from influenza, Herpes zoster, tuberculosis, typhoid fever, and hepatitis A and B (32). For these infectious diseases it is therefore of utmost importance to induce functional and long-lasting memory $CD8^{+}$ T cells. Several strategies are being pursued to enhance the efficacy of vaccines and to minimize adverse side effects (33,34). Live-attenuated vaccines have been proven highly efficient in eliciting T- and B-cell-mediated immunity, while conjugate and subunit vaccines have a very favorable safety profile but need to be supplemented with adjuvants to enhance immunogenicity (35). Adjuvants can be classified into antigen delivery systems [e.g., aluminium salts, microparticles, liposomes, oil-in-water emulsions, and immunostimulatory complexes (ISCOMs)] and immune potentiators [the saponin component QS21, 3-deacetylated monophosphoryl lipid (MPL) A, oligodeoxynucleotides-containing CpG motifs (CpG-ODNs), cytokines and nucleic acids]. The mechanisms of action of these adjuvants are to improve antigen processing and presentation, and to stimulate innate immunity components. In particular, antigen delivery systems convert soluble antigens into particulate material, which is more readily ingested by APCs. In contrast, immune potentiators stimulate innate immune components through evolutionary conserved pathogen recognition receptors or modulate T- and B-cell responses through the application of DNA encoding for cytokines, costimulatory molecules, or chemokines. However, only few adjuvants are licensed for human use. Aluminium salts have been used widely in humans to enhance specific antibody responses but they have little capacity to stimulate cell-mediated immunity (36). Until now, only two other vaccine adjuvants have been approved for use in human influenza vaccines: an oil-in-water emulsion (MF59®), which is used as an adjuvant in subunit influenza vaccines, and a virosomal influenza vaccine. These adjuvanted vaccines demonstrate an improved immunogenicity in elderly persons with seroconversion rates up to 68% (37,38). Numerous other adjuvants are currently being tested in animal models and clinical trials. Immunostimulatory adjuvants may overcome the proposed age-related functional declines of innate and adaptive immune responses.