and either increased expression of activation markers or inhibitory receptors associated with functional exhaustion. The more activated and differentiated B cells are also responsible for increased secretion of immunoglobulins and increased susceptibility to Fas-mediated apoptosis. In more advanced disease, there is also the appearance of immature B cells associated with CD4+ T cell lymphopenia. Cognate B cell–CD4+ T cell interactions are abnormal in viremic HIV-infected individuals in that B cells respond poorly to CD4+ T cell help and CD4+ T cells receive inadequate co-stimulatory signals from activated B cells. In vivo, the aberrant activated state of B cells manifests itself by hypergammaglobulinemia and by the presence of circulating immune complexes and autoantibodies. HIV-infected individuals respond poorly to primary and secondary immunizations with protein and polysaccharide antigens. Using immunization with influenza vaccine, it has been demonstrated that there is a memory B cell defect in HIV-infected individuals, particularly those with high levels of HIV viremia. There is also evidence that responses to HIV and non-HIV antigens in infected individuals, especially those who remain viremic, are enriched in abnormal subsets of B cells that either are highly prone to apoptosis or show signs of functional exhaustion. Taken together, these B cell defects are likely responsible in part for the inadequate response to HIV as well as to decreased response to vaccinations and the increase in certain bacterial infections seen in advanced HIV disease in adults, as well as for the important role of bacterial infections in the morbidity and mortality rates of HIV-infected children, who cannot mount an adequate humoral response to common bacterial pathogens. The absolute number of circulating B cells may be depressed in HIV infection; this phenomenon likely reflects increased activation-induced apoptosis as well as a redistribution of cells out of the circulation and into the lymphoid tissue—phenomena that are associated with ongoing viral replication.

Monocytes/Macrophages Circulating monocytes are generally normal in number in HIV-infected individuals; however, there is evidence of increased activation within this lineage. The increased level of sCD14 and other biomarkers (see above) reported in HIV-infected individuals is an indirect marker of monocyte activation in vivo. A number of other abnormalities of circulating monocytes have been reported in HIV-infected individuals, many of which may be related directly or indirectly to aberrant in vivo immune activation. In this regard, increased levels of lipopolysaccharide (LPS) are found in the sera of HIV-infected individuals due, at least in part, to translocation across the gut mucosal barrier (see above). LPS is a highly inflammatory bacterial product that preferentially binds to macrophages through CD14 and Toll-like receptors, resulting in cellular activation. Functional abnormalities of monocyte/macrophages in HIV disease include decreased secretion of IL-1 and IL-12; increased secretion of IL-10 and IL-18; defects in antigen presentation and induction of T cell responses due to decreased MHC class II expression; and abnormalities of Fc receptor function, C3 receptor–mediated clearance, oxidative burst responses, and certain cytotoxic functions such as ADCC, possibly related to low levels of expression of Fc and complement receptors. Monocytes express the CD4 molecule and several co-receptors for HIV on their surface, including CCR5, CXCR4, and CCR3, and thus are potential targets of HIV infection. The degree of cytopathicity of HIV for cells of the monocyte lineage is low, and HIV can replicate in cells of the monocyte lineage with relatively little cytopathic effect. Hence, monocyte-lineage cells may play a role in the dissemination of HIV in the body and can serve as reservoirs of HIV infection, thus representing an obstacle to the eradication of HIV by antiretroviral drugs. In vivo infection of circulating monocytes is difficult to demonstrate; however, infection of tissue macrophages and macrophage-lineage cells in the brain (infiltrating macrophages or resident microglial cells) and lung (pulmonary alveolar macrophages) can be demonstrated easily. Tissue macrophages are an important source of HIV during the inflammatory response associated with opportunistic infections. Infection of monocyte precursors in the bone marrow may directly or indirectly be responsible for certain of the hematologic abnormalities in HIV-infected individuals. However, as with DCs, monocytes and macrophages express high levels of host restriction factors that likely help explain the low contribution of myeloid cells to the overall viral burden in HIV-infected individuals.

Dendritic and Langerhans Cells DCs and Langerhans cells are thought to play an important role in the initiation of HIV infection by virtue of the ability of HIV to bind to cell-surface C-type lectin receptors, particularly DC-SIGN (see above) and Langerin. This allows efficient presentation of virus to CD4+ T cell targets that become infected; complexes of infected CD4+ T cells and DCs provide an optimal microenvironment for virus replication. There was once considerable disagreement regarding the HIV infectibility and hence the depletion as well as the dysfunction of DCs themselves. However, since the recognition of myeloid (mDC) and plasmacytoid (pDC) subsets, there has been a better appreciation of specific DC dysfunction in HIV disease. pDCs are an important component of the innate immune system and secrete large amounts of IFN-α in response to viral infections. The numbers of circulating pDCs are decreased in HIV infection through mechanisms that remain unclear, and there are conflicting reports regarding the frequency of pDCs in lymphoid tissues, with some studies suggesting that their increased tissue presence and secretion of inflammatory cytokines such as IFN-α contributes to lymphoid hyperplasia. The mDCs or conventional DCs are involved in the initiation of adaptive immunity in draining lymph nodes by presenting antigen to T cells and B cells, as well as by secreting cytokines such as IL-12, IL-15, and IL-18 that activate other immune cells. There are also indications that the relatively low infectibility of DCs may be associated with the expression of host restriction factors, including APOBEC3G (see above).

Natural Killer Cells The role of NK cells is to provide immunosurveillance against virus-infected cells, certain tumor cells, and allogeneic cells (Chap. 372e). There are no convincing data that HIV productively infects NK cells in vivo; however, functional abnormalities in NK cells have been observed throughout the course of HIV disease, and the severity of these abnormalities increases as disease progresses. NK cells are part of the innate immune system and act by direct killing of infected cells and secretion of antiviral cytokines. In early HIV infection there is an increase in the activation of NK cells, and the capacity to secrete IFN-γ is maintained, although they manifest reduced cytotoxic function. During chronic HIV infection, both NK cell cytotoxicity and cytokine secretion become impaired. Given that HIV infection of target cells downregulates HLA-A and -B, but not HLA-C and -D molecules, this may explain in part the relative inability of NK cells to kill HIV-infected target cells. However, the NK cell impairments, especially in patients with high levels of virus replication, are associated with an expansion of an "anergic" CD56–/CD16+ NK cell subset. This abnormal subset of NK cells manifests an increased expression of inhibitory NK cell receptors (iNKRs) and a substantial decrease in expression of natural cytotoxicity receptors (NCRs) and shows a markedly impaired lytic activity. The overrepresentation of this abnormal subset of NK cells may explain in part the observed defects in NK cell function in HIV-infected individuals and likely begins to occur during primary infection. NK cells also serve as important sources of HIV-inhibitory CC-chemokines. NK cells isolated from HIV-infected individuals constitutively produce high levels of MIP-1α (CCL3), MIP-1β (CCL4), and RANTES (CCL5), although the impact of these chemokines on HIV replication in vivo is unclear. Finally, NK cell–DC interactions are important for normal immune function. NK cells and DCs reciprocally modulate each other's activation and maturation. These interactions are markedly impaired in HIV-infected individuals with high levels of plasma viremia.

GENETIC FACTORS IN HIV-1 AND AIDS PATHOGENESIS

PHENOTYPES OF SUSCEPTIBILITY AND RESPONSE TO HIV INFECTION It is well known that individuals vary in their susceptibility to acquiring HIV infection and that there is wide variation in both the steady-state level of HIV that is established soon after infection (virologic setpoint) as well as the rate at which HIV-infected patients progress to AIDS. Some striking examples include sex workers who remain uninfected despite repeated exposure to HIV; HIV-infected individuals who