cells have numerous fine cytoplasmic processes that resemble dendrites, from which they derive their name. Several features of dendritic cells account for their key role in antigen presentation. First, these cells are located at the right place to capture antigens—under epithelia, the common site of entry of microbes and foreign antigens, and in the interstitia of all tissues, where antigens may be produced. Immature dendritic cells within the epidermis are called *Langerhans cells*. Second, dendritic cells express many receptors for capturing and responding to microbes (and other antigens), including TLRs and lectins. Third, in response to microbes, dendritic cells are recruited to the T-cell zones of lymphoid organs, where they are ideally located to present antigens to T cells. Fourth, dendritic cells express high levels of MHC and other molecules needed for presenting antigens to and activating T cells.

A second type of cell with dendritic morphology is present in the germinal centers of lymphoid follicles in the spleen and lymph nodes and is called the *follicular dendritic cell*. These cells bear Fc receptors for IgG and receptors for C3b and can trap antigen bound to antibodies or complement proteins. Such cells play a role in humoral immune responses by presenting antigens to B cells and selecting the B cells that have the highest affinity for the antigen, thus improving the quality of the antibody produced.

Macrophages

Macrophages are a part of the mononuclear phagocyte system; their origin, differentiation, and role in inflammation are discussed in Chapter 3. Here, their important functions in the induction and effector phases of adaptive immune responses are discussed.

- Macrophages that have phagocytosed microbes and protein antigens process the antigens and present peptide fragments to T cells. Thus, macrophages function as antigen-presenting cells in T-cell activation.
- Macrophages are key effector cells in certain forms of cell-mediated immunity, the reaction that serves to eliminate intracellular microbes. In this type of response, T cells activate macrophages and enhance their ability to kill ingested microbes (discussed later).
- Macrophages also participate in the effector phase of humoral immunity. As discussed in Chapter 3, macrophages efficiently phagocytose and destroy microbes that are opsonized (coated) by IgG or C3b.

Natural Killer Cells

The function of NK cells is to destroy irreversibly stressed and abnormal cells, such as virus-infected cells and tumor cells. NK cells make up approximately 5% to 10% of peripheral blood lymphocytes. They do not express TCRs or Ig. Morphologically, NK cells are somewhat larger than small lymphocytes, and they contain abundant azurophilic granules. NK cells are endowed with the ability to kill a variety of virus-infected cells and tumor cells, without prior exposure to or activation by these microbes or tumors. This ability makes NK cells an early line of defense against viral infections and, perhaps, some tumors. Two cell surface molecules, CD16 and CD56, are commonly used to identify NK cells. CD16 is an Fc receptor for IgG, and it confers on NK cells the ability to lyse IgG-coated target cells. This phenomenon is known as *antibody-dependent cell-mediated cytotoxicity (ADCC)*. The function of CD56 is not known.

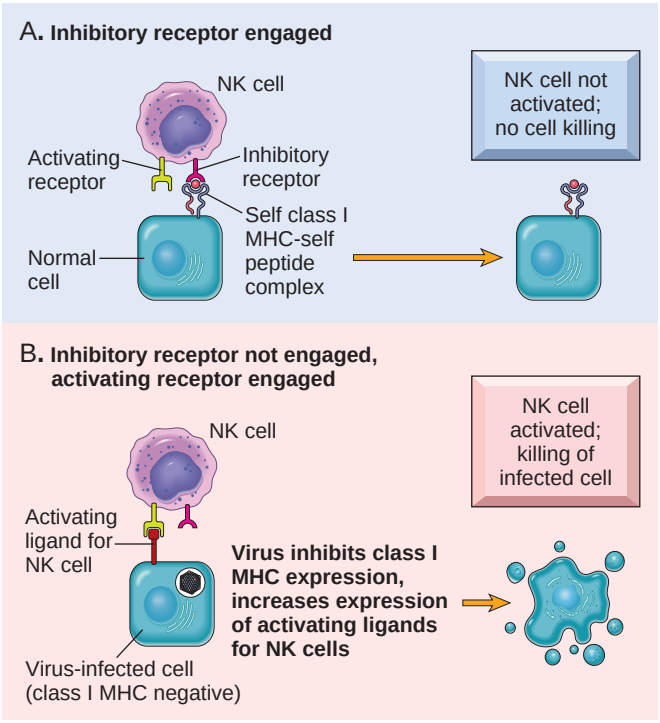

Figure 6-7 Activating and inhibitory receptors of natural killer (NK) cells. **A,** Healthy cells express self class I MHC molecules, which are recognized by inhibitory receptors, thus ensuring that NK cells do not attack normal cells. Note that healthy cells may express ligands for activating receptors (not shown) or may not express such ligands (as shown), but they do not activate NK cells because they engage the inhibitory receptors. **B,** In infected and stressed cells, class I MHC expression is reduced so that the inhibitory receptors are not engaged, and ligands for activating receptors are expressed. The result is that NK cells are activated and the infected cells are killed.

The functional activity of NK cells is regulated by a balance between signals from activating and inhibitory receptors (Fig. 6-7). There are many types of activating receptors, of which the NKG2D family is the best characterized. The NKG2D receptors recognize surface molecules that are induced by various kinds of stress, such as infection and DNA damage. NK cell inhibitory receptors recognize self class I MHC molecules, which are expressed on all healthy cells. The inhibitory receptors prevent NK cells from killing normal cells. Virus infection or neoplastic transformation often enhances expression of ligands for activating receptors and at the same time reduces the expression of class I MHC molecules. As a result the balance is tilted toward activation, and the infected or tumor cell is killed.

NK cells also secrete cytokines such as interferon-γ (IFN-γ), which activates macrophages to destroy ingested microbes, and thus NK cells provide early defense against intracellular microbial infections. The activity of NK cells is regulated by many cytokines, including the interleukins IL-2, IL-15, and IL-12. IL-2 and IL-15 stimulate proliferation of NK cells, whereas IL-12 activates killing and secretion of IFN-γ.