**Cross-presentation and Cross-priming of Tumor Antigens**

Cancer cells frequently stimulate Signal 1 alone, and inefficiently stimulate Signal 2. Accordingly, cancer cells may preferentially induce tolerance. Hence, tumor antigens must be presented through antigen-presenting cells to initiate and sustain anti-tumor immune responses. This is achieved by a process called APCs such as DCs can efficiently prime T cells, where they display MHC antigen complexes (Signal 1) together with co-stimulatory molecules (Signal 2), which activate naïve T cells in a process called cross-priming. This process can also cause T cell unresponsiveness or cross-tolerance (Chapters 7 and 11 in Immunology IV).

Since individual B and T lymphocytes are antigenically committed to a specific unique antigen, their clonal expansion upon recognition of foreign antigens is required to obtain sufficient antigen-specific B and/or T lymphocytes to achieve an appropriate immune response. Although the kinetics of primary adaptive immune responses are slower than innate immune responses, the differentiation of lymphocyte subsets into long-lived and short-lived memory cells during the primary immune response results in larger responses upon subsequent exposure to the same antigen (Figure 2 and Chapter 6 in Immunology IV).
Figure 2. Schematic representation of the clonal expansion and generation of subsets of lymphocytes differentiating into long-lived and short-lived memory cells during the course of a primary adaptive immune response, resulting in larger T and B cell responses upon subsequent exposure to the same antigen. [Reproduced with permission from Bellanti, JA (Ed). Immunology IV: Clinical Applications in Health and Disease. I Care Press, Bethesda, MD, 2012]

**T Cytotoxic and NK Cell Killing of a Cancer Cell**

Two of the major cytotoxic killing mechanisms of tumors are carried out by either CD8+ CTL cells or NK cells (Chapters 1 and 3 in Immunology IV). Shown in **Figure 3** is a schematic representation of the
The mechanism of destruction of a cancer cell by a CTL cell. After generation of mature CTL cells resulting from the APC-antigen/T cell interaction as described previously, the presence of the tumor peptide-loaded MHC-I molecule on the surface of the cancer cell is required for effective tumor cell killing. In this scenario, where the cancer cell retains the MHC-I molecule, the CTL cell is activated to kill the cancer cell by apoptosis.

Figure 3. Schematic representation of the role of T cytotoxic cells in the killing of a cancer cell that retains the MHC-I receptor. The tumor-specific antigen (TSA) is processed by an APC following which the processed TSA is then displayed on a MHC-I molecule and presented to a CTL cell, which is then activated to kill the cancer cell by apoptosis. [Reproduced with permission from Bellanti, JA (Ed). Immunology IV: Clinical Applications in Health and Disease. I Care Press, Bethesda, MD, 2012]

During the course of malignant transformation of a normal cell to a malignant cell, the cancer cell may lose the MHC-I molecule on its cell membrane as part of its evasion strategy to elude its destruction by the CTL. In this scenario, the NK cells are now called into play. Shown in Figure 4 is a schematic representation of the mechanisms of killing of a tumor cell by the NK cell. Normally, NK cells display two types of receptors: (1) a killer-activating receptor (KAR) with specificity for a number of cell surface ligand molecules; and (2) a killer-inhibiting receptor (KIR) with specificity for a MHC-I ligand. The interaction of a NK cell with a normal cell consists of the binding of both of these receptors with their respective ligand molecules, which are found on the cell membrane of a normal cell; the binding of the KAR with a KAR activation ligand (L) on a cell leads to an activation signal that enhances the killing activity of the cell, and conversely the binding of the KIR with an MHC-I molecule ligand results in an inhibitory signal restraining the killing activity of the cell. Since the inhibitory activity of the KIR-MHC-I interaction is greater than the killing activity of the KAR-L interaction, no reaction is seen when a NK cell encounters a normal cell. In the event of the loss of expression of a MHC-I molecule by the cancer cell, since the NK interaction with the cancer cell now can only occur through the KAR ligand, the cancer cell will be killed by the unopposed KAR activation pathway. The
apoptotic killing mechanism involves the assembly of a membrane-associated perforin cylindrical structure into which the granzymes deliver their death-dealing blow (Chapters 1 and 3 in Immunology IV).

Figure 4. Schematic representation of the mechanisms by which the NK cell discriminates between the non-killing of a normal cell and the killing of a cancer cell that has lost its MHC-I receptor. In the NK cell interaction with a normal cell, the inhibitory activity of the KIR-MHC-I interaction overrides the killing activity of the KAR-L interaction, and no NK killing of a normal cell occurs. In the cancer cell interaction, since there is no opposing KIR-MHC-I binding, the unopposed enhanced killing activity by the KAR-L interaction leads to successful NK cell killing of the cancer cell by apoptosis. [Reproduced with permission from Bellanti, JA (Ed). Immunology IV: Clinical Applications in Health and Disease. I Care Press, Bethesda, MD, 2012]

An alternative mechanism of destruction of the tumor cell by an NK cell can occur by an ADCC
mechanism where the Fab portion of an IgG antibody produced by B cells binds to the surface TSA and bridges to an Fc receptor on the NK cell by attachment through its Fc portion of the antibody molecule (Chapters 1 and 3 in Immunology IV). Shown in Figure 5 is comparison of these two mechanisms of killing of a cancer cell by a NK cell.

Figure 5. Panel A: Comparison of the two mechanisms of killing target cells by NK cells. Panel B: Direct NK cell killing of a cancer cell by a perforin/granzyme mechanism. Panel C: In contrast to NK killing by an ADCC mechanism. [Reproduced with permission from Bellanti, JA (Ed). Immunology IV: Clinical Applications in Health and Disease. I Care Press, Bethesda, MD, 2012]