c. T Cells and NK Cells Kill Cancer Cells

Most T cells reside in tissues, such as lymphoid tissues, intestines, lungs, and skin, while a small percentage resides in the bloodstream. At birth, all T cells are naive, and memory T cells arise and develop in response to exposure to antigens. By the second decade of life, in humans, about 35% of the T cells in the bloodstream are memory T cells (32).

Upon interaction with dendritic cells (DCs), naive $CD4^+$ T cells and naive $CD8^+$ T cells differentiate into antigen-specific T cells, where CD4 + T cells become Th1 cells, Th2 cells, or Th17 cells, and $CD8^+$ T cells become effector cytotoxic T cells (cytotoxic T lymphocytes, CTLs) (33).

Immune response against cancer cells by effector cytotoxic T cells is by way of adaptive immunity, while immune response against cancer cells by NK cells, also called "natural killer cells," is by way of innate immunity. NK cells received their name because of their ability for spontaneous "natural" cytotoxicity against cancer cells and virus-infected cells. The name also invokes the fact that NK cells can kill their targets without need for any adaptive immune response (34).

Cytotoxic T cells and NK cells each independently can kill cancer cells by direct contact, where an immune synapse is formed.

Where the cells contact each other, the target cell can be killed by way of degranulation, where fusion of an intracellular vesicle (the granule) with the plasma membrane results in release of perforin and granzyme (35,36). Perforin creates momentary pores in the target cell, allowing granzyme to enter, and once inside the target cell, granzyme activates apoptosis and the target cell is killed. The pores, which are only 10 nanometers in diameter, are rapidly repaired. The immune system uses this method for killing cancer cells, and also for killing cells that are infected with viruses.

Cytotoxic T cells and NK cells also kill target cells, with direct contact, by way of another mechanism, namely by way of the ligands, FasL and TRAIL (37). These ligands transmit signals to the corresponding receptors on the target cell, and the target cell is killed. Swann and Smyth (38) provided an elegant colored drawing showing cytotoxic T cells, NK cells, and other immune cells, busily attacking a tumor.

d. Immune Evasion With Tumor-Associated Macrophages

Immune response against tumors is also mediated by another type of white blood cell, the macrophage. Macrophages occur as two subsets, M1 macrophages and M2

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