CANCER IMMUNOEDITING

The concept of cancer immunoeediting tries to explain the evolution of the relationship that exists between cancer cells and the immune system during the development malignancy. This process has three distinct stages: elimination, equilibrium and escape. Elimination is equivalent to immune surveillance, in which immune system have a protective role against the development and growth of tumors. Despite evidence supporting this concept, tumor cells arise and grow progressively. This progression is driven by a selection of variant cells that can survive in normal conditions, and the elimination phase provides a selective pressure that generates immune-resistant cells. This stage of equilibrium is reached when the immune system can control tumors but no longer eradicate them. With this continued selection, dormant tumors may develop to the phase of immune scaphe, in which cells can kill, evade, or tolerate the immune system.

PD-1 Receptor

PD-1 expression is induced by TCR activation signals. When PD-1 binds with its ligands, PD-L1 or PD-L2, a signal which inhibits cell proliferation, cytokine production and cytotoxic activity of T cells is transmitted and the immune response is attenuated.

PD-1 interactions have different functions:
- Control the induction and maintenance of peripheral tolerance
- Regulate humoral immune response
- Control the induction of central tolerance

PD-1 and immune evasion of tumor cells

Tumor cells express more levels of PDL-1 or PDL-2 than normal tissues. In vitro experiments with tumor cells overexpressing PD-L1 demonstrated that expression of this ligand suppresses the cytotoxic activity of CD8+ and increases T lymphocyte apoptosis.

In addition, IFN-γ induces the expression of PD-L1 ligands on the surface of several tumor cell lines, and the advantage of tumor effector functions is that IFN-γ secreted by T lymphocytes for tumor destruction induces PD-L1 expression and avoids antitumor immune responses, which promotes tumor progression.

Mechanisms of anti-PD-1 and anti-PD-L1 immunotherapy

Blockade of PD-1 or its ligands increase T cells and IFN-γ at the tumor site and decrease the immunosuppressive myeloid-derived suppressor cells (MDSC).

The cytotoxic T lymphocytes promote:
- Effective immune response
- Prevent the induction of anergy
- Prevent the induction of apoptosis
- Decrease regulatory T cells levels
- Induce tumor regression
- Lead to tumor cell death by the NK cell-mediated antibody-dependent cell cytotoxicity (ADCC) pathway

Blockade of this pathway is not expected to stimulate de novo immune response but it is useful to enhance immune responses against tumor antigens.

References


