

ROLE OF IMMUNE CHECKPOINTS IN CANCER THERAPY

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The immune system developed certain mechanisms to control overreaction. The negative regulators of immune system are necessary for maintaining peripheral tolerance and inhibiting autoimmune diseases. Important immune checkpoint molecules of T cell are cytotoxic T lymphocyte antigen-4(CTLA-4), programmed cell death protein-1 (PD-1), lymphocyte activation gene-3 (LAG-3) etc. They exhibit their function by reducing tumor response and limiting T cell activity and proliferation. CTLA-4 and PD-1 have distinct mechanisms to inhibit immune and antitumor responses. They act in different stages of immune response. Cancer specific T cell shows co-expression of checkpoint receptors. Recent immunotherapy uses immunomodulatory monoclonal antibodies to block these checkpoint receptors for treatment of cancer. Ipilimumab, human monoclonal antibody blocking CTLA-4, was approved in 2011 for treatment of melanoma. Later other antibodies were developed to block PD-1 (nivolumab, pembrolizumab) and PDL-1, ligand of PD-1, (atezolizumab, durvalumab). After receiving several preclinical and clinical experimental successes, it was found that combination therapy of specific monoclonal antibodies with specific drugs or vaccines and combination of multiple immune checkpoint blockade are more effective than monotherapy for treatment of several cancers. Blockade of multiple checkpoint receptors leads to improved immune function against cancer.
