(Intron A®) was approved by the FDA in 1997 for non-Hodgkin's lymphoma, and it was previously approved for hairy cell leukemia and AIDS-related Kaposi's sarcoma. The function of DCs, which are the most important APCs that initiate the primary antitumor effector T-cell response, is interfered by cytokines, chemokines, and metabolites produced by tumor cells. The tumor-induced hypoxia stimulates immunosuppressive cells such as macrophages to produce proangiogenic factors that cause numerical and functional defects of DCs with impaired capabilities for antigen uptake, diminished cell motility, and impaired ability to activate naive T cells. Direct interaction between tumor cells and tumor-infiltrating lymphocytes may result in an impaired TCR signaling that inhibits the lytic function of cytotoxic T lymphocytes. In addition, the expression by tumor cells of ligands such as the Fas ligand or tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) may deliver death signals to activated T cells even at distant sites from the tumor.

Two types of immune cells with suppressive capacity on CTLs are currently known: Tregs and myeloid-derived suppressor cells (MDSCs).[42]

3.1 REGULATORY T CELLS

Tregs are a subpopulation of $CD4^+CD25^+$ T lymphocytes, considered the most powerful inhibitors of antitumor immunity, that confer cell growth and metastatic advantages. Their defects contribute to the induction of severe autoimmune diseases such as rheumatoid arthritis, whereas their stimulation induces the secretion of immunosuppressive cytokines that directly inhibit effector T cells and convert CDs into suppressive APCs. Treg depletion, suppression of Treg function, inhibition of its tumoral homing, and exploitation of T-cell plasticity are strategies to counter these effects.

Treg depletion may be achieved by chemical or radiation lymphoablation, mAbs directed against CD25 (such as those used to prevent rejection in organ transplantation) and immunotoxins.[43] Aldesleukin (Proleukin®) is a modified human IL-2[44] that was approved by the FDA in 1992. It was the first approved immunotherapy treatment for metastatic melanoma and is used in renal cell carcinoma.

The engineered protein denileukin diftitox (Ontak®), which combines IL-2 with the diphtheria toxin, received accelerated approval by the FDA for treatment of persistent or recurrent $CD25^+$ cutaneous T-cell lymphoma. Ontak® interacts with the high-affinity IL-2 receptor (CD25/CD122/CD132) on the cells surface and inhibits cellular protein synthesis.[45] Metronomic cyclophosphamide (metronomic refers to very low nontoxic doses of chemotherapy drugs delivered frequently for a prolonged period of time) may also induce Treg depletion.[46] A clinical trial involving pancreatic ductal adenocarcinoma (PDAC) patients, for which single-agent immunotherapies failed due in part to the barrier to immune infiltration and function that provides the tumor microenvironment, has shown that the allogeneic vaccine GVAX, in combination with metronomic cyclophosphamide, induces the formation of intratumoral tertiary lymphoid aggregates, resulting in the upregulation of immunosuppressive mechanisms including the PD-1/PD-L1 pathway. This study provides the first example of immune-based therapy converting a "nonimmunogenic" neoplasm into an "immunogenic" neoplasm by inducing infiltration of T cells and development of tertiary lymphoid structures in the tumor microenvironment.[47]

Suppression of Treg function may be achieved with anti-CTLA4 antibodies such as ipilimumab or tremelimumab, the antibody DTA-1, directed against the glucocorticoid-induced tumor necrosis factor receptor,[48] and the anti-RankL monoclonal antibody denosumab (Xgeva®, Prolia®), used for the treatment of osteoporosis. RankL is a member of the tumor necrosis factor (TNF) cytokine family that