Controlling T cell senescence in the tumor microenvironment for tumor immunotherapy

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Understanding molecular mechanisms involved in creating and sustaining the tumor suppressive microenvironment is critical for the development of novel antitumor therapeutic strategies. We have identified the induction of T cell senescence as a novel mechanism utilized by human tumor cells to induce immune suppression, and provided a new strategy using TLR8 ligands to reverse tumor immunosuppressive effects for tumor immunotherapy.

It is now well recognized that the tumor suppressive microenvironment created by malignant tumors is a major obstacle for effective antitumor immunity and successful tumor immunotherapy. Tumor cells can utilize different strategies, including recruitment of regulatory T (Treg) cells and tumor-derived macrophages and myeloid suppressor cells (MSCs), production of suppressive factors (IL-10, TGF-β, and IDO), and expression of immune inhibitory molecules (FasL and PD-L1), to inhibit tumor-specific T cell proliferation and functions in the tumor microenvironment. A better understanding of these molecular processes within the immune suppressive microenvironment is critical for the development of novel tumor vaccines and therapeutic strategies active against human cancers.

Increasing evidence shows that significant accumulation of senescent CD8+CD28null T cells has been found in certain types of cancer patients, strongly suggesting that it might be a strategy utilized by malignant tumors to evade immune surveillance. Senescent T cells were initially characterized in age-associated dysregulation of the immune system during the normal aging process. We recently found that human naturally occurring CD4+ Treg and tumor-derived γδ Treg cells can strongly suppress naïve/effector T cells through the induction of responder T cell senescence. In the current study, we further showed that multiple types of tumor cells, including breast cancer, melanoma, colon cancer, prostate cancer, ovarian cancer, and head and neck cancer, can also utilize the same mechanism as Treg cells and directly induce T cell senescence.Senescent T cells develop significant phenotypic alterations, such as permanent loss of CD28 expression, cell cycle arrest, and secretory proinflammatory and suppressive cytokines. More importantly, senescent T cells have exhibited functional changes, including defective killing abilities and the development of potent suppressive activity (Fig. 1). In addition, our in vivo adoptive transfer studies further confirmed that tumor-bearing microenvironments induced both adoptively transferred human naïve T cells and tumor-specific effector T cells to become senescent T cells possessing suppressive function. These studies clearly indicate that senescent tumor-infiltrating T cells are dysfunctional and could indirectly amplify and maintain the immunosuppressive effects mediated by tumor cells and Treg cells in the tumor microenvironment. These results suggest a potential mechanism for the failures seen in multiple clinical trials of tumor vaccines and adoptive T cell therapies. In addition, the possibility of blocking the induction of tumor cell senescence and restoring the effector function of senescent T cells are critical goals for enhancing antitumor immunity.

Dissecting molecular mechanisms used by tumor and Treg cells in the generation of senescent T cells will open new avenues to restoring T-cell function and will help in the design of novel vaccines for cancers. Metabolic dysregulation of tumor cells is one of the key factors involved in tumor-induced immune suppression. Tumor cells create a hypoxic microenvironment, resulting in accumulation of adenosine and cAMP within the tumor sites. These hypoxia-derived metabolites are potent immunosuppressors that can protect tumor cells from antitumor immune responses mediated by tumor-specific T cells. In our efforts to identify the molecules responsible for the induction of T cell senescence mediated by different types of tumor cells, we found that tumor-derived endogenous cAMP is responsible for the induction of senescence in T cells. We further demonstrated that tumor cells can transfer cAMP to targeted T cells via gap junctions, significantly increasing cAMP levels in senescent T cells. Notably, human Treg cells can also induce responder T cell senescence, and cAMP is a key component of Treg cell suppression. These novel studies identifying cAMP-mediated T cell senescence not only identify mechanistic links between tumor immunosuppression, hypoxia, and metabolic dysregulation, but also should lead to novel strategies capable of augmenting immune responses directly against cancer.

Our studies strongly indicate that the induction of T cell senescence possessing...
potent suppressive function is a general phenomenon utilized by malignant tumors to escape immune responses. Therefore, development of strategies to prevent the generation of senescence and control the fate and function of tumor-specific T cells is critical for antitumor immunity. Recent strategies, including depletion of CD4+ Treg cells or targeting immune checkpoint molecules CTLA-4 or PD1, have been utilized in clinical trials for cancer immunotherapy, and have yielded promising results. However, these strategies may concurrently eliminate activated effector T cells, prevent effector T cell activities and induce Treg cell replenishment. Thus, alternative novel strategies targeting more specific checkpoint molecules or interrupting tolerogenic pathways are needed. Identification of this novel suppressive mechanism utilized by tumor and Treg cells in our recent studies further suggests that blockage of senescence in tumor-specific T cells is also a critical checkpoint to control tumor suppression, which will provide a novel alternative target for cancer immunotherapy. We have previously demonstrated that human Toll-like receptor 8 (TLR8) signaling completely reversed the suppressive functions of naturally occurring CD4+CD25+ Treg and tumor-derived Treg cells. In addition, our more recent studies have shown that TLR8 ligand signaling in tumor cells and Treg cells can block the induction of senescence in naive and tumor-specific effector T cells and reverse their suppressive effects in vivo, resulting in enhanced antitumor immunity (Fig. 1). These studies provide new insights relevant for the development of strategies to prevent and/or overcome tumor-induced immune suppression for tumor immunotherapy.

In summary, our studies strongly indicate that differential induction of naive/effector T cells into senescent cells possessing potent suppressive activity is a novel mechanism mediated by human tumor cells and Treg cells to induce immune suppression. Importantly, TLR8 signaling in tumor cells and Treg cells can block the induction of senescence in naive and tumor-specific effector T cells and reverse their suppressive effects in vitro and in vivo, leading to other useful strategies for senescence prevention.}

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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In summary, our studies strongly indicate that differential induction of naive/effector T cells into senescent cells possessing potent suppressive activity is a novel mechanism mediated by human tumor cells and Treg cells to induce immune suppression. Importantly, TLR8 signaling in tumor cells and Treg cells can block the induction of senescence in naive and tumor-specific effector T cells and reverse their suppressive effects in vitro and in vivo, which could lead to other useful strategies for senescence prevention.

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