New Era of Regulatory T Cells in Tumor Immunity: Insights in Cancer Immunotherapy

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The clinically prognostic impact of tumor-infiltrating lymphocytes (TIL) has been a longstanding debate. TIL have been used to demonstrate how the host immune system recognizes and attempts to eliminate malignant cells.[1] In spite of their tenacious presence in the antitumor tug-of-war, cancer remains one of the major causes of human death. In adoptive immunity against a variety of human cancers, TIL have been recognized widely to be relevant to patient outcome. In cases in which TIL are involved in patient outcome in cancer, T lymphocytes are recognized as the main effectors of the antitumor immune response.[1–5] Previously, we have demonstrated that human cancer cells might alter the functional composition of antitumor effector cells, including CD8+ cytotoxic T cells, within the tumor milieu.[1–3] We have defined predominant Th2/Tc2 patterns of cytokine expression in a subset of CD3+ CD8+ T cell in human cancer.[2] We have illustrated further that certain cancer-derived mediators are responsible for the immunosuppressive conditions of TIL in human cancer, and are associated highly with prognostic significance clinically.[3,4] The regulation of the cytolytic function, especially natural killer (NK)-like cytotoxicity, of CD3+CD8+ cytotoxic T lymphocytes in human cancer has been stratified, which signifies the possibility of further cancer immunotherapy.[3–5] Moreover, recent studies have revealed that a subset of CD4+ T cells, referred to as CD4+CD25+ regulatory T (Treg) cells, might accumulate in the cancer microenvironment and restrain tumor-specific T-cell responses, thereby hindering tumor rejection.

Generally, Treg cells are characterized by elevated surface CD25 and intracellular Forkhead P3 (FoxP3) expressions.[6] These cells exist in noticeably higher proportions within TIL and/or regional lymph node lymphocytes of patients with cancer.[6,7] The presence of infiltrating CD4+ CD25+ Treg cells is controversial in anti-cancer immunity and even destructive to host defense against the tumor. This is despite the abundance of effector T lymphocytes, including CD8+ T cells and non-regulatory CD4+ T-helper cells, in cancer patients. It has been shown that Treg cells enriched in FoxP3, glucocorticoid-induced tumor necrosis factor receptor, and cytotoxic T-lymphocyte-associated antigen-4 potentially suppress the peripheral effector T cells.[6]

Increasing evidence has shown that elevated proportions of CD4+ Treg cells are present in various types of human cancer and thus abrogate antitumor immunity. Essentially, tumor-specific Treg cells require ligand-specific activation and cell-to-cell contact to exert their destructive activity on tumor-specific effector cells, which includes decreased cytotoxicity, proliferation, and Th1 cytokine secretion.[6,7] Recent studies have linked Toll-like receptor (TLR) signaling to the functional

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control of Treg cells. Treg cells can modulate multiple cell types, including T cells, B cells, dendritic cells (DC) and NK cells, by using diverse suppressor mechanisms. By now, certain factors that regulate Treg cell proliferation and function, including TLR ligands, have also been identified. It has been shown that TLR-8 signaling might regulate directly the suppressive function of CD4+ and CD8+ Treg cells.[8] Studies also have demonstrated that tumor cells can recruit these Treg cells to hold back antitumor immunity in the tumor microenvironment, which consequently limits the efficiency of possible cancer immunotherapy.[6–8]

It is thought that TLR-mediated recognition of specific structures of invading pathogens initiates innate as well as adaptive immune responses through DC. In cancer, Treg cells seem to induce immune tolerance by suppressing host immune responses against self or non-self antigens. Tumor-specific Treg cells recently have been identified and characterized, which has provided compelling evidence that such antigen-specific Treg cells can induce tumor-specific local immune tolerance.[9] Innovative evidence has suggested that TLR signaling may directly regulate the suppressive function of Treg cells. Linkage of TLR signaling to the functional control of Treg cells may shift the balance between CD4+ T-helper and Treg cells, thus improving the outcome of cancer immunotherapy.[10]

Strategies for modulating the effect of Treg cells on current immunotherapeutic and cancer targeting regimens have been proposed.[11–13] Recent evidence has suggested that TLR signaling may regulate the suppressive function of CD4+ CD25+ Treg cells in local and systemic immune responses. TLR signaling has been proposed to shift the balance between CD4+ T-helper and Treg cells, and subsequently influence the outcome of the immune response.[11] For possible immunotherapy, this Treg immunomodulation pathway may have potential applications in the treatment of graft rejection, autoimmune diseases, infectious diseases and cancer.[12]

In cancer immunotherapy, an increasing number of studies of Treg cells in patients with cancer stress the role of these cells in associated disease progression.[11–13] Essentially, Treg cells express certain TLRs. The activation and suppressor function of Treg cells are modulated by the binding of the respective TLR ligands. Similar to the double-edged nature of anti-cancer immunity, TLR ligands are proposed to induce suppression or enhancement of Treg cells. Furthermore, recent studies have shown that mature DC can override Treg-mediated suppression both *in vitro* and *in vivo*.[12,13] Naturally occurring Treg cells suppress T-cell responses by cell-contact-dependent mechanisms, whereas induced regulatory cells, including the T inducible regulatory type 1 cells, secrete inhibitory cytokines such as transforming growth factor-β and interleukin (IL)-10.[14] The interplay between Treg and antigen-responsive T cells is modulated by DC.[14,15] manipulation of mature DC that are activated through TLR recognition receptors can also induce the secretion of pro-inflammatory cytokines, including IL-6, and thus render responder T cells refractory to the suppressive effect of Treg cells.[13]

On the contrary, multiple immunosuppressive mechanisms subsist, noticeably diminish the anticancer immune responses and dampen the clinical application of current immunotherapeutic regimens. Modulation of Treg cells sheds new light on the reversal of cancer-mediated immunosuppression before immunotherapy can be applied successfully. Several studies have indicated that Treg cells inhibit effective antitumor immune responses and that removal of Treg cells facilitates tumor elimination.[12–15] Clinically, numerous studies of Treg cells in cancer patients also have indicated the key role of Treg cells in associated cancer progression.[14,15] Indeed, much evidence has shown that the Treg cells can shape the immune response to tumors, hold back effective tumor immuno-surveillance, and thus promote cancer invasion and metastasis.[12–15] Recently, active immunotherapy with therapeutic cancer vaccines has now progressed from the laboratory to clinical applications. Advanced insights into the distinctiveness of the regulatory elements of the immune system, especially Treg

cells, can show additional possibilities to enhance anticancer immunity and thereby increase the chance of cancer patient survival.[14–16]

In addition, a number of molecular regulators of T-cell-receptor signaling, either positive or negative, have been proposed in the context of Treg cell maturation. Among these, major histocompatibility complex class II modulation, self-ligands expressed by epithelial cells, and thymic stromal lymphopoietin seem to have synergistic roles.[17] Additionally, Treg cells can express FoxP3 as a transcriptional repressor of IL-2 and other cytokines, and thus retain the anergic and suppressor function of these cells. Treg cells play an important role in the control of autoimmunity, therefore, therapeutic strategies have focused on the enhancement of Treg cell function in specific autoimmune diseases.[17]

Conclusion

Strategies for therapeutic targeting of Treg cells and their potential effect on current cancer immunotherapy are under intensive investigation. By now, certain factors that regulate Treg proliferation and function, including TLR ligands, have been identified and proposed as potential immunotherapeutic regimens. Exploration of the mechanisms of Treg cell modulation gives rise to opportunities for controlling the function of Treg cell subsets, and thus gives scope for effective immunotherapy of cancer.

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In an era where immune therapies are becoming a treatment backbone in many tumour types, epigenetic modifiers could play a crucial role in modulating tumoursâ€™ immunogenicity and sensitivity to immune agents. Optimal trial design, including window of opportunity trials, will be key in the success of this approach, and clinical evaluation is ongoing.Â Combining epigenetic and immunotherapy to combat cancer. Cancer Res. 2016; 76: 1683-1689.Â EZH2 is crucial for both differentiation of regulatory T cells and T effector cell expansion. Sci Rep. 2015; 5: 10643. Regulatory T Cells and Cancer. Download PDF Copy. By Dr. Catherine Shaffer, Ph.D.Reviewed by Afsaneh Khetrapal, BSc.Â That is the role of regulatory T (Treg) cells. Tregs in cancer. One important role of the immune system is monitoring for cells that have become malignant, and could potentially lead to cancer, and eliminating those cells. Tregs play a role in the immunosurveillance process, at times hindering efficient eradication of tumors.Â Since Tregs generally suppress immune responses, this can become an obstacle to effective cancer immunotherapy. Treg depletion is increasingly being considered as an adjuvant therapy for a cancer vaccine approach. Some approaches for targeting Tregs in cancer therapy include In addition, we also discuss new immune checkpoint targets in cancer therapy.Â A clearer understanding of the regulatory roles of these receptors and elucidation of the mechanisms of T cell dysfunction will provide more insights for rational design and development of cancer therapies that target immune checkpoints. This article reviews recent advance(s) in molecular understanding of T cell dysfunction in tumor microenvironments.Â To eradicate tumor cells and induce antitumor immunity, T cells are able to recognize tumor antigens presented to T cell receptors (TCRs) by antigen-presenting cells (APCs). After binding to TCR, a second signal (signal two, also called costimulatory signal) is needed for T cell activation. Treg cell function in relation to tumor immunity. T-cell receptor repertoire of Treg cells. The T-cell receptor (TCR) repertoire of Treg cells is broad and skewed to a certain extent to recognizing self-antigens. That is, in the course of T-cell selection in the thymus, a developing Treg cell exhibits a higher TCR affinity than a conventional T (Tconv) cell for the MHC/self-peptide ligand that selects both11.Â Recent progress in cancer immunotherapy targeting Treg cells, either deliberately or inadvertently, suggests that molecules relatively specific to Treg cells are good candidates for Treg depletion or functional modulation. These molecules include CTLA-4, GITR, CCR4, PD-1, OX-40, and LAG3, as well as aforementioned CD25 and CD15s (Figure 2). T-cell agonists in cancer immunotherapy. Yeonjoo Choi1, Yaoyao Shi2Â Neoantigens are encoded by the mutated DNA of tumor cells, and their peptide epitopes are distinct from those derived from the normal human genome.7 They are processed and then displayed in major histocompatibility complexes on the surfaces of tumor cells and antigen-presenting cells (APCs).8 These neoantigen peptide-major histocompatibility complexes can be recognized by the TCRs of antigen-specific T.Â Thirty patients with advanced cancer (most common subtypes: melanoma and gastrointestinal...