Regulation of tumor immunity.

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Description

Innate and adaptive immunity play vital roles in immune surveillance and tumor demolition. However, increasing evidence suggests that tumor-permeating immune cells may have a dual function: inhibiting or supporting tumor growth and development. Although regulatory T (Treg) cells persuade immune tolerance by destroying host immune responses against self- or no self-antigens, thus playing critical roles in inhibiting autoimmune diseases, they might inhibit antitumor immunity and promote tumor growth. Recent studies demonstrate that raised proportions of Treg cells are present in various types of cancers and suppress antitumor immunity. Furthermore, tumor-specific Treg cells can prevent immune responses only when they are exposed to antigens presented by tumor cells. Therefore, Treg cells at tumor sites have harmful effects on immunotherapy directed to cancer.

The tumor microenvironment (TME) may be preeminent conceptualized as an ecosystem included of cancer cells interacting with a multitude of stromal constituents such as the extracellular matrix (ECM), blood and lymphatic networks, fibroblasts, adipocytes, and cells of the immune system. At the center of this crosstalk between cancer cells and their TME is the bioactive lipid lysophosphatidic acid (LPA). High levels of LPA and the enzyme producing it, termed autotoxin (ATX), are present in many cancers. It is also well recognized that LPA drives tumor progression by promoting angiogenesis, proliferation, survival, invasion and metastasis. One of the hallmarks of cancer is the capacity to modulate and escape immune recognition and abolition. Despite the profound role of LPA in regulating immune functions and inflammation, its role in the context of tumor immunity has not received much attention until newly where developing studies highlight that this signaling axis may be a means that cancer cells adopt to evade immune detection and abolition. One mechanism of cancer immune elusion is the suppression of anti-tumor immunity by immune regulatory T cells. Recent studies of these cells, especially CD4+CD25+ T cells and NKT cells, have discovered molecular and cellular mechanisms of immunosuppression. Mouse studies have shown that either eliminating immune regulatory T cells or blocking an immune regulatory pathway persuaded by such cells unmasks natural tumor immune surveillance and progresses responses to cancer vaccines. Studies of the corresponding T-cell populations in human cancer patients support a similar role for immune regulatory T cells in immunosuppression, indicating that blocking immune regulatory T-cell activity might develop the efficacy of tumor vaccines or the immunotherapy of cancer.

The goal of cancer vaccines is to persuade antitumor immunity that ultimately will reduce tumor liability in tumor environment. Several methods involving dendritic cells- (DCs)-based vaccine incorporating different tumor-associated antigens to persuade antitumor immune responses against tumors have been tested in clinical trials worldwide. Although DCs-based vaccine such as fusions of whole tumor cells and DCs has been demonstrated to be clinically safe and is efficient to improve antitumor immune responses for inducing effective immune response and for breaking T-cell tolerance to tumor-accompanying antigens (TAAs), only a limited success has occurred in clinical trials.

Recent studies have revealed that Foxp3+CD25+CD4+ regulatory T cells (Tregs), which are physiologically involved in the maintenance of immunological self-tolerance, play acute roles for the regulation of antitumor immune responses. For example, a large number of Foxp3+Tregs penetrate into tumors, and systemic exclusion of Foxp3+Tregs increases natural as well as vaccine-induced antitumor T-cell responses. Tregs are enrolled to tumor tissues via chemokines, such as CCL22 binding to CCR4 expressed by Tregs. They appear to expand and become activated in tumor tissues and in the draining lymph nodes by identifying tumor-associated antigens as well as normal self-antigen expressed by tumor cells. These results indicate that cancer vaccines targeting tumor-associated self-antigens may potentially expand/activate Tregs and hamper effective antitumor immune responses, and that tumor immunity can therefore be enhanced by depleting Tregs, attenuating Treg suppressive function, or rendering effector T cells refractory to Treg-mediated suppression.

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