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Immunological profiling as a means to invigorate personalized cancer treatment

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Immunotherapy has taken off but has not yet reached its cruising altitude and is certainly far from its final destination. Identifying the unique immunological profile of individual cancer patients will provide critical clues for the design of optimal strategies that rectify tumor-induced immune imbalances.

Immunotherapy, Ready for Take-Off

For a long time, stimulating the patient's immune system to attack tumors has been viewed as a rather meaningless intervention, an assumption that has recently changed.[1] Indeed, anticancer monoclonal antibodies, vaccines and cell-based immunotherapeutic approaches have shown great clinical potential, yet the development of these agents is still in its infancy. Recently, sipuleucel-T (Provenge™; Dendreon Corporation) and ipilimumab (Yelvoy™, Bristol-Meyers Squibb) have been approved by FDA for use in cancer patients. Both these agents, which exert antineoplastic effects as they potentiate the function of immune effector cells, have been shown to improve the survival of cancer patients in randomized Phase 3 clinical trials, reigniting the enthusiasm about cancer immunotherapy.[2] Thus, immunotherapy is now considered as the third generation strategy against cancer, after conventional chemotherapy and targeted agents.[3]

F(l)ight Plan

Immunotherapy attempts to stimulate or restore the natural capacity of the immune system to fight cancer. Within the oncoimmunology field, much attention is attracted by therapeutic strategies aimed at activating effector and memory T cells, as the secretion of their cytotoxic granules can directly kill malignant cells. In line with this notion, the infiltration of neoplastic lesions by effector and memory T cells has been associated with improved disease-free and overall survival in patients affected by multiple types of cancer.[4] Several approaches have been designed that attempt to increase the number of tumor-reactive T cells, for instance the adoptive transfer of tumor-infiltrating T cells (TILs) expanded in vitro or that of peripheral blood T cells that have been genetically engineered with new functions and specificities. The administration of antibodies specific for cytotoxic T-lymphocyte antigen 4 (CTLA4) and programmed cell death 1 (PD1) also promotes the cytotoxic activity of T cells as it blocks the delivery of immunosuppressive signals.[5] Furthermore, the stimulation of dendritic cells (DC) in vivo as well as the administration of DCs pulsed ex vivo with tumor-derived material increase the number and activity of multiple T-cell subsets.[6] Despite promising results achieved in some patients, the long-term effects of direct and indirect T-cell activation approaches are limited, and these strategies often fail to control established solid tumors. Such a limited therapeutic efficacy is partly caused by the emergence of cancer cell variants that have lost the expression of target antigens and by a broad spectrum of tumor-derived factors and immunosuppressive cells that impair the effector functions of TILs.

Flight Path and Obstacle Clearance for Take-Off

The tumor microenvironment (i.e., the site at which neoplastic lesions develop) and macroenvironment (i.e., lymphoid tissues and the blood) contain a variety of immune cells that can influence disease progression in opposing ways. We have recently provided a summary of immune cell types that play a critical role in this setting as well as of their dynamic interactions within established neoplastic lesions.[7] In summary, cancer cells produce an large repertoire of factors (e.g., chemokines, prostaglandins, metabolites) that lead to the activation and recruitment of immune cells to the tumor site. As a consequence, neoplastic lesions contain significant amounts of immune cells that can promote either tumor regression or tumor progression (**Fig. 1**). Tumor-infiltrating immune cells that normally favor tumor regression include natural killer (NK) cells, natural killer T (NKT) cells, B cells, and multiple subsets of T lymphocytes ($CD8^+$ cytotoxic

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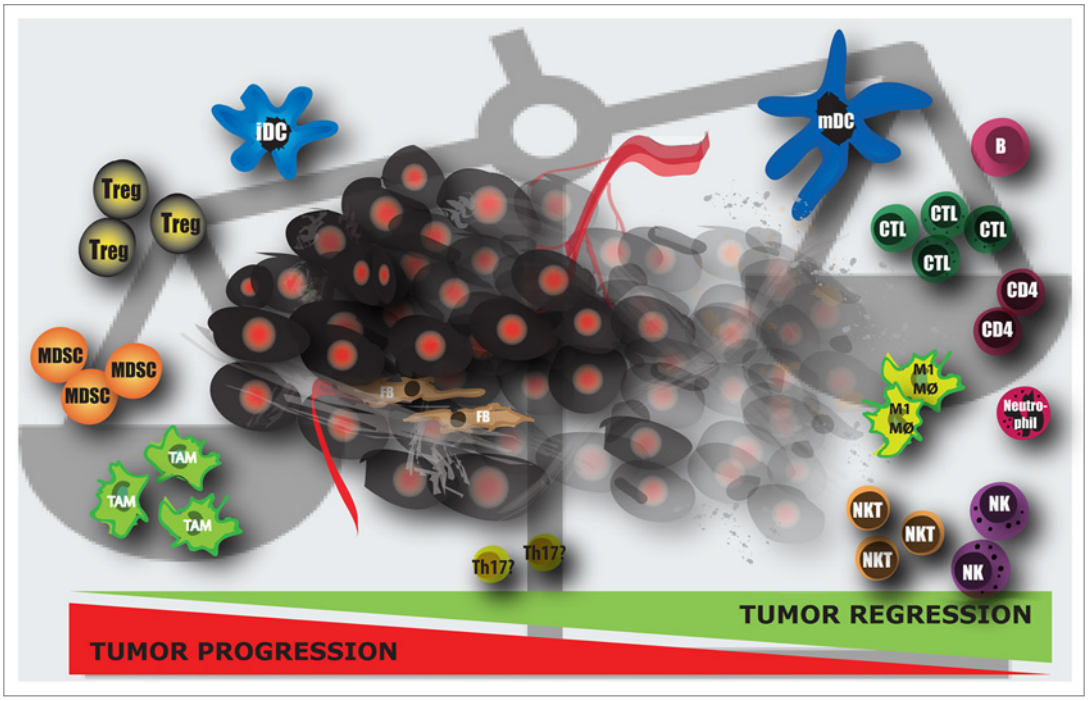

Figure 1. Immunological imbalances in the microenvironment of growing tumors. The tumor microenvironment consists of malignant cells (in black) as well as of non-transformed stromal cells, including endothelial cells and their precursors (pericytes), smooth muscle cells, and fibroblasts (FBs) of various phenotypes located within the connective tissue. In addition, neoplastic lesions are heavily infiltrated by immune cells including natural killer (NK) cells, natural killer T (NKT) cell, neutrophils, several subset of B and T lymphocytes, myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), tumor-associated macrophages of the M1 (Ø) or M2 (TAMs) phenotype, immature dendritic cells (iDCs) or mature dendritic cells (mDCs). Based on their functions, these cells can be subdivided into cells with a potentially positive impact (right) or a detrimental effect (left) on antitumor responses. It is still unclear what kind of effect T_H17 helper T cells exert in the tumor microenvironment. The net result of the interactions between these tumor-infiltrating cells and their products not only determines the outcome of antitumor immune responses but also influences the survival and proliferation of malignant cells as well as their invasive, angiogenic and metastatic potential (Adapted from ref. 7).

T cells, $CD4^+$ helper T cells, γδ T cells). Conversely, regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSC) generally promote tumor progression. Of note, the net effect of neutrophils, macrophages, and DCs on malignant cells largely depends on tumor type and stage as well as on specific microenvironmental conditions, such as the presence of soluble mediators and oxygen availability. Indeed, specific microenvironmental cues not only can polarize macrophages and neutrophils from an M1/N1 (antitumor) into an M2/N2 (tumor-supporting) subtype, but also can convert immunostimulatory DCs into tolerizing DCs, which robustly accelerate tumor growth. In conclusion, malignant and immune cells engage in a complex and dynamic signaling network that governs processes including tumor growth, invasion, angiogenesis and metastasis, hence impacting on the clinical course of the disease. It has been shown that the immune contexture (i.e., the type, density and location of tumor-infiltrating immune cells) can predict the clinical outcome of patients affected by multiple types of cancer, but with consistent intra-patient variations. It is therefore critical to identify the unique immunological profile of individual patients as a means for improving the efficacy of current immunotherapies.

Getting to Cruising Altitude

Personalized medicine must face three main challenges: (1) the complexity of malignant disease, (2) the complexity of the immune system and (3) the individuality of patients. A better understanding of the interactions between malignant and immune cells is crucial for elucidating the mechanisms that underpin tumor progression.[8] This is a central point because no single mechanism account alone for the complicated interactions between cancer cells and the immune system. To move forward in this direction, we might have to step away from analyzing the impact of a single immune cell type on a given tumor, and rather focus on immune cells as a whole and on their mutual interactions within the tumor microenvironment at specific stages of disease. Tumors are now classified by clinicians based on their anatomical location and histopathological features. However, there are initiatives that attempt to include immunological parameters into such classification such as the so-called Immunoscore (TNM-Immune).[9] Exciting technological advances now allow to obtain deep insights into the complex network of complex interactions that govern the tumor microenvironment. Super-resolution microscopy and the coupling of flow cytometry with microscopy or mass spectrometry are examples of these technical developments.[10] The characterization of the immunological profile of individual patients will provide valuable

insights into the contribution of each type of immune cells to tumor repression or progression at specific disease stages. This approach may allow us to determine why some patients are resistant to specific therapeutic options and to distinguish aggressive vs. indolent diseases. Moreover, modulating the immune system on a personalized basis offers an additional means of tailoring therapeutic interventions and hence ameliorate anticancer therapy. This is perhaps the way that will allow immunotherapy to get to cruising altitude and reach its final destination.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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