OncoImmunology 1:3, 261–262; May/June 2012; © 2012 Landes Bioscience

The immune microenvironment as a guide for cancer therapies

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After a long period of disputed history made of great hopes and subsequent disillusions, the field of oncoimmunology has now reached an unprecedented level of recognition and respectability, both in the scientific world and in the medical universe. This results from the merge of two streams of thought.

The first stream resulted from the availability of recombinant strains of mice lacking some or all components of the immune system, sometimes crossed with mice transgenic for oncogene expression, yielding the demonstration that the lack of immune components favors spontaneous tumor development. These experiments have generated the 3E's theory, which describes the three phases of tumor development, paraphrased as elimination, equilibrium, and escape. At the initiation of oncogenesis, most nascent tumor cells would be **eliminated** by the immune system. Only after genetic and phenotypic editing, prospective cancer cells may form a tumor that establishes an **equilibrium** with the immune surveillance system. Finally, tumor cells will undergo further (epi)mutations and **escape** immune control. This theory implies that advanced tumors become resistant to immune attack and advanced cancer patients should therefore not respond to immunotherapy.

The second stream, however, resulted from the success of immunotherapeutic approaches in advanced cancers including metastatic disease. Thus, monoclonal antibodies recognizing tumor cell associated antigens were proven efficient in lymphoma (CD20), colorectal (EGF-R) and breast (HER2-neu) cancer. Their beneficial effect is mediated, at least partly, through immune stimulation, for instance by activating NK cells via the FcγRIII (CD16) receptors and by inducing a memory T-cell response against the targeted antigen. Monoclonal antibodies raised against lymphocyte "checkpoint" receptors (CTLA-4, PD1, CD137) or their ligands (PDL-1) were reported to increase patient survival in metastatic melanoma, colorectal, pancreatic cancers or lymphoma. That the anti-tumor effect was indeed the consequence of unlocking the immune system is supported by the concomitant induction of autoimmune reactions in patients treated with anti-checkpoint antibodies and by the fact that responding metastatic sites become highly infiltrated by $CD8^+$ T cells. Therapeutic vaccination of patients with metastatic, hormone refractory prostate cancer resulted in significant increase in overall survival accompanied by a specific immune response to the immunizing prostatic antigens. Finally, cellular therapies with precursor or differentiated T cells, sometimes engineered to express a TCR that recognizes a tumor-associated antigen, can induce spectacular tumor regressions and prolong overall survival. Beyond these "classical" immunotherapies, a recent revolutionary concept suggests that chemotherapies are effective to induce prolonged overall survival only if they stimulate an anticancer immune response, for instance by inducing immunogenic tumor cell death that de facto converts the cancer into a therapeutic vaccine. Established in murine models, this concept is supported in man by the fact that polymorphisms of molecules involved in immunogenic chemotherapies are associated with patient survival. Also, some anti-angiogenic therapies may modulate the patient immune system by down-regulating suppressor cells. Therefore, a large body of murine models and clinical trials is largely supportive of the fact that the immune system is involved in tumor control and that its manipulation may result in increased survival, even in patients with advanced cancer.

The effectiveness of immunotherapies requires the stimulation of anticancer immune responses. It has been established for a long time that, except at the terminal stage or in heavily pretreated patients, cancer patients maintain a functional immune system capable of protecting them from infections. The last decade has witnessed the analyses of large cohorts of cancer patients, allowing to demonstrate that the tumor's immune microenvironment influences clinical outcome. Thus, a high density of memory T cells with a Th1 cytokine pattern and cytotoxic phenotype is a major positive prognostic factor correlating with increased survival of patients with colorectal, breast, urothelial, lung, gastric, pancreatic, ovarian, bladder, hepatocellular, cervical carcinomas, as well as with melanoma. This observation has led to the proposal of a new prognostic classification based on the immune pattern of the tumor microenvironment. This immune pattern is predictive of survival at all stage of cancer progression. For instance, in colorectal cancer, 95% of the patients with local disease (no lymph node or distant metastases) exhibiting high infiltration of $CD8^+$ and memory cells ($CD45RO^+$) of the tumor were alive after 5 y, as compared with 27% with low densities of these cells. Even at the disseminated stage, patients with a high memory T cell infiltrate in their resected hepatic metastases respond better to chemotherapy and exhibit a better overall survival than

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Submitted: 02/07/12; Accepted: 02/07/12
http://dx.doi.org/10.4161/onci.19651

patients with a low T cell infiltrate in their metastatic sites.

Altogether, these data support the concept that an efficient immune reaction may be shaped in the tumor microenvironment, then circulate as memory cells in the organism and finally delay recurrence post therapy and cancer-associated death. The question therefore arises of which patients would benefit from immunotherapeutic approaches. This problem is far from being trivial because, once resolved, it will result in the selection of patients for immunotherapy, particularly in early stage cancers. Treating an unselected cohort of early-stage patients for which the expected survival time is $> 95\%$ at 5 y is unlikely to yield statistically meaningful results unless very large trials are envisaged. In contrast, patients with a depressed immune system and advanced, aggressive cancer are unlikely to respond to any kind of therapy including immunotherapy. A definite proposal on which patients should experience immuntherapy is therefore difficult to establish, and murine models that reflect different interactions between cancer and the immune system should be designed and studied.

Before robust pre-clinical data guide future immunotherapies, however, several rules could be proposed for the further evaluation and optimization of anticancer immunotherapies. The first rule would be to obligatorily characterize the immune pattern of the tumor in all patients that are renrolled in the trial, thus allowing to establish retrospective classifications. The second rule would be to launch prospective trials in which the immune pattern is established for each patient. The third rule would be to preferentially treat early-stage patients with a low density of intratumoral memory T and CD8 cells with the aim of obtaining a clinical response within a short timeframe. Conversely, at the metastatic stage, only patients with signs of an efficient anticancer immune response should be included in innovative clinical trials.

We can anticipate that appropriate mouse models as well as intelligently designed clinical trial will fine tune optimal antineoplastic therapies as they demonstrate an ever more important role of the anticancer immune response.