Memory T-Cell Responses and Survival in Human Cancer: Remember to Stay Alive
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Abstract
Cancer is a major public health problem worldwide. Accumulating evidence suggests that tumor-host interactions may in part impact on tumor progression. However, the role of inflammation and adaptive immune reaction in cancer emergence, local and metastatic invasion and recurrence are still not clearly defined. Pro-inflammatory mediators are suspected to favor tumor growth and angiogenesis and naturally generated T cells with antigenic specificity to tumor associated antigens were usually in a state of anergy. Nevertheless, experiments in mouse and human showed a significant association between high density of tumor infiltrating T cells and improved cancer prognosis. Recently, the global analysis of colorectal cancer microenvironment demonstrated that a strong and coordinated Th1 adaptive immune response within primary tumors dramatically reduced the risks of relapse events. Interestingly the absence of early signs of metastatic invasion (lymphovascular emboli) correlated with a significant increase of the density of memory T cells in situ. This chapter presents the arguments supporting the existence of immunosurveillance mechanisms in human cancer. We will discuss the potent role of memory T cells in cancer immunity as well as the opportunities of therapeutic strategies uncovered by this new area of investigation.

Introduction
Many developments have occurred in prevention and treatment of cancer, but death from this disease is still common. Of the 58 million people who died worldwide in 2005, 7.6 million died of cancer. Based on projections, cancer deaths will continue to rise with an estimated 9 million people dying from cancer in 2015 and 11.4 million dying in 2030 (http://www.who.int/cancer/en/). Regardless of a great biological heterogeneity among malignancies, six major check points allowing tumors to adapt to their environment can basically describe cancer progression: (i) growth factor and (ii) proliferation-inhibiting signals autonomy, (iii) apoptosis escape, (iv) unlimited replication potential and—for carcinoma—(v) angiogenesis and (vi) primary tumor expansion and metastatic invasion.1 Despite extensive characterization of the intrinsic2 and environmental1 underlying mechanisms, markers of the oncogenic process remain poorly predictive of patient survival and fail to prove their reliability in clinical use. Thus cancer prognosis is still estimated by yet imprecise classical anatomopathological parameters. For instance, the accuracy of current tumor-node-metastasis UICC-TNM staging3 in colorectal cancer has remained largely unchanged.

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since 1932 Dukes’ original classification. This lack of elements for relapse prediction improvement led to the investigation of the impact of nontumoral parameters on patient survival.

For immunologists, a hallmark of tumorogenesis is immune escape. Because the immune system is in constant interaction with tumors, the ability to circumvent and adapt to immnosurveillance mechanisms dramatically improves local and metastatic cancer progression. Paradoxically, the immune system itself can participate in immune escape. Under the pressure of immune reaction, a darwinian selection of variant tumor cells that are resistant to immune-surveillance mechanisms can occur. This is the model of immunoediting or immune shaping of tumors. Inflammation is now commonly considered as a tumor-promoting factor. Cancer cells can take advantage of the release into their environment of pro-inflammatory mediators such as TNFα, IL-1, IL-8 and IL-6 to increase their own growth and metastatic invasion and induce angiogenesis. Thus, innate immune cells through inflammation-dependant mechanisms like tumor associated macrophages (TAMs) favor tumor progression. Furthermore, inflammatory conditions can alter local immune responses. Indeed, intratumoral Type 2 macrophages (M2) were shown to produce high amounts of immunosuppressive cytokines IL-10 and TGFβ but low levels of Th1 cytokine IL-12.

By contrast, experiments in mice revealed that immune responses mediated by IFNγ and cytotoxic mediators such as perforin secreted by lymphocytes are involved in cancer immunosurveillance of solid tumors and lymphoma. Local release of IFNγ can induces antiproliertive, proapoptotic and angiostatic mechanisms leading to tumor cell death. Subsequent tumor antigen uptake, processing and presentation by APC to T cells can lead to antitumoral Th1 adaptive immune response induced and supported by IFNγ. Consistently, in human cancer, infiltrating cytotoxic T cells were associated with improved clinical outcome and survival in melanoma, ovarian cancer and colorectal cancer. In this chapter we will discuss the role of memory T cells in human cancer and the opportunities of therapeutic strategies uncovered by this new area of investigation. Because memory T cells are the final actors of the immune reaction cascade, they could represent a critical marker of antitumoral activity that may help establish cancer patient prognosis. Furthermore, due to strong cytokine secretion and cytotoxicity memory T cells may directly be involved in the control of tumor progression and metastatic invasion.

Characteristics of Tumor Antigen-Specific T Cells

Molecular identification of specific tumor antigenic peptides that started 20 years ago was decisive for the acknowledgment of adaptive immune evasion. The first human tumor associated antigen (TAA) was discovered by the team of T. Boon in melanoma. The existence of TAA-specific T cells is now confirmed in an increasing number of malignancies (more information available at http://www.cancerimmunity.org/peptidedatabase/Tcell epitopes.htm). TAA can be classified in 2 major groups: unique antigens and shared antigens. Unique tumor antigens result from point mutations in genes that are expressed ubiquitously but that are restricted to an individual patient or to very few patients. On the other hand, shared antigens are present on many independent tumors. They can be further divided into four groups: shared tumor-specific antigens, differentiation antigens, overexpressed antigens and viral and bacterial antigens. Shared Tumor-specific antigens correspond to peptides encoded by “cancer-germline” genes, such as MAGE, which are silenced in normal tissues but expressed in many tumors. Differentiation antigens are not tumor-specific because they are also expressed in the normal tissue of origin of the malignancy such as tyrosinase, which is expressed in normal melanocytes and in most melanomas. Overexpressed antigens are expressed in a wide variety of normal tissues but overexpressed in tumors. One of the most studied antigen of this group is the proto-oncogene HER-2/neu which is overexpressed in many epithelial carcinoma (ovary, lung, breast, etc.). Viral and bacterial TAA are encoded by a number of pathogen agents such as Epstein-Barr virus (EBV) and human papilloma virus (HPV) that are associated with human malignancies.

The quality of adaptive immune responses is tightly dependant of the quality of the T-cell repertoire that can be mobilized. Because TAA expression is generally weak, a high frequency of