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http://dx.doi.org/10.1016/j.annder.2013.09.651

CONF15
Field cancerization and dormant epithelial cancer: Stromal mesenchyme takes the stage
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The vast majority of epithelial cancers is limited to in situ lesions that, for internal organs like breast, prostate or lung, can remain undetected for the whole life of an individual. The reason(s) why only a minor fraction of these lesions progresses into malignancy is not understood. In fact, many if not most of genetic changes found in invasive and metastatic tumors can be already present in pre-malignant lesions, raising the question of whether such changes are of primary causative significance or merely permissive for later cancer-spreading events. A related key issue raised by deep sequencing analysis of tumors is which of the many identified mutations has a driver initiating function in the carcinogenic process [1]. An extreme view is that none of these mutations is by itself a driver of cancer development and that it is the “ecological cellular environment” that restrains or unleashes tumor growth [2,3].

Changes in tumor stroma are most frequently viewed as secondary to changes in the epithelium. However, recent evidence indicates that they may play a primary role [4]. Such a possibility would help explain not only dormancy of most epithelial cancers, but also field cancerization, a condition of major clinical significance linked with intrinsic inhibitory controls on T cell proliferation and activation. The concept of cancer immunosurveillance, first coined by Schreiber’s group and thereafter investigated in a variety of mouse tumor models has been corroborated by the demonstration of a clinical relevance of intratumoral effector memory Th1/Tc1 cells in the prognosis of distinct human malignancies. Hence, inducing anti-tumor T cells and promoting T cell trafficking into tumor beds appears to represent a mandatory condition to prolong patients’ survival. An array of T cell co-stimulatory receptors and T cell negative regulators act in concert to control T cell activation, proliferation and effector functions. CD28 and CTLA-4 molecules feature among the best characterized T cell co-stimulatory and co-inhibitory molecules. CD28 provides co-stimulatory signals to T cell receptor engagement by binding to B7-1 and B7-2 ligands on antigen-presenting cells, while CTLA-4 provides a negative signal downregulating T cell functions.

The CTLA-4 blocking antibody ipilimumab has been approved by the U.S. Food and Drug Administration and the European Medical Agency in 2011 for the treatment of advanced melanoma because the antibody could induce durable objective responses in 15–20% of the cases. A number of preclinical studies—partly confirmed in early clinical trials—unraveled the basic mechanisms of the bioactivity of this first in-class product. Blocking the interaction between CTLA-4 with its known ligands B7-1 and B7-2 releases intrinsic and extrinsic inhibitory controls on T cell proliferation and activation (Walusas T.L., Immunity 1994, Peggs K.S., Immunol Rev 2008, Krummel, JEM 1995), unleashing cell cycle, cytokine production and intratumor accumulation of effector CD4+ and CD8+ T cells. CTLA-4 is a negative and positive regulator of IL-2 transcription (Krummel and Allison, JEM 1995, Blair P.J., J1998) and TGF release from CD4+ T lymphocytes (Chen W., JEM 1998), respectively. Hence, CTLA-4 loss or inhibition reduced regulatory T cell (Treg) function

References
[1] Eifert C, Powers RS. From cancer genomes to oncogenic drivers, field cancerization, a condition of major clinical significance linked with...