

Shaping an efficient adaptive immune microenvironment in human cancer

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Abstract

The importance of immune reaction in controlling tumor invasion and metastasis has been debated but is of seminal importance for identifying novel targets for cancer treatment through immunointervention. The participation of chronic inflammation in tumor promotion is well established and recognized but the involvement of tumor-rejecting immune responses is largely disregarded. Based on the analysis of immuno-compromised animals, the group of R.D. Schreiber has established that tumors arise and grow in all mice deficient for both adaptive and innate immunity, bringing experimental evidence to the immunosurveillance theory.

In man, epidemiologic evidence of higher incidence of cancers in immunodeficient individuals or in allografted patients also supported the theory but no direct evidence of the impact of immune reactions among the factors controlling clinical outcome had been established.

We addressed the question of the role of the "in situ" type, location and functional orientation, i.e. the "immune contexture" in three human cancers, two arising in immunoactive sites (colorectal and lung) and one in an immunological sanctuary (primary intra-ocular lymphoma). Using high throughput analysis of the components of the immune system, we first established that the presence of high adaptive immune infiltration in the center and in the margin of colorectal tumors was the strongest prognosticator of disease free survival, recurrence and overall survival above the classical tumor associated factors, such as age differentiation and lymph node involvement. Similar results were obtained in non small cell lung cancers, both adenocarcinomas and squamous cell, with the additional characterization of tumor-associated lymphoid islets as being the putative location of an anti-tumor immune reaction. In primary intraocular lymphoma, where there is no pre-existing inflammation or immunity in the eye, the tumor also attracts a TH1 and CD8 immune infiltration with shared characteristics with the "efficient" TH1/CD8 reaction in colorectal and lung carcinomas.

We believe that the fact that adaptive immune reactions present in three different human cancers are major prognosticators of clinical outcome supports the hypothesis of efficient immune responses which control in the long term the metastatic potential of circulating tumor cells and represent targets and tools for immunointervention. The mechanisms underlying the shaping of an efficient immune response are being deciphered.