special session: evasion, activation and manipulation of the cancer immuno response

IMMUNOTHERAPY FOR CANCER: NEW CHALLENGES AND OPPORTUNITIES FOR PRECISION MEDICINE

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Immunotherapy of cancer is presently one of the areas where major medical breakthroughs are witnessed, with dazzling results reported by several groups recently. Two approaches stand out. On one hand, neutralizing antibodies that disable key inhibitory receptors regulating T lymphocyte function, such as CTLA-4 and PD-1, enable the potent activation of effector T cells against tumors. On the other hand, the adoptive transfer of autologous tumor-infiltrating lymphocytes (TILs) has been successful in melanoma, but could find applications in other tumor types as well. A major breakthrough in T cell engineering relates to the development of autologous engineered T cells generated ex vivo through the insertion of exogenous receptors that recognize cancer cells, such as cloned T cell receptors (TCRs) or chimeric antigen receptors (CARs). Although successful in many patients, these powerful therapies do not work in others. There is an acute need therefore to understand the factors affecting response to immunotherapy. The microenvironment of tumors with pre-existing TILs is conducive to T cell homing. Thus, in these tumors, a main barrier to successful immunotherapy is T cell function rather than homing. Checkpoint blockade therapy seems a rational approach in this patient subset, and combinatorial approaches aimed at correcting multifactorial T cell suppression are expected to enhance the efficacy of checkpoint blockade. Lack of TILs denotes a tumor microenvironment that is prohibitive to T cell homing, which may be due to the establishment of a vascular endothelial barrier, deregulation of chemokine expression etc. Pharmacologic intervention to reverse these mechanisms will be necessary to allow successful engraftment of T cells in these tumors. Clearly, identification of relevant targets and development of robust biomarkers are necessary for the rational development of precision immunotherapy, and tumor heterogeneity will be an important challenge.

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