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Institutionen för Onkologi-Patologi

Tumor-mediated changes in the immune system of cancer patients

– a balancing act between effectors and suppressors

AKADEMISK AVHANDLING

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ABSTRACT

Tumors and immune cells interact in many ways: immune cells can recognize and even kill tumor cells, while the tumor on the other hand can induce cells of the immune system to participate in tumor-mediated immune subversion.

We studied immunosuppressive effects that human tumors exert on immune effector cells, particularly T cells, by inducing suppressive myeloid cells and decreasing T cell functional capacity.

Increased numbers of myeloid-derived suppressor cells (MDSC) have been found in tumor-bearing individuals in response to cancer-derived factors. We characterized a $CD14^{+}HLA-DR^{-/low}$ MDSC population in patients with melanoma that could strongly suppress T cell function. Suppressive activity was dependent on cell-cell contact, arginase-1 expression, oxidative stress, and STAT3 signaling. Melanoma MDSC exhibited a mixed phenotype including markers of both mature and immature cells. Due to their monocyte-like characteristics, we wondered whether the presence of MDSC could interfere with the generation of monocyte-derived dendritic cells (DC) for vaccine use. We found that melanoma MDSC exerted a dose-dependent negative effect on DC quality. The removal of MDSC from monocytes prior to DC generation could therefore be advisable in order to improve vaccine efficacy in diseases where $CD14^{+}HLA-DR^{-/low}$ cells have been observed.

Tumor-mediated immunosuppression has mostly been studied in patients with advanced cancer, thereby under-representing the group of early-stage cancer patients that should have a better chance to mount anti-tumor immunity and benefit from tumor immunotherapy.

We found that even patients with early-stage breast cancer exhibit signs of tumor-induced immune modulation. Expression of the ζ -chain, an important transducer of activating signals in T and NK cells, was down-regulated in patients compared with controls, but normalized after surgical tumor removal. Loss of ζ -chain expression was detectable in the blood, but strongest in the tumor, suggesting it to be mediated by tumor-derived factors. Further, circulating T cells of breast cancer patients were more differentiated than those of controls and exhibited signs of altered homing capacity. Tumor-associated T cells were dominated by effector memory cells that showed signs of activation, but were accompanied by indicators of immunosuppression.

The findings presented here show that various mechanisms of tumor-mediated immunosuppression are active in patients with early- as well as late-stage cancers. Understanding such tumor-immune interactions is the first step towards the design and optimization of immunotherapeutic strategies for the treatment of cancer.