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Meeting Abstract

Control of tumor immunity by the microenvironment: Overcoming the endothelial barrier

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Abstract

The clinical success of immunotherapy of tumors is still rather limited. Here we show that the tumor vasculature contributes to this failure. In general, the vasculature of solid tumors displays an aberrant morphology characterized by dilated and fragile vessels, intensive vessel sprouting, and loss of hierarchical architecture. Such an aberrant vasculature is also found in Rip.Tag mice developing autochthonous insulinomas in a multi-step process, therefore resembling the clinical situation. Vaccination against the Tag tumor antigen or transfer of tumor-specific T lymphocytes fails to eliminate the tumors, because the aberrant tumor endothelium forms a barrier against infiltration by tumor-specific lymphocytes. However, induction of an inflammatory environment in the tumor, e.g. by irradiation or immunostimulatory CpG oligonucleotides, will result in activation of the endothelia and in efficient infiltration of effector cells into the tumor tissue and tumor eradication.

Gene expression profiling identified RGS5 (regulator of G protein signalling 5) as a master gene that seems to be involved in the barrier function as suggested by its selective overexpression in pericytes of the tumor vasculature. Interestingly, tumors developing in RGS5 knockout mice display a normalized tumor vasculature. Moreover, this normalized vasculature permits strong T cell infiltration resulting in tumor eradication.

In conclusion, we suggest that for successful immunotherapy of cancer vaccination or adoptive T cell transfer should be combined with an anti-angiogenic therapy resulting in modulation or normalization of the tumor vasculature, and, thereby, to enhanced T cell infiltration. These observations open the way for novel therapeutic interventions.