The controversial role of TNF in melanoma

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\textbf{ABSTRACT}

Tumor necrosis factor (TNF, formerly TNF-\textalpha) was first characterized in the 70s as a cytotoxic molecule for cancer cells. Today, more than 40 y later it is still used for treatment of locally advanced tumors of the extremities in combination with melphalan (reviewed in\textsuperscript{1}). However, only in the last decade we are starting to appreciate its pleiotropic roles in cancer biology. Multiple recent reports have shown that TNF associated inflammation as well as its direct effects on tumor cells may actually be cancer promoting. In melanoma, preclinical models have shown that TNF can induce cell invasion\textsuperscript{2} and angiotropism\textsuperscript{3}, thus increasing the likelihood of intravasation and hematogenous dissemination; dedifferentiation, and thereby impaired sensitivity to melanocyte-differentiation antigen (MDA)-directed CD8\textsuperscript{+} immune responses;\textsuperscript{4} trigger effector CD8\textsuperscript{+} T cell death impairing accumulation of CD8\textsuperscript{+} T cells in the tumor microenvironment.\textsuperscript{5} Importantly, TNF inhibition prevents lung metastatization in animal models\textsuperscript{6} and, in contrast to earlier reports, it is now demonstrated that chronic treatment with TNF inhibitors does not increase the risk of developing melanoma in human subjects.\textsuperscript{7}

Our recent studies add additional insights to the puzzling roles of TNF in cancer, pointing out tumor-specific CD4\textsuperscript{+} T cells as one major source of TNF in the tumor microenvironment of metastatic melanoma in humans driven by tumor MHC class II expression.\textsuperscript{8}

Of note, aberrant expression of MHC class II has repeatedly been reported in melanoma and other tumors. Tumor-antigens (TA) presented in association with MHC class II molecules may trigger activation of TA-specific CD4\textsuperscript{+} T cells in the tumor microenvironment, and lead to direct recognition of MHC II\textsuperscript{+} cancer cells. Under physiological conditions and in the absence of a local inflammatory response, expression of MHC class II molecules occurs only in hematopoietic cells and thymus epithelium. This suggests that dysregulated gene-networks leading to abnormal transcription of class II transactivator (CIITA) are responsible for MHC class II expression.

We provide evidence that the accumulation of melanoma-specific CD4\textsuperscript{+} T cells is promoted by constitutive de novo aberrant expression of MHC class II on tumor cells. In contrast to melanoma-specific CD8\textsuperscript{+} T cells, the vast majority of these tumor specific CD4\textsuperscript{+} T cells were mono-functional with TNF as principal function.

During immune attack of melanoma, activation of CD8\textsuperscript{+} T cells lead to release of large quantities of IFN\gamma in the tumor microenvironment. Our data indicate that, in tumors enriched with melanoma-specific CD4\textsuperscript{+} T cells, IFN\gamma induced upregulation of MHC class II molecules increase tumor-recognition and activation of resident CD4\textsuperscript{+} T cells, with local release of TNF which in turn impairs CD8\textsuperscript{+} T cell function (Fig. 1).

Importantly, downregulation of MHC class I with reduced response to IFN\gamma has been previously characterized as a major immune escape mechanism.\textsuperscript{9} Our data indicate that this immune escape pathway is exclusively activated in tumors which are not able to attract a sufficient TNF-producing CD4\textsuperscript{+} T cell pool.

Thus, our results indicate that a novel mechanism of suppression of CD8\textsuperscript{+} T cell response may be linked to aberrant expression of MHC class II. However, they also indicate that only a fraction (roughly corresponding to 40%, that we named “melanoma subset I”) of melanoma seems to use this immune-escape pathway efficiently, and suggest that the remaining tumors (or “melanoma subset II”) may instead suppress CD8\textsuperscript{+} T cell recognition through reduced upregulation of MHC class I in response to IFN\gamma.

One previous small clinical trial has investigated the safety and biological activity of infliximab, a TNF inhibitor, in patients with advanced cancers. However, there were no objective responses reported but, at best, disease stabilization in one out of three patients with advanced melanoma.\textsuperscript{10}
Based on these premises and given the pleiotropic roles of TNF, we believe that it is unlikely that strategies blocking TNF may result in marked clinical efficacy if used as monotherapy. However, novel strategies based on selective targeting MHC class II-related immune escape in the tumor microenvironment may instead reach more success.

Importantly, the immune suppressive role of MHC class II may not be limited to the mechanisms described above. Immune inhibitory receptors found on the surface of T cells such as LAG-3 may bind to MHC class II molecules, transmitting immune suppressive signals. Strategies to counteract this mechanism are currently explored in clinical trials (clinicaltrials.gov identifier: NCT01968109 and NCT02061761).

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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