ST18

The role of Calcineurin-NFAT axis in tumour microenvironment in melanoma mouse model

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Abstract:
The tumor microenvironment (TME) is a complex system consisting of a heterogeneous set of cells, including stromal cells, tumor endothelial cells, innate and adaptive immunity cells. The tumor has the ability to shape the microenvironment that surrounds it, reprogramming the cells in order to favor their own survival, growth and spread. In light of the known function of NFAT in activating the immune response, we are trying to understand the role of the calcineurin-NFAT axis in TME.

For this purpose, we blocked the site of interaction of NFAT with calcineurin in B16 melanoma cell line using a specific peptide that binds the calcineurin site PxIxIT and we compared their behavior both *in vitro* using B16 murine melanoma cells and *in vivo* using C57BL / 6 mouse model.
We assessed the impact on tumor infiltrate and immune cells exhaustion status and the correlation to anti- PD1 treatment responsiveness. In addition, we wanted to determine the activated signaling responsible for the boosted immune response.

The analysis of the tumor infiltrate in calcineurin-NFAT impaired B16 tumors revealed an increased recruitment of CD8+T progenitor exhausted cells (PD-1int TCF1+ TIM3), which is canceled the by treatment with anti-CXCR3 antibodies, suggesting an important role of this receptor for their recruitment. CXCL9 and CXCL11, two ligands of this receptor, are upregulated *in vitro* by the stem niche in calcineurin-NFAT impaired B16 cells, so we hypothesized that the recruitment of the progenitor-exhausted CD8+T observed *in vivo* is mediated by the stem component of the tumor. In accordance with the literature, describing the involvement of CD8+T cells in the response to anti-PD-1 therapy, we observed that the calcineurin-NFAT impaired B16 tumors are more responsive to anti-PD-1 treatment. In addition, we saw that interleukin (IL)-15 promotes T-CD8+ cell proliferation and survival and influences their effector functions in calcineurin-NFAT impaired B16 tumors.
Finally, our aim is to evaluate the influence of the imapirement of the calcineurin-NFAT axis on the metatstasis of the B16 cancer cells.

This study identifed the dynamic interactions between the stem niches within the tumor and the TME immune cells. These interactions could be exploited to induce a patients' immune response against tumors or to increase anticancer drugs efficiency.