Reactivation of tumor associated macrophages via proprotein convertase 1/3 inhibition

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Tumors are highly heterogeneous both histologically and molecularly. Tumor heterogeneity can be explained in part by the wide diversity of stromal cells found in the tumor microenvironment. Macrophages are part of them and can represent up to 30% of the tumor mass in certain tumor types. In the tumor immune suppressive environment, macrophages are changed from their primary function to participate to the tumor growth. They are involved in angiogenesis, metastasis and immune suppression of T lymphocytes. Thus, a therapeutic strategy targeting macrophages which have a pivotal role in tumor seems to be a good option. Our idea is to switch tumor macrophages phenotype toward an antitumor one.
Previous studies have demonstrated that PC1/3 knock-out mice challenged with lipopolysaccharides (LPS) are more susceptible to septic shock characterized by high plasmatic levels of proinflammatory cytokines. In this work, we have analyzed the role of the proprotein convertase 1/3 (PC1/3) in macrophages' phenotype switching in a macrophages cell line inhibited for PC1/3.
We have demonstrated that inhibition of the proprotein convertase 1/3 (PC1/3) together with Toll-Like Receptor 4 (TLR4) stimulation in macrophages triggers an increase of their pro-inflammatory response. TLR4 signaling pathways can be enhanced leading to the secretion of pro-inflammatory factors and antitumor factors. Secreted factors by these PC1/3 inhibited macrophages decrease cancer cells viability and invasion. Our recent results have also shown that a peptidic inhibitor of PCs has also anti-tumor properties and could be used as a therapeutic agent in addition to TLR ligand in targeted therapy via macrophages reactivation.
Because TLR4 is a key actor in immuno-oncology, control of macrophages' activation by PC1/3 represents a promising and potent anti-tumor therapy.

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