Targeting tumor-infiltrating myeloid cells for prostate cancer therapy

Project

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Abstract

We will pursue a novel therapeutic approach, based on specifically targeting the interaction between tumor-infiltrating myeloid-derived suppressor cells (MDSCs) and prostate cancer cells. Our recent studies demonstrate that tumor-infiltrating MDSCs allow tumor cell senescence evasion and tumor immune tolerance, and that they fuel tumor growth following an androgen receptor (AR) blockade, at least in part by secreting IL-23 (Calcinotto *et al.*, 2018). We will use genetically engineered mouse models of different genetic backgrounds, patient-derived tumor models, and samples from translational studies focusing on an anti-IL-23 antibody and an AR antagonist to identify the best treatment modality for metastatic castration-resistant prostate cancer (mCRPC) patients. In particular, we will focus on the identification of novel regulators of MDSC recruitment and function, and will validate active therapeutic interventions reversing these processes. Our studies will provide key answers to unresolved questions, namely:

1) How do tumors with different genetic backgrounds recruit MDSCs?
2) Which factors secreted by MDSCs control tumor growth?
3) What is the best therapeutic intervention to remove or inhibit the function of these immune subsets in prostate cancer?
4) Is targeting IL-23 sufficient to reverse the impact of MDSCs on tumor growth, or are drug combinations needed to maximize antitumor activity?

Proposal Keywords

Clinical trial, immunotherapy, mechanisms of therapeutic resistance, novel targeted therapy