Potentiation of the Cancer Immunotherapy with low dose chemotherapy

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Abstract

Background

Cancer is characterized by accumulation of genetic alterations and loss of normal cellular regulatory processes. These events result in expression of tumor-associated and tumor-specific antigens, which may activate anti-cancer immune responses. However, the tumor microenvironment induces T cell tolerance, thereby contributing to uncontrolled tumor growth. We recently found that IgA-producing plasmocytes confer resistance to the immunogenic chemotherapeutic agent oxaliplatin in mouse models of prostate cancer (PC) by inhibiting the activation of cytotoxic T cells (CTL). Immunosuppressive plasma cells (ISP), which are also found in human-therapy-resistant PC, are generated in response to TGFb, and their functionality depends on PD-L1 expression and IL-10 secretion (*Shalapour et al., Nature, 2015*). However, the exact mechanism through which these cells are generated and how they suppress CTL effector functions remain unclear and their elucidation are the major goals of the current study.

Methods

Using the autochthonous transgenic adenocarcinoma of the mouse prostate (TRAMP) model of metastatic PC and subcutaneous transplantation of mouse Myc-CaP (MC) and Ovalbumin (Ova)-expressing newly developed PC cell lines, we examined how ISP are generated in response to low-dose oxaliplatin, and how low dose chemotherapy can potentiate cancer immunotherapy. We also conducted proteomic and transcriptomic analyses of cancer cells treated with Oxaliplatin or Cisplatin, which is not immunogenic, to understand the underlying mechanism the immunogenic activity of low dose oxaliplatin.

Results

Consistent with the market differences in their immunogenic activity, Oxali and Cis exert differential effects on RNA and protein expression, as determined by RNA-seq and Mass spectroscopy analysis (MS). The differential expressed RNAs and proteins are involved in autophagy, ER stress signaling and the IFN gamma response pathway. Optimal suppression of $CD8^+$ T cell proliferation by ISP required expression of IL-10 or PD-L1. IL-10 expression by B cells was also required for their ability to produce IgA, indicating that IL-10 autocrine signaling is involved in control of the IgA expression, which requires class switch recombination (CSR). The IgA CSR, was also dependent on follicular helper T cells, which may act through PDL1/PD1 signaling, consistent with these findings, depletion of $CD4^+$ T cells restored the response to low-dose Oxaliplatin, which promotes the tumor-directed CTL activation.

Conclusion

We suggest that elimination or inhibition of tumor infiltrating IgA^+ plasmocytes or T_{FH} may be the key to successful immunotherapy of PC, as long as an immunogenic chemotherapeutic, such as oxaliplatin, is also used. Other drugs which mimic the effect of Oxaliplatin on gene expression may turn out to also have strong immunogenic activity.

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