Antigen shedding into the circulation contributes to tumor immune escape

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Abbreviations: CEA, carcinoembryonic antigen; LSECs, liver sinusoidal endothelial cells

Tumors develop in constant interaction with the immune system, which influences both oncogenesis and tumor progression. This process has been conceptualized by the theory of cancer immunoediting, which involves an elimination, an equilibrium and an escape phase. During cancer immunoediting, tumors eventually develop ways to escape efficient antitumor immunity. One such ways is to create immunomodulatory conditions within the tumor microenvironment. The local production of immunosuppressive factors such as transforming growth factor β (TGFβ) and interleukin-10 (IL-10), the induction of enzymes that consume essential nutrients for immune cell function (e.g., IDO, Arg-I), and the local activation or recruitment of immunosuppressive cell types (e.g., regulatory T cells, myeloid derived suppressor cells) can all contribute to limit immune responses.

In many clinical settings, the presence of tumor-associated antigens in the serum of patients is being used for diagnostic and sometimes prognostic purposes. For instance, in colorectal carcinoma (CRC) patients, the levels of the carcinoembryonic antigen (CEA) in the serum has clinical relevance and is used as a prognostic maker. Interestingly, we could detect a similar antigen presentation to CD8+ T cells was restricted to LSECs and CD8+ T cells

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shedding their antigens into the bloodstream may not only directly diminish antitumor CD8+ T-cell responses, but also may be able to modulate antitumor CD4+ T cell responses. As many tumor-associated antigens can be detected in the circulation of cancer patients (e.g., α-fetoprotein, CA-19–9 or CA-125), we postulate that the inhibition of antitumor CD8+ T-cell immunity via antigen cross-presentation by LSECs might represent a general mechanism of tumor immune escape that operates alongside immunosuppressive mechanisms within the tumor microenvironment.

Figure 1. (A) The tumor carcinoembryonic antigen (CEA) circulating in the blood stream can be taken up by the mannose receptor (MR) and cross-presented by liver sinusoidal endothelial cells (LSECs). (B and C) Antigen recognition by naïve CD8+ T cells on LSECs leads to proliferation and expansion of CD8+ T cells and the emergence of an antigen-experienced CD8+ T-cell population that has upregulated CD44 but is CD25– and remains CD62Lhigh. (D) LSEC-induced CD8+ T cells are retained in the T-cell repertoire but are unable to produce interleukin-2 (IL-2) and interferon γ (IFNγ) and hence cannot mount a cytotoxic response to antigen-bearing target cells. As a consequence, CEA-specific LSEC-primed CD8+ T cells are unable to eradicate tumor cells in vivo. The induction of such incapacitated CD8+ T cells by LSECs is dependent on expression of the co-inhibitory molecule B7H1.

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