Regulatory T cells constitute 5–10% of peripheral CD4+ T cells and play an essential role in the active suppression of autoimmune responses, in both humans and rodents. Increasing evidence suggests that CD4+ regulatory T cells that infiltrate neoplastic lesions also play a significant role in the suppression of antitumor immunity and may represent a key mechanism by which tumors foster immune privilege. Recently, a circulating subset of thymic-derived regulatory T cells that constitutively express FOXP3 as well as inducible costimulator (ICOS) and that inhibit T-cell proliferation by an interleukin (IL)-10-dependent effect on antigen-presenting cells (APCs) has been identified in healthy subjects.1 Of note, the survival, proliferation and immunosuppressive functions of these cells are strictly dependent on ICOS-mediated, rather than on CD28-mediated, co-stimulation.1 Several studies have recently demonstrated that ICOS+FOXP3+ regulatory T cells abundantly infiltrate several human neoplasms, indicating that this cell subset plays a key role in tumor-elicited immunosuppression (and hence in disease progression).

Plasmacytoid dendritic cells (pDCs), a rare subset of circulating dendritic cells, have also been detected in the microenvironment of many solid tumors. Whereas pDCs are known to participate in antiviral immunity as they respond to viral infections by producing high levels of Type I interferons (IFNs), the role of these cells within the tumor microenvironment has remained unclear. Tumor-infiltrating pDCs appear to maintain a non-activated state and generally do not produce Type I IFNs, reflecting either the lack of activation stimuli in situ or the active inhibition of pDC functions by malignant cells.6 Similar to high levels of regulatory T cells, abundant tumor infiltration by pDCs has also been associated with poor clinical outcomes,2,7 suggesting a potential link between pDCs and ICOS+ regulatory T cells constituting strong predictors of disease progression and poor clinical outcome in patients affected by ovarian,2 breast3 and thyroid cancer.4 The intratumoral levels of ICOS+FOXP3+ regulatory T cells were found to predict cancer progression more robustly than the abundance of all tumor-infiltrating regulatory T cells, indicating that this cell subset plays a key role in tumor-elicited immunosuppression (and hence in disease progression).

Plasmacytoid dendritic cells and regulatory T cells in the tumor microenvironment

A dangerous liaison

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Tumor-infiltrating plasmacytoid dendritic cells (pDCs) have been associated with poor patient prognosis. We have recently uncovered the ability of pDCs to activate and expand a subset of tumor-infiltrating FOXP3+ regulatory T cells that express inducible costimulator (ICOS), providing new insights into the mechanisms that govern the escape of cancer from immunosurveillance.

Although the ability of pDCs to stimulate ICOS+FOXP3+ regulatory T cells requires MHC-T-cell receptor (TCR)
interactions, the nature of the antigen presented by pDCs is currently unknown. It is generally accepted that pDCs have a limited capacity to internalize exogenous antigens by phagocytosis and that they may rather be specialized in presenting endogenous molecules. However, tumor-infiltrating pDCs were found to induce a strong expansion of ICOS⁺FOXP₃⁺ regulatory T cells in cancer patients, raising the possibility that they also present tumor-associated antigens (Fig. 1). Interestingly, a recent study has shown that pDCs are indeed able to take up exogenous tumor-derived antigens via specific receptors.

Taken together, these findings provide novel insights into the factors that mediate cancer-elicited immunosuppression and identify new molecular targets for therapeutic interventions. In this setting, one therapeutic strategy would be to block ICOS-L/ICOS co-stimulation, to reduce the expansion and functions of ICOS⁺ regulatory T cells within the tumor microenvironment. Alternatively, the recruitment of pDCs into neoplastic lesions could be specifically targeted. EOC cells have been shown to produce large amounts of the CXCR4 ligand CXCL12 (also known as stromal cell-derived factor1, SDF1), which directly recruits pDCs into the tumor microenvironment.⁶ In line with our model, inhibitors of CXCL12-CXCR4 signaling axis have previously been shown to reduce tumor growth in mouse models of EOC.⁹,¹⁰ Finally, Toll-like receptor (TLR)7 or TLR9 ligands could be used to promote robust antitumor immune responses by virtue of their capacity of activating pDCs to produce type I IFNs and of differentiating pDCs into cytotoxic effector cells.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.
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