The two faces of regulatory T cells in cancer

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Regulatory T cells (Tregs) that expand in human colon cancer express retinoid-related orphan receptor γt (RORγt) and exert potent T-cell suppressive functions while mediating pro-inflammatory effects. Similar Tregs expand and drive a vicious cycle of inflammation in murine polyposis. Targeting RORγt in Tregs interrupts such a cycle and protects mice against polyposis, suggesting that a similar intervention may provide therapeutic benefits to colon cancer patients.

Regulatory T Cells are Attractive Targets for Anticancer Immunotherapy

The infiltration of colon cancer (CC) lesions by lymphocytes is an independent predictor of increased patient survival.¹ In addition, CC patients exhibit natural CD8⁺ T-cell responses that recognize and can eliminate tumor cells in an antigen-specific manner.² These observations have raised the hope that immunosurveillance mechanisms might keep neoplastic cells at bay and that vaccination or surveillance mechanisms might keep neoepithelial cells within a glandular organ in an antigen-specific manner.² These observations have raised the hope that immunosurveillance mechanisms might keep neuroepithelial cells at bay and that vaccination or surveillance mechanisms might keep neoplastic cells at bay and that vaccination strategies might efficiently eradicate CC.² Still, immunotherapeutic approaches have not generated consistent therapeutic benefits for CC patients so far. FOXP3⁺ regulatory T cells (Tregs) expand in cancer patients, have preferential access to neoplastic lesions and hinder antitumor CD8⁺ T-cell responses. Interestingly, Tregs differ significantly from effector T cells with regard to their T-cell receptor (TCR) repertoire, and therefore tend to recognize different antigens than effector T cells.² An elevated number of tumor-infiltrating Tregs has been associated with poor clinical outcomes in cohorts of patients affected by multiple types of cancer, encouraging therapeutic strategies aiming at the elimination of Tregs. There is however much controversy about the actual role of Tregs in cancer. Recent findings challenge the view that Tregs are always deleterious and rather suggest that high densities of intratumoral Tregs can correlate with better clinical outcomes in patients affected by CC and several other cancers.³ The ability of Tregs to control inflammation explains their protective role in cancer. Oncogenic events and the breakdown of the epithelial barrier cause inflammation, which provides both fuel and protection to growing tumors.¹ In CC, a deregulated T helper 17 (Th17) response to microbial products contributes to tumor growth, and Th17 cytokines are elevated both in human CC and in murine polyposis, a setting in which the inhibition of these cytokines exert consistent protective effects.⁵ In humans, persistent Th17 inflammation predisposes to inflammatory bowel disease, and tumor infiltration by IL-17-expressing lymphocytes negatively correlates with patient survival in CC.⁴ Tregs suppress Th17 cells in an interleukin (IL)-10 dependent manner.⁵ However, when activated under inflammatory conditions, Tregs can acquire different functional properties and emerge as a prominent pro-inflammatory cell subset, hence converting into cells that they normally suppress, Th17 cells. The conversion of Tregs into Th17 cells does not seem to be highly deleterious in cancer, as it would presumably reduce the abundance of Tregs. However, cancer is marked by significant increases in both systemic and tumor-infiltrating FOXP3⁺ Tregs.

Different Subsets of Regulatory T Cells Can Protect or Promote Colon Cancer

Observations in support of a protective role of Tregs in CC have been obtained in mouse models. The adoptive transfer of Tregs from healthy mice protect against experimental colitis as well as against microbial-associated colitis and cancer.¹⁰ Furthermore, the transfer of Tregs protects against polyposis in mice that are genetically predisposed to develop this disease.⁷ Such a protection is generally attributed to the capacity of Tregs to suppress inflammatory reactions that are inherent to preneoplastic settings, including those driven by mast cells, macrophages and granulocytes, and to reduce the levels of Th17 cytokines, leading to the active regression of polyps.⁵ However, the fact that endogenous Tregs expand and are recruited to murine polyps without any apparent detrimental effect for the latter is confounding. Obviously, there must be functional differences between Tregs isolated from healthy and polyp-ridden mice. Indeed, Tregs isolated from the latter not only do not inhibit inflammation and polyposis but also have a tendency to mediate opposite effects while remaining able to potentently suppress T-cell responses.³ We have recently demonstrated that pro-inflammatory Tregs can be discriminated from their counterparts as they co-express FOXP3 and retinoid-related

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orphan receptor γt (RORγt), which is the signature transcription factor of Tγt cells. When we compared the effects of the ablation of Tγt cytokines with those of the ablation of RORγt, the latter was by far more protective. The significance of pro-inflammatory Tregs in the etiology-pathology of polyposis became evident when the Treg-specific ablation of RORγt was found to hinder inflammation and exert cytoprotective effects. The ablation of RORγt in the T-cell compartment also exacerbated T-cell responses against polyps. We concluded that the acquisition of pro-inflammatory properties by Tregs is a turning point that allows for the uncontrolled escalation of T-cell suppressive and polyposis-promoting inflammatory reactions.

Our observations have direct implications for human cancer. We indeed detected Tregs exhibiting the phenotype and functional properties described above in the peripheral blood and tumors of CC patients. The expansion of RORγt Tregs in patients was strictly tumor-dependent.

In line with this notion, the abundance of RORγt+ Tregs dropped upon the surgical removal of primary tumors in non-metastatic patients. There were however a few cases making exception, and in these patients RORγt+ Tregs persisted post-surgery. We are now following surgerized patients to see whether the persistence of pro-inflammatory Tregs may convey prognostic information. Based on results obtained in mouse models, we predict that the pharmacological inhibition of RORγt will provide clinical benefits to cancer patients. The administration of a novel, first generation RORγt inhibitor for 2 weeks reduced the number of polyps arising in ApcΔ7168 mice, opening the path to clinical trials targeting the plasticity of Tregs in cancer patients. The same inhibitor was shown to restore the anti-inflammatory properties of Tregs isolated from CC patients. We conclude that the expression of RORγt by Tregs is causatively related to CC and that its inhibition can convey therapeutic benefits (Fig. 1).

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