Neuropilin 1 guides regulatory T cells into VEGF-producing melanoma

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Abbreviations: iTreg, induced Treg; NRP1, neuropilin 1; nTreg, naturally occurring Treg; Treg, regulatory T cell; VEGF, vascular endothelial growth factor; WT, wild-type

Owing to their potent immunosuppressive functions, CD4+CD25+ regulatory T cells (Tregs) are involved in the maintenance of immune homeostasis and control several facets of immunity, including autoimmune, anti-pathogen and antitumor responses.

High levels of Tregs have been found in neoplastic lesion as well as in the peripheral blood of cancer patients, and such an increase has been shown to correlate with poor prognosis in patients affected by breast, gastric and ovarian carcinoma.

Murine models of Tregs depletion, for instance obtained with anti-CD25 antibodies or in transgenic DEREG (Depletion of Regulatory T cells) mice, provide further support to the notion that Tregs interfere with effective antitumor immune responses and hence contribute to oncogenesis and tumor progression. Murine T cells exhibit an immunosuppressive phenotype in vitro. The thymus-derived naturally occurring Tregs (nTregs), a heterogeneous population of induced Tregs (iTregs) has been described. Moreover, Yadav et al. and Weiss et al. have recently proposed that the expression of NRP1 may be useful for distinguishing nTregs from iTregs generated in vivo from naïve T cells under several circumstances, including via the physiologically relevant mucosal route. However, whether and how NRP1 de facto contributes to Treg function remain unclear.

In a recent study, we have investigated the role of NRP1 expressed by Tregs on the development and progression of tumors in mice. We observed an impaired tumor growth in mice bearing a T cell-specific ablation of Nrp1. This phenotype was accompanied by an increased antitumor CD8+ T-cell response, suggesting that NRP1 is directly involved in the functions of Tregs. Interestingly, in vitro studies revealed that Nrp1-deficient Tregs exhibit a similar inhibitory activity than Nrp1-expressing Tregs obtained from WT mice. These results led us to conclude that NRP1 is not involved in the intrinsic immunosuppressive function of Tregs. However, a growing body of evidence indicates that inhibitory molecules expressed by Tregs and the underlying molecular mechanisms are essential, but not necessarily sufficient, for efficient immunosuppressive Treg functions in vivo. Indeed, an effective immunosuppression in vivo requires the appropriate co-localization of suppressor and effector cells. Tumors themselves promote their own progression by creating an immunosuppressive environment that facilitates their escape from immunosurveillance.

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NRP1 acts as a co-receptor for the vascular endothelial growth factor (VEGF), and NRP1-expressing endothelial cells migrate toward VEGF gradients. Tumors produce high amounts of VEGF, and we detected elevated levels of Nrp1-expressing Foxp3+ Tregs within tumors transplanted in WT mice. Hence, we propose that tumor-derived VEGF...
interaction may stand out as a new therapeutic strategy that might be superior to Treg depletion with regard to the development of autoimmune side effects, at least for the treatment of melanoma. We assume that blocking the tumor-derived VEGF-dependent trafficking of NRP1+ Tregs would not affect the function and number of Tregs systemically. Indeed, we did not observe any changes in the frequencies of Tregs in tumor-draining lymph nodes or in peripheral lymphoid organs of tumor-bearing mice bearing a T cell-specific \( \text{Nrp1} \) ablation or VEGF-deficient tumors. However, whether the NRP1/VEGF-mediated trafficking of nTregs is a tumor-specific phenomenon or is also involved in other inflammatory immune responses will have to be carefully determined in future experiments.

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