Pulling the Strings of the Tumor Microenvironment

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Macrophages are in the spotlight of cancer immunotherapy research because they exert a wide spectrum of protumorigenic functions. In this issue, Pfirschke and colleagues report that macrophage targeting pulls the strings of the tumor microenvironment, ultimately leading to a coordinated antitumorigenic immune reaction in a lung carcinoma mouse model.

See related article by Pfirschke et al., p. 40 (4).

Macrophages are heterogeneous and versatile immune cells displaying a continuum of functional cell states (1). They frequently represent one of the most dominant immune-cell populations in the tumor microenvironment, and their intratumoral presence is linked with tumor progression and poor survival (2, 3). Macrophages are therefore among the most studied targets for novel immunotherapies. However, responses to macrophage-targeting therapies have been limited to defined cancer types, highlighting the need for a better elucidation of the cellular and molecular mechanisms controlling macrophage function in the cancer context (2).

In this issue, Pfirschke and colleagues elegantly show how macrophage targeting reeducates $CSF1R^+$ cells, ultimately unleashing a collective antitumoral immune reaction (4). Using the KP1.9 cell line–based orthotopic mouse model of non–small cell lung cancer, the authors report that CSF1R inhibition (CSF1Ri) with the small molecule BLZ945 reduces tumor burden in the lungs. Consistent with previous studies (3), this treatment does not deplete $CSF1R^+$ cells; rather it initiates their transcriptional rewiring. Upon CSF1Ri, monocytes and macrophages reduce their expression of protumorigenic genes and gain gene signatures associated with antigen presentation and lymphocyte activation, suggesting involvement in a complex network of cellular interactions.

By studying the $CSF1R^-$ cellular compartment, Pfirschke and colleagues reveal an indirect effect of CSF1Ri that reshapes immune cell cross-talk in the tumor microenvironment. This includes an increase of immune-activating interactions between $CSF1R^+$ monocytes and macrophages with lymphocytes. *In vivo* depletion of $CD8^+$ T cells and natural killer (NK) cells abrogates CSF1Ri-dependent protection against tumor growth, indicating that effective antitumor immunity is unleashed upon CSF1Ri. In addition, there is upregulation of the effector gene *Ifng* in NK cells in CSF1Ri-treated tumors as compared with controls. Together with the lack of tumor control in CSF1Ri-treated *Ifng*-deficient mice, these findings indicate that the reeducation of $CSF1R^+$ cells by treatment with BLZ945 induces antitumorigenic IFNγ production by NK cells. Knowing that lymphocyte-derived IFNγ can induce IL12 production in dendritic cells (DC), and having observed enhanced *Il12b* expression in DCs upon CSF1Ri and an increase in lymphocyte interactions with DCs, the authors investigate the role of IL12 in CSF1Ri-treated tumors. Accordingly, intratumoral IL12 protein levels increase upon CSF1Ri, and both IL12 and DCs are required for the antitumor effect of CSF1Ri.

Collectively, CSF1Ri rewires cellular interactions among $CSF1R^+$ and $CSF1R^-$ cells in lung tumors and induces a licensing mechanism mediated by lymphocyte-derived IFNγ and DC-derived IL12, ultimately enabling effective antitumor immune responses.

This study exemplifies how innovative research techniques, including single-cell RNA-sequencing (scRNA-seq) and intravital microscopy, can be powerful tools when combined with more traditional functional approaches. Pfirschke and colleagues exploit scRNA-seq to provide a comprehensive picture of the intricacy of the tumor microenvironment, and how this is changed upon macrophage targeting, and they interrogate their datasets to generate and validate complex research hypotheses. Next to this, intravital imaging, *in vivo* targeted cell depletion, and the use of transgenic mice provide further confirmation with a noteworthy holistic approach.

This comprehensive and timely study conveys an important message about the complexity of heterotypic intercellular cross-talk in the tumor microenvironment and demonstrates that, by pulling the strings of one immune cell population, a coordinated response of the whole tumor microenvironment can be triggered. Moreover, the notion that tumor-associated macrophages orchestrate intercellular cross-talk reinforces their attractiveness as targets for novel immunotherapies. Cutting-edge technologies, such as single-cell -omics, represent a valuable help to improve current macrophage-targeting therapies by, for instance, facilitating the choice of promising combinatorial strategies or the prediction of patient response.

Authors' Disclosures

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