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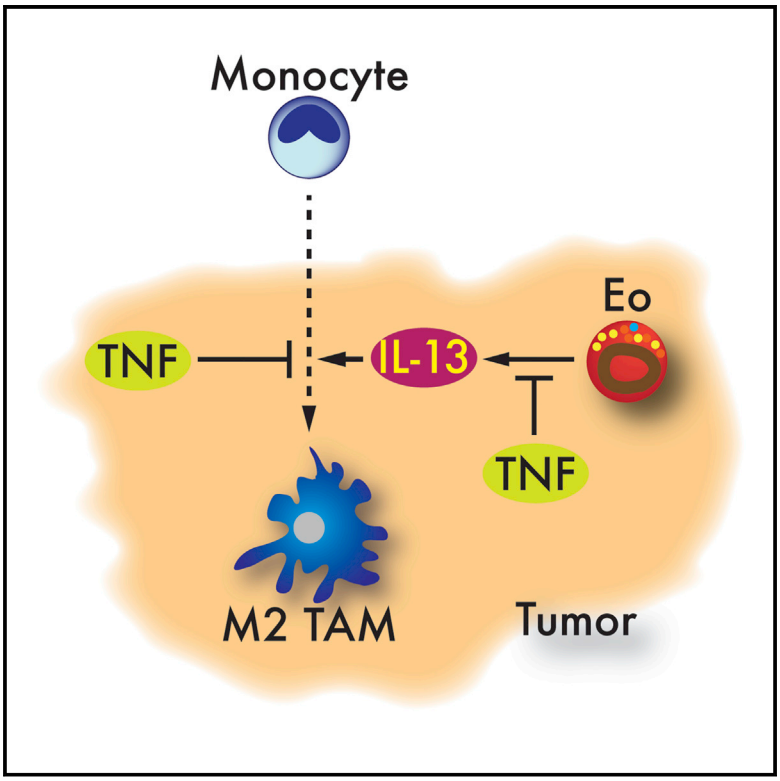
TNF Counterbalances the Emergence of M2 Tumor Macrophages

Graphical Abstract



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In Brief

Macrophage "polarization" in cancer involves heterogeneity between the M1 and M2 phenotypes. Most research and clinical data link M2 macrophages to pro-tumor activities. Kratochvill et al. show that TNF is essential for suppressing the number of M2 tumor macrophages. TNF also blocks IL-13 production, a pro-M2 cytokine, from activated eosinophils.

Highlights

- Tumor-associated macrophages (TAMs) are heterogeneous populations
- Loss of type I TNF receptor signaling causes a rise in M2 gene expression in TAMs
- TNF mediates a global anti-M2 pathway
- TNF suppresses IL-13 production from activated eosinophils

Accession Numbers

GSE59047
GSE68817

Kratochvill et al., 2015, Cell Reports *12*, 1902–1914
September 22, 2015
http://dx.doi.org/10.1016/j.celrep.2015.08.033

OPEN ACCESS
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Cell Reports
Article

TNF Counterbalances the Emergence of M2 Tumor Macrophages

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SUMMARY

Cancer can involve non-resolving, persistent inflammation where varying numbers of tumor-associated macrophages (TAMs) infiltrate and adopt different activation states between anti-tumor M1 and pro-tumor M2 phenotypes. Here, we resolve a cascade causing differential macrophage phenotypes in the tumor microenvironment. Reduction in TNF mRNA production or loss of type I TNF receptor signaling resulted in a striking pattern of enhanced M2 mRNA expression. M2 gene expression was driven in part by IL-13 from eosinophils co-recruited with inflammatory monocytes, a pathway that was suppressed by TNF. Our data define regulatory nodes within the tumor microenvironment that balance M1 and M2 populations. Our results show macrophage polarization in cancer is dynamic and dependent on the balance between TNF and IL-13, thus providing a strategy for manipulating TAMs.

INTRODUCTION

Macrophages are the most-abundant non-tumor-cell-populating cancers, and their numerical presence is correlated with poor clinical outcomes (Dannenmann et al., 2013; Gajewski et al., 2013; Galon et al., 2013; Zhang et al., 2012). The large numbers of macrophages in tumors raises a simple but unanswered question: what are macrophages doing in tumors? One possibility is macrophages seed tumors to repair tissue they detect as damaged. In cancer, malignant tissue looks like "self," thereby escaping detection by immune cells. It therefore is hardly surprising macrophages are recruited to tumors if they are performing their normal "cleanup" functions. In doing so, macrophages may aid and abet an enemy within as proposed by Dvorak in the "wounds that don't heal" model (Bissell and Hines, 2011; Dvorak, 1986).

Given that clinical and mouse model data frequently correlate macrophages with pro-tumor activities, several different tactics have been used to deplete or interfere with macrophage viability or recruitment including tyrosine kinase inhibitors or monoclonal antibodies targeting the colony-stimulating factor 1 receptor (CSF-1R), CD11b, or antibodies targeting CCL2, a chemokine for monocyte recruitment to tumors (Ahn et al., 2010; Bonapace et al., 2014; Pyonteck et al., 2013; Ries et al., 2014). However, the anti-macrophage activity of these drugs is not limited to macrophages in tumors. Macrophages are required for normal homeostatic functions and populate all tissues of the body. Therefore, gross targeting of monocytes and/or macrophages is likely to cause toxicities in tissues dependent on macrophages such as the gut, lungs, and heart (Epelman et al., 2014). Unanticipated side effects such as tumor rebound when drug therapy ceases have been reported (Bonapace et al., 2014). Macrophages are also critical for cell corpse disposal and tissue repair after chemotherapy, irradiation, or surgery. In these therapies, macrophages have time-dependent pro- and anti-tumor functions (De Palma and Lewis, 2013; Klug et al., 2013; Ma et al., 2013; Nakasone et al., 2012; Predina et al., 2013). Collectively, targeting specific pro-tumor macrophage functions rather than macrophages per se could be a valuable addition to standard-of-care therapies.

Macrophages and dendritic cells are "plastic" because their inflammatory mediator production is tailored for responsiveness to specific environmental cues (Murray and Wynn, 2011a; Wynn et al., 2013). Macrophages alter their effector and defense mechanisms across a spectrum between "M1" pro-inflammatory phenotypes—characterized by destructive anti-intracellular pathogen free radical and inflammatory cytokine production—and "M2" states—displayed by tissue-resident macrophages and macrophages encountering worms and fungi (Murray et al., 2014; Wynn et al., 2013). M2 macrophages express genes involved in tissue repair and resolution and have