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Origin and Role of a Subset of Tumor-Associated Neutrophils with Antigen-Presenting Cell Features in Early-Stage Human Lung Cancer

Highlights

- Lung tumors accumulate a subset of TANs with a granulocyte and APC hybrid phenotype
- APC-like hybrid neutrophils are able to stimulate the anti-tumor T cell responses
- IFN-γ and GM-CSF are requisite factors for the development of hybrid neutrophils
- Ikaros negatively regulates the development of hybrid neutrophils from progenitors

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In Brief

Singhal et al. identify a subset of tumor-associated neutrophils (TANs) that can cross-present tumor antigens and activate anti-tumor T cells in stage I/II human lung cancer. The induction of these hybrid TANs from progenitors requires GM-CSF and IFN-γ and reduction of Ikaros.

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Origin and Role of a Subset of Tumor-Associated Neutrophils with Antigen-Presenting Cell Features in Early-Stage Human Lung Cancer

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SUMMARY

Based on studies in mouse tumor models, granulocytes appear to play a tumor-promoting role. However, there are limited data about the phenotype and function of tumor-associated neutrophils (TANs) in humans. Here, we identify a subset of TANs that exhibited characteristics of both neutrophils and antigen-presenting cells (APCs) in early-stage human lung cancer. These APC-like "hybrid neutrophils," which originate from $CD11b^{+}CD15^{hi}CD10^{-}CD16^{low}$ immature progenitors, are able to cross-present antigens, as well as trigger and augment anti-tumor T cell responses. Interferon-γ and granulocyte-macrophage colony-stimulating factor are requisite factors in the tumor that, working through the Ikaros transcription factor, synergistically exert their APC-promoting effects on the progenitors. Overall, these data demonstrate the existence of a specialized TAN subset with anti-tumor capabilities in human cancer.

INTRODUCTION

Tumor-associated inflammation contributes to cancer development and progression and is often associated with a high degree of inflammatory cell infiltration (Grivennikov et al., 2010). Tumor-associated neutrophils (TANs) represent a significant portion of tumor-infiltrating cells and accumulate in many types of cancers, including lung cancer (Carus et al., 2013; Ilie et al., 2012). Although the role of TANs in tumor development is beginning to be investigated in murine models, it remains largely unexplored in humans.

In murine studies, it appears that TANs can exert both pro-tumor and anti-tumor effects (Brandau, 2013; Fridlender et al., 2009). Numerous studies have shown that neutrophils can promote tumor progression by degrading matrix, immunosculpting, stimulating tumor cell proliferation, increasing metastasis, and enhancing angiogenesis (Houghton, 2010; Piccard et al., 2012). However, they can also exert anti-tumor functions such as inducing tumor cell death via their powerful antimicrobial killing machinery (Dallegri and Ottonello, 1992; van Egmond and Bakema, 2013) and by producing factors to recruit and activate cells of the innate and adaptive immune system (Mantovani et al., 2011). Given these varying effects of mouse TANs on tumor growth, the paradigm of anti-tumor "N1 neutrophils" versus pro-tumor "N2 neutrophils" was proposed (Fridlender et al.,

Significance

Tumor-associated neutrophils (TANs) represent a significant fraction of the inflammatory cells in the tumor microenvironment; however, the contribution of these cells in inhibiting or promoting tumor expansion in humans remains unclear. Although the concept of neutrophil phenotypic and functional diversity has emerged in murine tumor models, it is unknown whether TAN subsets with different functions exist in humans. Here, we provide evidence that early-stage lung tumors can induce the formation of a unique subset of TANs that can trigger and support anti-tumor T cell responses. These findings demonstrate the potential anti-tumor role of TANs in early-stage cancer and may provide opportunities to boost the anti-tumor efficacy of cytotoxic T lymphocytes.