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Promoting metastasis: neutrophils and T cells join forces

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The role neutrophils play in cancer is a matter of debate as both pro- and anti-tumor functions have been documented. In a recent publication in *Nature*, Coffelt *et al*. identify a new mechanism where neutrophils and T cells cooperate to generate metastasis-supporting immune suppression.

Neutrophils are an important component of the innate immune system and play a critical role in fighting infections and inflammation. However, they are also propagated and mobilized by tumors and accumulate at the tumor bed and in pre-metastatic and metastatic tissues where they exert important effects. There are conflicting reports regarding the role that neutrophils play in cancer. Neutrophils have been shown to have tumoricidal properties and can kill tumor cells either by direct cytotoxicity or via antibody-dependent cell-mediated cytotoxicity (ADCC). A number of reports have also shown that neutrophils can recruit and activate T cells, inducing acquired anti-tumor immune responses. On the other hand, neutrophils were shown to possess *bona fide* pro-tumor properties including the promotion of tumor angiogenesis, supply of pro-tumor cytokines, stimulation of growth by neutrophil elastase, and promotion of immune evasion by immunosuppression of T cells [1]. Confusion about the role of neutrophils in cancer might be explained by the realization that neutrophil precursors have some plasticity [2] and that multiple neutrophil subsets with differing properties likely exist within tumors, which are driven by factors in the tumor microenvironment, such as TGFβ [3]. It appears that early on in tumor growth, both murine and human neutrophils tend to inhibit the primary cancer growth and actually recruit and activate $CD8^+$ T cells [4, 5] (Figure 1), however, as tumors become larger and the microenvironment changes, the neutrophils (along with other tumor-associated cell types, such as macrophages) begin to become immunosuppressive and inhibit T cell activity [2, 6, 7].

In addition to their role in influencing primary tumor growth, interesting new observations have been made about the role of neutrophils in cancer metastasis. In recent years, it has become apparent that while tumor cell-autonomous traits play a key role in the metastatic process, the normal stromal cells that surround and interact with tumor cells also play a critical part in the metastatic cascade.

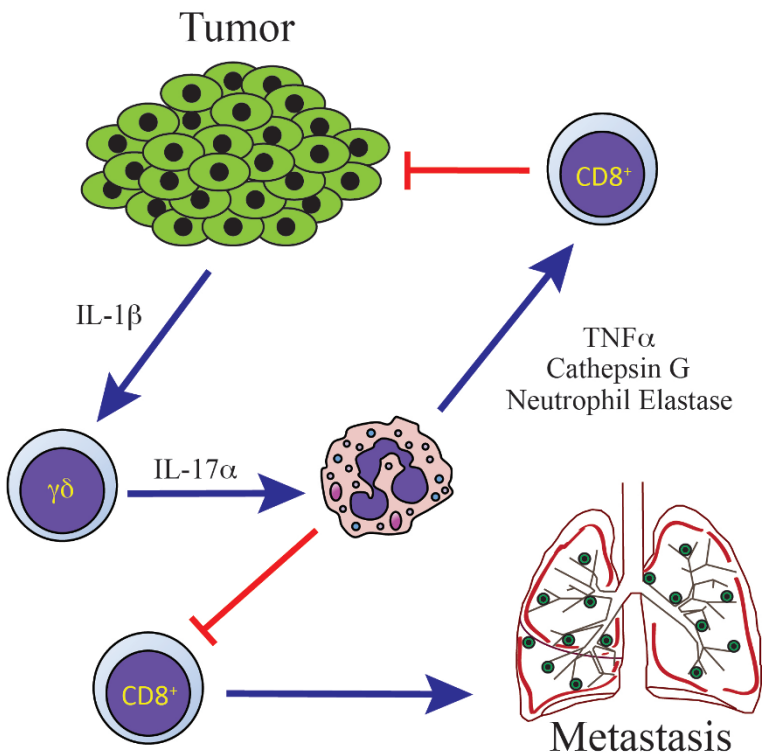

Figure 1 The consequences of the interplay between neutrophils and lymphocytes on tumor growth and metastatic progression. Neutrophils were previously shown to possess both tumor-promoting and tumor-limiting properties. Neutrophils have the capacity to propagate cytotoxic $CD8^+$ cells, through secretion of factors such as TNFα, cathepsin G and neutrophil elastase, thereby limiting primary tumor growth. Coffelt *et al*. [10] identified a tumor-promoting cascade where tumor-secreted IL-1β stimulates the secretion of IL-17α from γδ T cells. Consequently, neutrophils acquire a suppressive phenotype and inhibit the propagation of cytotoxic $CD8^+$ cells, ultimately enhancing metastatic seeding in the pre-metastatic lung.

Again, the role of neutrophils in metastasis is unclear. We, and others, recently reported that tumor-stimulated neutrophils possess anti-metastatic activity and actively limit metastatic seeding by direct elimination of tumor cells at the pre-metastatic site [8, 9].

In contrast to these studies, Coffelt *et al*. [10] recently presented data to show that neutrophils could enhance metastasis in the highly aggressive KEP mouse model of metastatic breast cancer. They elegantly show that depletion of neutrophils in this model leads to a dramatic reduction in spontaneous lung metastases. They further show that the combined depletion of both neutrophils and $CD8^+$ cells results in reversal of the metastatic phenotype, implicating $CD8^+$ cells and neutrophils as partners in crime. Looking for the mechanism through which tumors induce this metastasis-enhancing process, the authors found that several cytokines capable of inducing IL-17α release from γδ T cells are significantly increased, and showed that IL-17α was indeed required for upregulation of G-CSF, which in turn, regulated both neutrophil mobilization and activation of the immunosuppressive neutrophil phenotype (Figure 1). Finally, the authors demonstrated that it is tumor-secreted IL-1β that stimulates the release of IL-17α, inducing the unique immune suppressive phenotype in neutrophils which acquire the ability to suppress $CD8^+$ cytotoxic T cells and directly support metastatic spread. This complex mechanism may thus be perturbed by eliminating γδ T cells, IL-17α or neutrophils, firmly supporting the author's conclusions.

Interestingly, while this novel mechanism involving the interplay between tumor-stimulated neutrophils and two distinct T cell subsets has profound implications for metastatic spread, it apparently has no significant implications for primary tumor growth.

This study raises a number of interesting issues. Are IL-1β, γδ T cells or IL-17α important in other tumors? Are these results generalizable to other mouse models and to human tumors? It is unclear why the results of this paper are so different than other reports showing that neutrophils prevent metastasis [8, 9]. Tumor type, location, size, and the timing of interventions are all likely to be important. Regardless, this paper is a sophisticated demonstration of how tumor cells, innate immune cells and adaptive immune cells have the potential to interact in a specific tumor model. This study thus provides an interesting paradigm that should be examined in other systems.

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