The Yin-Yang of Tumor-Associated Neutrophils

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Cancer-related inflammation is a key component of the tumor microenvironment. A report in this issue of *Cancer Cell* now indicates that tumor-associated neutrophils in lung cancer can polarize to either "N1" or "N2" phenotype that inhibits or promotes cancer development, respectively.

Inflammatory cells and mediators are a key component of the tumor microenvironment (Mantovani et al., 2008) and cancer-related inflammation has been proposed to represent the seventh hallmark of cancer. Among inflammatory cells, the "big eaters," tumor-associated macrophages (TAMs), have long been credited to play a key role in tumor progression (Mantovani et al., 2008; Pollard, 2004). Macrophages can exert dual functions in the context of tumors. M1 macrophages activated by interferons and bacterial products can elicit tumor- and tissue-destructive reactions by targeting cancer cells and the tumor vasculature. At the other end of the spectrum, in response to tumor-derived or lymphocyte-derived signals (e.g., Hagemann et al., 2006; DeNardo et al., 2009), TAMs infiltrate neoplastic tissues and are set in an M2, alternative activation mode (Mantovani et al., 2002). TAMs affect virtually all aspects of tumor progression, ranging from cancer cell proliferation and survival, to angiogenesis, to response to hormones (Mantovani et al., 2008). A report by Fridlender et al. (2009) now highlights that the "small eaters" (microphages), neutrophils, can be no less important in tumor progression.

Neutrophils are short-lived white blood cells derived from bone marrow myeloid precursors. Attention has long been focused on their short-term antimicrobial and tissue-damaging function. However, cytokines, including some involved in tumor progression such as IL-1, dramatically prolong their survival and reprogram their function. Moreover, polymorphonuclear leukocytes (PMN) are themselves a conspicuous source of inflammatory cytokines (Cassatella, 2006). Previous studies have already shown that PMN can promote cancer in particular by affecting the angiogenic switch (Pekarek et al., 1995; Nozawa et al., 2006). Fridlender et al. (2009) now report that in lung cancer and mesothelioma models, including an orthotopic primary one, TGF-β blockage is associated with activation of a $CD8^+$ T cell-dependent effector arm that involves neutrophils as effectors. Under conditions of TGF-β-mediated immunosuppression, $CD8^+$ T cell activation results in increased recruitment of neutrophils, their "N1" polarization, and antitumor activity. Conversely, in the presence of TGF-β, depletion of "N2" polarized neutrophils results in tumor growth retardation. Interestingly, preliminary data suggest that at least part of the neutrophil-attracting chemokines is derived from TAMs, suggesting a "ménage a trois" involving T cells, macrophages, and PMN. The N1-N2 polarization of TAN was born out by limited transcription analysis with similarities to corresponding macrophage populations, for instance in terms of arginase levels. Thus, in models of lung cancer, infiltrating neutrophils are driven by TGF-β to acquire a polarized N2 protumor phenotype. After TGF-β inhibition, a shift to N1 occurs with acquisition of antitumor activity in vitro and in vivo.

Interestingly, in a parallel set of studies, TGF-β was also associated with myelomonocytic cell-attracting chemokines and myeloid cell recruitment. In a mammary carcinoma model, deficiency in the type II TGF-β receptor was associated with chemokine-mediated recruitment of myeloid cells (Yang et al., 2008). These in turn promoted metastasis via metalloproteinase. Thus, TGF-β, a tumor suppressor (but at times a promoter) frequently involved in human tumors and associated with metastasis, appears to be generally linked to regulation of chemokine production and myelomonocytic cell recruitment in tumors.

The new findings raise a number of questions and suggest that the role of neutrophils in cancer-related inflammation may need careful reappraisal. The N1-N2 polarization proposed by Fridlender et al. (2009) mirrors the M1-M2 polarization of macrophages. It will be important to assess whether and to what extent neutrophil plasticity indeed mirrors macrophage polarization, by defining for instance the effect on these cells of interferon-γ and IL-4 produced mainly by Th1 and Th2 cells, respectively. Cancer is associated with the expansion of the myeloid compartment and with the appearance of a heterogeneous set of immunosuppressive cells operationally defined as myeloid-derived suppressor cells (MDSC; Gabrilovich and Nagaraj, 2009). The TAN characterized in the present study have clear features of mature neutrophils. Yet, the general question remains as to the differentiation in tumor tissues of MDSC and as to the nature of the ultimate effectors (neutrophils? macrophages?) of MDSC-suppressive function. There are considerable differences between mouse and human in terms of transcriptional profiles associated with macrophage polarization, e.g., arginase expression. Therefore, the existence and properties of N1-N2 in humans will have to be carefully investigated. Finally, the present results call for a reappraisal of infiltration, polarization, and prognostic significance of neutrophils in human cancer.

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Imatinib Resistance and Progression of CML to Blast Crisis: Somatic Hypermutation AIDing the Way

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Very little is known about how acquired oncogenic mutations arise. In this issue of *Cancer Cell*, Klemm and colleagues present evidence supporting a role for the antibody diversification enzyme activation-induced deaminase (AID) in the generation of mutations associated with disease progression and drug resistance in chronic myeloid leukemia.

Chronic myeloid leukemia (CML) is a clonal disease of hematopoietic stem cells (HSCs) that occurs as a result of a reciprocal translocation between chromosomes 9 and 22 (Quintas-Cardama and Cortes, 2009). This rearrangement gives rise to the Philadelphia (Ph) chromosome that, at the molecular level, contains a genomic fusion between the *BCR* gene from chromosome 22 and the *ABL1* gene from chromosome 9. *ABL1* encodes the Abelson tyrosine kinase, and its enforced expression from the *BCR-ABL1* gene fusion drives the pathogenesis of Ph^+ leukemias through phosphorylation of a wide range of substrates that regulate cell proliferation, differentiation, migration, survival, and DNA repair. Clinically, CML follows a triphasic course, with the majority of patients presenting in chronic phase characterized by an accumulation of myeloid progenitor cells and mature granulocytes in the bone marrow and peripheral blood. If untreated, the chronic phase can last several years before progressing to an accelerated phase characterized by increasing disease burden and frequently accompanied by the acquisition of additional genetic defects. The accelerated phase can last weeks to months and signals the imminent development of blast crisis, the final phase of CML. Clinically, blast crisis behaves like acute leukemia and can have an immature myeloid, pre-B lymphoblastic, or mixed-lineage phenotype (Garcia-Manero et al., 2003). The molecular mechanisms involved in the evolution of this complex disease from chronic phase to blast crisis remain largely unknown, although it is clear that genetic changes in addition to the Ph chromosome are required.

Approved by the FDA in 2001, the tyrosine kinase inhibitor imatinib was the first drug to be designed specifically to target a molecular defect associated with cancer and has revolutionized the management of CML. Imatinib binds to the catalytic domain of the ABL1 kinase, preventing ATP binding and trapping it in an inactive conformation (Druker, 2008). Newly diagnosed chronic-phase CML patients treated with imatinib demonstrated a complete hematologic response of 96% at one year and an overall survival of 89% at five years (Druker et al., 2006). However, approximately 6% of chronic-phase patients relapse and develop resistance to imatinib and many patients who are first treated during accelerated phase or blast crisis demonstrate imatinib resistance (Druker, 2008). In the majority of cases, imatinib resistance is due to point mutations in *BCR-ABL1* that change the conformation of the ABL1 kinase domain, preventing imatinib binding. Many of these mutations can be overcome by treatment with next-generation tyrosine kinase inhibitors such as dasatinib or