La mala educación of Tumor-Associated Macrophages: Diverse Pathways and New Players

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Inflammation is a key component of the tumor microenvironment. Two reports published in this issue of *Cancer Cell*, Andreu et al. and Erez et al., shed new light on pathways and players involved in the orchestration of cancer-related inflammation.

Recruitment of myelomonocytic cells is a hallmark of cancer-related inflammation (Mantovani et al., 2008; Pollard, 2004). Tumor-associated macrophages (TAMs) have served as a paradigm for the cancer-promoting actions of hematopoietic cells (Allavena et al., 2008). TAMs in established progressing tumors generally fail to express antitumor activity and have properties of alternatively activated or M2-like cells, oriented to the promotion of tissue remodeling, angiogenesis, and taming of protective adaptive immunity. Other cells in the myelomonocytic lineage including $Tie2^+$ monocytes, the operationally defined myeloid-derived suppressor cells (MDSCs), and mature neutrophils share properties and protumor functions with TAMs (Fridlender et al., 2009; Mantovani et al., 2008; Ostrand-Rosenberg, 2008).

What signals orchestrate the protumor functions of TAM? Tumor cells produce molecules that orchestrate mononuclear phagocyte functions such as colony stimulating factor-1 (CSF-1) or interleukin-10 (IL-10) (Hagemann et al., 2006; Mantovani et al., 2008; Pollard, 2004) (Figure 1). A report in this issue of *Cancer Cell* (Erez et al., 2010) now shows that in a mouse model of multistage squamous epithelium carcinogenesis driven by HPV, tumor cells also reprogram fibroblasts to promote inflammation. Cancer-associated fibroblasts (CAFs) acquire proinflammatory properties and promote tumor growth, angiogenesis, and macrophage recruitment. Conditioning of CAF is orchestrated by tumor cells as well as by immune cells as discussed below. Interestingly, an inflammatory signature is present also in fibroblasts from selected human tumors (breast and pancreas) characterized by a desmoplastic response. Hence, fibroblasts have now emerged as new players in cancer-related inflammation (CRI) capable of considerable plasticity and of shaping the function of TAMs (Erez et al., 2010).

In the same model of multistage carcinogenesis, lymphocytes were found to orchestrate cancer-related inflammation by remote control. Antibodies produced by B cells with the help of $CD4^+$ T cells localize in the matrix and drive the construction and function of an inflammatory microenvironment. Dissection of this pathway has now shed new light on its cellular and molecular components (Andreu et al., 2010).

The effector function of antibodies is mediated by Fcγ receptors (FcγRs) or by complement. As true for other components of immunity, complement can also act as a double-edged sword in cancer. Complement components have indeed been implicated in the recruitment of cancer-promoting myelomonocytic cells (Markiewski et al., 2008). Unequivocal evidence is now presented that in this model of epithelial carcinogenesis, antibody-mediated cancer promotion is FcγR dependent (Andreu et al., 2010). The pathway that emerges can be summarized as follows (Figure 1): B cells produce antibodies directed against components of the extracellular matrix. FcγR engagement leads to mast cell-dependent

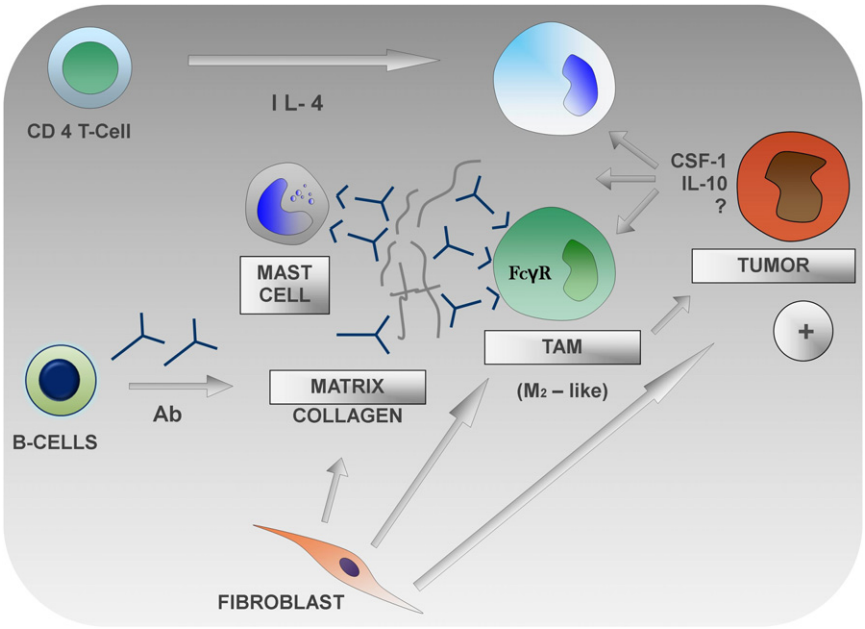

Figure 1. A Schematic Representation of Diverse Pathways that Orchestrate the Protumor Function of Myelomonocytic Cells
In different models of carcinogenesis, macrophage polarization is orchestrated by different cells and molecules (Th2-derived IL-4 or B cell-derived antibodies and immune complexes). TAM can therefore differ (light blue or green) but they share M2-like cancer-promoting properties.

promotion of angiogenesis and myelomonocytic cell recruitment. Macrophages directly enhance tumorigenicity in an FcγR-dependent fashion. Interestingly, here the culprit of tumor promotion was on mature TAMs rather than on immature elements in the myelomonocytic pathway such as MDSC. Tumor-promoting TAMs have a M2-like transcriptional profile. B cell-instructed innate cells are a source of IL-1, which activates the proinflammatory properties of CAF (Erez et al., 2010).

The TAM profile reported by Andreu et al. and previous profiles (Mantovani et al., 2008) include T cell-attracting anti-angiogenic chemokines (CXCL10 and CXCL11). This finding emphasizes the yin-yang dual potential of the macrophage-tumor cell interplay (Allavena et al., 2008; Mantovani et al., 2008; Ostrand-Rosenberg, 2008).

These observations raise important general issues. B cells are a valuable target in the therapy of autoimmune disorders. Therefore, the definition of a B cell/antibody/FcγR/macrophage pathway in cancer-promoting inflammation identifies potential targets for therapeutic intervention. Similarly, IL-1-blocking strategies are available or being developed for inflammatory disorders, and in both here and elsewhere (Dinarello, 2009), IL-1 is emerging as a key player in CRI.

Myelomonocytic cells are part of a common pathway of inflammation-mediated cancer promotion (Allavena et al., 2008; Mantovani et al., 2008; Pollard, 2004). However, the subsets involved (from classic mature macrophages or neutrophils to immature myelomonocytic cells) differ considerably in different settings (e.g., Andreu et al., 2010; DeNardo et al., 2009; and Fridlender et al., 2009). In a mouse model of metastatic breast cancer, DeNardo and colleagues (DeNardo et al., 2009) reported that macrophage M2 polarization and tumor promotion is driven by T cell-produced IL-4. Thus, not only can the subsets be different but so can the orchestrating signals in different tumors (Figure 1). Therefore, careful dissection of the players, conductors and themes in different human cancers will be required for the clinical exploitation of our understanding of CRI at the bedside.

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Discovery of Novel Transcriptional and Epigenetic Targets in APL by Global ChIP Analyses: Emerging Opportunity and Challenge

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Identifying transcriptional program(s) deregulated by oncoproteins is key to understanding the molecular basis of the disease. In this issue of *Cancer Cell*, two studies by Martens et al. and Wang et al. provide global blueprints for transcriptional targets and epigenetic modifications mediated by PML-RARα in acute promyelocytic leukemia.

Acute promyelocytic leukemia (APL) is characterized by the expression of RARα fusions and unique sensitivity to all-*trans* retinoic acid (ATRA) treatment. As a result, it has been the paradigm for studying differentiation therapies and more recently for epigenetic therapies. In the past decades, a tremendous amount of effort has been made to identify the aberrant