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Article

$CD4^+$ T Cells Regulate Pulmonary Metastasis of Mammary Carcinomas by Enhancing Protumor Properties of Macrophages

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SUMMARY

During breast cancer development, increased presence of leukocytes in neoplastic stroma parallels disease progression; however, the functional significance of leukocytes in regulating protumor versus antitumor immunity in the breast remains poorly understood. Utilizing the MMTV-PyMT model of mammary carcinogenesis, we demonstrate that IL-4-expressing $CD4^+$ T lymphocytes indirectly promote invasion and subsequent metastasis of mammary adenocarcinomas by directly regulating the phenotype and effector function of tumor-associated $CD11b^+Gr1^-F4/80^+$ macrophages that in turn enhance metastasis through activation of epidermal growth factor receptor signaling in malignant mammary epithelial cells. Together, these data indicate that antitumor acquired immune programs can be usurped in protumor microenvironments and instead promote malignancy by engaging cellular components of the innate immune system functionally involved in regulating epithelial cell behavior.

INTRODUCTION

Clinical and experimental studies have established that chronic infiltration of neoplastic tissue by leukocytes, i.e., chronic inflammation, promotes development and/or progression of various epithelial tumors (de Visser et al., 2006; Mantovani et al., 2008); however, the organ-specific cellular and molecular programs that favor protumor, as opposed to antitumor, immunity are incompletely understood. Although some subsets of leukocytes certainly exhibit antitumor activity, including cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells (Dunn et al., 2006), other leukocytes, most notably mast cells, B cells, dendritic cells, granulocytes, and macrophages, exhibit more bipolar roles, by virtue of their capacity to either hinder or potentiate tumor progression (de Visser et al., 2005; Mantovani et al., 2008).

Breast cancer development is characterized by significant increases in the presence of both innate and adaptive immune cells, with B cells, T cells, and macrophages representing the most abundant leukocytes present in neoplastic stroma (DeNardo and Coussens, 2007). Retrospective clinical studies in human breast cancer have revealed that high immunoglobulin (Ig) levels in tumor stoma (and serum), and increased presence of extra follicular B cells, T regulatory (T_{reg}) cells, and high ratios of CD4/CD8 or T_H2/T_H1 T lymphocytes in primary tumors or in draining lymph nodes (LNs) correlate with tumor grade, stage, and overall patient survival (Bates et al., 2006; Coronella-Wood and Hersh, 2003; Kohrt et al., 2005); thus, some facets of adaptive immunity might indeed be involved in fostering cancer development in the breast.

However, experimental studies have demonstrated that macrophages in primary mammary adenocarcinomas regulate

SIGNIFICANCE

DeNardo and colleagues demonstrate a tumor-promoting role for T_H2-$CD4^+$ T lymphocytes that elicit protumor, as opposed to cytotoxic bioactivities of tumor-associated macrophages and enhancement of prometastatic epidermal growth factor receptor signaling programs in malignant mammary epithelial cells. This work reveals a protumor regulatory program involving components of the acquired and cellular immune systems that effectively collaborate to promote pulmonary metastasis of mammary adenocarcinomas, and identifies cellular targets, namely $CD4^+$ T effector cells and IL-4 for anticancer therapy.

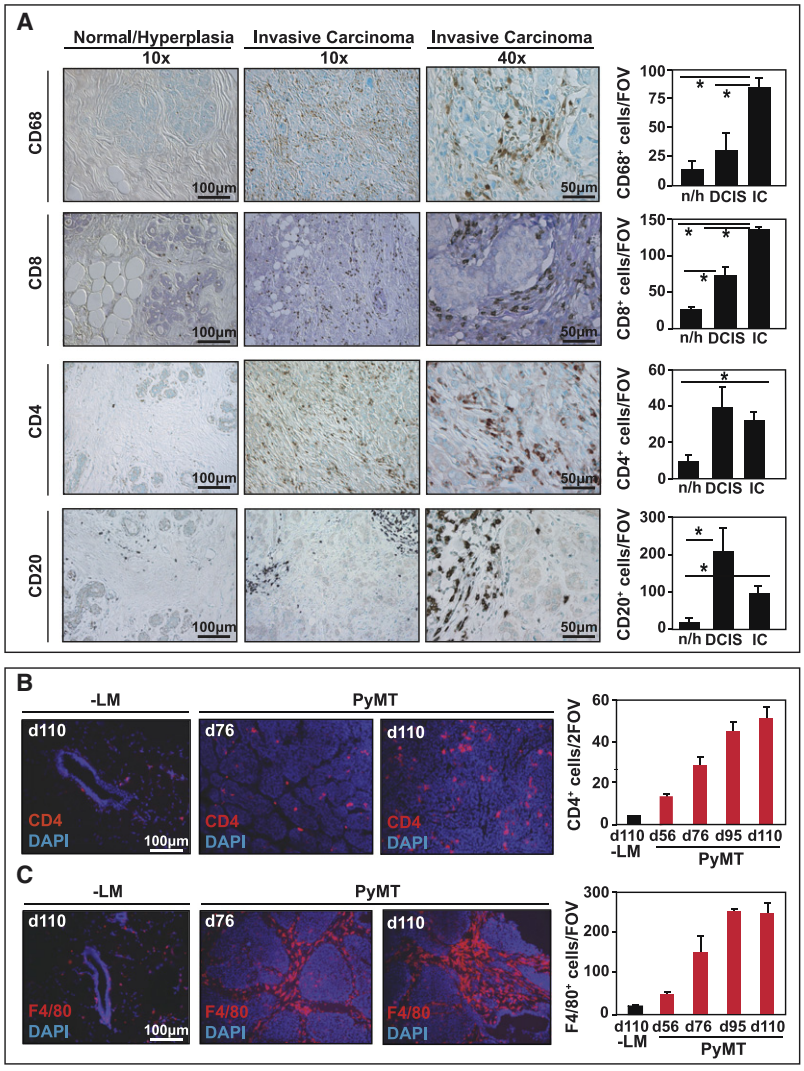

Figure 1. Concomitant Recruitment of Adaptive and Innate Immune Cells in Breast Cancers

(A) The number of $CD68^+$, $CD20^+$, $CD4^+$, and $CD8^+$ cells was analyzed in patient samples of normal/hyperplastic breast tissue (n/h; n = 9), ductal carcinoma in situ (DCIS; n = 6), and invasive ductal carcinomas (IC; n = 150) using tissue microarrays. Representative 10× and 40× images are shown and the average number of positive cells as depicted reflects the mean number of cells in each disease stage, evaluated by counting all high power fields (20×) per tissue section (1.1 mm)/two sections/patient. *p < 0.05 by Mann-Whitney.

(B, C) $CD4^+$ and $F4/80^+$ cell presence was evaluated during MMTV-PyMT mammary tumor development and is depicted by representative images in normal mammary tissue (-LM) and tumors from 76 and 110-day-old *PyMT* mice. $CD4^+$ or $F4/80^+$ cells were quantitatively assessed and data reflects the mean number of positive cell evaluated in 10 high-power fields (20×) per tumor, n = 4 mice per group.

Graphs are depicted as mean values and standard error of the mean (SEM) in all panels.

late-stage carcinogenesis by virtue of their proangiogenic properties (Lin and Pollard, 2007), as well as foster pulmonary metastasis by providing epidermal growth factor (EGF) to malignant mammary epithelial cells (MECs) and thereby enhancing their invasive (and metastatic) behavior (Pollard, 2004). Based on these seemingly disparate observations, we sought to determine whether adaptive immunity also fosters malignancy in the breast by regulating the phenotype or effector functions of tumor-associated macrophages (TAMs) and either activating their protumor properties or alternatively by suppressing their antitumor capabilities. To address this, we utilized an aggressive transgenic mouse model of murine mammary adenocarcinoma development (*MMTV-PyMT* mice) (Guy et al., 1992) where late-stage carcinogenesis and pulmonary metastasis are regulated by colony stimulating factor (CSF)-1 and tissue macrophages (Lin et al., 2001). We evaluated *MMTV-PyMT* mice harboring homozygous null mutations in genes regulating development of specific lymphocyte subtypes and found that $CD4^+$ T cells potentiate pulmonary metastasis of mammary adenocarcinomas indirectly by enhancing aspects of protumor immunity mediated by TAMs.

RESULTS

$CD4^+$ T Cells Regulate Pulmonary Metastasis of Mammary Adenocarcinomas

As observed in several types of solid tumors, human breast adenocarcinomas are characterized by infiltration of both innate and adaptive immune cells (Figure 1A). Immunohistochemical (IHC) detection of $CD68^+$ myeloid cells (macrophages), $CD4^+$ and $CD8^+$ T cells and $CD20^+$ B cells in human breast cancer reveals an increase in each cell type paralleling cancer development (Figure 1A). Given the critical role of adaptive immunity in regulating innate immune cell effector function in chronic inflammatory diseases, and in some mouse models of cancer development (de Visser et al., 2005), we hypothesized that B and/or T lymphocytes might exert a functional role in regulating protumor properties of myeloid cells during mammary carcinogenesis. Because infiltration of $CD4^+$ T cells and $F4/80^+$ macrophages increases progressively during mammary carcinogenesis in MMTV-polyoma middle T (*PyMT*) mice (Figures 1B and 1C), similar to human breast cancer development (Figure 1A), we addressed this hypothesis by generating *PyMT* mice harboring homozygous null mutations in the recombinase activating gene-1 (*RAG1*) functionally impairing development of B and T cells, i.e., *PyMT/RAG1*$^{-/-}$, and compared them for characteristics of neoplastic progression to *PyMT* mice lacking B cells, i.e., *PyMT/JH*$^{-/-}$, versus selective subsets of T cells, i.e., *PyMT/CD4*$^{-/-}$, *PyMT/CD8*$^{-/-}$ and *PyMT/CD4*$^{-/-}$*/CD8*$^{-/-}$ mice. Strikingly, we found no gross histopathological or quantitative differences between these cohorts when evaluated for primary tumor latency, tumor burden, or tumor angiogenesis as a function of complete or selective lymphocyte deficiency (Figures 2A–2D; see Figure S1 available online). In contrast, selective loss of $CD4^+$ T cells in either *PyMT/RAG1*$^{-/-}$, *PyMT/CD4*$^{-/-}$*/CD8*$^{-/-}$,

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