Inflammatory lymphangiogenesis in postpartum breast tissue remodeling

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Like many cancers, mammary carcinomas use lymphatic vessels to disseminate, and numerous clinical and experimental studies have documented a strong correlation between peritumoral lymphangiogenesis and tumor dissemination. At the same time, many other factors can affect the incidence, invasiveness, and mortality of breast cancer, including lactation history. Although lactation reduces overall cancer risk, patients diagnosed within 5 years of pregnancy have an increased incidence of metastatic disease. In this issue of the JCI, Lyons and colleagues demonstrate that postpartum breast tissue remodeling during involution coincides with inflammatory lymphangiogenesis. In mouse models, cyclooxygenase-2 (COX-2) inhibition during involution reduced the risk of cancer metastasis and correlated with decreased lymphangiogenesis. In addition to lymphangiogenesis, COX-2 inhibition reduces many of the immune-suppressive features of the tumor microenvironment, including development of myeloid-derived suppressor cells and regulatory T cells; therefore, these results support the notion that inhibiting COX-2 during lactation weaning may lessen the incidence of breast cancer metastasis.

Lymphangiogenesis in cancer, inflammation, and tissue remodeling

Lymphatic vessels are common routes for tumor cell metastasis, and sentinel lymph node metastasis is a major prognostic indicator of breast cancer outcome. Since the identification of lymphatic-specific growth factors VEGF-C and VEGF-D and their receptor VEGFR-3, numerous studies have demonstrated striking correlations between tumor-associated lymphangiogenesis, or peritumoral lymphatic expansion, and metastasis (1). Originally the correlation between lymphangiogenesis and tumor metastasis was attributed to increased accessibility for tumor cell dissemination, but recent studies have shown that tumor-associated lymphangiogenesis provides many immune-suppressive features to the tumor microenvironment and can pacify tumor-specific cytotoxic T lymphocytes as well as drive deletional tolerance of naïve T cells (2, 3).

On the other hand, lymphangiogenesis is not specific to the tumor microenvironment and generally accompanies all types of inflammation, particularly in late or chronic stages, including chronic infections, wound healing and tissue remodeling, autoimmune diseases like Crohn’s disease, and the resolution phase of acute inflammation (3, 4). Lymphangiogenesis is driven by a host of inflammatory cells that secrete VEGF-C, including mast cells, neutrophils, macrophages, activated stromal cells, angiogenic blood endothelium, and B cells (3). These cells can upregulate their production of VEGF-C or VEGF-D upon exposure to prostaglandin E2 (PGE₂), which plays many important and complex roles in the tumor microenvironment.

Function and consequences of inflammatory lymphangiogenesis

During inflammation, lymphangiogenesis often involves hyperplasia of preexisting lymphatic vessels, increased vessel diameters, and decreased organization and patterning. The expanded lymphatic network in inflamed tissues often resembles the vascular plexus of the liver sinusoids or bone marrow vasculature. It remains controversial whether these altered vessels have increased transport functions — draining fluid or carrying cells to the lymph node — but several recent studies have suggested other functions of lymphatic expansion. First, as mentioned above, VEGF-C and VEGF-D are triggered in later stages of inflammation. PGE₂ is a key driver of inflammatory lymphangiogenesis through its actions on inflammatory cells that secrete VEGF-C and VEGF-D. Moreover, upregulation of PGE₂ is considered to be key for the resolution of inflammation and dampening cytotoxic immune responses; therefore, the activated lymphatic endo-

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inflammatory cells drive lymphangiogenesis, lymphangiogenesis also alters the local immune cell repertoire. It was first suggested a decade ago that COX-2 could drive inflammatory or tumor-associated lymphangiogenesis. At this time, activation of the E-prostaglandin-enriched hyperplasia could therefore increase the relative importance of these functions by increasing LEC surface area. Finally, VEGF-C triggers LECs to upregulate CCL21 (6), a lymphoid homing chemokine that attracts not only dendritic cells and naive T cells but also regulatory T cells. Thus, while the lung likely serves immune-suppressive roles in such an environment. Second, lymphatic endothelial cells (LECs) have been shown to suppress dendritic cell maturation, secrete suppressive cytokines and factors like IDO, and directly activate naive T cells for deletional tolerance (3); lymphatic hyperplasia could therefore increase the relative importance of these functions by increasing LEC surface area. Finally, VEGF-C triggers LECs to upregulate CCL21 (6), a lymphoid homing chemokine that attracts not only dendritic cells and naive T cells but also regulatory T cells. Thus, while inflammatory cells drive lymphangiogenesis, lymphangiogenesis also alters the local immune cell repertoire.

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Lactation, involution, and breast cancer

Among the many risk factors in metastatic breast cancer are pregnancy and lactation history due to the important changes induced both hormonally as well as physically in the breast tissue. In multiple studies and meta-analyses, lactation has been correlated with reduced breast cancer risk, especially in genetically predisposed women (15). On the other hand, cancers that develop in women within 5 years of childbirth have an increased risk of metastasis and mortality compared with those that develop later. When lactation ends, dramatic changes in the breast occur to remodel the milk-producing ducts back into a quiescent state in a process termed involution. This remodeling of the breast tissue has been a major focus of the Schedin lab, who demonstrated previously that various features of the inflammatory environment accompanying involution drive cancer susceptibility and in particular promote more invasive and metastaic cancer development in rodents (16, 17). Specifically, these features include collagen remodeling, which contributes to a stiffer extracellular matrix, an established risk factor for disease (18); alternatively activated macrophages, which promote immune suppression; and COX-2 expression, which drives the synthesis of PGE2 (10). Because lymphangiogenesis accompanies this remodeling process, the results of Lyons and colleagues (10) indicate that COX-2–dependent inflammatory processes might be addressed before therapeutic strategies can be designed and clinically implemented. First, how is the normal physiological process of involution affected by inhibiting the inflammatory processes that drive this remodeling? Can involution proceed normally if COX-2 is inhibited, and would the resulting breast return to a normal quiescent state? Second, as lymphangiogenesis and other COX-2–driven events contribute immune-suppressive functions in the tissue, would autoimmune reactions be a risk of attenuating this program?

Finally, it will be important to determine whether lymphangiogenesis actually drives the more invasive breast cancer in these patients or merely correlates with the inflammation that supports its onset. Would specifically blocking lymphangiogenesis during this weaning period give the same efficacy as more generally inhibiting all COX-2–dependent inflammatory processes? Lymphangiogenesis can be inhibited specifically by antibody-mediated blockade of VEGFR-3, which prevents LEC proliferation but does not destroy pre-existing lymphatic vessels (19). Such inhibitors have been widely shown in mouse models to prevent metastasis, although their effects on the overall tumor immune microenvironment are poorly understood. Such function-blocking antibodies might also be interesting potential targets in the prophylactic context of the targeted window during involution.

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