Fibrosis, cancer and the premetastatic niche

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The onset and development of breast cancer is known to be a complex process involving reciprocal interactions between multiple cell types within the body. Epithelial, endothelial, mesenchymal and hematopoietic cells act together to alter and shape the microenvironment of the tumor to modulate the initiation, progression and dissemination of cancer. Their actions result in a dramatically altered extracellular matrix (ECM) from both a biochemical, but also biomechanical context. As such, over the past decade, solid tumors have become increasingly recognized as discrete organs, showing a complexity that approaches and perhaps even exceeds that of healthy tissue. These significant changes are the result of normal homeostatic mechanisms gone awry and as such make targeting them incredibly difficult.

Tumors develop as a result of the dysregulation of multiple signaling networks governing fundamental cell processes such as apoptosis, proliferation, differentiation and migration. All of these cellular processes are inherently important to tumor initiation, progression and metastasis. One of the critical regulators of these is the ECM, and more importantly, ECM

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dynamics within the tumor microenvironment. Biological regulation of cellular behavior and phenotype by the ECM is rapidly emerging as a major research area. The ability of cells to sense and respond to changes in biochemical and biomechanical cues provided by ECM is now considered an important factor in determining cancer onset and progression to metastasis.

Under normal conditions, homeostasis, the secretion of new and breakdown of old ECM components is tightly controlled, and this balance helps to maintain normal order and structure within organs. Early on in tumorigenesis, this homeostasis is upset and the ECM begins to change in both its biochemical as well as its biomechanical properties. In the case of breast cancer, it has been shown that these desmoplastic changes, driven primarily by collagen I accumulation, are a key component of the tumor microenvironment [1] and act to drive malignant transformation [2], but also drive tumor progression [3,4] and ultimately metastasis [5,6]. Yet this disruption to homeostatic ECM mechanisms is not confined to the primary tumor site. Indeed, the tumor is capable of eliciting changes within the ECM in sites of future

KEYWORDS

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• microenvironment • niche

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metastasis, so-called premetastatic niches [7–10]. Many of these changes we see during the formation of premetastatic niches; the recruitment of immune cells, the secretion of ECM components and ECM-modifying enzymes, are highly reminiscent of changes observed in another pathological disease, namely that of fibrosis.

Fibrosis is a huge clinical problem, and affects millions of people worldwide. The links between cancer and fibrosis are strong. Indeed, it is well known that underlying tissue fibrosis is closely correlated with the onset of cancer in organs such as the liver and the lung. For example, it has been shown that fibrotic breast disease is associated with a predisposition to breast cancer [11], and environmentally induced fibrotic disorders of the lung can increase incidence of lung cancer [12]. To that end, it has been proposed that the treatment of underlying fibrosis in such cases would lead to an improvement in cancer associated prognosis [13]. In our work last year, we showed that tissue fibrosis may pose a serious clinical problem in patients harboring unrelated primary tumors [6]. The presence of pathological organ fibrosis in both the lung and the liver increases the ability of circulating breast cancer cells to colonize and grow in these organs, suggesting that breast cancer patients with unrelated organ fibrosis may present a poorer metastasis-free survival. This work is supported by others who showed that in the liver, myofibroblast activation is associated with the arrival of melanoma cells into the liver, leading to enhanced colonization of the organ [14]. That the onset of tissue fibrosis is capable of modulating tumor cell behavior at secondary sites is also supported by work showing that developing tissue fibrosis is capable of re-activating already disseminated dormant tumor cells [15]. Together, this body of work illustrates how collagen remodeling and changes in both the biochemical as well as biomechanical properties of the local microenvironment may be capable of modulating the behavior of tumor cells at secondary metastatic sites.

Given the significant overlap in pathways associated with fibrosis and cancer, we should simultaneously evaluate agents that target the tumor microenvironment and fibrosis for potential roles in both settings. When considering adjuvant therapies for metastatic breast cancer, just as antifibrotic therapies are being proposed for highly fibrotic primary tumors, it may also be necessary to treat patients with antifibrotic

therapies aimed at disrupting the establishment and development of metastases. Even better would be to target commonalities in mechanisms behind tumor initiation and progression and the onset and development of fibrosis. A key family shown to play a pivotal role in these two diseases in the lysyl oxidase (LOX) family of proteins, in particular LOX and LOX-like 2 (LOXL-2) [16,17]. Both of these proteins have been shown to be important in ECM remodeling and homeostasis, and to play critical roles in both breast cancer and fibrosis [6,7,18–20] driving the accumulation of collagen fibers. Indeed, a role for LOX and LOXL-2 has been shown in chronic hepatic fibrosis, arterial fibrosis and chemotherapy-induced kidney fibrosis in human patients [21], as well as liver and lung fibrosis in mouse models [6,18]. While targeting fibrosis has proved problematic in the past, several therapeutic approaches are being explored and clinical trials with a LOXL-2 targeting antibody [18] are in Phase II for fibrosis and beginning in cancer patients. Data would suggest that as well as targeting the primary tumor cells directly, these therapies would also disrupt aberrant remodeling of the ECM at the primary tumor site and secondary metastatic sites thereby improving the prognosis of patients. Recent work by Gilkes and colleagues has also shown that primary tumor hypoxia leads to the increased breast cancer tumor cell secretion of collagen prolyl hydroxylases that are critical for collagen deposition and desmoplasia, and leads to enhanced metastasis to lymph nodes and lungs in human xenograft models [22].

While we are still uncovering more about the interplay between organ fibrosis and cancer metastasis, it is clear that new challenges are yet to emerge. For example, blocking aberrant changes in the ECM may prove beneficial, but sustained inhibition may adversely affect normal programs of wound healing. Knowing who, when and how long to treat with antifibrotic therapies in the cancer context may prove problematic as the long-term side effects of such treatments are currently unknown. However, in time it is likely that we will be able to block the pro-tumorigenic and pro-metastatic changes in the ECM without disrupting normal regenerative processes to improve the prognosis and outcome of breast cancer patients.

Author contributions

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