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AUTHOR'S VIEWS

Stress-induced metastatic niches in breast cancer

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ABSTRACT

Interactions between disseminated cancer cells and the microenvironment in secondary organs are essential for the development of metastasis in most malignancies. Metastasis-initiating cells and their progeny can impose changes in the microenvironment leading to the formation of a metastatic niche that supports malignant growth at secondary sites. Our recent findings indicate that stress responses play a crucial role in generation of metastatic niches in breast cancer by modulating the extracellular matrix and promoting interactions with reactive fibroblasts.

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Stress is a collective term over physiological responses to events that perturb cellular homeostasis. The ability to respond to stress is mediated by evolutionary conserved signaling pathways that are important to reacquire homeostasis.[1] Cellular stress responses are of high relevance to cancer biology, as cancer cells face numerous stress-inducing insults during their lifespan. This includes oncogenic-, replicative- and endoplasmic reticulum stress as well as diverse stress signals induced by the microenvironment. During metastatic colonization of secondary organs, disseminated cancer cells that are released from primary tumors face an unfavorable microenvironment that can lead to their elimination. Indeed, evidence suggests that most disseminated cancer cells, that reach a secondary site, perish at early stages of colonization.[2] Cancer cells that can initiate metastasis must therefore have intrinsic ability to survive in an antagonistic environment. In addition, metastasis-initiating cells may have the capability to instruct changes in the microenvironment leading to the formation of a supportive metastatic niche. Although not fully understood, the knowledge on the molecular composition of metastatic niches is rapidly expanding.[3]

Evidence indicates that c-Jun N-terminal kinase (JNK) signaling pathway may play a major role in the formation of metastatic niches in the lungs. JNK is a member of the family of mitogen-activated protein kinases (MAPKs) and is one of the key mediators of stress signals in cells.[4] Previously, we showed that breast cancer cells with metastasis-initiating properties have active JNK signaling and depend on it for metastatic progression.[5] When activated in breast cancer cells, JNK induces numerous genes associated with mammary stem cell properties and wound healing including tenascin C (*TNC*) and osteopontin, officially termed secreted phosphoprotein 1 (*SPP1*), that encode distinct glycoproteins within the extracellular matrix (ECM). In metastasis, these proteins have a pleiotropic function, affecting cancer cells in an autocrine manner and exerting changes in stromal physiology. Both TNC and SPP1 promote metastatic progression and are associated with poor clinical outcome in breast cancer patients.[5–7]

Recently, we revealed new means by which JNK signaling affects the metastatic microenvironment. We showed that JNK induces pro-metastatic interactions between metastasis-initiating breast cancer cells and fibroblasts during the development of pulmonary metastasis.[8] Fibroblasts form a heterogeneous group of mesenchymal cells that are frequently observed in a reactive state in breast cancer. Whereas the role of reactive fibroblasts in cancer at the primary site has been recognized for years,[9] their role in secondary organs during metastatic colonization is still ambiguous. We analyzed the dynamic transcriptome of metastasis-associated fibroblasts isolated from mouse lungs harboring metastasis at distinct stages. Our study revealed a crosstalk between breast cancer cells and reactive fibroblasts in lungs, that is initiated by JNK-induced interleukins-1α and 1β (IL-1α/β) production by the cancer cells leading to upregulation of C-X-C motif chemokine ligands 9 and 10 (CXCL9/10) in fibroblasts via interleukin 1 receptor type 1 (IL-1R1) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling.[8] This paracrine axis promotes proliferation of disseminated cancer cells by CXCL9/10-mediated activation of C-X-C motif chemokine receptor 3 (CXCR3) and thus fuels metastatic colonization of the lungs.

In established breast tumors, JNK activity is not observed homogeneously within cancer cell populations. Our results suggest that only a minor population within growing primary tumors exhibits JNK activity and consequently the ability to eventually modify the pulmonary microenvironment.[5] However, a major enrichment is observed in the JNK-positive population during metastasis initiation, as vast majority of cancer cells exhibits JNK signaling in micrometastases. Notably, upon growth, metastatic nodules (macrometastases) reestablish heterogeneity where modest populations of JNK-positive cells are primarily observed at the invasive front.[5,8]

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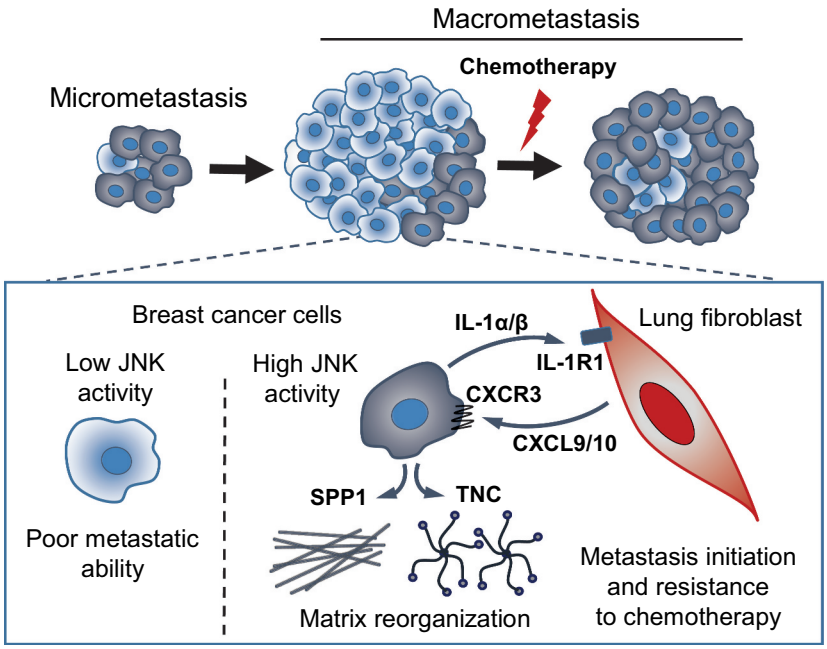

Figure 1. Stress signaling in breast cancer cells favors the generation of pulmonary metastatic niches. During metastatic colonization of the lungs, breast cancer cells with high c-Jun N-terminal kinase (JNK) activity are enriched at early stages i.e. in micrometastases. However, the majority of cancer cells in macrometastases exhibit low JNK activity, with JNK-positive cells mostly at the invasive front. JNK signaling promotes metastasis by inducing expression of interleukins-1α and 1β (IL-1α/β), tenascin C (TNC) and secreted phosphoprotein 1 (SPP1) in cancer cells, directly via the c-Jun transcription factor. Secreted IL-1α/β induce expression of C-X-C motif chemokine ligands 9 and 10 (CXCL9/10) in fibroblasts via interleukin 1 receptor type 1 (IL-1R1) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling. In turn, CXCL9/10 bind C-X-C motif chemokine receptor 3 (CXCR3) on metastasis-initiating cells and fuel metastatic growth in the lung. JNK-induced TNC and SPP1 promote cancer cell survival during metastatic colonization. JNK is activated by chemotherapy leading to further support of the metastatic niche and thus limiting therapeutic efficacy.

The majority of JNK-positive breast cancer cells also expresses CXCR3 and is thus able to respond to CXCL9/10 secreted by reactive fibroblasts. In line with these results, the JNK target genes *TNC* and *SPP1* are likewise prominently expressed in cancer cells at the invasive front.[6,7] This is intriguing in the light of JNK signaling promoting mammary stem cell features, because TNC and SPP1 are both recognized components of normal stem cells niches, indicating that under stress, JNK signaling promotes both stem cell properties and a supportive niche for breast cancer cells.

Acquired tumor resistance to treatment options such as chemotherapy is a major challenge in the battle against cancer. JNK signaling can be induced in response to chemotherapy. In a mouse model of breast cancer metastasis, chemotherapy induces JNK activity in metastatic nodules in lungs. Macrometastases, in which only a minor cell population exhibits JNK activity, respond to chemotherapy in a striking manner by inducing JNK signaling in most cancer cells within the nodule.[5] Considering the role of JNK signaling in maintaining stem cell properties and metastasis-initiating ability of breast cancer cells, the response to chemotherapy suggests a substantial plasticity of cancer cells that can be regulated by stress. Interestingly, studies on normal stem cells within the skin epidermis suggest that stem cell plasticity can expand in response to stress during wound healing of the skin.[10] However, it is unknown whether this response of normal stem cells is mediated by the JNK pathway. Notably, because breast cancer cells induce JNK signaling in response to a number of chemotherapeutics, in parallel to cytotoxic actions, the establishment of a metastatic niche in the lungs is facilitated, thus impairing therapeutic efficacy.[5] The findings show that cancer cells can benefit from chemotherapy-induced stress signals to counteract cytotoxic effects of the therapy.

Our findings emphasize the importance of JNK signaling in the generation of metastatic niches by promoting ECM reorganization and a crosstalk with reactive fibroblasts; summarized in (Figure 1). Importantly, the cellular outcome of JNK signaling is highly context dependent and thus different malignant entities may respond distinctly to the pathway activation. Considering the various circumstances that lead to stress in cancer cells during metastatic progression, our evidence suggests that specific cancer cells may not only be able to survive under these conditions, but can even take advantage of the resulting signals.

Disclosure of potential conflicts of interest

The author declares that he has no conflict of interest.

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