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Short Communication

Metabolic Reprogramming and Morphological Signatures in Breast Cancer Stem Cells

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DESCRIPTION

Breast cancer stem cells represent a subpopulation of tumor cells with enhanced self-renewal capacity, tumor-initiating potential, and resistance to conventional therapies. These cells contribute significantly to disease progression, metastasis, and recurrence, making them a critical focus for research. The biology of breast cancer stem cells is tightly linked to both metabolic adaptations and distinctive morphological features, which together govern their survival, proliferation, and interaction with the tumor microenvironment. Understanding how metabolic reprogramming influences cellular morphology and histological characteristics provides insight into the mechanisms driving tumor aggressiveness and therapeutic resistance.

Metabolic reprogramming is a hallmark of cancer and is particularly pronounced in breast cancer stem cells. These cells exhibit remarkable metabolic plasticity, allowing them to adapt to fluctuating nutrient availability and hypoxic conditions within the tumor microenvironment. Unlike differentiated tumor cells, which often rely predominantly on glycolysis or oxidative phosphorylation, breast cancer stem cells can switch between metabolic pathways depending on environmental cues and energy requirements. Enhanced glycolytic flux provides rapid Adenosine Triphosphate (ATP) generation and supports biosynthetic processes required for proliferation. At the same time, reliance on oxidative phosphorylation supports survival in nutrient-depleted or hypoxic niches and maintains redox balance, facilitating resistance to oxidative stress. This dual metabolic flexibility underpins the ability of breast cancer stem cells to sustain stemness, evade apoptosis, and initiate secondary tumors at distant sites.

The metabolic phenotype of breast cancer stem cells is closely associated with their morphological signatures. Cells with heightened glycolytic activity often exhibit a rounded, amoeboid morphology with reduced cytoplasmic-to-nuclear ratio and compact cytoskeletal organization. This shape facilitates migration through dense extracellular matrices and contributes to metastatic potential. Conversely, cells favoring oxidative phosphorylation tend to display elongated, spindle-like morphology with pronounced actin stress fibers, extensive filopodia, and focal adhesion structures. These features correlate with increased invasiveness and enhanced interaction with stromal elements. Morphological plasticity, driven by metabolic state, allows breast cancer stem cells to transition between quiescent and proliferative states, migrate, and establish secondary lesions, highlighting the functional significance of the metabolic-morphology link.

The tumor microenvironment plays a pivotal role in modulating both metabolism and morphology of breast cancer stem cells. Hypoxia, nutrient gradients, and mechanical stiffness of the extracellular matrix influence metabolic pathway selection, cytoskeletal arrangement, and cell shape. Hypoxic conditions favor glycolytic metabolism and promote the formation of rounded, compact cells capable of collective migration and resistance to apoptosis. Well-vascularized, oxygen-rich niches support oxidative phosphorylation, leading to elongated, invasive morphologies and enhanced interaction with stromal fibroblasts, endothelial cells, and immune elements. Stromal signals, including growth factors, extracellular matrix proteins, and cytokines, further reinforce the link between metabolism and morphological adaptation, facilitating tumor progression and metastatic dissemination.

Metabolic intermediates themselves regulate cytoskeletal dynamics and epigenetic modifications, further linking metabolism to cellular morphology. Accumulation of glycolytic metabolites such as lactate can acidify the microenvironment, modifying extracellular matrix stiffness and promoting rounded, invasive morphologies. Conversely, tricarboxylic acid cycle intermediates influence acetylation, methylation, and other epigenetic marks, modulating gene expression programs that control cytoskeletal organization, adhesion molecule expression, and cell polarity. These epigenetic-metabolic interactions manifest histologically as variation in cell shape, nuclear morphology, and tissue architecture, reinforcing the connection between metabolism and observable tumor features.

Therapeutic targeting of metabolic pathways in breast cancer stem cells is a promising strategy due to their reliance on metabolic flexibility for survival and adaptation. Inhibitors of

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glycolysis, oxidative phosphorylation, or key regulators of metabolic plasticity can selectively impair stem cell function, reduce tumorigenicity, and sensitize cells to chemotherapy or radiation. Histopathological assessment before and after treatment can reveal metabolic and morphological changes, including reduced cellular density, loss of spindle morphology, decreased cytoplasmic projections, and increased apoptotic features. Monitoring these changes provides insight into treatment efficacy and underscores the importance of linking metabolic profiling with morphological evaluation in clinical practice.

Integration of advanced imaging, histopathology, and metabolic analysis enhances understanding of breast cancer stem cell biology. Techniques such as metabolic flux analysis, live-cell imaging, fluorescence lifetime microscopy, and three-dimensional culture models allow direct assessment of metabolic states, cellular mechanics, and morphological dynamics. Combining these data with immunohistochemical markers and tissue architecture evaluation facilitates a comprehensive understanding of how metabolic reprogramming drives tumor morphology and contributes to progression, metastasis, and therapy resistance. This multidimensional approach supports precision oncology, enabling identification of high-risk subpopulations and optimization of therapeutic strategies.

CONCLUSION

Metabolic reprogramming and morphological signatures in breast cancer stem cells are intimately linked and collectively influence tumor behavior, progression, and therapeutic response. Glycolytic and oxidative phosphorylation-dominant states dictate cell shape, cytoskeletal organization, nuclear architecture, and interaction with the microenvironment. Morphological heterogeneity observed in histopathological sections reflects underlying metabolic diversity, providing functional and diagnostic insights.

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