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REVIEW

The tumor microenvironment as driver of stemness and therapeutic resistance in breast cancer: New challenges and therapeutic opportunities

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Abstract

Background Breast cancer (BC), the second most common cause of cancer-related deaths, remains a significant threat to the health and wellness of women worldwide. The tumor microenvironment (TME), comprising cellular components, such as cancer-associated fibroblasts (CAFs), immune cells, endothelial cells and adipocytes, and noncellular components such as extracellular matrix (ECM), has been recognized as a critical contributor to the development and progression of BC. The interplay between TME components and cancer cells promotes phenotypic heterogeneity, cell plasticity and cancer cell stemness that impart tumor dormancy, enhanced invasion and metastasis, and the development of therapeutic resistance. While most previous studies have focused on targeting cancer cells with a dismal prognosis, novel therapies targeting stromal components are currently being evaluated in preclinical and clinical studies, and are already showing improved efficacies. As such, they may offer better means to eliminate the disease effectively.

Conclusions In this review, we focus on the evolving concept of the TME as a key player regulating tumor growth, metastasis, stemness, and the development of therapeutic resistance. Despite significant advances over the last decade, several clinical trials focusing on the TME have failed to demonstrate promising effectiveness in cancer patients. To expedite clinical efficacy of TME-directed therapies, a deeper understanding of the TME is of utmost importance. Secondly, the efficacy of TME-directed therapies when used alone or in combination with chemo- or radiotherapy, and the tumor stage needs to be studied. Likewise, identifying molecular signatures and biomarkers indicating the type of TME will help in determining precise TME-directed therapies.

Keywords Breast cancer · Tumor microenvironment · Targeted therapeutics · Cancer-associated fibroblasts · Tumor-associated macrophages · Immunotherapy · Cancer stemness

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