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Investigating The Role Of Mesenchymal Cell-Mediated Paracrine Signaling In Breast Cancer Cell Proliferation And Invasion In A Heterotypic 3D Co-culture Model

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Abstract:

Breast cancer (BC) is a complex heterogenous and fatal disease. Increased expression of proliferation marker, Ki-67 and mesenchymal-like phenotype resulting from the epithelial-mesenchymal transformation (EMT) highlight transformation of *in situ* ductal carcinoma (DCIS) into invasive breast cancer (IBC) associates with poor prognosis in patients. Previous indirect 2D co-culture studies have demonstrated that mesenchymal stem cells (MSCs) promote BC progression through secretion of paracrine factors including growth factors, cytokines and chemokines. In order to investigate this aspect of the tumour microenvironment in a more relevant 3D co-culture model, spheroids incorporating breast cancer cells (BCCs), both cell lines and primary BCCs expanded as patient-derived xenografts, and MSCs were established. MSCs in co-cultures were shown to enhance proliferation in BCCs and altered the native cytoskeletal arrangement of actin filament in estrogen receptor (ER)/progesterone (PR) receptor-positive BCCs. In addition, co-culture resulted in downregulation of E-cadherin in parallel with upregulation of the EMT-relation transcription factor, SNAIL. Cytoplasmic relocalization of SnON, a negative regulator of TGF-β signalling, and of β-catenin, involved in Wnt signalling, was also observed in BCCs in co-cultures in contrast to monocultures. In addition, the β-catenin inhibitor, 3-[[(4-methylphenyl)sulfonyl]amino]-benzoic acid methyl ester (MSAB), mediated reduced growth and invasion in the co-cultures. This study highlights the potential role for SnON as a bio-marker for BC invasiveness, and the importance of interactions between TGF-β and Wnt signalling, involving SnON. Such pathways may contribute towards identifying possible targets for therapeutic intervention in BC patients.

During cancer development, there is active recruitment of mesenchymal stem cells (MSCs) from bone marrow to the TME where MSCs are educated by cancer cells to form cancer-associated fibroblast (CAF)-like cells. The presence of several growth factors and chemokines including hepatocyte growth factor (HGF), monocyte chemotactic protein-1 (MCP-1), interleukin-6 (IL-6), transforming growth factor-beta (TGF-) and CCL-5 in MSC-conditioned medium in 2D suggests that, once within the TME, MSCs secrete growth factors that promote tumour growth, epithelial-mesenchymal transition(EMT) and invasion through direct paracrine actions and remodelling of extracellular matrix; thus activated signalling axes identified in this way may provide therapeutic targets.

However, studying the impact of MSC-driven paracrine signalling on BC progression in 2D may not be an ideal approach. In 3D, extracellular matrix (ECM) supports cells through focal adhesion and participates in cell signalling by promoting interaction between growth factors and cell surface receptors. In addition, in 2D cell culture systems, lower numbers of gap junctions prevent exchange of ions and secondary metabolites and block removal of waste materials. Alternatively, in vivo xenograft models have been used but cross-species interaction between human tumour and murine stromal cells may mask the real signalling axes activated in cancer cells by human MSCs. In contrast, 3D spheroids potentially provide a useful system for modelling heterotypic interactions, overcoming some of these problems, and are increasingly being used for drug screening and drug penetration studies. In spheroids, cells grow in aggregates that result in cell–cell interactions and, under some conditions, the nutrition and oxygen gradients observed in real tissue. In addition, potential for incorporation of ECM facilitates cell–matrix interaction.

A high stroma–tumour ratio has been shown to be a poor prognostic indicator for breast cancer patient overall survival and distant metastasis-free survival. Uncontrolled cell proliferation is an indication of the onset of neoplasia and a risk factor in patients, while epithelial-mesenchymal transformation (EMT) facilitates invasion. Therefore, understanding the molecular mechanisms underlying breast cancer progression and the role of the stroma in driving it is important.

Biography:

Amarnath Pal has completed his PhD from the University of Nottingham, United Kingdom and his academic work includes preclinical models of cancer therapy, breast cancer, stem cell biology and the tumour microenvironment. In 2015, he received the prestigious International Vice Chancellor Scholarship and honored with 'Best PhD research student talk' award at Nottingham breast cancer research center (NBCRC) in 2019. He served as a student ambassador at EACR for 3 years and recently published his PhD research work in a journal 'Cancers'. He is immensely interested to collaborate with a team pursuing research in cancer stemness and drug resistance.

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