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Perspective

Investigation of Novel Secretory Proteins Regulating miRNA Mechanisms

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ABOUT THE STUDY

Breast cancer was diagnosed more frequently than lung cancer in 2021, making for 11.7% of all cancer cases. Additionally, there was a 9.3% increase from 2018 to 2020 in the number of breast cancer-related fatalities worldwide. As breast cancer patient survival is 99% when diagnosed in the localised stage, adding accessible, non-invasive, cost-effective technologies to routinely screen for breast cancer alongside current procedures is one strategy to deal with the rise in breast cancer incidence and deaths.

The complexity of breast cancer has resulted in the development of customised treatment plans that depend on the tumour grade, stage, and presence or absence of hormone receptors (HR); estrogen receptor (ER) and progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). 73% of breast tumours that have been diagnosed are of the luminal A subtype (HR+/HER2-), followed by 12% triple-negative (HR-/HER2-), 11% luminal B (HR+/HER2+), and 4% HER2-enriched (HR-/HER2+) tumours. Precision medication and individualised therapy can increase patient survival. However, in most nations, standard mammography screening for breast cancer detection begins around age 50. Finding early detection biomarkers is a major focus of breast cancer research due to rising rates of breast cancer in younger populations.

Growth factors, ligands, and other chemicals are secreted by cells in order to interact and communicate with nearby cells. These secretions undergo oncogenic transformation, which alters their chemical composition and creates a unique tumour microenvironment (TME) that could affect the outcome of metastasis. The collection of proteins that cells secrete into extracellular space is known as the secretome. It contributes significantly to the human proteome (13%–20%) and is crucial for cell motility, cell signalling, and cell-cell communication. Additionally, secretory proteins control a variety of cancer characteristics, and as more secreted proteins are present in physiological fluids close to tumours, they can be found in blood. The secretome therefore contains a variety of regulatory mechanisms that affect cancer and carcinogenesis.

Short non-coding RNAs called miRNAs control the expression of genes after transcription. Nearly every element of cancer genesis and progression in breast cancer is correlated with miRNA dysregulation. Inflammatory enzyme Cyclooxygenase-2 (COX-2) is overexpressed in poorly metastatic luminal two oncogenic miRNAs, miR526b and miR655, are upregulated in the MCF7 breast cancer cell line. miR526b and miR655 overexpression in weakly metastatic luminal Breast cancer characteristics such Epithelial to Mesenchymal Transition (EMT), cell migration, invasion, activation of Cancer Stem Cells (CSCs), tumor-associated angiogenesis, lymphangiogenesis, oxidative stress, and hypoxia responses were encouraged by the breast tumour cells MCF7 and SKBR3. In addition, miRNA-overexpressed cell secretions and metabolites increased the angiogenic potential of primary endothelium HUVECs and caused oxidative stress, tumor-associated angiogenesis, and lymphangiogenesis in poorly metastatic MCF7 cells.

Oncogenic miRNAs including miR526b and miR655 encourage aggressive breast cancer characteristics and change cells in the TME. We have discovered that the phenotypes of cells present in TME are altered by cell-free miRNA and miRNAhigh tumour cell secretory proteins. It may be possible to understand the methods by which miRNA regulate TME and find potential biomarkers by analysing the cell secretomes of miR526b and miR655 in ER-positive breast cancer cell lines. Large-scale secretome analyses can be challenging since many extracellular proteins are signalling molecules that are detected at low levels and may not be chosen because of a higher threshold. However, our approach, which combines large sensitivity mass spectrometry with nano-high performance liquid chromatography, ensured thorough, sensitive secretome analysis.

Reactive oxygen species (ROS) overproduction by miR526b and miR655 has been demonstrated to cause oxidative stress, and ROS levels were further increased by hypoxia in cells that overexpressed these miRNAs. Additionally controlled by secretory marker production by tumour cells, these miRNA-induced actions. Apoptosis is frequently triggered by DNA damage caused by ROS generation, and hypoxia affects the apoptotic pathways in tumours that are growing aggressively.

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Here, we found that the regulation of apoptosis and cell redox homeostasis were the two biological processes that were most enrichedly regulated by the eight secretome indicators. Instead of inducing apoptosis in breast cancer cells with high levels of miRNA, hypoxia encourages oxidative stress, cell migration, and tube formation. Secretome indicators control the levels of ROS, apoptosis, and the hypoxic response, supporting the regulation of these processes by miR526b and miR655 in breast cancer.