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Detection of Proteins and their Therapeutic Effects in patients with Triple-Negative Breast Cancer

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Introduction

Tumor-secreted substances such as cytokines, growth factors, proteases, inhibitors of proteases, membrane and extracellular vesicle proteins, peptide hormones, and metabolic proteins are all examples of extracellular matrix (ECM) proteins; these are actively included in cancer secretion. To prevent chemotherapy-dependent cytotoxicity, tumor-promoting factors known as TCS are released by cancer cells. Lung cancer is the most prevalent cause of cancer mortality, while breast cancer is the most common cancer among women. A novel way of classifying breast cancer emerged because of the development of gene expression profiling. Breast cancer has been classified into five categories using a DNA microarray molecular taxonomy: luminal types A and B, HER2/neu type, normal breast, and basal type (Figure 1) [1, 2]. Whereas basal-type breast cancers (BLBC) are triple-negative" breast cancers because they are negative for the three indicators estrogen receptor, progesterone receptor, and HER2/neu gene amplification. Luminal-type tumors are continuously estrogen receptor-positive and have a good prognosis (TNBCs). This feature has resulted in a widespread synonymy mistake where TNBCs and BLBCs are interchangeable.

Much of the biological variation in human cells and malignancies is caused by variations in transcriptional processes. Each cell has signaling

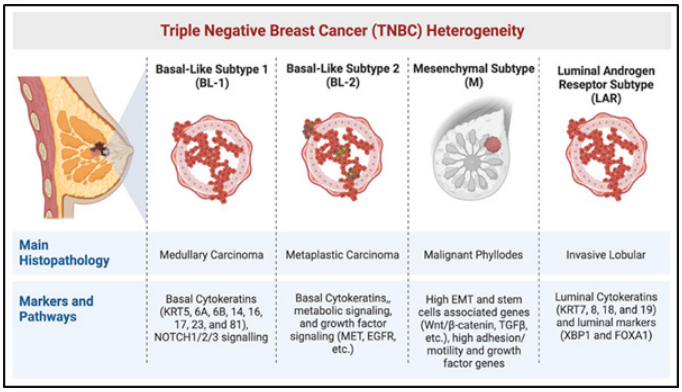

Figure 1: TNBC heterogeneity, showing TNBC subtype's main histopathology, markers, and signalling pathways [2].

regulatory mechanisms that transmit information about the identity of the cell to the surrounding environment, which controls how much each gene in the genome is expressed. In the United States and around the world, breast cancer is the most common kind of cancer among women. Molecular subtypes of breast cancer can be distinguished based on differences in gene expression, prognosis, and available treatments. Because of its propensity to develop resistance to conventional chemotherapy after an initial positive response, triple-negative breast cancer (TNBC) poses a clinical challenge. This subtype of breast cancer lacks the expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2), making it ineligible for ER and HER2 targeted therapy; instead, patients must rely on conventional chemotherapy [3, 4]. High test scores, a poor prognosis, and an early age are linked to BLBC. Such instances are frequently recognized clinically using the triple-negative phenotypic description (ER, PR, and HER-2, all negative).

For typical pathology specimens, BLBC-positive markers that are easily accessible include EGFR and cytokeratin 5/6. Although patients initially react well to chemotherapy, resistance to chemotherapy drugs develops in 50% to 80% of TNBC patients, which is a substantial contributor to breast cancer mortality. Determining and characterizing additional molecular processes and downstream pathways significant for TNBC onset, chemotherapy resistance, and recurrence is thus an urgent unmet need. The interaction of released substances with the tumor cells or surrounding tumor microenvironment is one mechanism that may affect the emergence of chemoresistance in TNBC (TME). There are groups of co-expressed genes that have been found, and their mRNA level variation has been linked to physiological variational traits. Based on significant variations in their gene expression patterns, tumors can be divided into subtypes. For cancer patients, chemotherapy is a prominent kind of treatment. The tumor returns after chemotherapeutic treatment and does not respond to fresh chemotherapy treatments (chemoresistance). Chemotherapy exposure can also change the kinds and amounts of TCS constituents. Therapy-induced TCS is the name of this syndrome.

Other Enzymes and The TNBC Components

Cancer cells release substances that affect nearby cells' behavior

and can promote enhanced proliferation and metastasis. Cells MCF-7 receptor-positive for estrogen and progesterone, TNBC cells MDA-MB-231, DT22, and DT28, and untransformed MCF-10A mammary epithelial cells were cultivated in 3D cultures to better understand the significance of these variables in oncogenesis and disease development. In a conditioned medium, spectral samples were employed as substitutes for the levels of protein expression (CM). The immunomodulatory proteins SAA1 and thrombospondin (THBS1), as well as the growth factor TGF-1, were shown to be more robustly expressed in TNBC CM compared to MCF-7 CM using this metric [5]. Vascular modulation stands out among the cytokines and growth factors released by TNBC. For instance, brain-derived neurotrophic factor is a growth factor that encourages the migration of tumor and endothelial cells [6, 7]. In contrast, one of the primary secreted substances that prevent TNBC cells from proliferating *in vitro* is SLIT3, which is produced by CD36 stromal fibroblasts [8]. Vasoconstriction is regulated by END1, which is produced by TNBC. TNBC is an inflammatory type that has a short patient survival time and increases cancer angiogenesis. We investigated the function of the cell surface protein Syndecan-1 in tumor angiogenesis using a 3D cell culture system. With the reduction of angiogenesis factors in the tissue factor pathway, angiogenesis is decreased by downregulating syndecan-1. TNBC is characterized by increased angiogenesis, metastasis, and a dismal prognosis. A poor prognosis is linked to dysregulation of the signaling coreceptor Syndecan-1 and the cell surface heparan sulfate proteoglycan. In SUM-19, MDA-MB-68, and MDA-MB-231 cells, the elimination of syndecan-1 siRNA decreased the development of HUVEC tubular networks. The angiogenesis group had lower VEGF-A and tissue factor production that was inhibited by syndecan-1. In SUM-19, MDA-MB-231, and MDA-MB-68 cells, qPCR independently verified the expression of F3, F7, F2R/PAR1, F2RL1/PAR2, VEGF-A, EDN1, IGFBP1, and IGFBP2. In at least three investigations, the secretion of TNBC has been shown to contain vascular endothelial growth factor (VEGF). A variety of sources, such as syndecan-1-depleted TNBC cells [9], interstitial fluid from mouse TNBC xenograft tumors [10], and mesenchymal stem cells generated from adipose tissue treated with CM from TNBC cells, have been found to contain VEGF.

Studies have demonstrated that TNBC cells produce TGF. Whereas it decreases VEGF-A signaling [11] and cooperates with VEGF to influence angiogenesis in a TGF receptor subclass-dependent way [12], the function of TGF in angiogenesis is yet unknown. Another TGF-superfamily member, NODAL, was discovered in TNBC's secretome [13]. VEGF's angiogenic activity is stimulated by the fetal developmental protein NODAL, which is reactivated in numerous cancer types [14]. Further altering the tumor microenvironment, NODAL also stimulates fibroblasts linked to cancer cells [15]. HMGA1 secretion contains an intriguing protein. A chromatin structural protein called HMGA1 generally controls the transcription of genes. Its recent discovery that it can bind to the RAGE receptor, however, raises the possibility of a novel function as an immune modulator closely linked to the related protein HMGB1 [16, 17]. Compared to cells that had syndecan-1 knocked down, The same study demonstrated that syndecan-1 facilitates TNBC cell metastasis in the brain by cardiac injection in mice and that TNBC cells have the capacity to pass the blood-brain barrier.

Epithelial cells always express the transmembrane heparan sulfate proteoglycan known as syndecan-1 (Sdc-1/CD138), It functions as a coreceptor for several chemokines, cytokines, and growth factors [18]. Angiogenesis, cell adhesion, proliferation, migration, invasion, and metastasis are just a few of the crucial cancer-related activities that Sdc-1 helps to develop; In ductal breast cancer *in situ*, co-expression of Sdc-1, E-cadherin, and c-Met is a hallmark connected to (lymphatic) angiogenesis-related components [19]. Nevertheless, it is yet unclear how tumor-endothelial contact affects the role of tumor cell-independent Sdc-1 expression in the control of angiogenesis. Moreover, the function of Sdc-1 in breast cancer angiogenesis has not been examined using objective screening techniques. Consequently, the objective of this work is to clarify the underlying molecular processes and examine the impact of Sdc-1 expression suppression on angiogenesis in TNBC cells using a 3D co-culture paradigm. The CTSD proenzymes that haven't been digested can, however, be "guided" to endosomes before being released. CTSD experiences autoactivation in the acidic tumor microenvironment. Breast cancer metastasis is linked to high extracellular CTSD expression [20]. Moreover, the pro-form of CTSD interacts with numerous proteins and performs other functions in cell signaling [21]. While cathepsin Z (CTSZ), a cysteine protease that has not been well explored in breast cancer, is overexpressed in hepatocellular carcinoma, where it promotes EMT, and the production of proteins involved in matrix remodeling. The advanced clinical stage also coincides with CTSZ expression in CTSZ [22]. Proteases that are closely associated with Alzheimer's disease include amyloid-precursor protein (APP) and amyloid-precursor-like protein 2 (APLP2). The secretase [23] cleaves the secreted form of APP, also known as protease nexin-2, which is a component of the TNBC secretion known as serine peptidase inhibitor E1 (SERPINE1), also known as plasminogen activator inhibitor 1 (PAI1). SERPINE1/PAI1 small molecule inhibitors in xenograft tumors, two of these inhibitors cause apoptosis and disturb the tumor vasculature [24]. In a rat model of Alzheimer's disease, one of these small compounds significantly decreased amyloid-plaque in the cortex and hippocampus, which enhanced learning and memory [25]. Four tissue inhibitors belonging to the metalloproteinase (TIMP) family (TIMP1) have comparable but overlapping binding partners. MMPs are often inhibited by them through reversible competitive inhibition. TIMPs have also been discovered to be involved in adipogenesis, the growth of different epithelial and connective tissues, and lung branch morphogenesis. Moreover, TIMP3 was discovered in TNBC's secretion. TIMP3 has a tumor-suppressive function in numerous cancer processes and is downregulated in many malignancies. They are also very much controlled by microRNAs.

Characteristics of the Molecule

Gene expression profiling studies have discovered the unique molecular subtype of breast cancer known as BLBC. Because of its distinct clinicopathological features and aggressive behavior, BLBC has drawn a great deal of interest from researchers. This is based on the expression of markers that are specific to the female ductal epithelium's basal layer.

Apoptosis and TP53

Cell cycle regulation depends on the tumor suppressor gene TP53, which is situated on the short arm of chromosome 17 [26]. By causing cell cycle arrest, enabling time for DNA repair, or activating the Bax gene, p53 works as a checkpoint to ensure that cells repair damaged DNA before cell division begins. Hence, faulty p53 expression can result in aberrant cell proliferation and reduced cell death, which can result in cancer. Through a mechanism regulated by MDM2 and jun kinase, the proteasome quickly degrades p53 in healthy cellular settings [27]. The overexpressed protein's half-life is markedly extended following cellular stress, such as exposure to DNA-damaging chemicals, and p53 accumulates in the nucleus of afflicted cells. The most typical

genetic alterations that have been found are TP53 mutations, which are present in around 50% of all human malignancies [28]. 0–20% of breast tumors had TP53 mutations [29]. The mutation, which is linked to a poor prognosis and treatment resistance, is assumed to be an early occurrence in carcinogenesis.

BLBC and BRCA1

Breast cancer in its early stages is linked to mutations in these genes. Breast cancer development before the age of 70 is 10–20 times more likely in people who carry BRCA gene mutations. While research has linked TNBC to BRCA1-related malignancies, no gene-phenotype correlation has been found for tumors linked to the BRCA2 gene. Moreover, according to gene expression profiling research, over 70% of malignancies linked to BRCA1 fall into the basal-like group. A lot of random BLBCs have also been shown to have altered BRCA1 activity and function loss. A subpopulation of BLBCs with lower BRCA1 messenger RNA levels and promoter methylation in the range of 10–20% of BLBCs. Moreover, it has been discovered that BLBC overexpresses ID, a bad transcriptional regulator of the BRCA1 promoter.

Angiogenesis

A key phase for the growth and progression of cancer is the creation of fresh blood vessels from the blood vessels that already exist [30]. As a result, preventing angiogenesis is crucial in the fight against cancer. Many signals generated by cells in the tumor microenvironment and several signaling pathways, including vascular tissue factor, basic fibroblast growth factor, and endothelial growth factor, closely regulate the complicated process of angiogenesis [31]. The interaction between angiogenic factors and proteoglycan co-receptors on the cell surface is the key determinant of their activity. CD109, a GPI-anchored co-receptor and negative regulator of TGF, is another surface antigen. Furthermore, the soluble form of CD109 binds to TGF and prevents TGF signaling. In TNBC compared to non-TNBC, CD109 protein expression is much greater, and CD109 expression is connected to greater clinicopathological features and a worse surgical outcome [32].

Immunohistochemistry

Each of the 17 formalin-fixed, paraffin-embedded tissue slides was subjected to conventional streptavidin-biotin complex immunohistochemistry for the detection of ER, PR, HER2, EGFR, and CK5/6. A dilution of the ER antibody (Clone SP1, Lab Vision) was used. 1:250 for 8 min of microwave antigen retrieval in a citrate buffer filter at a pH of 6.0, in accordance with the conventional CC1 technique. The EGFR PharmDx kit (DAKO) was used for EGFR staining, and proteinase K was used for enzymatic antigen retrieval for 5 min. Breast cancer subtypes are identified by immunohistochemical surrogates (ER, PR, HER2, EGFR, and CK5/6) using a five-biomarker strategy. In the two systems, BLBC was characterized differently. All commonly examined biomarkers, including ER, PR, and HER2, are base-like negative using the TNP technique (ER-PR-HER2). The five-biomarker method separates TNP into 2 groups: triple-negative patients (ER-PR-HER2), which also express either EGFR or CK5/6 positively, and (5NP), which is triple-negative and does not express EGFR or CK5/6. Breast cancer patients' prognosis and treatment planning are frequently based on the use of HER2/neu, progesterone receptor, and oestrogen receptor biomarkers in clinical practice.

Conclusion

In addition to proteins involved in cellular metabolism that are typically connected to one another include cytokines, growth factors, ECM proteins, secreted proteases (and their regulators), membrane proteins (either shed from the cell surface or integrated into extracellular vesicles), peptide hormones, and these molecules cover a wide range of protein functions. Although its function in angiogenesis is less apparent, the TGF superfamily appears to be significant, and the essential angiogenic protein VEGF appears to be particularly significant in TNBC. Small-molecule medications and anti-VEGF antibodies are currently on the market and must unquestionably be included in the TNBC therapy plan [33]. Immune modulation is another recurring subject. TNBC secretion contains several cytokines that regulate the immune response, such as chemokines and pro-inflammatory proteins. These chemicals can alter endothelial cell function, allowing cancer cells to spread both inside and outside. The ECM proteins secreted by TNBC are quite varied. Several ECM proteins have been revealed to perform unanticipated functions in cellular responses and immunological control in addition to their structural and sticky features. The enzymes released by TNBC are numerous. The proteases oversee modifying the ECM and turning on certain ECM elements. Our review included a major section on the plasminogen-plasmin system. The activation or control of this signaling pathway is influenced by several known proteins released by TNBC, which in turn affect the inflammatory response and vascular dynamics. These are inhibitors of these enzymes in addition to the proteases that TNBC secretes. Among the secreted factors, TIMPs and other proteins that affect MMPs are widely distributed. These proteins are thought to control tumor invasion in some way [34].

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