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Role of ATP usage in Breast cancer and metastasis

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Abstract
Breast cancer is still a major global health concern, and one of the main causes of death for those who have it is metastasis. Although a great deal of study has illuminated many facets of the biology of breast cancer, little is known about the complex interactions between cellular energetics, namely the use of adenosine triphosphate (ATP), and tumour growth and metastasis. With the goal of providing insights into possible treatment paths, this research study aims to clarify the complex role that ATP utilisation plays in promoting breast cancer metastasis. In this paper we examined the basic principles that underlie the synthesis and use of ATP in both healthy and malignant cells. Sometimes called the *"energy currency"* of the cell. One of the main characteristics of cancer cells is their dysregulated ATP metabolism, which allows them to continue proliferative signalling, avoid growth suppressors, and withstand cell death. Determining therapeutically targetable vulnerabilities requires an understanding of the abnormal ATP utilisation pathways unique to breast cancer cells. We also investigated the complex relationship with a particular emphasis on metastasis between ATP utilisation and significant markers of cancer progression. Cancer cells migrate from the main tumour to remote locations through a complicated, multi-step process called *metastasis*, which is regulated by a number of cellular and molecular factors. Furthermore, the tumour microenvironment has a significant impact on the behaviour and propensity for metastasis of cancer cells due to its altered ATP levels and signaling. This article will additionally address new developments in ATP utilisation pathway targeting as a possible treatment approach to prevent breast cancer metastases. The preclinical models of breast cancer have shown the ability of inhibitors of important ATP production-related enzymes, such as glycolysis and oxidative phosphorylation, to reduce the spread of metastatic cancer while improving treatment results. To further improve therapeutic efficacy and disrupt the metastatic cascade, purinergic signalling pathways which regulate ATP release and extracellular signaling, can be potentially targeted. To sum up, the untangling of the complex function that ATP utilisation plays in the advancement and spread of breast cancer is highly promising in terms of creating novel therapeutic approaches. The objective of this research is to improve patient outcomes and help with the ongoing fight over metastatic breast cancer by clarifying the molecular mechanisms underlying ATP-dependent actions in cancer cells and their peritoneum.

Keywords: Breast cancer, ATP metabolism, Metastasis, Tumor microenvironment, Purinergic signalling

Introduction

Background on Breast cancer

Breast cancer, a global leading reason of mortality especially in women, resulted in approximately 570,000 fatalities in 2015. Annually, over 1.5 million women (about the population of WestVirginia), constituting 25% of all female cancer cases, are diagnosed with breast cancer worldwide. In the U.S. alone, breast cancer comprised around 30% of new cancer diagnosis among women in 2017. Unfortunately, its metastatic nature, spreading to organs like the liver, brain, lung, and bone, renders it largely incurable. However, early detection significantly improves prognosis, with a 5-year relative survival rate exceeding 80% for patients in North America [1, 2].

Screening methods such as mammography have effectively reduced mortality rates, with newer techniques like Magnetic Resonance Imaging (MRI) showing promise due to their higher sensitivity. Various factors like gender, age, hormonal influences, genetic predisposition, lifestyle choices etc. lead to risk of developing cancer. Despite its increasing prevalence, advancements in early detection programs and medical treatments have decreased mortality rates. Biological therapies offer hope for improved treatment outcomes [3]. Breast tumor development is influenced by microenvironmental factors like macrophages and stromal effects. Inflammatory conditions induced by these factors promote angiogenesis and immune evasion, contributing to tumor progression. Differential DNA methylation patterns in tumor-associated microenvironments suggest a role for epigenetic changes in cancer development [4].

Lately, the discovery of Cancer Stem Cells (CSCs) in tumors has shed light on tumor initiation, metastasis, and recurrence. CSCs, characterized by self-renewal and resistance to conventional treatments, may originate from normal stem or progenitor cells. Understanding the signaling pathways involved in CSC behavior, such as Wnt, Notch, Hedgehog, and others, is crucial for developing innovative therapeutic strategies [5]. Cancer's stem cell theory as well as stochastic theory propose different ideas about how breast cancer starts and spreads. According to the cancer stem cell theory, all types of breast tumors come from progenitor cells, which can change genetically or epigenetically to create different tumor types. In contrast, the stochastic theory suggests that any breast cell can become cancerous through random mutations, eventually forming a tumor. While both theories have evidence supporting them, neither fully explains how breast cancer initially forms [6].

Types of breast cancer (Based on location):

Non-invasive breast tumor cells: remain well within the ducts and they don't extend into the nearby connective and fatty tissues of the breast. The most common type,

accounting for 90% of cases, is ductal carcinoma in situ (DCIS). A Less common one is lobular carcinoma in situ (LCIS), which is related to an elevated risk of developing an invasive breast tumor.

Invasive Breast cancer cells: on the other hand, breach the walls of ducts and it spreads into nearby connective and fatty tissues of breast. This metastatic behavior allows cancer cells to potentially spread to other organs or lymph nodes, although invasiveness is not a prerequisite for metastasis [7].

More prevalent Breast cancer:

Lobular carcinoma in situ (LCIS, lobular neoplasia): Cancer which remains confined to its site of origin without spreading is termed "in-situ." This LCIS involves a significant increment in cell number within the lobules of the breast; these are the glands involved in milk production**.**

Ductal carcinoma in situ (DCIS): DCIS is one of the most prevalant non-metastatic form of breast carcinoma which is limited to the ducts in the breast. Take example of ductal comedocarcinoma.

Lobular carcinoma infiltrating (ILC): Invasive lobular carcinoma (ILC), originates in the glands which produce milk, or lobules, in breast. It sometimes metastasizes to other areas in the body. It accounts for approximately 10% to 15% of all breast cancers [8].

Invasive ductal carcinoma (IDC): Infiltrating ductal carcinoma (IDC), referred to as invasive ductal carcinoma, originates in ducts of breast which produce milk. It infiltrates ductal walls and spreads into nearby fatty tissue of breast, and it has a potential to metastasize to different parts of the body. IDC accounts for approximately 80% of all diagnosed cases in breast cancer, resulting in it being the most prevelant [9,10].

Correlation of ATP production with Breast cancer

It has been reported that breast tumours overexpress ATP synthase. Larger, poorly differentiated, and advanced stages of tumours are associated with the α subunits, one of the the polar F1-part of mitochondrial H+-ATP synthase consists of five subunits. Nonetheless, a data indicates that there is no noteworthy distinction in the β-F1-ATP synthase expression levels between normal and BC breast tissues. However, there is evidence that decreased the catalytic β expression of component (synthase β-F1-ATP) is associated with the advancement of cancer and the resistance of cancerous cells to conventional anticancer treatments. In cancer cells, there exists an inverse correlation between the amounts of β-F1-ATP synthase and aerobic glycolysis. The majority of ATP synthase inhibitors frequently exhibit intolerable in *vivo* toxicity. Some of them, meanwhile, may still be employed as anticancer medications. For instance, at high concentrations, oligomycin A affects the F1-portion of ATP synthase and reduces its ability to transfer protons. Oligomycin significantly reduces the lung metastatic seeding of BC, indicating the functional significance of OXPHOS in its invasiveness and emphasising its ability as a therapeutic target for stopping BC patients' metastatic dissemination [11, 12]. Aurovertin B reduces the functioning of ATP synthase and inhibits proliferation of breast cancer (BC). This effect is observed with minimal impact on wild type epithelial cells (MCF-10A). Similarly, citreoviridin, belonging to the same group as aurovertin, fights lung cancer cells and inhibits both lung cancer and breast cancer cell growth and proliferation by acting on β subunit of the F1-ATP synthase [13].

Rhodamine123 stops the development of the breast cancer colonies by targeting FoF1-ATP synthase complex, resulting in depletion of ATP. Conversely, benzodiazepine (Bz-423) induces production of superoxide (O2-) from mitochondrial respiratory chain, directly inhibiting F1-ATP synthase and initiating apoptosis. Previous done studies showed that the transcription factor (RUNX2) leads to glycolytic switching in the BC cells by upregulating genetic elements involved in the glycolytic pathways. While RUNX2 reduces the pyruvate dehydrogenase (PDH) activity, knockdown of RUNX2 enhances the mitochondrial oxygen utilization rate by enhancing PDH functioning, a crucial part in pyruvate utilization within the TCA cycle. Based on these findings, inhibiting RUNX2 is hypothesized to disrupt the reliance of tumor cells on glycolysis, thereby impeding BC growth and progression. Utilizing Computer-Assisted Drug Design (CADD), small compounds were screened to target RUNX2 and prevent its binding to specific DNA regions. This approach led to the identification of CADD52 as an important inhibitor of the RUNX2-DNA binding [14, 15].

Emergence of ATP synthase as a promising target in the cancer therapy

Decades ago, Warburg observed, cancer metabolism undergoes significant alterations, leading to metabolic reprogramming, which is now recognized as a hallmark of cancer. Novel classes of drugs are being developed to target this reprogramming, with several undergoing clinical trials. Mitochondria play a crucial part in cancer metabolism. For example, cancer cells without mitochondria need to reconstruct oxidative phosphorylation from the host stroma to form tumors. Additionally, the mitochondrion is implicated in conferring resistance to therapy in tumor stem cells and contributing to the resilience of pancreas cancer to suppression of KRAS-lead signaling. Complex V, also known as mitochondrial ATP synthase, serves as the crucial final enzyme in oxidative phosphorylation (OXPHOS) within the mitochondrion, responsible for ATP generation. Ectopically expressed ATP synthase, abbreviated as EAS, was identified in 1994 on surface of the tumor and vascular endothelial cells. presence of EAS has been associated with drug resistance, metastasis, and tumor angiogenesis [16].

MAS (mitochondrial ATP synthase) in tumor

Aberrant expression of genes encoding for subunits and mutations in the genes of mitochondrial ATP synthase (MAS) subunits have been linked to cancer. Downregulation of miRNAs targeting ATP5A1 and ATP5B is believed to contribute to increased mRNA levels related to MAS F1 in glioblastoma cancer cells as well as cells of endothelium involved in microvascular invasion [17].

ADP5B

Downregulated miR-450a, which stops ATP5B expression, has been associated with increased metastasis in ovarian cancer, implying a potential role of ATP5B in promoting

ovarian cancer invasiveness. Conversely, overexpression of ATP5B is inversely correlated with overall survival and metastasis-free survival in prostate, breast, and thyroid cancers. Breast cancers with HER2 positivity that have developed resistance to HER2-targeted treatments have also been observed to exhibit increased ATP5B expression. These reports suggest that ATP synthase has a crucial role to play in sustaining the malignant tumor growth. Aberrant expression of genes encoding mitochondrial ATP synthase (MAS) subunits and abnormalities in these genes have been related to cancer [18].

ADP5B

Downregulation of miR-450a, which targets ATP5B expression, has been associated with increased metastasis in ovarian cancer, indicating a potential role of ATP5B in promoting ovarian cancer invasiveness. Conversely, overexpression of ATP5B is inversely correlated with overall survival and metastasis-free survival in prostate, breast, and thyroid cancers. Additionally, breast cancers with HER2 positivity that have developed resistance to HER2-targeted treatments exhibit increased ATP5B expression. These findings suggest that ATP5B may be playing an important role in promoting metastasis and reducing survival in various cancers [19].

ADP5A1

ATP5A1 overexpression has emerged as a potential biomarker for diagnosing, prognosing, and assessing treatment response in various cancers. In clear cell renal cell carcinoma, ATP5A1 overexpression is associated with disease progression, while in breast cancer, it is linked to tumor spread and metastasis. Moreover, elevated ATP5A1 levels are positively correlated with early tumor initiation in prostate cancer and chromosomal instability, TP53 mutation, and SNPs promoting tumor growth in colorectal cancer. In hepatocellular carcinoma, ATP5A1 contributes to the anti-cancer effect, as observed with dihydroartemisinin. Periplocin inhibits lung cancer formation by downregulating critical proteins like ATP5A1. Changes in ATP levels also signal carcinogenesis onset and provide insights into tumor location and microenvironment. Additionally, mitochondrial ATP synthase (MAS) can regulate the inflammatory astrocyte response, which isassociated with glioma initiation [20].

Cancer therapy based on ATP synthase targeting

A novel approach to cancer treatment involves investigating ATP synthase inhibitors, having the crucial role of ATP synthase in driving malignancy. Various categories of inhibitors, including polyketides, polyphenolic phytochemicals, polyenic α-pyrone derivatives and various proteins, have been developed and studied. Some of these compounds were initially utilized like antibiotics, n infectious diseases, as anti-obesity medications but have shown subsequent antiangiogenic and anticancer properties. Despite promising preclinical research, the development of ATP synthase inhibitors for clinical cancer treatment is still in its early stages, with none having entered the market yet [21].

Polyketide inhibitors

Polyketides are bioactive compounds naturally occurring in various microorganisms. Polyketide synthase synthesizes polymers of ketides, with macrolides being a type of polyketides known for their anti-tumor properties. Examples include oligomycin, apoptolidin, and cytovaricin. Oligomycin, formed from, Streptomyces, is a particular inhibitor of ATP synthase. It attaches to the Fo c portion and, in higher concentrations, to F1 portion, blocking ATP production. The oligomycin sensitivity-conferring protein (OSCP) subunit is necessary for ATP synthase to be sensitive to oligomycin, as it has been shown to effect cell survival in various carcinomas.

Apoptolidin

Apoptolidins are microbial secondary metabolites available in isoforms A–D, exhibiting a high degree of specificity in inducing apoptosis in certain cancer cell lines. They inhibit proliferation by targeting mitochondrial ATP synthase (MAS) among their biological targets. This study conducted by Ishmael and colleagues demonstrates that not all macrolides function in the same manner.

Cytovaricin B

Twenty years ago, this chemical was screened as a JAK-STAT signalling pathway inhibitor; currently, its broader effects on tumour cells are being investigated [22]

Oestrogen and polyphenolic phytochemicals

Natural plant substances with phenol groups and anticancer qualities are called polyphenolic phytochemicals. A lot of them block ATP synthase. How many phenol groups there are and position of the hydroxyl groups decrfeases the inhibition strength. Some polyphenols occur naturally in many different plants, primarily in berries, grapes, and white tea. These phytoestrogens have anti-inflammatory, antioxidant, and cardioprotective properties and anti-tumor characteristics. Piceatannol and resveratrol offer a multitude of preventive and therapeutic alternatives for various cancer types. They attach themselves to a non-polar pocket that lies in between hydrophobic interior of the b subunit and non-polar C terminal region of g subunit. Resveratrol encourages the demise of human phéochromocytoma cells in this manner [23].

EGCG

Green tea contains a lot of epigallocatechin gallate (EGCG), a catechin that prevents ATP hydrolysis. EGCG promotes apoptosis and growth suppression in the cancerous pleural mesothelioma cells, bladder urothelial cells, and hepatocellular carcinoma cells. Through a number of molecular signalling pathways, including MAS inhibition, EGCG helps prevent a variety of chronic diseases, including Curcumin neurodegenerative disorders [24]

Curcumin

Zingiberaceae Curcuma longa is an herbal remedy having anticancer properties. The roots and stalks of the plant are the source of this natural polyphenol, which is known as a MAS inhibitor. Numerous malignancies are inhibited by it, including as lung, prostate, breast, cervical, and liver cancers. It has an impact on many signaling pathways, with NF-kB (nucleus kB) signaling being significantly suppressed. It was recently revealed that MAS inhibition,

which is independent of NF-kB signaling, reduced ATP levels in *vivo* and in *vitro* concurrently with oxygen consumption [25].

The metabolic mechanism of Breast Cancer

Cancer ranks among the most common malignant tumors all over the world and is one of the causes of carcinoma-related mortality among women. Over 90% of carcinoma-related deaths are attributed to breast cancer rather than primary tumor. According to a SEER-based study, 30–60% of women with breast cancer are prone to developing metastases in different parts of body. Increasing evidence suggests that carcinoma is not just a genetic disorder but also a metabolic one, with oncogenic pathways supporting rapid tumor growth through energy management and anabolism. Consequently, metabolic reprogramming is recognized as a distinguishing feature of cancer. Importantly, metabolic reprogramming with the intricate regulatory pathways similarly influence development and metastasis of breast cancer. Breast cancer comprises 4 primary molecular subtypes: HER2-positive, luminal B, luminal A, and the triple negative breast cancer (TNBC), representing a highly heterogeneous disease. Each subtype exhibits distinct metabolic genotypes and phenotypes, affecting their proliferation and metastatic potential. For instance, TNBC cells typically display limited mitochondrial respiration and heightened glycolysis. In contrast, HER2-positive tumors demonstrate increased lipid and glutamine metabolism. However, metabolic alterations may vary across breast cancer subtypes depending on the interactions between cancer cells and the complex microenvironment [26]. This review presents an overview of current understanding of the interplay between metabolic reprogramming and metastatic pathways in breast tumor. By delving deeper into the metabolic mechanisms related to metastasis of breast cancer, there is potential to uncover new avenues for anticancer treatment development.

Glucose metabolism

Normal cells in a state of rapid proliferation activate multiple signaling pathways in response to external growth cues. This leads to the suppression of oxidative phosphorylation and the promotion of glycolysis and anabolic processes to support the cell development. Cancerous cells, even in the absence of external signals, exploit this system to fulfill their developmental requirements. Unlike normal cells, which consistently display a negative correlation between glycolysis and OXPHOS, cancer cells often exhibit varying degrees of coexistence between these two metabolic modes. Moreover, while glucose-derived pyruvate is primarily converted to adenosine triphosphate (ATP) via OXPHOS through the tricarboxylic acid (TCA) cycle in normal cells, glycolysis serves as the primary energy source for most cancer cells, even in oxygen-rich environments [27].

Tumor cells demonstrate a dual metabolic nature, capable of transitioning from the aerobic
glycolysis to the OXPHOS, an oxidative method, phenotype in response to lactic acidosis. Additionally, some cancers exhibit a 2 compartment tumor metabolism, also referred to
as metabolic coupling or the reverse of the Warburg effect, where nearby cancer cells are sustained by glycolytic metabolism in stroma associated with malignancy. This metabolic phenotype not only contributes to chemotherapy resistance but also explains why some cancer cells display paradoxical characteristics of increased mitochondrial respiration and decreased glycolytic rates. Furthermore, the hypoxic environment in breast cancers promotes the production of ROS. HIF-1, an inducer of hypoxia response, can enhance glucose metabolism to maintain redox equilibrium [28].

In addition to glycolysis and the kreb's cycle, the pentose phosphate pathway (PPP) provides an alternative route for oxidatively breaking down glucose. Various molecular subtypes of breast cancer exhibit differential expression patterns of PPP-related proteins. For example, higher expression levels of 6-phosphogluconolactonase (6PGL) and glucose-6-phosphate dehydrogenase(G6PD) indicate that the HER2 subtype of breast cancer is more active in PPP than other subtypes. Additionally, there is a suggestion of a positive relation between expression of G6PD, transketolase (TKT) and reduced relapse-free surviving ability in breast cancer [29].

Amino acid metabolism

In addition to providing energy, glutamine and its intermediates in metabolism, like antioxidants glutathione (GSH) and NADH, also help cells withstand oxidative stress, thereby promoting the growth and spread of cancer cells. Some tumor cells exhibit "glutamine addiction," depending on the exogenous glutamine for living. For instance, in response to lactic acid stimulation, c-MYC stimulates production of ASCT2 and GLS-1, promoting glutamine usage and metabolism in tumor cells. A metabolic study uncovered that the glutamate-to-glutamine ratio (GGR) was elevated in breast tumor tissues compared to normal tissues, particularly in tumors lacking estrogen receptor (ER) expression. Moreover, a significant correlation was observed between GGR levels and tumor grade as well as ER status. HER2-positive breast cancer exhibited higher expression levels of glutamine metabolism-associated peptides compared with other subtypes, including glutamate dehydrogenase (GDH), alanine-serine-cysteine transporter 2 (ASCT2), and glutaminase (GLS)-1. These findings suggest that HER2-positive breast malignancy displays heightened glutamine catabolism activity. With glutamine, heightened serine/glycine catabolism, closely intertwined with folate metabolism, is correlated with enhanced tumor cell proliferation and adverse patient outcomes. Dysregulated immune system and tolerance, these are common in malignancy and are influenced by tryptophan and arginine. Breast tumor environments upregulate arginase activity, the key enzyme responsible for catalyzing L-arginine, forming an immune-suppressive milieu unfavorable for T cell activity [30, 31].

Lipid metabolism

Metabolism of lipid plays a pivotal part in growth and mobility of breast cancer. tumor cells actively engage in cholesterol and lipid metabolism by enhancing usage of exogenous lipids as well as lipoproteins, while promoting de novo lipid and cholesterol production. De -novo fatty acid synthesis (FAS) is particularly important for meeting the heightened demand for membrane metabolism in rapidly proliferating tumor cells. FAS, a critical enzyme involved in fatty acid [FA] formation, is often overexpressed in the breast tumor, contributing to disease, recurrence, and bad prognosis. This increased FAS functioning underscores its

significant role in breast cancer evolution. Remarkably, Fatty Acid Synthase (FASN) expression levels are greatest in HER2-positive breast malignancy and minimalistic in Triple-Negative Breast Cancer. Additionally, signal transduction pathways involving phosphatidylinositol-3-kinase (PI3K), AKT,
mTOR, and mitogen-related protein kinase (MAPK) may regulate the expression of FASN. In the hypoxic conditions, breast tumor cells activate AKT and SREBP-1, leading to the upregulation of the FASN gene. Both the mTOR inhibitor rapamycin and inhibition of the MAPK pathway have been shown to reduce expression of FASN in breast cancer cells [32].

An Overview of metastasis in the breast cancer

The production of metastases in distantly located organs is a complex, multi-step process known as tumor metastasis, which involves sequential events such as local invasion, intravasation, transit through blood vessels or lymphatics, extravasation, and colonization. Crucially, the relation between tumor cells and the tumor microenvironment (TME), comprising extracellular matrix (ECM), soluble factors, immune system cells, endothelium, fibroblast cells, and fat storage cells, among other non-cancerous cell types, play a pivotal role in determining organ-specific colonization. Breast cancers typically exhibit the parallel metastatic model, indicating that cancer cells initiate spreading early in tumor development and may progress independently of the advancement of primary tumors, in addition to the linear metastatic model [33].

Research suggests that genetic alterations present in breast tumor cells that have metastasized to the bone marrow often differ from those in the corresponding tumors. Various breast cancer types display preferences for specific metastatic sites, each controlled by unique genetic mechanisms. The organ-specific spread of metastasis is influenced by the molecular characteristics of target tissues and breast malignancies. While all subtypes of breast cancer can metastasize to bone, the luminal A subtype is related with an elevated risk of bone recurrence, and compared to different types, the luminal B type is more likely to have bone relapse as the initial site of recurrence. Additionally, compared to HER2-positive cancers, incidence of bone metastases is substantially elevated in luminal type tumors (80.5%). Conversely, basal-like and luminal B subtypes exhibit higher rates of lung-specific metastases. Regarding liver metastases, the HER2-positive subtype is more prevalent than the HER2-negative subtype. In a separate study, basal-like tumors demonstrated significantly lesser rates of hepatic and bone metastases but higher rates of mobility to different parts of the body compared to other types [34].

Mechanism of metastasis

During the initial stage of tumor mobility, tumor cells are removed from the primary tumor and insert into the circulation from the stroma. for escaping the primary tumor to infiltrate surrounding tissues, these cells undergo epithelial-mesenchymal transitions (EMT), reducing strong cell adhesion. EMT and stem cell characteristics are closely associated with cancer metastasis. Regional migration of tumor cells relies on integrin-mediated adhesion and interactions with matrix constituents. Additionally, cancer cells can easily enter the systemic circulation through intratumoral blood capillaries, which exhibit enhanced permeability [35].

After leaving the initial tumor site and entering into bloodstream, breast cancer cells encounter the initial challenge presented by the wall of blood vessel, particularly of endothelial cells. Certain organs, like the liver and bone marrow, have microvessels with sinusoidal structures and high permeability, facilitating the spread of cancer cells. Elevated selectin ligand expression by tumor cells is closely related to poor prognosis and the mobility of metastases. The induction of angiopoietin-like 4 (ANGPTL4) in tumor cells enhances their stoppage and progression in lungs and enables breast cancer cells to breach the lung wall and form the pulmonary metastases. This process is mediated by the transforming growth factor-beta (TGFβ)/small mother against decapentaplegic (SMAD) signaling processes in cancer cells. Additionally, target cell tissues release chemokines that regulate adhesion, cytoskeletal rearrangement, initiate signal process, and induce directed cell migration. [36].

pre-metastatic niche

Through intricate interactions among the stromal parts of organs and initial tumors, a conducive environment known as the pre-metastatic niche may form in the secondary tissues as well as organs prior to the emergence of metastases. A recently published report proved the significance of tumor-mobilized bone marrow-derived cells (BMDCs) in creating a milieu favorable for lung metastasis. Substances released by the primary tumor, influence bone marrow mesenchymal stem cells (BMDCs), prompting them to migrate to anticipated location of metastasis prior to the arrival of disseminated cancer cells. According to a report., HIF-1 serves as an important regulatory factor in the formation of a metastatic niche for breast cancer by activating multiple members. Additionally, suppression of prostaglandin endoperoxide synthase (PTGS) by Dickkopf (DKK)-1-2 induces the recruitment of neutrophils and macrophages to lung metastases via stopping signaling in cancer cells. Conversely, this mechanism promotes metastasis from the breast to the bone by influencing osteoblasts' classical WNT signaling [37].

Organotropism

Subvariants and distinct gene signatures of metastatic cancerous cells are associated with site- specific breast cancer metastasis. The genetic expression of such genes inside the initial tumor will help in predicting the organotropic metastasis of patient. Functional investigations have discovered numerous important genetic elements that play a crucial part in organotropic metastasis of breast tumor. A prevelant location for metastases of breast cancer is the bone. The excessive resorption of bone mediated by osteoclasts is typically associated with osteolytic-type lesions and bone metastases. Tumor cells of breast are drawn to the bone and then adhere to it due in part to integrin complexes like αvβ3, α4β1, and α5. Breast cancer bone metastasis can be facilitated by signaling via the SMAD pathway, which may have redirected into a strong pro-metastatic factor due to certain clinical, genetic, and functional data. Furthermore, the expression of VEGF and CXCR4 can be independently stimulated to induce bone metastases of breast cancer by hypoxia and TGFβ signaling. Brain is the second prevelant site when breast cancer

metastasizes. Breast cancer brain metastases can be found in the leptomeningeal region or the parenchymal brain (around four out of five). In order to live, CTCs must cross blood-brain barrier, interact with surrounding milieu, and establish brain metastatic colonies. In order to accelerate transendothelial migration of tumor cells, CD44, VEGF, and CXCR4 can compromise endothelial integrity [38, 39, 40].

Metastasis driven by extracellular ATP via S100A4 formation by tumor cells and fibroblasts

Extracellular ATP is a significant pro-invasive component, and we have explored a potential mechanism in our work. It is seen that in fibroblasts and breast cancer cells, ATP increases the expression and release of S100A4 in the cells. In addition to inducing intracellular S100A4-mediated stimulation of mobility of breast cancer cell, ATP improved the capacity of breast tumor cells for conversion of fibroblast cells into the CAF-like cells, which produced S100A4 to again stimulate the mobility of cancer cell. Apyrase and niclosamide treatments were able to prevent inoculation tumors from spreading to the liver, lung and kidney in a mouse-based model. Additionally, the cancer-associated factor (CAF) produced by these treated tumors showed reduced ability to stimulate the mobility of breast tumor cells [41].

All together, the data show the extracellular ATP stimulates connections among fibroblasts and breast tumor cells, and then cooperate by producing S100A4, which worsens the spread of breast cancer. Growing research is being done on the role that the cancer-supporting microenvironment which is home to stromal cells such as immunological, and fibroblast cells and different signaling molecules play in the initiation and spread of tumors. Tumor metastasis is facilitated by the mutual molecular exchanges that occur between the stromal cells underneath the tumor cells. Although ATP's function in signal transduction outside the cell is quite recent, it is recognized as an intracellular source of energy. Extracellular ATP is undetectable in healthy tissues but can be produced by dying cells, produced by tumor cells, or infiltrated immune cells. In the tumor microenvironment, it can reach hundreds of micromoles. Extracellular ATP mostly engages in P2 receptor-mediated interactions and is responsible for a variety of bio-chemical processes in cancers, such as cellular invasion, proliferation, and termination. It does this by activating P2Y2 and/or P2X7, which in turn controls the amounts of several molecules associated to the epithelial-mesenchymal invasion and tranasition. We used microarray of cDNA in MCF-7 cells to try to find potential downstream genetic elements of extracellular ATP production. It was observed that ATP treatment increased the function of S100A4 mRNA. In the investigations that followed, we discovered that ATP increased the extracellular secretion and intracellular expression of S100A4 in fibroblasts and breast tumor cells. We postulated that ATP-driven cancer metastasis may be influenced by the combined action of extracellular S100A4 produced by fibroblasts and intracellular S100A4 of cancer cells [42].

Adaptation of energy metabolism of breast cancer's brain metastases

Since there is currently no treatment that can stop or reverse breast tumor from reaching to the brain, brain metastases are among the most dreaded side effects of the disease. Novel therapeutic approaches are contingent upon a precise understanding of the characteristics of tumor cells that permit the proliferation of breast tumor cells in the brain tissue. Large-scale proteome study revealed that the brain-derived cells have a distinct protein expression profile and a higher propensity for brain metastasis in *vivo* [43].

Elevated expression of enzymes connected to the kreb's cycle, glycolysis, and oxidative phosphorylation implies, glucose oxidation is source of energy for brain metastatic cells. The cells also shown increased glutathione system and pentose phosphate pathway activation, which can reduce the generation of ROS brought on by an enhanced oxidative metabolism. These modifications increased the brain metastatic cells' resistance to medications that alter the cellular oxidation-reduction equilibrium. Crucially, there is a clear correlation between the metabolic changes and increased survival and motility of cancerous cells in the brain microenvironment. The most dreaded consequence of breast cancer is brain metastasis. Breast tumors are the primary cause of metastatic brain disorder in women, with brain lesions being detected in about 20% of patients with advanced breast cancer. Though no current treatment regimen significantly influences brain metastases from breast cancer, the prevalence of brain metastasis rises as patients live long after improved cancer therapy. Most of the time, palliative care only prolongs survival for a few weeks or months, and it frequently has a negative effect on quality of life. Therefore, in order to create effective regimens to stop and treat this level of disease, it is essential to get a deeper knowledge of the nature and functioning of breast tumor cells that generate brain metastasis [44].

The invasive characteristics of metastatic tumor cells and capacity to draw in different blood vessels received a lot of attention in the past. Nevertheless, little is known about the innate processes that enable metastatic cancer cells to endure also multiply in desired target organs. In order to provide insight into the biological characteristics that support survival of cancer cell in the distinct brain environment. The circulation is the primary route via which metastatic breast tumor cells invade the brain. As a result, we extracted cancer cells from the brain and reintroduced the cells into the bloodstream of immunosuppresed animals. We used multidimensional proteomic analysis, or MudPIT, to analyze the protein profiles of the original cell line and its brain or bone homing variants in order to identify factors that contribute to breast tumor cell proliferation in brain. These cells have unique regulation of over 300 proteins. The majority of such proteins are engaged in the metabolic activities and stress response of cells. Our in *vitro* cell function investigations, transcriptional validation, and proteome results demonstrate that brain metastatic cells produce energy through increased mitochondrial respiratory pathways and employ antioxidant defense mechanisms [45].

Metabolic alterations seen in brain cancerous cells could be an indication of the tumor cells' propensity for or adaptation to the brain environment, a steady, high energy requirement is nearly fully satisfied by glucose breakdown. Our findings offer fresh proof that energy metabolism pathways used by brain metastatic breast cancer cells differ from anaerobic glycolysis, which is the major energy metabolism process used by most tumor cells in oxygen deficient tumor microenvironments. Moreover, a connection between the energy metabolism and gene regulation of brain metastatic

breast tumor cells may be established by their redox status. Our findings support the idea that focusing on tumor energy metabolism is viable treatment for brain metastases of breast cancer. They also highlight importance of comprehending the metabolic state of metastatic cells [46].

Conclusion

ATP metabolism plays a critical and multifaceted role in the development and progression of breast cancer, particularly in the context of metastasis. As the central energy molecule in cells, ATP supports various processes that enable cancer cells to proliferate, migrate, invade, and establish secondary tumors. The altered energetic demands of malignant cells, along with the dysregulation of ATP-generating pathways such as glycolysis and oxidative phosphorylation, contribute significantly to their aggressive behavior. Furthermore, ATP's role extends beyond intracellular energy supply to influence the tumor microenvironment and intercellular communication via purinergic signaling. Understanding these mechanisms opens new opportunities for targeted therapies aimed at disrupting the metabolic pathways that cancer cells rely on for metastatic progression. By focusing on ATP utilization, researchers and clinicians may uncover novel strategies to suppress metastasis and improve outcomes for patients with breast cancer. Continued investigation into these energy-dependent processes is essential for the development of effective, metabolism-based treatments that could complement existing therapies and ultimately reduce mortality in breast cancer.

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