International Journal of Advanced Scientific Research
www.allscientificjournal.com
ISSN: 2456-0421
Received: 03-04-2025, Accepted: 04-05-2025, Published: 19-05-2025
Volume 10, Issue 2, 2025, Page No. 25-32

Role of Anaerobic respiration derived lactic acid in severing malignant breast cells

Hritik Chaudhary, Siddhant Mavi
Department of Life science, Sharda University, Greater Noida, Uttar Pradesh, India

Abstract
Anaerobic respiration, a metabolic process occurring in the absence of oxygen, leads to the production of lactic acid as a byproduct. Traditionally, lactic acid was considered a mere metabolic waste product, but its involvement in cancer progression has garnered increasing attention. In breast cancer, the accumulation of lactic acid due to the tendency of cancer cells to favor glycolysis over oxidative phosphorylation, creates an acidic microenvironment. Lactic acid affects malignant breast cells by inducing cellular stress responses that can lead to apoptosis (programmed cell death) and altering cellular signaling pathways. In normal conditions, somatic cells including mammary epithelial cells undergo oxidative phosphorylation (OXPHOS) for the production of energy to carry out normal metabolic activities, but in some specific conditions such as hypoxic condition cells may switch from aerobic OXPHOS to anaerobic glycolysis leading to lactate production, this phenomenon is referred to us Warburg's effect. When a normal cell transforms into a malignant cell due to different oncogenic factors, its metabolism also tends to change, for example the uptake of glucose by the tumor cells is abnormally increased and after its metabolism through the glycolytic pathway,instead of going into Krebs cycle and oxidative phosphorylation leading to energy generation, a huge portion of it gets converted into lactic acid even under normal aerobic conditions or normoxic conditions ; this phenomenon is referred to as metabolic switch. Certain oncogenic genetic alterations, over-expression of some enzymes and enhanced activity of some metabolite transporters are thought to be the reasons for this shift, which are explored briefly in this review. Also the effect of lactic acid in key immunological processes and modulations of certain immune cells related to tumor development are also reviewed. Recent advancements suggest that targeting lactic acid production or its effects could provide new avenues for breast cancer treatment, either by exploiting its ability to induce cancer cell death or by counteracting its tumor-promoting properties. This review focuses on the emerging evidence suggesting that lactic acid, traditionally viewed as a mere waste product, may influence the behavior of cancer cells. Understanding the mechanisms by which lactic acid affects breast cancer cells could provide novel insights into metabolic interventions and improve therapeutic strategies for managing malignant breast tumors.

Keywords: Warburg's effect, metabolic switch, glycolysis, OXPHOS, metastasis, tumor microenvironment

Introduction

Breast cancer is an important global health issue, which is affecting millions of humans throughout the world every year. It arises when abnormal cells in breast begin to grow uncontrollably, forming a malignant tumor which has the capability to invade nearby tissues and/or to move to various parts of the body. While breast cancer mostly affects women, men may also develop this disease, though it is much less common [1]. The cases of breast cancer have been on the rise, largely due to increased awareness, improved diagnostic techniques, and lifestyle factors. World Health Organization (WHO) refers to it as, one of the most common cancers globally, surpassing even lung cancer in terms of new cases. Early diagnosis and advances in the treatment have significantly improved survival rates, but still breast cancer is one of the leading causes of mortality related to cancer, especially among women [2].

Environmental factors also play a crucial role in mitigating the risk of breast cancer. Research has indicated that exposure to certain chemicals, radiation, and some lifestyle choices such as improper balanced diet and physical exercise can influence susceptibility to the disease. For instance, studies have shown that alcohol consumption, smoking, and obesity are related to the increased instances of the disease. Conversely, regular physical activity and a healthy diet may lower the risk [3]. Screening and early detection are pivotal in managing breast cancer. Mammography, a type of X-ray imaging, is the most commonly used screening tool and has been shown to reduce mortality rates by detecting tumors before they become symptomatic. The recommended age to begin regular mammograms varies by guidelines but typically starts around age 40 to 50, depending on individual risk factors. Along with mammography, some other screening methods such as ultrasound and MRI may be employed based on specific circumstances [4].

Background on Breast cancer

Breast cancer, a global leading reason responsible for mortality especially in women, resulted in approximately 570,000 fatalities in 2015. Annually, over 1.5 million women (about the population of West Virginia), 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 [5]. 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. Despite its increasing prevalence, advancements in early detection programs and medical treatments have decreased mortality rates.

Biological therapies offer hope for improved treatment outcomes [6].

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 [7]. Lately, the discovery of Cancer Stem Cells (CSCs) in cancer 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 [8].

Correlation of Lactic Acid with Development and Metastasis of Breast Cancer

The research done by Warburg in the early twentieth century, on the correlation of tumor development with enhanced glucose metabolism and lactic acid formation has proven to be very insightful and a lot of valuable research followed afterwards shedding more light on the topic. As a result of thorough research we now know that the supply of oxygen in the tumor cells is restricted and there is an improper management in the supply and usage of available oxygen in the tumor microenvironment, which leads to the creation of hypoxic environment in tumor cells. It is important to find out the exact causes and impact of tumor hypoxia on cancer patients and it can also help us to develop better diagnostic approaches for cancer. In the last few decades there have been a tremendous effort to uncover these answers but we were lagging in the research regarding glycolysis and lactate metabolism and its association with tumor development and even metastasis, but now this area is gaining some momentum and in this review article we will shed some light on the same [9].

Metabolic Switch in Tumor Cells

In normal conditions, somatic cells including mammary epithelial cells undergo oxidative phosphorylation (OXPHOS) for the production of energy to carry out normal metabolic activities, but in some specific conditions such as hypoxic condition cells have the tendency to switch from the aerobic OXPHOS towards anaerobic glycolysis leading to lactate production, this phenomenon is referred to us Warburg's effect [10].

When a normal cell transforms into a malignant cell due to different oncogenic factors, its metabolism also tends to change, for example the uptake of glucose by the tumor cells is abnormally increased and after its metabolism through the glycolytic pathway, instead of going into krebs cycle and oxidative phosphorylation leading to energy generation, a huge portion of it gets converted into lactic acid even under normal aerobic conditions or normoxic conditions; this phenomenon is referred to as metabolic switch. To fulfil this enhanced requirement of glucose by tumor cells, continuous supply of glucose needs to be maintained and this is done by GLUT (glucose transporters) which are a kind of transmembrane proteins responsible for the transfer of glucose into the cells from the extracellular environment. GLUT has many isoforms but GLUT 1 is crucial in case of glucose transportation in malignant breast cells. In some experiments, silencing of GLUT1 results in reduced tumor development and proliferation which clearly indicates its importance in glucose uptake and metabolic shift of tumor cells. It can also be used as a target point for development of therapeutics for breast cancer [11].

Certain oncogenic genetic alterations, overexpression of some enzymes and enhanced activity of some metabolite transporters are thought to be the reasons for this shift. There are a number of discovered oncogenes and tumor suppressor genes which are responsible for this metabolic shift, one of the most crucial out of these genes are HIF (Hypoxia inducible factor)-1-regulated genes which leads to increased glycolysis in tumor cells and formation of lactic acid independent of the oxygen availability, which is in accordance with Warburg's research. HIF-1 transcription factor controls the GLUT1 expression, increasing its activity in tumor cells thereby helping in the metabolic shift of tumor cells.

Enzyme lactate dehydrogenase (LDH) is a crucial enzyme involved in the process of glycolysis, it converts pyruvate to lactate and vice versa. This enzyme has many isoforms which are LDH-1(H4), LDH-2(H3M1), LDH-3(H2M2), LDH-4(H1M3) and LDH-5(M4). LDH-5 is seen to be expressed higher than normal in case of breast cancer which is correlated with short survival and mortality among breast cancer patients and it is also related with the cerebral metastasis of breast cancer. Levels of expression of LDH-1 is also enhanced in malignant breast cells but its relation with physiology and functional mechanism of breast cancer is not yet completely understood. There may be different reasons for their overexpression but one thing is clear that it leads to enhanced production of lactic acid in tumor cells which is further related to the development and proliferation of breast cancer. It is experimentally found that the suppression of LDH-1 and LDH-5 in case of hypoxic (oxygen deprived) malignant breast cells, leads to the reduction in growth of tumor and this can also be utilized as a point of interference while developing therapeutics for breast cancer [12].

Importance of Glycolysis in Tumor Formation and Development

Conversion of glucose is the main source of cellular energy. Cells go through aero in order to support a particular Tumor microenvironment that promotes local development of tumor and its metastasis to different organs, cancer cells recruit nearby non-tumor/normal cells during tumor cell development. These cancerous cells form an abnormal organoid structure by interacting with host cells oxidation when there is enough oxygen present, converting glucose to carbon dioxide and water. This is the primary method of sugar oxidation and the primary way that cells produce energy, glucose or glycogen decomposes to produce lactate and energy when anaerobic circumstances are present. Anaerobic glycolysis is the term for this process [13].

Glycolysis has three primary characteristics:

1. In anaerobic environments or in cells without mitochondria, such as erythrocytes and hyperthyroid cells, it is the sole method of producing ATP. In these conditions, pyruvate is transformed into lactate
2. When oxygen is present, glycolysis generates pyruvate, which then enters the mitochondria's (TCA)tricarboxylic acid cycle, for ATP production

3. A variety of metabolites from the glycolytic and TCA cycles can also participate in the production of NADPH and the intermediaries needed for the synthesis of different biomolecules such as glycogen, lipids, nucleotides, and proteins [14].

In order to move to distant sites for metastasis, malignant tumor cells proliferate excessively and separate from nearby cells. This calls for a lot of energy as well as biosynthetic precursors that speed up invasion, migration, and cell division. Early tumor growth causes hypoxia and the elevation of hypoxia-inducible transcription factor expression because it surpasses the local blood supply's diffusion limit. By increasing the synthesis of enzymes involved in glycolysis, glucose transportation proteins (GLUT), and mitochondrial metabolic inhibitors, metabolism of cancerous cells often shifts to glycolysis due to the consequent decreased reliance on aerobic respiration. Through modifications to their energy metabolism, tumor cells acquire a robust capacity to endure in an unfriendly setting. This process, referred to as "metabolic reprogramming," is primarily brought on by increased glycolysis [15].

Normally differentiated cells use mitochondria-mediated glucose oxidative phosphorylation to enhance ATP generation in oxygenated environments. On the other hand, even in an environment with adequate oxygen, tumor cells rely on glycolysis to provide energy because they consume too much glucose and produce enormous amounts of lactate. This mechanism is also referred to as the Warburg effect or aerobic glycolysis [16].

Flow of Lactate Transport and its Metabolism in Breast Cancer

Evidence suggests that the concentration of lactate or lactic acid is found to be much larger in the cancerous cells as compared to its normal physiological concentration or its concentration in blood. And as we move towards more severe cases of breast cancer the concentration of lactate increases with the grade of the tumor. Earlier scientists used to think that lactate is merely a waste product of anaerobic glycolysis but after extensive research, we now know that lactate is an important tumorigenic factor and it plays an evident role in development of cancer and its progression, it can acta a biosynthetic precursor molecule, a signalling molecule or a regulatory molecule for extracellular acidosis of TME (tumor microenvironment) [17].

As the progression of cancer takes place and our normal breast cells have a metabolic shift towards becoming tumor cells, the intracellular concentration of lactate increases in these cells, but it can only increase to a certain level upto which it will help in tumor development in different ways, but beyond that level it can be toxic for cell and lead to inhibition of tumor progression. So it needs to be eliminated from the cells through designated pathways. Lactic acid is transported through the plasma membrane through monocarboxylate transporters (MCTs). these are a class of transmembrane proteins which are passive transporters, they transport lactate anions in conjugation with protons into the extracellular environment down the concentration gradient, leading to an accumulation of lactate in TME and acidosis of the extracellular environment, which helps in tumor progression in different ways [18].

Two main classes of MCT involved in tumor development are MCT 1 and MCT 4, MCT 1 can be involved in influx or efflux of lactate from different cells depending on the cell type and mechanism involved whereas MCT 4 is responsible for the efflux of lactate from the cells into the TME (tumor microenvironment).

In accordance with the warburg's effect, normal breast cells are transformed into tumor cells leading to a shift in metabolism and thereby increasing the production of lactate in these cells as can be seen in figure 1. After transformation to tumor cells the uptake of glucose increases drastically by the tumor cells for supporting the abnormal growth of malignant cells and their uncontrolled cell division for tumor development. These tumor cells also require a continuous enhanced supply of oxygen but the RBCs in our blood are only able to provide a certain amount of oxygen, leading to the development of hypoxic conditions in these cells [19].

All these conditions promote enhanced aerobic glycolysis of glucose in these cells leading to an enhanced production of lactate. This lactate starts accumulating inside these cells and then it is transported to the tumor microenvironment by monocarboxylate transporter, MCT4 with a symport of protons leading to accumulation of lactate in TME and its acidosis. The lactate produced by the stromal cells is transported into the tumor microenvironment with the help of monocarboxylate transporter, MCT1. And then alternatively the lactate present in the TME can be transported back to the tumor cells with the help of G-protein coupled receptors, GPR81. Where it can stimulate the production of more lactate by aerobic glycolysis in tumor cells. This process is referred as reverse warburg effect, but its existence and mechanism is still under debate [20]

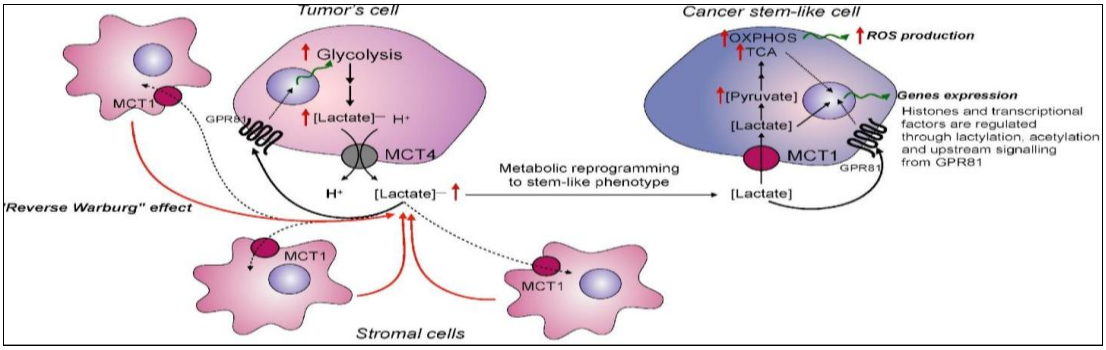

Fig 1: Illustration of Lactate's contribution to the development of cancer stem-like phenotypes. Lactate buildup in the TME causes a metabolic reprogramming of the tissue and influences stromal cell lactate production (reverse Warburg effect). Furthermore, through the lactylation of transcriptional factors and histones, lactate may directly affect the expression of genes. (Courtesy: https://www.mdpi.com/2072-6694/14/19/4552)

There is also an alternate underlying mechanism involved in this process, the development of cancer stem-like cells (CSCs), these are a subclass of tumor cells which have the ability of self renewal, proliferation to form multiple cancer cells and differentiation to form certain different types of cells involved in cancer development. Excess lactate from the tumor microenvironment enter certain tumor cells through monocarboxylate transporter, MCT1 and upon entering it gets converted into pyruvic acid and then this pyruvate enters the krebs cycle and further oxidative phosphorylation (OXPHOS), producing different intermediates at various levels and also phosphorylation of nucleotides for energy production. Certain histone proteins and transcriptional factors are regulated via acetylation by acetyl coenzyme A of TCA cycle or directly via lactylation from the intracellular lactate or via upstream signalling through GPR81 by lactate in TME. All these modifications are leading to the conversion of cancer cells to cancer stem-like cells thereby leading to enhanced tumor progression [21].

The Tumor Microenvironment (TME)

Normal tissues maintain an equilibrium between cell division and apoptosis. When this equilibrium is upset, a number of benign and malignant neoplastic disorders may arise. A dynamic non-homogenous collection of cancer or cancer stem cells makes up the TME, a cellular niche that also constantly modifies resident and infiltrating host cells, secretory factors, and extracellular matrix. This niche encompassesthe intracellular microenvironment (the nucleus and the cytosol) of these cancer cells as well as the conformation, functioning, and the metabolic processes of the cancer-host tissue. The cancerous cells themselves are one of the cellular components of the tumor microenvironment (TME), along with adipocytes, fibroblasts, lymphocytes, dendritic cells, tumor vascular system, and cancer-related fibroblasts. Each of these cells has a distinct immune capacity that will dictate the cancer cells' ability to remain viable and their impact on nearby cells [22].

Different chemokines and cytokines are examples of extracellular components of the tumor microenvironment. Together, these cellular and extra-cellular elements create a complex tumor micro-environment that promotes cancer growth in a synergistic manner. Patients, primary and metastatic cancers, and even individual cancers at different stages differ in their parenchymal and mesenchymal cell morphology, phenotype, and function. In order to support a particular Tumor micro environment that promotes local cancer development and progression to different organs, cancer cells recruit nearby non-tumor cells during cancer cell proliferation. These tumor cells form an abnormal organoid structure by interacting with host cells [23].

Lactic Acid and Metastasis of Breast Cancer

Breast cancer is considered to be one of the major prevailing and challenging malignancies around the world. Its complexity is amplified when considering metastatic progression, where cancer cells spread from primary tumor to different organs. An emerging area of research has highlighted the role of metabolic byproducts, particularly lactic acid, in the development and transfer of breast cancer. It is important to study the influence of lactic acid on breast cancer metastasis, delving into the mechanisms through which it promotes tumor spread and the potential therapeutic implications [24].

Lactic Acid Production in Cancer: An overview

Lactic acid is a byproduct of anaerobic glycolysis, which is a metabolic pathway that converts glucose into energy without the use of oxygen. While normal cells primarily utilize oxidative phosphorylation (OXPHOS) for energy formation, tumor cells often show enhanced glycolytic activity, even when the oxygen is abundant. This phenomenon is referred to as the Warburg effect, resulting in elevated levels of lactic acid within the tumor microenvironment (TME). In breast cancer, high rates of glycolysis and subsequent lactic acid production are frequently observed. This metabolic shift supports rapid tumor growth and survival by providing essential substrates for biosynthesis and by modulating the tumor microenvironment. The accumulation of lactic acid contributes to an acidic extracellular milieu, which influences various aspects of tumor biology, including metastasis [25].

Mechanisms Linking Lactic Acid to Metastasis

Lactic acid affects metastasis through several key mechanisms:

1. Acidic Microenvironment and Tumor Invasion

The acidic microenvironment created by excess lactic acid performs a crucial part in promoting the metastasis of breast cancer. Acidic conditions can enhance the activity of proteolytic enzymes like matrix metalloproteinases (MMPs), which degenerate the components of the extracellular matrix. This degradation facilitates cancer cell invasion and migration by breaking down physical barriers that typically confine cancer cells to their original location.

Moreover, the low pH can influence cellular behavior by altering adhesion properties. Cancer cells exposed to acidic conditions are often more motile and invasive, as the acidic environment can modify cell to cell and cell to matrix interactions. These changes enhance the capability of cancer cells to penetrate the nearby tissues and then enter our bloodstream or the lymphatic system [26].

2. Induction of Epithelial-Mesenchymal Transition (EMT)

Lactic acid has been proven to induce epithelial-mesenchymal transition (EMT), a process through which epithelial cells acquire mesenchymal, fibroblast-like properties. EMT is associated with increased invasiveness and metastatic potential. During EMT, cancer cells lose their epithelial characteristics, such as tight junctions and polarity, and gain migratory and invasive traits. The acidic environment induced by lactic acid can activate signaling pathways involved in EMT. These pathways promote the expression of mesenchymal markers and reduce the expression of epithelial markers, facilitating cancer cell detachment and movement [27].

3. Modulation of Immune Response

Lactic acid influences the immune landscape of the tumor microenvironment, which can impact metastatic progression. The accumulation of lactic acid can stop the functioning of different cells of the immune system, including cytotoxic T cells and natural killer cells (NKC), thereby reducing the ability of our immune system to target

and remove tumor cells. This immune suppression allows cancer cells to evade immune surveillance and enhances their capacity for metastasis. Additionally, lactic acid can induce the polarization of macrophages towards a pro-tumor phenotype. Tumor-associated macrophages (TAMs) in this polarized state can support tumor growth, angiogenesis, and metastasis. By influencing immune cell function and macrophage polarization, lactic acid contributes to a microenvironment that favors cancer progression [28].

4. Angiogenesis and Metastatic Niche Formation

Lactic acid also impacts angiogenesis, which is the process of formation of new blood vessels, for supporting the tumor development. Tumor cells produce lactic acid in high quantities, which can promote the process of angiogenesis, by enhancing the expression of certain factors which are pro-angiogenic, such as vascular endothelial growth factor (VEGF). Enhanced blood supply supports the growth of primary tumors and provides a route for cancer cells to enter systemic circulation [29].

5. Pre-metastatic niche formation

Furthermore, the acidic microenvironment can influence the formation of metastatic niches in distant organs. The presence of lactic acid in these organs can condition the microenvironment to support the survival and colonization of disseminated cancer cells. This phenomenon, known as pre-metastatic niche formation, involves changes in the extracellular matrix, immune cell infiltration, and vascular remodeling, all of which facilitate the establishment of secondary tumors.

Lactic acid plays a multifaceted role in breast cancer metastasis, influencing tumor invasion, EMT, immune response, and angiogenesis. Its impact on these processes underscores the importance of metabolic factors in cancer progression. As research continues to unravel the complexities of lactic acid's role in metastasis, novel therapeutic strategies targeting metabolic pathways and the tumor microenvironment may give a hope for improving outcomes for breast cancer patients. Understanding and manipulating these metabolic interactions holds the capability to significantly increase treatment efficacy and reduce the burden of metastatic disease [29, 30].

Lactate influenced metastasis of breast cancer

Research has shown that the presence of lactate helps in the migration of tumor cells, as was evident by the Boyden chamber experiments where addition of lactate to different cancer cell lines leads to a concentration-dependent random migration of the cancer cells. And not only single cells but a bulk or mass of tumor cells also respond to the introduction of lactate in a similar manner, which can be observed through various techniques such as time lapse video microscopy. Although this relationship between lactate and tumor cell migration has been established, the molecular mechanisms involved in the same are not yet completely understood. Serum LDH levels, lactate levels, and tumor lactate generation have been recognized as predictive indicators of bad and improper clinical prognosis for a long time now, in a variety of human epithelial malignancies, which includes breast cancer. In fact, lactic-acidosis caused by an excess of or buildup of serum lactate due to the metabolic shift of tumor cells towards the enhanced production of lactate by aerobic glycolytic pathways, often results in the death of people suffering from metastatic breast cancer or other forms of metastatic disease [31, 32, 33].

Role of lactate in macrophage polarization, inflammation and cancer

Lactate was always considered as a by-product of the metabolic reactions other than a key bioactive compound but recent experimentations suggest the important role of lactic acid in cancer progression and metastasis. It plays a key role in maintenance of the macrophage metabolism, in tumors the excessive production of lactate supports the polarization of tumor-associated macrophages (TAM), helping in the development of breast cancer. Macrophages are induced into distinct phenotypes in several human disorders as a result of infection, malignancies, metabolism, and activation of the immune system. M1/M2 macrophages retain an intermediate state during normal settings; disease development results from a change from M1 to M2 or vice versa. Based on various cues from the microenvironment, macrophages have the ability to transform into several phenotypes and carry out distinct activities. Both M1-phenotypes (classically activated macrophages, or CAM) and M2-phenotypes (alternatively activated macrophages, or AAM) of macrophages were identified by the researchers. M1 and M2 macrophages are in a state of dynamic equilibrium under normal physiological settings [34, 35].

In addition to promoting the generation of inflammatory factors and reactive oxygen species (ROS) and some nitrogen intermediates, classical M1-type macrophages also control the immune response through Th1 and Th17 cells, which has pro-inflammatory, bactericidal, and anti-tumor effects. Angiogenesis and lymphangiogenesis, that are necessary for tissue and wound healing, inhibition of the acute inflammatory response, and immune regulation and inflammation suppression, are processes carried out by M2-type macrophages. Tumor stroma is home to a large population of macrophages known as tumor-associated macrophages (TAMs). Macrophages develop M2-phenotypes in the tumor microenvironment, which promote tumor growth. They sustain angiogenesis, encourage matrix disintegration, encourage tumor development and dissemination, and impede tumor-opposing adaptive immune responses. In addition to preventing T cell growth and cytotoxic T cell response, TAMs also contribute to the immunosuppressive environment [36].

According to a recent study, TAM (tumor associated macrophages) proliferation during epithelial-mesenchymal transition was fueled by lactic acid. In similar studies a connection was found between a tumor's macrophages and the lactic acid the tumor released. It was also discovered that lactic acid stimulates M2-like macrophage polarization.Furthermore, vascular endothelial growth factor (VEGF) expression was elevated by lactic acid-polarized macrophages, creating a positive feedback loop that accelerated angiogenesis which is a very crucial step in the development and proliferation of tumor.These research findings showed that lactic acid can, through dose-dependent metabolic reprogramming, cause monocytes to develop into M2 macrophages, which will aid in the formation of tumors in the surrounding microenvironment. In conclusion, this suggests that treating disorders that pose a serious risk to life can benefit from lactic acid targeting. Furthermore, lactic acid plays a significant role in disorders associated with inflammation and is implicated in the

control of macrophage morphologies and activities. This suggests that disorders associated with inflammation may be efficiently treated by using the metabolism of lactic acid. To demonstrate the connection between lactic acid and macrophages and its potential for disease therapy, further clinical trials and scientific data should be acquired [37].

Suppression of Immune Cells by Lactate Accumulation in Tumor Microenvironment

The tumor microenvironment possesses various cell types such as tumor cells, fibroblast cells, various vascular cells such as modified endothelial cells and different immune cells. The enhanced glycolysis and lactate production by tumor cells and secretion of lactate into tumor microenvironment disrupts or modifies the activities of different cells in tumor microenvironment, especially a diminished immune response or immunosuppression of different immune cells is observed.

1. T Lymphocytes

Also referred to as T cells, these cells are formed in bone marrow by the differentiation of lymphoid progenitor cells and they mature in thymus, an endocrine gland which remains active in humans upto a certain age. The are majorly of types T helper cells and T cytotoxic cells which helps in the combat with foreign particles in their own ways. Certain T lymphocytes such as cytotoxic CD8+ T lymphocytes (CTLs), depends on glycolysis for their proliferation and for the activation of their function but due the increased competitive glycolysis by tumor cells these cells get less than required amount of glucose for glycolytic activation of their effector function, as a result a decrement is observed in their function [38].

The regulated effluence of lactate is from these CTLs is also important for their proper functioning but due to the accumulation of lactate in the tumor microenvironment, these cells are unable to secrete their intracellular lactate into the TME because it depends on the differential gradient of lactate in TME and CTL cytoplasm. Furthermore, the enhanced lactate production by tumor cells also leads to mitochondrial dysfunction in T cells and it leads to the enhanced ROS (reactive oxygen species) by these cells, ultimately pushing these cells towards a programmed cell death or apoptosis [39].

2. Natural killer cells (NKC)

These are a type of lymphocytes which are a component of innate immune response. When they encounter any foreign cell or cancerous cell in the body they secrete different proteins called cytokines which direct different immune cells towards that entity and help in its elimination from the body. The enhanced level of lactate in tumor microenvironment leads to the suppression of cytotoxic activity of NK cells through different mechanisms such as downregulation of the activity of IFN-g, perforin, granzyme, and the activating receptor Nkp46. Also the enhanced lactate production by tumor cells also leads to decreased tumor infiltration by NK cells, decreased proliferation of NK cells and mitochondrial dysfunction in NK cells which also leads to the enhanced ROS (reactive oxygen species) by these cells, ultimately pushing these cells towards a programmed cell death or apoptosis [40].

3. Dendritic cells

These are a type of APCs, antigen presenting cells, which have the function of antigen capturing, its processing and presentation on their surface to CD4+ T cells, which will further help in the elimination of foreign entity from the body. Enhanced lactate concentration leads to decreased functionality of dendritic cells by interfering in different mechanisms such as maturation of dendritic cells, activation of dendritic cells, antigen presentation by dendritic cells to T cells, type 1 IFN response and antigen elimination by dendritic cells [41].

4. Myeloid-derived suppressor cells (MDSCs)

These immunosuppressive immune cells and their formulation and expression leads to decreased T cell proliferation and T cell function, it also hampers with the T cell receptor signalling, further impairing the activity of T cells. Enhanced glucose metabolism and lactate production and both intracellular and TME accumulation of lactate by tumor cells leads to enhanced expression of MDSC genes leading to increased production and development of MDSCs, thereby suppressing the functioning of T cells [42].

5. Tumor Associated Macrophages (TAM)

In the breast tumor micro environment (TME), tumor-associated macrophages (TAMs) are the most prevalent immune cells and play an important role in breast cancer progression. Throughout the development and advancement of breast cancer, TAMs contribute to tumor growth by enhancing angiogenesis, facilitating cancer cell metastasis, inducing cancer stemness, influencing energy metabolism, and aiding in immune system suppression. They drive breast cancer progression by fostering tumor cell invasion and metastasis, supporting angiogenesis, promoting cancer stemness, regulating metabolic processes, and modulating T cell activity [43].

Conclusion

In conclusion, the correlation between lactic acid production and the development and metastasis of breast cancer has emerged as a key area of research, shedding light on the complex interplay between tumor metabolism and tumor progression. Lactic acid, produced during anaerobic glycolysis, is a hallmark of the Warburg effect, a metabolic adaptation that allows cancer cells to remain viable and prosper even under low oxygen conditions. Elevated lactic acid levels are not only indicative of altered metabolic states within tumor cells, but they also actively contribute to tumorigenesis and metastatic spread. The accumulation of lactic acid in the tumor microenvironment leads to acidosis, which can modify the behavior of both cancer cells and surrounding stromal cells. This acidic microenvironment promotes angiogenesis by increasing the expression of hypoxia-inducible factors (HIFs) and various pro-angiogenic molecules, enabling tumors to grow larger and become more invasive. Furthermore, lactate has been shown to enhance the epithelial-mesenchymal transition (EMT), a crucial process that allows cancer cells to lose their adhesive properties and acquire a more migratory and invasive phenotype, facilitating the spread of tumor cells to distant organs.

In addition to direct effects of lactic acid on cancer cells, it also influences the immune microenvironment, suppressing anti-tumor immune responses and aiding in immune evasion. It interferes with the function of immune cells such as T-cells and natural killer cells, further contributing to the tumor's ability to evade detection and elimination by the

host immune system. Given these findings, lactic acid production is emerging as a critical factor in both the initiation and progression of breast cancer, particularly in promoting metastasis. Targeting the mechanisms involved in lactate production, transport, or its downstream signaling effects offers a potential therapeutic strategy to halt the spread of cancer. Further investigation into lactate's role in tumor biology, as well as the development of targeted therapies to modulate its production or effects, could lead to new treatment options for breast cancer patients, particularly those with metastatic disease. Ultimately, this research underscores the need for a more nuanced understanding of tumor metabolism and its implications for cancer treatment, as targeting metabolic pathways such as lactate production may hold the key to improving patient survival and preventing metastasis in breast cancer.

References

1. Jheeta S. The Landscape of the Emergence of Life. Life,2017:7(2):206–216.
2. Kunnev D. Origin of Life: The Point of No Return. Life,2020:10:269.
3. Olson KR, Straub KD. The Role of Hydrogen Sulfide in Evolution and the Evolution of Hydrogen Sulfide in Metabolism and Signaling. Physiology (Bethesda, Md.),2016:31(1):60–72.
4. Bahrami H, Tafrihi M. Understanding the Warburg Effect Yields New Insights into the Metabolic Control of Cancer. Journal of Cancer Research Updates,2023:12:44–48.
5. Bose S, Le A. Glucose Metabolism in Cancer. Advances in Experimental Medicine and Biology,2018:1063:3–12.
6. Kump LR. The Rise of Atmospheric Oxygen. Nature,2008:451(7176):277–278.
7. Gregory TR. Understanding Natural Selection: Essential Concepts and Common Misconceptions. ResearchGate,2020.
8. Schirrmeister BE, Gugger M, Donoghue PCJ. Cyanobacteria and the Great Oxidation Event: Evidence from Genes and Fossils. Palaeontology,2015:58(5):769–785.
9. Ma'ayan A. Complex Systems Biology. Journal of the Royal Society Interface,2017:14(134):20170391.
10. Bich L, Pradeu T, Moreau J. Understanding Multicellularity: The Functional Organization of the Intercellular Space. Frontiers in Physiology,2019:10:1170.
11. Cooper MG, Housman RE. The Cell: A Molecular Approach. Sinauer Associates,2009.
12. Rasnitsyn A. Cancer: A Throwback to Ancient Cells? Cells,2019.
13. Bahrami H, Tafrihi M, Mohamadzadeh S. Reversing the Warburg Effect to Control Cancer: A Review of Diet-Based Solutions. Journal of Current Oncology and Medical Sciences,2022:2(3).
14. Edwards G. Uranium: Known Facts and Hidden Dangers. The World Uranium Hearing Conference,1992.
15. National Cancer Institute. What Is Cancer? National Cancer Institute,2021.
16. Chiaradonna F, Scumaci D. Cancer Metabolism as a New Real Target in Tumor Therapy. Cells,2021:10(6):1393.
17. Aranda-Anzaldo A, Dent MAR. Is Cancer a Disease Set Up by Cellular Stress Responses? Cell Stress & Chaperones,2021:26(4):597–609.
18. Fares J, Fares MY, Khachfe HH, Salhab HA, Fares Y. Molecular Principles of Metastasis: A Hallmark of Cancer Revisited. Signal Transduction and Targeted Therapy,2020:5(1):28.
19. Luengo A, Li Z, Heiden MV. New Clarity on the Warburg Effect. National Cancer Institute,2021.
20. Otto AM. Warburg Effect(s) – A Biographical Sketch of Otto Warburg and His Impacts on Tumor Metabolism. Cancer & Metabolism,2016:4:5.
21. Warburg O. On the Origin of Cancer Cells. Science (New York, N.Y.),1956:123(3191):309–314.
22. Liberti MV, Locasale JW. The Warburg Effect: How Does It Benefit Cancer Cells? Trends in Biochemical Sciences,2016:41(3):211–218.
23. Apple S. An Old Idea, Revived: Starve Cancer to Death. The New York Times Magazine, 2016.
24. Bahrami H, Greiner T. The Alkaline Diet and the Warburg Effect. ResearchGate, 2020.
25. Bunz F. Principles of Cancer Genetics. Springer,2016.
26. Bahrami H, Tafrihi M. Improving Natural Resistance to Cancer: An Overview of Metabolic Pathways in Cancer Cells Integrated with Regional Cancer Incidence Statistics. Jentashapir Journal of Cellular and Molecular Biology,2023:14(3).
27. Adewale O, Basiru A, Ojo O, Adewale O, Olayide I, Emuowhochere R. Biology of Glucose Metabolization in Cancer Cells. Journal of Oncological Sciences,2017:3:45–51.
28. Choi SYC, Collins CC, Gout PW, Wang Y. Cancer-Generated Lactic Acid: A Regulatory, Immunosuppressive Metabolite? The Journal of Pathology,2013:230(4):350–355.
29. Drochioiu G. The Influence of Respiratory and pH Imbalance in Cancer Development. International Journal of Biochemistry Research & Review,2014:16:386–409.
30. Dong L, Krewson EA, Yang LV. Acidosis Activates Endoplasmic Reticulum Stress Pathways through GPR4 in Human Vascular Endothelial Cells. International Journal of Molecular Sciences,2017:18(2):278.
31. Ibrahim-Hashim A, Estrella V. Acidosis and Cancer: From Mechanism to Neutralization. Cancer Metastasis Reviews,2019:38(1-2):149–155.
32. Lee S, Griffiths JR. How and Why Are Cancers Acidic? Carbonic Anhydrase IX and the Homeostatic Control of Tumour Extracellular pH. Cancers,2020:12(6):1616.
33. El-Kenawi A, Gatenbee C, Robertson-Tessi M, Bravo R, Dhillon J, Balagurunathan Y, et al. Acidity Promotes Tumour Progression by Altering Macrophage Phenotype in Prostate Cancer. British Journal of Cancer,2019:121(7):556–566.
34. Bahrami H, Tafrihi M. Global Trends of Cancer: The Role of Diet, Lifestyle, and Environmental Factors. Cancer Innovation,2023:2(4):290–301.
35. Ahmad F, Cherukuri MK, Choyke PL. Metabolic Reprogramming in Prostate Cancer. British Journal of Cancer,2021:125(9):1185–1196.
36. Schwingshackl L, Morze J, Hoffmann G. Mediterranean Diet and Health Status: Active Ingredients and Pharmacological Mechanisms. British Journal of Pharmacology,2020:177(6):1241–1257.

37. Maruca A, Catalano R, Bagetta D, Mesiti F, Ambrosio F A, Romeo I, et al. The Mediterranean Diet as Source of Bioactive Compounds with Multi-Targeting Anti-Cancer Profile. European Journal of Medicinal Chemistry,2019:181:111579.
38. Bahrami H. Nutrition for Cancer Prevention and Control: A Review of Dietary Risk Factors and Protective Measures. Journal of Cancer Screening and Prevention,2023:2(4).
39. O'Keefe SJD, Li JV, Lahti L, Ou J, Carbonero F, Moha mmed K, et al. Fat, Fiber and Cancer Risk in African Americans and Rural Africans. Nature Communications,2015:6:6342.
40. Jin Z, Wu M, Han R, Zhang X, Wang X, Liu A, et al. Ra w Garlic Consumption as a Protective Factor for Lung Cancer: A Population-Based Case-Control Study in a Chinese Population. Cancer Prevention Research (Philadelphia, Pa.),2013:6(7):711–718.
41. Wang Y, Liu B, Han H, Hu Y, Zhu L, Rimm EB, et al. A ssociations Between Plant-Based Dietary Patterns and Risks of Type 2 Diabetes, Cardiovascular Disease, Cancer, and Mortality – A Systematic Review and Meta-Analysis. Nutrition Journal,2023:22(1):46.
42. Leitzmann C. Vegetarian Diets: What Are the Advantages? Forum of Nutrition,2005:57:147–156.
43. Hovannessian AT. Raw-Eating: A New World Free from Diseases, Vices and Poisons. Ter Hovannessian, 2000.