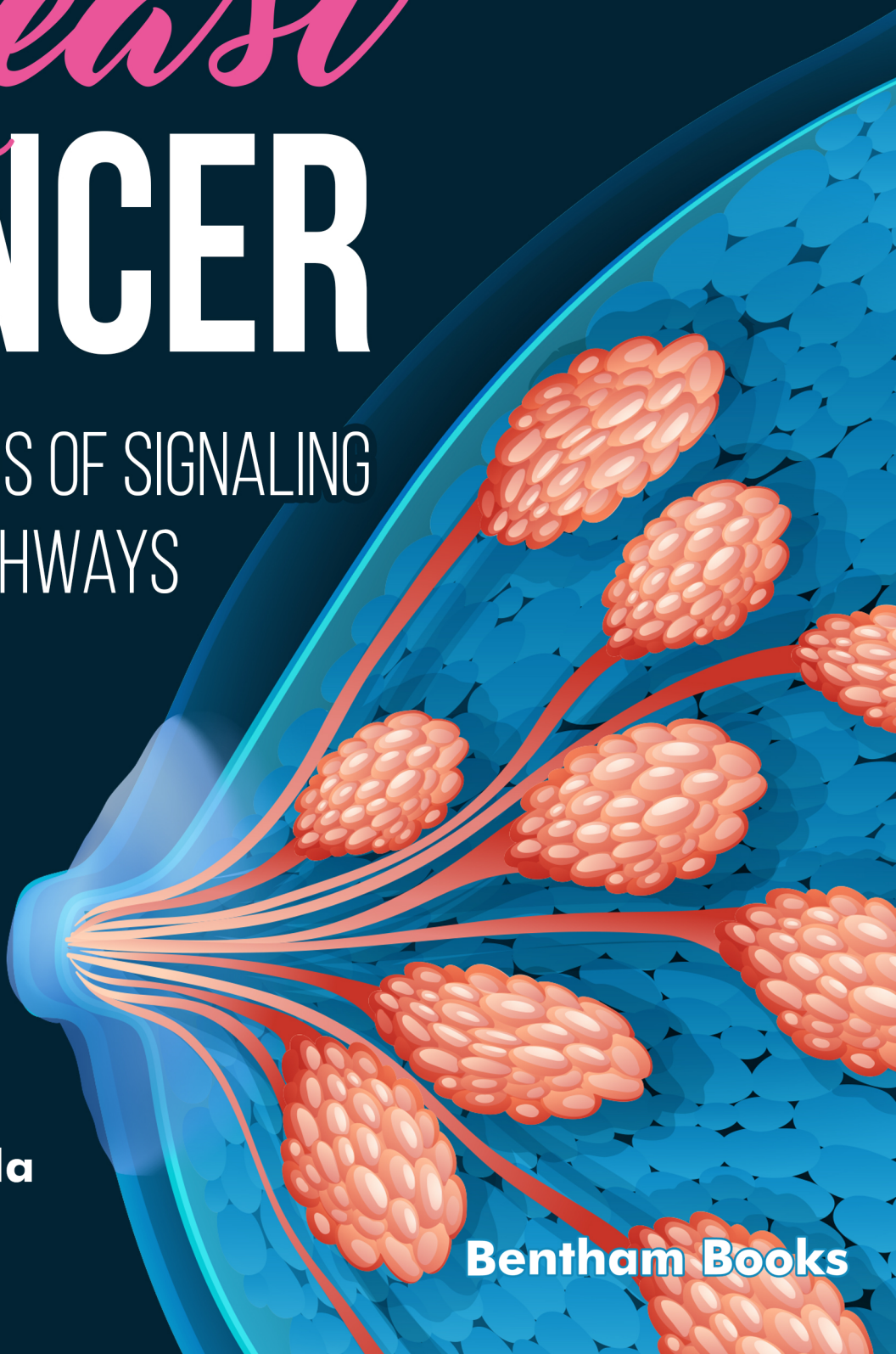
DIABETES AND *Breast* CANCER

AN ANALYSIS OF SIGNALING PATHWAYS



Editor: **Asis Bala**

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Diabetes and Breast Cancer: An Analysis of Signaling Pathways

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Diabetes and Breast Cancer: An Analysis of Signaling Pathways

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FOREWORD

I am happy to introduce Dr. Asis Bala, a valued scientist, for his book on “Diabetes and Breast Cancer: An Analysis of Signaling Pathways”, which is a real advancement in the field.

Prof. Didier JAMBOU, MD, PhD
Laboratoire d'Hematologie
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PREFACE

Research has shown that breast cancer patients with diabetes experience worse clinical outcomes compared to those without diabetes, indicating a possible link between diabetes and breast cancer cell progression and migration. The exact reasons for this association are still being studied, but it is believed that factors such as hyperglycemia and hyperinsulinemia in type 2 diabetes may play a role. To better understand this link between diabetes and breast cancer, it is important to thoroughly investigate the signaling pathways involved. By doing so, biomedical scientists may be able to develop more effective treatments that target these mechanisms. The main focus of this book is to provide a detailed analysis of the signaling cross-talk between diabetes and breast cancer, with the goal of facilitating future drug development and improving patient outcomes. This book elucidates the critical signaling mechanisms and signaling Analysis to cross-talk between Diabetes and Breast Cancer. The key features include-

- Explains the role of critical regulatory signaling for Breast cancer progression during diabetes and obesity-associated conditions.

- Covers and explores the Genetic similarity between type 2 Diabetes and breast cancer.

- Systematically explains the signaling analysis to insulin for breast cancer cell invasion and migration and explores the possible pharmacological target for its concomitant management.

- Outline the Pharmacogenomics and Precision medicine approaches in relation to Diabetes and Breast Cancer.

This book is designed to provide valuable insights into the complex signaling mechanisms that link diabetes and breast cancer. This book is a useful resource for biomedical scientists in academia, the bio-pharmaceutical and biotechnological industries, as well as individual researchers and PhD scholars. By delving into the intricacies of this cross-talk, the book aims to facilitate the development of future drugs that can target these signaling pathways more effectively. Furthermore, as the first of its kind, this book will serve as a go-to reference for academics and students seeking a comprehensive understanding of this crucial field.

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This book would not have been possible without the tireless efforts of many researchers, and I am pleased to acknowledge the contributors who have willingly taken on the many demands placed upon them. We had the pleasure of partnering with Bentham Science Publishers, and we cannot thank them enough for their invaluable support. They approached the task with efficiency and perfection.

I would also like to extend a special thanks to Prof. Ashis Kumar Mukherjee, Director, Institute of Advanced Study in Science and Technology (IASST) and Department of Science & Technology (Govt. of India) for the continuous encouragement and support.

Lastly, I am grateful to my family for granting me the time and space needed to work on this book.

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CHAPTER 1

Interplay between Diabetes and Breast Cancer: A Brief Report

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Abstract: Cancer and diabetes are two of the most prevalent and complicated diseases. Several epidemiological studies have found a link between type 2 diabetes and an increased risk of breast cancer. This chapter aims to highlight the advances in understanding the mechanisms that connect diabetes and breast cancer. Alterations in glucose metabolism, hyperinsulinemia, insulin resistance, changes in the hormonal environment, and substrate availability create a metabolic environment that is particularly favourable for the growth of tumours. Therefore, it is vital to understand the correlation between diabetes mellitus and breast cancer. A precise analysis of these relationships could help in finding biomarkers that can predict disease risk and prognosis, and aid in selecting appropriate, evidence-based diagnostic and therapeutic approaches.

Keywords: Breast cancer, Hyperlipidemia, Insulin resistance, Inflammatory cytokines, RAGEs, Signalling pathway, Type 2 diabetes.

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INTRODUCTION

Chronic diseases in the twenty-first century are an existential threat to human health due to dietary overload or excessive energy consumption [1]. In developed nations, the prevalence of type 2 diabetes has been gradually increasing for decades and now affects 10% of the population [2]. Diabetes mellitus is regarded as a global pandemic and the tenth leading cause of mortality globally. Studies have shown that diabetes is associated with the development of several types of cancers, including breast cancer. Women with diabetes are 23% more likely to develop breast cancer than non-diabetic women [3]. Type 2 diabetes brings about changes to cellular and overall metabolism, which foster an environment that promotes the progression of breast cancer [4]. Several pathways that connect type 2 diabetes to breast cancer, such as the activation of insulin-like growth factor pathway, hyperinsulinemia, high estrogen levels, higher leptin quantities, and lower adiponectin values, activation of AKT pathway, immune responses such as elevated levels of proinflammatory cytokines like tumor necrosis factor-a (TNF-α) have been identified through multiple studies [4 - 6]. This chapter provides an overview of the key metabolic changes associated with type 2 diabetes and how breast cancer cells use cellular metabolism modifications to promote abnormal growth and proliferation. These findings offer insights into the comorbid situation and may be used to design several therapeutic approaches for treating breast cancer in diabetic patients in the near future. The development of breast cancer during the diabetic condition is influenced by several key factors.

Insulin Resistance

One of the main characteristics of type 2 diabetes is insulin resistance [7]. The hormone insulin, produced by the pancreatic β-cells, helps to regulate blood glucose levels by facilitating glucose absorption and storage [7, 8]. Insulin binds to the insulin receptor (IR), which activates the glucose transporter 4 (GLUT4) and facilitates glucose uptake into tissues like skeletal muscle, adipose tissue, and liver. Insulin resistance is such a condition when a certain concentration of insulin is present but has a lower biological impact than anticipated [9]. Insulin primarily affects metabolism and cell growth by binding to the insulin receptor (IR) and activating its tyrosine kinase activity, leading to the phosphorylation of the receptor substrate [10]. When the IR/PI3K/Akt signalling pathway is activated, mTOR is also phosphorylated and activated. The activation of this pathway encourages cancer cell survival, proliferation, invasion, migration, differentiation, angiogenesis, and metastasis. Additionally, the activation of the IR/PI3K/Akt signalling pathway triggers -catenin translocation into the nucleus and raises vascular endothelial growth factor (VEGF) levels, which affects the behaviour of tumour cells [7 - 10].

Inflammatory Cytokines

Type 2 Diabetes Mellitus (T2DM) is often characterized by chronic low-grade inflammation that leads to an increase in local and systemic cytokine levels, including Interleukin 6 (IL-6), C-reactive protein (CRP), tumour necrosis factor (TNF)-α, and adiponectin [11, 12]. Cytokines like IL-6 may substantially affect the development of cancer through signaling cascades [13, 14]. The signalling pathways of IL6, Janus kinase 2 (JAK2), and Signal Transducer and Activator of Transcription 3 (STAT3) are essential for the invasion and metastasis of malignant tumours [13]. The JAK2/STAT3 pathway is required for the development of breast cancer (BC) cells, which are human CD44+CD24- stem cells. JAK2/STAT3 is linked to the development of tumour cachexia and can cause a systemic inflammatory response [14]. IL-6 activates JAK2, one of the non-receptor tyrosine kinases, after binding to membrane receptors these phosphotyrosine residues serve as docking sites for the recruitment of the STAT3 protein, which functions as a cellular IL-6 mediator [12]. After activation, the oncogene STAT3 reacts to extracellular inputs and the JAK2 pathway. The two STAT3 monomers tyrosine phosphorylate, form a dimer, travel to the nucleus, attach to the target gene of STAT3-specific DNA response element, and trigger transcription of the gene. Thus, IL-6 promotes the activation of the JAK2/STAT3 pathway in its downstream cascade, which helps to promote carcinogenesis by controlling angiogenesis, cell cycle progression, and immune system escape of tumour cells [13]. IL-6 is also produced by tumour cells when STAT3 is overactive, creating a positive feedback loop. The abnormal activation of JAK2/STAT3 signaling mediated by IL-6 is strongly associated with the metastasis of human breast cancer [13, 14].

Oxidative Stress

Oxidative stress or an altered redox system develops from the excessive production of reactive oxygen species (ROS) or reactive nitrogen species (RNS) that aren't eliminated by endogenous antioxidants [15]. Although these ROS usually participate in cell signaling, high levels of superoxide radical (O2), hydroxyl radical (HO), and nonradical hydrogen peroxide (H2O2) can cause damage and harm to cells and tissues [15, 16]. Malondialdehyde (MDA), which is an indication of free radical-mediated lipid peroxidation, has been linked to an increase in antioxidant enzymes in people with type 2 diabetes (T2D) [17]. This connection may result from an adaptive response to prooxidants in the diabetic state [16, 17]. In this favorable environment, ROS can trigger carcinogenesis by acting as chemical effectors in the setting of a redox imbalance [17, 18]. ROS plays a significant role in the epigenetic regulation of cancer cells because they have been linked to both aberrant DNA hypermethylation and hypomethylation

CHAPTER 2

Neuroinflammatory Mechanism of Neuropathic Pain in Breast Cancer and Diabetes

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Abstract: The understanding of the complex relationship between the immune and nervous systems has significantly evolved in recent years. It is now recognized that the inflammatory response and interactions between these two systems play crucial roles in the development and progression of neurodegenerative diseases and injuries. The immune and nervous systems are intricately connected, with bidirectional communication pathways that allow them to influence each other's functions. This cross-talk is mediated by various signaling molecules including cytokines, chemokines, and neurotransmitters. Neuropathic pain is a debilitating condition that arises as a result of damage or dysfunction in the central nervous system (CNS) or peripheral nervous system (PNS). Neuropathic pain is a common pathological symptom of cancer and diabetes. Neuropathic pain can be generated by resulting injury to peripheral or central neurons through various neural pathways, ion channels, receptors, and neurotransmitters. In this article, we elaborate on the recent progress in the understanding of mechanism of the neuroinflammation. First, we provide current knowledge of neuroinflammatory molecules and their association with neuroinflammation. Subsequently, we describe recent advances in the understanding of the pathophysiology of neuropathic pain in PNS and CNS, emphasizing breast cancer and diabetes. Finally, we highlighted the current challenges of molecular understanding and diagnosis regarding targeted therapies for the treatment of neuropathic pain.

Keywords: Metabolic disorder, Neuroinflammation, Neuropathic pain, Neurodegenerative disease, Tumor microenvironment.

INTRODUCTION

The International Association for the Study of Pain has characterized pain as "a disagreeable sensory and emotional encounter linked to real or potential harm to bodily tissues" [1]. Neuropathic pain is a term used to describe pain that results

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from damage or disease affecting the somatosensory system. It encompasses a diverse range of pain syndromes and can be associated with a wide array of both peripheral and central nervous system disorders [2]. The mechanisms underlying neuropathic pain in these conditions are multifaceted and frequently involve neuroinflammatory processes. It can manifest in various disease states, including cancer and diabetes, and is characterized by persistent and often severe pain that is challenging to manage [3].

Cancer-related neuropathic pain is a frequently encountered issue, stemming from either the disease itself or as a result of the acute or chronic consequences of cancer treatment. For instance, chemotherapy-induced peripheral neuropathy affects approximately 90% of patients undergoing neurotoxic chemotherapy [4]. As per the data from the International Diabetes Federation, there are currently 382 million people worldwide suffering from diabetes [5]. Diabetes is recognized as one of the primary causes of diabetic neuropathy [6], a common complication characterized by nerve damage resulting from prolonged hyperglycemia, whereas in cancer, neuropathic pain can result from tumor-related nerve compression or infiltration, as well as the adverse effects of cancer treatments, such as chemotherapy-induced peripheral neuropathy [7].

Neuroinflammation is a specific term used to describe inflammatory conditions occurring within the nervous system. This phenomenon can lead to the significant issue of neuropathic pain, a condition characterized by pain resulting from damage or malfunction in the nervous system [8]. The neuroinflammatory mechanisms contributing to neuropathic pain in these conditions involve the activation of glial cells, the release of pro-inflammatory cytokines, and alterations in neuronal function [9, 10]. These processes create a state of heightened sensitivity within the nervous system, leading to the development and maintenance of neuropathic pain. Understanding these neuroinflammatory mechanisms is crucial for developing targeted therapies that can alleviate neuropathic pain and improve the quality of life for patients with cancer and diabetes. This brief overview sets the stage for a more in-depth exploration of these mechanisms in the context of neuropathic pain associated with cancer and diabetes.

NEUROINFLAMMATION

Neuroinflammation is a type of broad immune response, majorly of the CNS, involving cells like microglia and astrocytes. Increasing evidence suggests that neuroinflammation is one of the fundamental causes of several CNS diseases including Alzheimer's disease (AD), Parkinson's Disease (PD), and Multiple sclerosis (MS) [11]. Nonetheless, there is a debate surrounding whether

neuroinflammation plays a harmful or advantageous role in the development of CNS diseases [12, 13]. This hinges on the production of pro-inflammatory mediators versus anti-inflammatory mediators and/or growth factors during various stages of neuroinflammation. Neuroinflammation increases the susceptibility to cancer development and encourages all phases of tumorigenesis. Specifically, pro-tumorigenic inflammation supports cancer by impeding antitumor immunity, influencing the tumor microenvironment (TME), and delivering direct signals and functions that promote tumor growth to epithelial and cancer cells [14].

Neuroinflammation can be observed in both PNS, comprising peripheral nerves and ganglia, and the CNS, comprising the spinal cord and brain. It is marked by the infiltration of leukocytes and elevated production of inflammatory mediators within these areas [15, 16]. Neuroinflammation represents a localized type of inflammation, making it more efficient at triggering and maintaining pain compared to systemic inflammation. Emerging targets include chemokines, which facilitate interactions between neurons and glial cells, lipid mediators that act on neurons and glia to resolve inflammation, as well as other molecules that control neuroinflammation, such as proteases and WNT signaling molecules [14]. However, its clinical detection remains challenging, and further studies are necessary to determine the cellular prerequisites that modulate inflammation [14].

Neuroinflammatory Molecules

The blood-brain barrier (BBB), which is the endothelial layer, plays a pivotal role in comprehending how peripheral inflammation can lead to prolonged and detrimental neuroinflammation [10]. Initially, it was believed that inflammatory cytokines and other proteins were too large to access the brain from the bloodstream, but over the past two decades, various transport mechanisms have been discovered. BBB active transport systems have been observed facilitating the passage of tumor necrosis factors (TNFs) and interleukins (ILs) into the brain [17]. Certain regions with incomplete barrier properties at the blood-brain interface, known as circumventricular organs, serve as concentrated sites for cytokine transport [18]. Notably, cytokines like TNFα, IL-6, IL-1β, and others can compromise the integrity of the BBB, making it more permeable and allowing the entry of immune cells into the brain [19, 20]. Cytokine levels are known to modulate BBB permeability by affecting the tight junctions in endothelial cells within the brain's vasculature [21]. High cytokine levels can upregulate inflammatory cytokines and COX-2 transcription in the endothelium [9]. Damage to essential tight junction proteins, such as occludin, can lead to increased tight junction permeability, potentially affecting their interaction with the cell cytoskeleton. Furthermore, peripheral cytokines can stimulate the vagus nerve,

CHAPTER 3

Insulin and Hypoxia in Breast Cancer Cell Invasion and Migration

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Abstract: Uncontrolled cell division resulting in cancer is a significant contributor to mortality rates, with breast cancer being the most common form affecting women. When the disease progresses, the uncontrolled cell division can spread through the bloodstream to other parts of the body, making treatment through chemotherapy and radiation therapy challenging. As such, there is an urgent need for the discovery of new drugs and targets to combat this disease. This chapter delves into the physiological role of insulin and hypoxia in breast cancer cell invasion and metastasis, which can potentially increase the druggability of the pathway. It is a valuable resource for those researching new druggable targets in these pathways.

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Keywords: Breast cancer, Cell invasion and migration, Correlation, Hypoxia, Insulin.

INTRODUCTION

Breast cancer is a widely prevalent cancer that primarily affects women, with approximately 1.3 million new cases reported each year [1]. Developing targeted treatments for this disease requires a thorough understanding of the mechanisms of invasion and metastasis [2]. Malignant cells are typically found in breast tissues, particularly in the lactiferous ducts and lobules of the mammary gland [3, 4]. While nodal metastases serve as a significant prognostic index, identifying molecular alterations in cancer cells has been proposed as a way to identify node-negative carcinomas at risk of recurrence [5]. Breast cancer can be caused by a variety of factors, including hereditary predisposition, dietary habits, female gender, age, ionising radiation exposure, and other breast conditions. The most common type of breast cancer is invasive ductal carcinoma, accounting for 70-80% of all cases, while non-invasive ductal carcinoma, also known as ductal carcinoma in situ (DCIS), accounts for the remaining 20% [3, 4]. The status of disease progression and optimal treatment for breast cancer is largely determined by molecular features associated with the cancer lesions, such as oestrogen and progesterone receptor expression and human epidermal growth factor receptor 2 (HER2/neu) [3, 4].

Breast cancer patients with diabetes suffer from significantly worse overall survival and clinical morbidity when compared to non-diabetic breast cancer patients. This suggests a link between diabetes and the progression and migration of breast cancer cells. Several possible causes have been hypothesized, including hyperglycemia and hyperinsulinemia in type 2 diabetes. However, the root cause of this association between diabetes and breast cancer is still not fully understood. Therefore, it is important to gain a deeper understanding of the signaling pathways that facilitate cross-talk between diabetes and breast cancer.

Hypoxia in Breast Cancer

Breast cancer frequently experiences hypoxia or oxygen deficiency, due to insufficient angiogenesis, which leads to reduced oxygen supply to the tumour cells [6]. Hypoxia inducible factor 1a regulates hypoxia in solid tumours [6]. Most solid tumours are characterized by abnormally low levels of oxygen or hypoxia [6]. Hypoxia is linked to malignant progression, invasion, angiogenesis, changes in metabolism, and an increased risk of metastasis [7, 8]. Tumours with very low oxygen levels exhibit resistance to chemotherapy and radiotherapy [9]. Hypoxia, or low oxygen levels, plays a significant role in breast cancer metastasis. Studies confirm that tumours containing large hypoxic regions are more likely to

metastasize [10 - 12]. Hypoxia can modify gene expression, activate or inactivate genes, and enhance genomic instability, mRNA translation, and protein stability, all of which contribute to the metastatic process [11]. This can cause changes in the expression of genes associated with metastasis, angiogenesis, and tumour aggressiveness, such as chemokine receptor-4, urokinase, plasminogen activator receptor, cell motility factor receptor, autocrine motility factor receptor, lysyl oxidase, vascular endothelial growth factor-C, interleukin-8, and osteopontin [13]. Hypoxia-induced gene expression changes are linked to poorer prognosis and an increased potential for metastasis in breast cancer [14]. Hypoxia also upregulates the cell surface protein carbonic anhydrase IX (CA IX), which has been associated with poorer outcomes in breast cancer patients [13].

From clinical evidence, it appears that hypoxia is a crucial factor in breast cancer metastasis. By understanding the molecular pathways involved in hypoxia-induced metastasis, we may be able to provide better prognostic and therapeutic information to breast cancer patients [15, 16]. In support of this hypothesis, clinical measurements using techniques like polarographic needle electrodes indicate that breast tumors have lower oxygen levels when compared to normal breast tissue [17]. This low-oxygen environment affects the expression of certain genes associated with breast cancer and can also influence post translational modifications in cells [18, 19]. Tumor cells have hypoxia because of poor oxygen supply to their vasculature, and the transcription factor Hypoxia-inducible factor 1 (HIF-1) helps cells adapt to hypoxic conditions. HIF-1 is overexpressed in breast cancer and is associated with increased blood vessel density, tumor aggressiveness, and poor prognosis [19]. The HIF-1 complex is made up of two subunits, HIF-α and HIF-β, with HIF-α being sensitive to oxygen levels. The activity of HIF-1 is regulated by oxygen levels and controls gene expression involved in angiogenesis, metabolism, and cell survival during hypoxic conditions [19, 20].

Hypoxic conditions can cause changes in both the extracellular and intracellular matrix [20]. The degradation of the intracellular matrix is interpreted as a tissue stress signal, which triggers the induction of angiogenesis through specialized pathways [21]. This correlation between hypoxia and the extracellular matrix suggests the importance of these pathways in the progression of breast cancer [22]. Fibrotic foci and estrogen receptor overexpression in breast tumors can result in a more aggressive cancer phenotype and poorer prognosis. Inflammation, particularly the role of interleukin-1b (IL-1b), is also implicated in breast cancer progression and tumor invasiveness [23 - 25].

CHAPTER 4

Genetic Similarity between Type 2 Diabetes and Breast Cancer: A Brief Report

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Abstract: Recent progress in genetics research has accelerated our comprehension of complex disorders such as type 2 Diabetes Mellitus and breast cancer. Genome-wide association studies on a large scale have facilitated our exploration of the underlying pathology. Individuals with type 2 diabetes are at a higher risk of developing several types of cancer as a result of common risk factors, such as obesity, poor diet, aging, and low levels of physical activity. While several susceptibility genes have been identified, we must consider tissue specificity and direction of effect when investigating the shared genetic aetiology. Techniques such as Mendelian randomisation allow us to unravel the link between the two diseases and answer critical questions. By deconstructing the type 2 Diabetes GRS and studying genetic variants in relation to their biological function, we may be able to evaluate the causal association between different groups and various cancer types. Genetic research also has the potential to investigate epigenetic modifications that contribute to the development of cancer. This work explores the association between the genetic similarity between type 2 diabetes and breast cancer.

Keywords: Breast cancer, Gene disease association, Type 2 Diabetes, co-signalling mechanism.

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INTRODUCTION

Insulin resistance in target organs and pancreatic β-cell dysfunction are the two main causes of relative insulin insufficiency that define type 2 diabetes. Patients under 25 years old with type 2 diabetes have particular challenges, since their complicated phenotypes may require decades of rigorous therapy to avoid the development and progression of microvascular and macrovascular problems [1]. Dysregulation of the metabolism of fats and proteins is a hallmark of type 2 diabetes mellitus (T2DM), which can be caused by either insulin resistance or inadequate insulin secretion. About 90% of cases of diabetes tend to fall under type 2 diabetes among the other types (type 1 and gestational diabetes). Both microvascular problems, such as neuropathy, nephropathy, and retinopathy, and macro-vascular problems, such as cardiovascular comorbidities, are very likely to occur in people with type 2 diabetes [2]. The intricate interaction of genetic, epigenetic, and environmental variables leads to type 2 diabetes. The first putative gene that was consistently linked to type 2 diabetes was PPARG, which codes for the nuclear receptor PPAR-γ. The PPAR- γ receptor is a very attractive candidate gene because it is a molecular target for thiazolidinediones, a family of insulin-sensitizing medications used to treat type 2 diabetes. Similarly, there are several other candidate genes that are prone to mutation giving rise to type 2 diabetes [3].

The most common cancer in women is breast cancer. Around 1.5 million women worldwide receive a breast cancer diagnosis each year, accounting for 25% of all cancer-stricken females. Breast cancer is a metastatic disease that frequently spreads to distant organs such as the liver, brain, lung, and bone [4]. Like other forms of cancer, breast cancer is caused by epigenetic changes, which have no effect on the original DNA sequence. These changes lead to aberrant transcriptional regulation, which modifies the expression patterns of genes involved in the survival, proliferation, and differentiation of cells. DNA methylation is frequently linked to certain histone changes that work together to alter chromatin structure and suppress the expression of certain genes. The development of novel approaches for breast cancer detection and therapy has been greatly influenced by the recent advances in the field of epigenomics, which have also had a significant impact on our understanding of the processes behind breast cancer [5].

Studies have shown that regardless of age, obesity, benign breast illness, reproductive variables, physical activity, and alcohol intake, women with type 2 diabetes had a slightly higher risk of breast cancer than those without the condition [6]. There are numerous scientific evidences, both preclinical and clinical, which suggest that there are common genes associated with the pathogenesis and development of type 2 diabetes and breast cancer. Diabetes is

known to increase the chance of developing endometrial cancer and pancreatic cancer [7].

INVOLVEMENT OF BRCA1 GENE IN DIABETES AND BREAST CANCER

Although obesity and hyperinsulinemia are well-known risk factors for breast cancer, and given that BRCA1 has a variety of metabolic functions, it is important for medical reasons to investigate how a damaged BRCA1 pathway affects the relationship between diabetes and breast cancer.

BRCA1, commonly known as the 'caretaker gene' is a tumour suppressor gene. It is mainly involved in the repairing of damaged DNA and chromosomal breaks found mainly in breast tissues. The BRCA1 protein interacts with histone deacetylase complexes *via* the C-terminal domain and RNA polymerase II through its interaction with the latter. In light of this, this protein is involved in transcription and double-strand DNA break repair. Mutated forms of this particular gene result in the loss of the tumour suppressive property leading to the development of breast cancer [8].

Due to a relaxation of the inhibitory effect of wild-type BRCA1 on acetyl-CoA carboxylase, a crucial enzyme in fatty acid synthesis, mutant BRCA1 has been linked to enhanced lipogenesis [9]. It has been seen that circulating fatty acids result in triglycerides production, inflammation, and the development of insulin resistance. Lack of insulin sensitivity develops due to mutation of BRCA1 resulting in reduced levels of IGF binding proteins. BRCA1 or BRCA2 mutation carriers had a twofold increase in diabetes risk in the 15 years following breast cancer diagnosis. It's important to note that the danger was considerably higher for women whose BMI was above 25 [10].

Moreover, during type 2 diabetes, there has been an increase in DNA methylation of the BRCA1 gene by 40 times. DNA methylation is responsible for silencing the expression of tumour suppressor genes by repressing the transcription of their promoter regions [11].

ROLE OF THE INSULIN RECEPTOR (IR) ENCODED BY THE INSR GENE

When our body experiences an elevation in the blood glucose level, insulin gets secreted from the pancreatic β cells. Although the liver, adipose tissue, skeletal muscle, and brain are the primary target tissues for insulin, IRs are widely expressed and may also be found in the heart, lung, pancreas, kidney, placenta, vascular endothelium, monocytes, granulocytes, fibroblasts, and erythrocytes. The

CHAPTER 5

Diabetes, Obesity, and the Risk of Breast Cancer: An Attempt to Decipher the Interconnections

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Abstract: Diabetes and obesity are linked to a higher risk of breast and other cancers. In addition to the direct effects of hyperglycaemia and insulin resistance on breast cancer cells, the complications of diabetes, obesity, and metabolic syndrome are characterised by a dysfunctional endothelium and increased inflammation in tissue phenomena that are intimately related and occur concurrently in breast cancer progression. However, the complexity of the underlying mechanisms, together with the interplay of diet and physical activity contributing to energy balance and the role of adipose tissue, hyperglycaemia, insulin resistance, and glucose intolerance, pose challenges to our understanding of the basis of this increased risk. In addition to being an established risk factor for postmenopausal breast cancer, abdominal obesity, also known as central obesity, may also raise the chance of triple-negative breast cancer, which is more common in premenopausal women. This chapter explains how various parameters like oestrogen, mammography, density, adipokines, insulin-signalling pathway activation, and inflammatory conditions, may play a part in this seemingly contradictory association. A key focus of this chapter is to better understand the impact of obesity and diabetes in the pathogenesis of breast cancer and, hence, provide some clarity into the interrelationships involved in between.

Keywords: Breast cancer, Diabetes, Hyperglycaemia, Insulin resistance, Obesity.

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INTRODUCTION

Breast cancer is one of the most common cancers and holds approximately 24.5% and 15.5% of all cancer cases and cancer deaths in women. With an estimated 2.3 million new cases worldwide, breast cancer is currently one of the most frequently diagnosed malignancies and the 5th cause of cancer-related deaths [1, 2]. The data derived from the Global Burden of Cancer (GLOBOCON) report for the year 2020 reveals that approximately one out of every eight instances of cancer diagnosed ultimately manifests as breast cancer [3]. The primary risk factors associated with the development of breast cancer encompass several key elements. These include advancing age, a personal history of breast cancer, histologic risk factors, familial and genetic predispositions, reproductive factors, utilisation of exogenous hormones and oral contraceptives, as well as exposure to tobacco and an early onset of menstruation [4, 5]. Metabolic syndrome (MetSyn) involves metabolic abnormalities, hypertension, central obesity, insulin resistance, and dyslipidaemia. Both inherited and acquired variables that contribute to the ultimate pathway of inflammation are involved in the aetiology of MetSyn [6]. The prevalence of diabetes, a metabolic condition characterised by increased amounts of glucose in the bloodstream, has seen a significant rise in recent years, paralleling the worldwide increase in obesity rates. Type 2 diabetes (T2D) and obesity have been found to be correlated with an elevated risk of postmenopausal breast cancer [7, 8]. The prevalence of type 2 diabetes, commonly referred to as the "silent pandemic," is growing around the world. Diabetes has been hypothesised to raise the risk of developing breast cancer through a variety of different biochemical mechanisms. These pathways include alterations in the hyperinsulinemia/insulin-like growth factor (IGF) axis, hyperglycaemia, fat-induced inflammation, and changes in sex hormone levels [9, 10]. Recent scientific investigations have revealed compelling evidence linking the presence of excess body weight and obesity to elevated susceptibility for the development of adenocarcinoma in various anatomical sites, including the oesophagus, gastric cardia, thyroid, pancreas, colon, rectum, endometrium, prostate, gallbladder, ovary, and breast, as well as multiple myeloma [11]. People who are obese are known to have adipose tissue that produces inflammatory cytokines and mediators, which creates an environment that is favourable for the progression of breast cancer and makes it easier for the disease to invade and spread [12]. The presence of obesity has consistently demonstrated a negative correlation with overall survival rates among individuals diagnosed with early-stage HER2+ breast cancer [13, 14]. Understanding the complex relationship between diabetes, obesity, and breast cancer is crucial because of the serious health consequences it bears. These three ailments are not independent things; rather, they are intricately tangled and have the potential to affect a person's general health and wellbeing [15]. Obesity raises the risk of diabetes and breast cancer and is often a result of

sedentary behaviour and poor food choices [12]. It fosters an environment that is favourable for the growth of cancer cells while also contributing to insulin resistance and inflammation, two major elements in the development of type 2 diabetes. Diabetes, which is characterised by high blood sugar, might hasten the spread of breast cancer by encouraging inflammation and changing hormone levels [9]. This chapter explores the intricate interrelationships among obesity, diabetes, and breast cancer, while examining the influence of obesity and diabetes on the development and progression of breast cancer. The chapter also addresses prospective treatment strategies, which comprise pharmaceuticals derived from diverse natural sources, repurposed medications, traditional therapeutic methods, dietary modifications, and surgical procedures.

PATHOPHYSIOLOGY OF BREAST CANCER IN NON-OBESE, NON-DIABETIC SUBJECTS

DNA damage and genetic abnormalities are the root causes of breast cancer, and exposure to estrogen can play a role in fostering these conditions. Sometimes, cancer-causing genes like BRCA1 and BRCA2 are passed down *via* families, individuals who possess the BRCA1/BRCA2 mutation are approximated to have a tenfold increased likelihood of developing breast cancer. The BRCA1 gene, situated on chromosome 17, functions as a tumor suppressor gene by encoding a nuclear protein that plays a crucial role in preserving the stability of the genome. In conjunction with other suppressor genes, signal transduction genes, and DNA damage-detecting mechanisms, this particular protein forms a protein complex that binds to RNA polymerase II and engages with histone deacetylase, thereby influencing the processes of transcription, DNA repair, or recombination. The BRCA1 protein, in conjunction with the BRCA2 gene product, a tumor suppressor gene situated on chromosome 13, plays a significant role in the process of repairing double-stranded DNA breaks by homologous recombination [16]. Thus, there is an increased chance of developing breast cancer if there is a family history of either ovarian or breast cancer. The immune system of a healthy person seeks out and destroys cells with faulty DNA or unnatural growth patterns. Breast cancer originates from an initial genetic alteration, which subsequently triggers a cascade of molecular modifications in the epithelial cells that line the ducts or lobules of the breast. Elevated concentrations of endogenous oestrogens, in conjunction with various growth factors, have been observed to expedite the progression of breast cancer at multiple stages. Additional significant factors contributing to the progression of breast cancer encompass the influence of exogenous oestrogens and early life occurrence, including environmental encounters with viruses, radiation, and toxins [17]. The P13K/AKT pathway and RAS/MEK/ERK pathway exert cellular protection through the inhibition media-

CHAPTER 6

FAT Cadherine and Wnt Signaling in the Progression of Breast Cancer with Hyperglycemia

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Abstract: Breast cancer has continued to be one of the most common causes of cancer death among females without sparing either those in modern societies or rural communities. Breast cancer is, in general, the uncontrolled cell growth in the mammary glands. This encompasses stromal and epithelial cells as the major cause of breast cancer. The disruption of communication between stromal and epithelial cells is one of the inducers of breast cancer. The mechanism surrounding this uncontrolled cell growth is postulated to be due to the role played by cadherin molecules and WNT signaling in mammary gland tumorogenesis and the hyperglycemia-driven modulation of the progression of breast cancer. Among different FAT cadherin molecules, repression of FAT4 mediates the Wnt signaling cascades, which regulate tissue homeostasis, vascularization, tumorigeneses, cell invasion, and metastasis. The epithelial-to-mesenchymal transition (EMT), which is promoted by transforming growth factor beta (TGF-beta) through the Wnt Signaling pathway, leads to the progression of breast cancer. This fundamental discussion may contribute to designing new signaling-targeted therapeutic approaches to mitigate breast cancer and associated factors for hyperglycemia.

Keywords: Breast cancer, Cadherins, Hyperglycemia, Hippo signaling pathway, Wnt signaling pathway.

INTRODUCTION

Breast cancer is the second leading cause of death worldwide and is the most frequent occurring malignancy in women. According to data from the Global

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Cancer Observatory, under WHO, in 2021, a total of 6,84,996 deaths and 22,61,419 new cases have been recorded worldwide [1]. According to the world life expectancy, the survival rate from breast cancer can vary between 21.39% and 1.49% depending upon the severity and age of the patient (*https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf*). Epidemiological observations showed a constant rise in new cases of breast cancer in both industrial and developing countries [2]. Its occurrence not only is triggered by several genetic changes, but also several lifestyle and environmental factors playing prime roles in the onset of breast cancer [3]. Besides, factors like age, obesity, altered regulation of female hormones, nulliparity, and late menopause may act as an inducer in the onset of breast cancer in postmenopausal women [4]. Extensive use of hormonal medications like contraceptive pills may play a potent risk factor in the onset of breast cancer [5]. Breast tumours are often benign and curable through surgery, but one-quarter of them are latent and insidious in character, thus allowing the tumour to grow slowly but with early metastasis [6]. There is a switch mechanism that transforms normal breast cells into cancerous ones. A switch in the molecular regulation of the mammary gland results in the development of tumours, mostly benign, but once they become malignant is a matter of great concern.

Cell-to-cell adhesions are important for the development of multicellular organisms and the processes of animal morphogenesis. Cell-to-cell adhesion and cell-microenvironment interactions mediated by cellular adhesion molecules (CAMs) are necessary for major cellular functions, such as apoptosis, cell growth, cell migration and cell differentiation [7]. A large superfamily of signaling proteins called cadherins consists of six types of proteins: classical, FAT, daschous, flamingo, protocadherins, 7-pass transmembrane, and desmosomal cadherins [8, 9]. These proteins operate as transmembrane receptors that mediate calcium-dependent homophilic and heterophilic interactions between cells [10]. Members of the cadherin superfamily provide cell-to-cell contact and communication in many different organ systems that are characterized by five repeated cadherin-specific motifs in their extracellular domains. This motif is approximately a 110-amino-acid peptide molecule that mediates homophilic interactions with other cadherin molecules, forming dimers that then interact with other dimers on neighboring cells [11]. These interactions are crucial for enhancing the cell's ability not only to interact with neighboring cells but also for inter-cell signaling. Any disruption in cadherin molecules or any miscommunication between cells can lead to the development of cancerous cells. The purpose of this review is to discuss the role and interrelationship of FAT cadherin molecules and interleukins in breast cancer development, as well as to report and establish target-specific phyto-modulation of the Wnt signaling pathway in breast cancer.

Treatment of breast cancer mainly relies upon chemotherapy, which includes the use of many chemicals that have been proven to indiscriminately damage both normal and malignant cells. Although, chemotherapeutic treatment may delay tumour progression significantly; nonetheless, recurrence is inevitable with an array of side effects, which contributes to high mortality rates Table **1**.

Table 1. Chemotherapeutic drugs often used in breast cancer treatment and their possible side effects (Laskar *et al.*, 2020; Liao *et al.* 2013).

Chemotherapeutic Agents	Side Effects
Cisplatin	Nephrotoxicity.
Cyclophosphamide	Infertility, loss of appetite, nausea, skin and nail discoloration, temporary hair loss, vomiting.
Doxorubicin	Alopecia, anaemia, Impaired cognitive function, infertility, low blood counts, nausea, and vomiting.
Epirubicin	Cardiotoxicity, hair loss, low blood counts, nausea, respiratory problems.
Methotrexate	Anaemia, diarrhoea, jaundice, loss of bone density, weight gain.
Paclitaxel	Alopecia, arthralgia, hypersensitivity, myalgia, nausea, peripheral neuropathy, vomiting.
Raloxifen	Flu, hot flashes, joint and muscle pain, rhinitis, thrombosis (deep vein thrombosis in rare cases).
Tomaxifen	Cardio-respiratory toxicity, Abnormal vaginal bleeding, tenderness as well as numbness in the face, head, and legs.

To overcome such fallacies, currently, a global focus is now on the use of phytomedicine against several tumor abnormalities. Phytomedicines are herbal medicines that use phytochemicals (non-nutritive plant chemicals with therapeutic and healing properties) that have existed since the advent of human civilization. Several phytochemical compounds have been proven to cease breast cancer development in different experiments. WHO reports that approximately 80% of the global population in developing countries rely on naturally available herbs and traditional medicine for their primary health care requirements [12]. Phytochemicals have also been responsible for the aberration of Wnt signaling, by increasing the activity of GSK-3β in the pathophysiological aspects of cancer and its metastasis [13]. Phytochemicals have also been shown to effectively moderate Wnt signaling pathways in many ways and thus are able to control breast cancer [14]. Although, the use of phytochemicals is reported to reduce the chances of development of side effects in patients and is also cost-friendly, but needs to be confirmed through more randomized clinical trials. The chapter has been written on a collection of published articles from several renowned scientific journals on

CHAPTER 7

Impaired Glucose Metabolism and Oxidative Stress of Diabetes Mellitus in Causation of Breast Cancer

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Abstract: Breast cancer (BC) and Diabetes Mellitus (DM) are medical conditions that are becoming more common in many developed nations. When compared with healthy individuals, diabetic people have an elevated risk of BC and more fatalities from the disease. This implies an association and that the two conditions share risk factors and pathophysiological pathways. Although the causal processes beneath this connection remain incompletely understood, plausible ties include hyperinsulinemia, insulin resistance, oxidative stress, chronic inflammation, hyperglycaemia, and hormonal. Each of these conditions has been proposed for fostering tumour progression in numerous manners. Although hyperglycaemia is one of the most extensively researched metabolic abnormalities in DM, the consequences of high blood sugar on malignancy have garnered less scrutiny than the influence of insulin, insulin-like growth factor-1 (IGF-1), oxidative stress, and chronic inflammation on the progression of cancer. The purpose of this chapter is to provide insight into the link between impaired glycaemic status and oxidative stress of DM with the causation, type, progression, and mortality of BC. Several unexplored areas exist, and new hypotheses may emerge in the days to come.

Keywords: Breast cancer, Diabetes mellitus, Glucose metabolism, Oxidative stress.

INTRODUCTION AND EPIDEMIOLOGY

Breast cancer (BC) is the most common cancer among women around the globe. BC is a complex and multifactorial disease. BC is caused by malignant cells that proliferate in an uninhibited manner, invading the surrounding tissue as well as spreading to any other area of the body (metastasis). Any area of the breast may

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be affected primarily, or the breast may be affected by cancer of any other location spreading to the breast. Over the past three decades, there has been an upsurge in its occurrence and mortality rates owing to an increase in the associated risk factors like obesity, diabetes mellitus (DM), nulliparity, sedentary lifestyle, alcohol dependence and smoking; improved cancer detection, and improved cancer registries and documentation. As per Globocan 2020, 2.3 million new cases of breast cancer have been reported worldwide, rendering it one of the most diagnosed cancers and the fifth-ranked cause of cancer-related mortality. Currently, 80% of patients with BC are above 55 years of age and often diagnosed with diabetes [1, 2]. The proportion of BC increases with age and is linked to hereditary factors, hormonal factors, and benign breast diseases as well as a family history of breast cancer. Over 20% of people in developed nations suffer from obesity. Obesity is another established risk factor for BC and has been associated with an elevated risk of postmenopausal breast cancer [3].

Type 2 diabetes mellitus (T2DM) is a serious health burden affecting more than 7% of adults and about 15% of geriatric demographics in developed nations. Among the elderly population, DM has been found to affect 10-20% of breast cancer patients [3]. Obesity and older age are risk factors for T2DM, which are also related to breast cancer. Research involving 38,000 women reported 15% of cases with diabetes and showed that they had a higher risk of developing an advanced stage of breast cancer in comparison to the non-diabetic group [4]. Several comparative cohort and case-control studies have observed a 10–20% higher probability of occurrence of BC linked to T2DM. Gestational diabetes, but not type 1 diabetes, could be associated with an elevated risk of BC. Furthermore, diabetes and its associated consequences might negatively impact cancer screening and treatment, thus affecting the patient's well-being [5].

In a meta-analysis to investigate the association between DM and the risk of BC, it was observed that the risk of breast cancer in women with T2DM was increased by 27%, although the risk was decreased by 16% after adjustment for body mass index (BMI) [6]. In another meta-analysis of primary observational studies, there was a 29% increased risk of BC in males with DM but was not statistically significant (OR 1.29, 95% CI 0.99–1.67) [7]. There is some epidemiological evidence that T2DM and its medications may differentially impact risk across the major breast cancer molecular subtypes and potentially have the greatest impact on the risk of triple-negative disease [8]. In breast cancer patients with T2DM prior to diagnosis, the mortality rate is increased compared to individuals without diabetes (hazard ratio 1.17). The mortality increased further when T2DM was diagnosed at or after the breast cancer diagnosis (hazard ratio 1.39) [9].

In another study, in spite of comparable accessibility to treatment, women with DM had a 40% higher all-cause and 25% higher cancer-specific mortality rate compared with those without DM. However, when adjusted for comorbidities such as cardiovascular disease, renal disease, and dementia, the excess all-cause mortality associated with diabetes decreased to 16%, and the difference in breast cancer-specific mortality was no longer significant. Therefore, diabetes-related morbidity is responsible for the poorer prognosis in BC with DM rather than DM itself [10].

MECHANISMS LINKING T2DM TO BREAST CANCER

T2DM, which has several aetiologies, is characterized by persistent hyperglycemia that occurs because of impairment of the main biomolecule metabolism, insufficient insulin synthesis, and action. Glycosuria, polydipsia, and polyuria are all common symptoms of T2DM. The consequences and associated complications of T2DM may result in several co-morbidities and lethal conditions such as organ damage in various ways, including the female breast [11]. The association of DM with BC has been demonstrated through three mechanisms: expression and stimulation of insulin, and insulin-like growth factor (IGF-1) pathways, and modulation of endogenous sexual hormones. Several studies have found evidence of a link connecting DM and BC [5]. The Warburg effect, a prolonged state of hyperglycemia that may raise the likelihood of BC, is another route that has been proposed [6]. Increased levels of inflammatory cytokines and IGF-1 are linked to hyperglycemia, which can have a direct or indirect impact on uncontrolled cell proliferation, apoptosis, and metastasis [12]. High blood sugar level stimulates many signalling pathways that work together to regulate the behaviour of cancer cells, including invasion, migration, multiplication, and resurgence [13], Fig. (**1**).

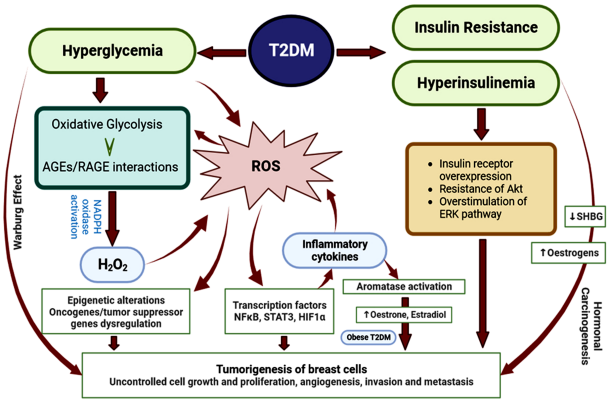

Fig. (1). Mechanisms linking T2DM to the risk of breast cancer.

CHAPTER 8

Role of Igf-Induced Tumour-Associated Macrophage (TAM) in Breast Cancer: Decoding the Signalling Cascade and Possible Target

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Abstract: Breast cancer (BC) is a multifactorial disease with a poor prognosis. Tumour-associated macrophages (TAMs), also known as TAMs, play a significant role in promoting tumour growth, facilitating angiogenesis, participating in tissue remodelling processes, and suppressing the adaptive immune response within breast tumours. TAMs usually located within the microenvironment of solid tumours or infiltrating the tumour's tissues, and their presence in BC is linked to an unfavourable clinical prognosis. The IGF signalling system, comprising IGF1, IGFBPs, and IGFR1, plays a key role in cancer development and progression, and its association with TAM in breast cancer has been extensively investigated. In this review, we delve into the interaction between TAM and IGF1 signalling in BC. We also proposed the concept of M2 polarization - as a possible alternative to cancer chemotherapy.

Keywords: Breast cancer, Insulin-like growth factor, Macrophage polarization, Macrophage, Tumor-associated macrophage, Tumour microenvironment, TAM.

INTRODUCTION

Breast cancer (BC) has gained significant global attention due to its alarming prevalence, as evidenced by the 2020 statistics from the World Health Organization (WHO), which reported a staggering 2.3 million newly diagnosed cases of breast cancer in women, resulting in 685,000 fatalities. This data highlights the fact that breast cancer has become the most widespread form of cancer worldwide, affecting the lives of approximately 7.8 million individuals by the end of 2020. According to the Global Cancer Statistics 2020: GLOBOCAN, which analysed cancer incidence and mortality rates across 185 countries, BC has now surpassed lung cancer as the most diagnosed malignancy, with an expected

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2.3 million new cases (11.7%). Other prevalent cancers include lung (11.4%), colorectal (10.0%), prostate (7.3%), and stomach (5.6%) [1].

BC typically affects the lobules, ducts, and connective tissue, exhibiting a wide range of physiological characteristics and clinical manifestations. It is a complex and multifaceted disease with diverse biological attributes, clinical implications, and molecular classifications. These classifications are often based on the presence or absence of specific hormone receptors as indicated by immunohistochemical analysis, including estrogen receptor positivity (ER^+), progesterone receptor positivity (PR^+), human epidermal growth factor receptor positivity ($HER2^+$), and the distinctive triple-negative breast cancer (TNBC), characterised by the absence of expression of any of the receptors [2]. Furthermore, TNBC is subdivided into six categories: luminal androgen receptor (LAR), immunomodulatory, mesenchymal, mesenchymal stem cell-like (MSL), basal-like 1 (BL-1), and basal-like 2 (BL-2) [3]. Additionally, breast cancer is classified into five commonly used molecular subtypes: Luminal A-like ($ER^+PR^+HER2^-Ki67^{low}$), Luminal B/$HER2^-$ like ($ER^+HER2^-Ki67^{high}$ or PR^-), Luminal B/$HER2^+$ like (ER^+HER2^+), HER2-type ($ER^-PR^-HER2^+$), and Triple negative/basal-like ($ER^-PR^-HER2^-$) [4, 5]. Genetic mutations in recognized but rare genes, including BRCA1, BRCA2, PTEN, TP53, CDH1, or STK11, can account for up to 25% of hereditary breast cancer cases, increasing the lifetime risk of developing breast cancer to as much as 80%. Rare, moderate-penetrance gene mutations in CHEK2, BRIP1, ATM, and PALB2 are linked to an additional 2%–3% of cases, doubling the risk [6].

Cancer development is intricately linked to complex signalling pathways that regulate normal cell growth and are often co-opted by cancer cells and cancer stem cells (CSCs). CSCs share similarities with normal stem or progenitor cells, including self-renewal potential and multi-lineage differentiation capacity, facilitating tumour growth and diversity [7]. Various signalling pathways, such as mitogen-activated protein (MAP) kinase [8, 9], PI3K/Akt/nuclear factor kappa B (NF-κB) [10, 11], transforming growth factor beta (TGF-β) [12, 13], hedgehog (Hh) [14, 15], Notch [16, 17], Wnt/-catenin [18], and Hippo pathways [19 - 21], can contribute to the generation of CSCs. Cancer stem cells possess the ability to self-renew and drive tumour growth [7, 22, 23]. Understanding the metabolic aspects of CSCs, particularly in breast cancer, remains an evolving area of research. Elevated insulin levels, often associated with obesity and diabetes, represent an independent risk factor for tumour development and recurrence in various cancer types, including breast cancer. The insulin/Insulin-like growth factor (IGF) signalling pathway activated by hyperinsulinemia promotes breast cancer development, as demonstrated in preclinical studies with mouse models [24].

Inflammation is commonly associated with cancer tissues, characterized by leukocyte infiltration and the presence of cytokines and chemokines. Tumour-associated macrophages (TAMs) play a significant role in influencing tumour growth and prognosis [25]. Hypoxic areas within tumours can trigger pro-angiogenic programs in TAMs, leading to the production of angiogenic molecules like vascular endothelial growth factor (VEGF), tumour necrosis factor -α (TNF-α), basic Fibroblast growth factor (bFGF), and CXCL8. This indirect pathway amplifies angiogenesis, further supporting tumour growth [26].

A better understanding of the role of TAM in tumours and its possible role in complex growth signal pathways are yet not discussed in detail. In this review, we delve into IGF signalling and its association with TAM in breast cancer. Herewith, we also proposed the concept of macrophage polarization – as a possible alternative to cancer chemotherapy. We hope the readers will find new insight and perspective about TAM in BC.

IGF SIGNALLING IN BREAST CANCER

IGFs, structurally composed of two subunits interconnected by disulfide bonds, bear a resemblance to insulin [27]. IGF1 and IGF2 are the primary types among several varieties of IGFs (Fig. **1**). These growth factors exert their physiological effects through three receptors: insulin-like growth factor 1 receptor (IGFR1), insulin-like growth factor 2 receptor (IGFR2), and insulin receptor (IR) [27, 28]. When IGF1 and IGF2 bind to their respective receptors, they activate tyrosine kinase, setting off a cascade of cellular responses. IGF1 exhibits affinity for IR/IGFR1 hybrid receptors, while IGF2 can bind to IGFR2, IR-A receptor, and IGFR1/IR-A hybrid receptors. IGFR2 primarily functions to reduce IGF2 bioavailability by directing IGF2 toward degradation [29]. IGFs typically form complexes with insulin-like growth factor binding proteins (IGFBPs) that protect them from degradation. Six soluble IGFBPs and IGFBP proteases have been identified to regulate IGF function [30].

Almost every type of cell expresses IGF1R and IGFs can promote growth and differentiation in a variety of tissues [31]. The IGF-1 receptor (IGF-1R) comprises two identical alpha (α) subunits and two identical beta (β) subunits in its structure (Fig. **2**). When insulin-like growth factor (IGF) binds to the IGF-1 receptor situated on the cell surfaces of specific target tissues, it triggers the activation of the receptor's tyrosine kinase activity. This activation, in turn, causes a change in the shape or configuration of the beta subunit of the receptor [32]. Src homology collagen (SHC) and insulin receptor substrates (IRSs) are two of the several substrates that are phosphorylated by an active receptor.

CHAPTER 9

Recent Advances in Medicinal Plant Research in the Concomitant Management of Diabetes and Breast Cancer

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Abstract: Both diabetes and breast cancer are well-established diseases with similar underlying causes that can be influenced by various risk factors. Research suggests that insulin can play a significant role in the spread of breast cancer cells. Moreover, certain medicinal plants have antidiabetic and anticancer properties, making them promising candidates for dual-acting therapies. This article provides a review of the current scientific literature on these plants, including a tabular summary of the findings. By exploring the potential of these medicinal plants further, there is a possibility of developing effective natural therapies to control the invasion and migration of breast cancer cells in diabetic patients.

Keywords: Anti-diabetic, Anti-cancer activity, Breast cancer cell, Concomitant effect, Ethnopharmacological phytomolecules, Invasion, Migration, Medicinal plants.

INTRODUCTION

Cancer and diabetes are among the leading causes of death in the United States, according to the National Center for Health Statistics report (2021) [1]. In 2020, the Centers for Disease Control and Prevention reported 1,603,844 new cancer cases and 602,347 deaths due to cancer in the United States. The country reported

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403 new cancer cases and 144 cancer deaths per 100,000 people. Among all types of cancer, breast cancer is the second most common cancer among women in the United States [2]. Each year, around 240,000 women and 2,100 men in the United States are diagnosed with breast cancer, and about 42,000 women and 500 men die from it [2]. Diabetes is a widespread chronic health issue, and currently, around 37.3 million people in the United States suffer from it [3]. Studies have indicated that diabetes is a risk factor for all-site cancer in women and men, but women are slightly more at risk than men [4]. Diabetes mellitus has been associated with a higher risk of breast cancer, along with other types of cancer [5 - 8]. Up to one-third of breast cancer patients have diabetes, and women with diabetes are 40% more likely to die from breast cancer than women without diabetes [9 - 11]. Similarly, women with diabetes are 23% more likely to develop breast cancer than women without clinical diabetes [8, 12]. Diabetes and breast cancer share similar risk factors, and diabetes induces several changes in different hormonal systems, such as insulin, insulin-like growth factors, estrogen, and other growth factors, which may affect the development of breast cancer [13].

Insulin appears to play a crucial role in the movement and spread of breast cancer cells. Women who possess traits associated with insulin resistance syndrome, such as obesity (postmenopausal), central obesity (premenopausal and postmenopausal), high levels of natural insulin, clinical diabetes, and physical inactivity, are at a higher risk for breast cancer [14]. Women with breast cancer who also have diabetes mellitus have a 17% greater chance of dying from breast cancer [15]. Furthermore, diabetic symptoms can mimic those of breast cancer and worsen the effects of the disease [16]. Various ethnopharmacological studies have shown that medicinal plants and phytochemicals can have anti-diabetic and anticancer effects on breast tumors in diabetic patients. This review article examines the scientific literature on medicinal plants and phytochemicals that have dual anti-diabetic and anticancer effects to help identify potential therapies for controlling the invasion and spread of breast cancer cells in diabetic patients. By analyzing the published literature on almost 60 medicinal plants in tabular form, this review aims to provide further insight into the potential of phytochemicals in preventing the spread of breast cancer cells in diabetic patients.

PATHOLOGY OF DIABETES MELLITUS

Diabetes mellitus is a chronic metabolic disorder that affects both the endocrine and metabolic systems [16]. A combination of genetic and environmental factors causes it. The disorder is characterized by elevated blood glucose levels or hyperglycemia, which occurs when the body cannot properly regulate blood sugar levels due to abnormalities in carbohydrate, protein, fat, electrolytes, and water metabolism. This can be caused by two primary factors: defective insulin

secretion by pancreatic β-cells or the inability of insulin-sensitive tissues to respond appropriately to insulin, or sometimes by a combination of both factors. Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision [17]. Chronic hyperglycemia can also lead to impaired growth and susceptibility to certain infections [16, 17].

There are two major types of diabetes: Type 1 Diabetes (T1D) and Type 2 Diabetes (T2D). T1D is an autoimmune disease that leads to the destruction of insulin-producing pancreatic beta cells, making the body unable to produce adequate quantities of insulin, which results in persistent hyperglycemia [17, 18]. Symptoms of T1D can develop at any age, but it is commonly known as insulin-dependent or juvenile diabetes. Long-term hyperglycemia may lead to diabetic ketoacidosis, which can be life-threatening. Life-long insulin replacement is required for such individuals. Genetics plays a pivotal role in the development of T1D, although environmental factors cannot be completely overlooked [18].

T2D is the most common form of diabetes and is also known as non-insulin-dependent mellitus, adult-onset diabetes, or simply diabetes mellitus. In this condition, the body develops insulin insensitivity or insulin resistance in the target tissues. As a result, the pancreas produces more insulin to reduce blood glucose levels. Eventually, the pancreatic beta cells are unable to make enough insulin to meet the body's needs. The risk factors for T2D include obesity, impaired glucose tolerance, insulin resistance, ethnic background, sedentary lifestyle, family history, age, polycystic ovarian syndrome, *etc.* Although T2D is commonly associated with adults, it can also affect kids and teens due to childhood obesity [18, 19].

PATHOLOGY OF BREAST CANCER & WORLD SCENARIO

Breast cancer is a prevalent disease among women, accounting for more than 1 in 10 new cancer diagnoses each year [19]. According to the World Health Organization (WHO), breast cancer caused 685,000 deaths globally in 2020. It has surpassed lung cancer as the most commonly diagnosed cancer among women, with an estimated 2.3 million new cases (11.7%), followed by lung (11.4%), colorectal (10.0%), prostate (7.3%), and stomach (5.6%) cancers [20]. Although both men and women are at risk of getting breast cancer, women are more prone to this disease. Early menarche, late menopause, and obesity in postmenopausal women increase the risk, and studies have shown that high concentrations of endogenous oestradiol are associated with an increase in risk [21]. A family history of breast cancer also significantly increases the risk ratio [22], with approximately 13-19% of patients diagnosed with breast cancer reporting a first-degree relative affected by the same condition [23]. Breast cancer

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Asis Bala

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