REVIEW

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EVOLUTION OF METFORMIN IN BREAST CANCER THERAPY IN LAST TWO DECADES: A REVIEW

Among women, breast cancer is one of the most prevalent cancers. The disease has a complex etiology, with multiple biological pathways contributing to its development. As insulin signaling has mitogenic effects, glucose is a necessary cellular metabolic substrate, and the growth and metastasis of breast cancer are closely related to cellular glucose metabolism. Anti-diabetic medications have drawn increased attention as a potential treatment for breast cancer. Metformin lowers cancer incidence and death rates in patients with type 2 diabetes, according to epidemiologic studies. Preclinical studies conducted in vivo and in vitro offer fascinating new insights into the cellular mechanisms underlying metformin oncostatic action. We present an overview of the mechanisms of anticancer effects of metformin and discuss its potential function as an adjuvant in the treatment of breast cancer.

Keywords: metformin, breast cancer, diabetes mellitus, insulin.

Cancer is considered a major danger to worldwide population health with steadily growing incidence [1]. The burden of cancer may be minimized by advances in the knowledge of optimal early detection, therapy, and follow-up care, as well as the identification of certain cancer biomarkers [2]. The most prevalent cancer in women is breast cancer (BC) worldwide [3]. The disease has a complex etiology, with multiple biological pathways contributing to its development. The growth and dissemination of BC are closely associated with the metabolism of glucose since glucose serves as a vital substrate for cell metabolism and insulin signaling has mitogenic properties [4]. Numerous anti-diabetic medications, including metformin, have been investigated for their anticancer potential due to the substantial correlation between diabetes and cancer incidence. A biguanide antihyperglycemic medication metformin is prescribed as a first-line treatment for type II diabetes mellitus. It affects various biological pathways, including AMP-inducible protein kinase (AMPK)-dependent and AMPK-independent pathways, and thus shows anticancer activity [5]. It primarily works by lowering the amount of glucose produced by the liver and activating AMPK (adenosine monophosphate-

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activated protein kinase) in the cells. For additional examination, clinical trials examining the impact of metformin on the assessment of body mass index (BMI), insulin, Ki-67, fasting blood sugar (FBS), and homeostatic models of insulin resistance (HOMA-IR) were chosen [6]. Metformin has been widely used in clinical studies over the past decade, and these studies have shown that metformin helps lower death and morbidity rates among diabetic patients with cancer, such as breast, ovarian, prostate, liver, pancreatic, lung, medullary thyroid, gastric, and colon cancers [7—10]. *In vitro* studies have shown that metformin suppresses the development of several human cancer cell lines by regulating glucose metabolism and the PI3K-AKT-mTOR signaling pathway [11, 12]. Usually, BC develops when cells lose their capacity to stop proliferating and become resistant or less effective in apoptosis. Phospholipase/Akt and mammalian target of rapamycin (mTOR) signaling molecules are expressed at high levels in BC cells, which decreases the cell capacity to undergo apoptosis [13].

Some molecular aspects of breast cancer pathogenesis

BC poses a serious threat to public health [4]. According to the American Cancer Society estimates, the incidence of BC rises with age, and approximately 1 out of 8 females is expected to acquire it during her lifetime [4]. A combination of genetic, lifestyle, and environmental factors interact to determine cancer risk in the equally complicated etiology of BC. BC is categorized as noninvasive or invasive. While ductal and lobular carcinomas are regarded as the invasive subtypes, ductal and lobular carcinomas *in situ* are among the non-invasive subtypes [4]. In females, ductal carcinoma typically accounts for 80% of the reported occurrences, while lobular carcinoma accounts for only 5%—10% of cases [14]. Nowadays, chemoradiotherapy and surgery are used to treat BC, and Trastuzumab (Herceptin®) is used to treat HER2+ tumors [15].

Apoptosis is a physiological process by which damaged cells that are exposed to toxic substances are removed. It helps in tissue regeneration and restores tissue function; this is followed by increased cell proliferation. Furthermore, until the toxic substance is eliminated, proliferation and inflammation may continue, not allowing the tissues to heal completely. Continued inflammation raises the possibility of dysplastic alterations in cells, which raises the chance of neoplasia [16]. Several investigations have been focused on the role of leukocytes, particularly cytotoxic T cells, in the development of tumors. These cells are thought to assist natural killer (NK) cells in the elimination of cancerous cells [17]. Anti-tumorigenic effects of the immune system depend on this process. In contrast, pro- and anti-inflammatory cytokines (IL-4, IL-5, IL-6, IL-10, and IL-13) are expressed when Th2-polarized $CD4^+$ T-helper cells are activated. This subsequently upregulates cell-mediated antitumor immunity and increases humoral immunity, which in turn promotes pro-tumoral humoral response [18—22]. The source of BC is the indistinguishable lobules type 1, which are made up of different cell types with different proliferation rates: ER– cells and ER+ cells. When metabolized by cytochrome P450 enzymes, endogenous 17 beta-estradiol (E2) can also function as a carcinogen, which can ultimately result in genomic alterations and transformed phenotypes seen in primary BCs, which spontaneously emerge. P450 cytochromes metabolize endogenous E2, activating the carcinogen benzo[a]pyrene (B[a]p) found in cigarette smoke [23]. The changes in DNA caused by B[a]P and E2 *in vitro* are similarly seen in invasive ductal carcinoma, ductal hyperplasia, and ductal carcinoma *in situ* [4]. The progression and invasion of BC are associated with transcriptional repressors, such as Polycomb Group Protein (EZH2), which conventionally regulates cellular memory. Kleer et al. [24] showed a substantial correlation between BC aggressiveness and EZH2 protein levels. Moreover, through the SET domain and histone deacetylase activity, EZH2 overexpression facilitated anchorage-independent growth and cell invasion. Because of the connections between dysregulated cellular memory, transcriptional repression, and neoplastic transformation, EZH2 might serve as a marker for both aggressive BC and neoplastic transformation. More extensive molecular research is necessary to fully comprehend the neoplastic transformation process underlying BC, as it is more intricate than previously believed. This will help identify strategies to block this process [24].

Diabetes and the risk of cancer

Additionally, diabetes is linked to severe cancer prognosis, progression, and fatality [25]. More pre-

cisely, patients with diabetes have higher amounts of bioavailable IGF-1, which raises their chances of developing cancer such as prostate, colorectal, and breast cancer [26, 27]. Metabolic disease known as type 2 diabetes mellitus (T2DM) has been linked to several malignancies. Hyperglycemia, insulin resistance, and hyperinsulinemia are its defining characteristics. Hyperglycemia supplies the metabolic substrate for cell proliferation, whereas these variables work together to enhance cell proliferation through the mitogenic effect caused by the insulin receptor and insulin-like growth factors (IGFs) [28]. In addition to causing an increase in local cytokine production, the inflammatory effects of hyperinsulinemia may make diabetics more vulnerable to the development of cancer [29]. Several extensive epidemiological investigations and meta-analyses have documented a rise in the occurrence of several malignancies in individuals with type 2 diabetes [30, 31]. According to a population-specific cohort study conducted by Ballotari et al. [32], patients with diabetes had a greater risk of cancer. Obesity was the reason for this association, revealed in people with type 2 diabetes (T2DM) but not type 1 diabetes (T1DM) [4].

Type-II diabetes mellitus and breast cancer

A recent study included 26,968 BC patients, 11.6% of whom had diabetes, and revealed that the possibility of BC and co-occurring complications of diabetes increased with time. The individuals with diabetes were more likely than non-diabetic individuals to be diagnosed with stage III—IV BC (OR 1.14, 95% CI 1.03—1.27; and 1.17, 95% CI 1.00—1.38) [33]. Moreover, there is a greater chance of screen-detected BC in diabetic women aged 45—69 (OR 1.13, 95% CI 1.02—1.26). *In vivo* comparative studies using mice given high- or low-glycemic index diets revealed that animals given high-glycemic index diets developed BC more quickly and had a greater tumor burden [34]. As the primary energy source for tumor growth, elevated glucose concentrations in the tumor microenvironment (TME) are associated with aggressive tumor proliferation [35, 36]. As a result, any anti-diabetic medication that reduces blood sugar, like metformin, may one day be used to treat cancer. There is conflicting information regarding how metformin affects the risk of cancer in T2DM patients [5]. Only three studies out of 46 were rated as low or unlikely for bias domains in a 2017 systematic review of metformin and cancer risk studies. These bias domains included outcome, exposure, control selection, baseline confounding, time-dependent confounding, immortal time, missing data, and censoring methods [37]. Consequently, the authors proposed that the data regarding the correlation between metformin and cancer risk in patients with type 2 diabetes are inadequate.

Mechanisms of metformin action

Metformin, which was derived from the plant *Galega officinali*, has been used for a long time to treat diabetes, but its exact mechanism of action is still unknown. It works in two ways: directly by inhibiting mitochondrial ETC/OxPhos and activating AMPK as a result, or indirectly by lowering systemic insulin levels by inhibiting hepatic gluconeogenesis. Tumor suppressor serine/threonine kinase 11 (STK11/LKB1) and calcium/calmodulin-dependent protein kinase kinase-2 (caMKK-2) phosphorylate AMPK upon activation, which enables AMPK to translocate cells from an anabolic to a catabolic state. Blocking glucose, lipid, protein synthesis, and cellular development, it thereby shuts down the ATP-consuming processes. In contrast, fatty acid oxidation and glucose uptake are encouraged to restore the ratio of AMP and ATP [38] knowledge of the physiology as well as physiopathology of hepatic energy metabolism is a prerequisite to our understanding of whole-body metabolism. Hepatic fuel metabolism changes considerably depending on physiological circumstances (fed *vs*. fasted state. Metformin mainly affects the mitochondria by inducing mitochondrial respiratory-chain complex 1 (MRCC1), which is found in hepatic cells, muscular tissues, endothelial cells, pancreatic beta-cells, and neurons, to be mildly and specifically inhibited [39—45]. Metformin also lowers the generation of reactive oxygen species (ROS) in the mitochondria by specifically blocking reverse electron transport through MRCC1 [46, 46]. ROS are key players in the physiology of both T2DM and BC, acting as significant mediators of genomic and cell damage. Thus, the ability of metformin to inhibit the production of ROS may offer advantages beyond its conventional use as an oral

hypoglycemic medication. In this regard, a number of studies have demonstrated that metformin has anticancer properties in diabetic BC patients. In contrast, there is a lack of research on the effectiveness of metformin and its usage in BC patients who are not diabetic, and inconsistent results have been observed [4].

Additionally, AMPK suppresses mTOR, a downstream growth factor activator in cancerous cells linked to the anticancer medication resistance [48]. Interfering with the mitochondrial electron transport chain and decreasing the mitochondrial membrane potential, metformin treatment also increases intracellular ROS. Metformin has anti-proliferative effects on MCF-7 cells that are dependent on both time and concentration, as demonstrated by Queiroz et al. [49]. Metformin activates AMPK and FOXO3a, increases oxidative stress, and has pro-apoptotic action, which leads to the cell cycle arrest. Metformin inhibits BC cell migration and proliferation by deregulating matrix metalloproteinases MMP-2 and MMP-9 and downregulating the oncogenic microRNAs miR-21 and miR-155 [50]. Moreover, metformin promotes a reduction in the total amount of CD68-positive, aromatase-positive macrophages in the tumor microenvironment and a decrease in fat buildup in the liver of treated rats. This study demonstrated that metformin affects the TME as well as whole-body metabolism. It also suggested that women who are at BC risk or have already developed BC may benefit greatly from metformin during the perimenopausal stage. Similar results have been obtained by other researchers in *in vivo* animal models of BC, showing lower tumor sizes and reduced proliferation [51, 52]. Metformin administration enhanced the percentage of low-grade tumors in a rat model of breast tumors generated by MNU, as shown by recent research by Bojkova et al. [53]. There was a substantial positive connection found between Ki-67 expression and histological grade. On the other hand, no variations in tumor incidence or frequency were noted. The reduced serum IGF-1 levels reflected the better histological profile of BC.

Conclusion

Considering that glucose is a necessary cellular metabolic substrate and that insulin signaling has mitogenic effects, the epidemiologic association between BC and disturbed glucose metabolism is intriguing from a molecular perspective. The underlying mechanism that unites BC and T2DM is hyperinsulinemia, which triggers multiple biochemical pathways that promote cell proliferation. Metformin lowers blood glucose levels of insulin by inhibiting mTOR pathways and activating AMP-activated protein kinase. Furthermore, it prevents cancer cells from proliferating and invading, which may reduce the spread of metastases [54]. Additionally, research has shown that metformin may help cancer cells prevent the development of resistance to trastuzumab, hormone therapy, and chemotherapy. Moreover, encouraging *in vivo* research indicates that metformin may work in a positive synergistic manner with naturally occurring antitumor substances like curcumin. In contrast, there have been contradictory clinical results published in the literature regarding the effectiveness and antitumor activity of metformin, which highlights the need for more studies [55, 56].

Further long-term double-blind randomized trials are necessary to investigate the specific function of metformin and its usage as an adjuvant in cancer therapy. Most recent studies devoted to the use of metformin in BC have shown conflicting results for the medication's effectiveness. However, these studies used various metformin doses and different follow-up durations. Nevertheless, it is evident that metformin has great potential as an antitumor agent.

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ЕВОЛЮЦІЯ ЗАСТОСУВАННЯ МЕТФОРМІНУ В ЛІКУВАННІ ХВОРИХ
НА РАК МОЛОЧНОЇ ЗАЛОЗИ ЗА ДВА ДЕСЯТИРІЧЧЯ: ОГЛЯД

Рак молочної залози є одним з найпоширеніших онкологічних захворювань у жінок. Захворювання має складну етіологію, і його розвиток пов'язаний з низкою біологічних процесів. Оскільки внутрішньоклітинні шляхи, які передають сигнал від рецептора інсуліну, приводять до активації мітогенних ефектів, а глюкоза є необхідним субстратом для клітинного метаболізму. Розвиток раку молочної залози та його метастазування тісно пов'язані із метаболізмом глюкози. Протидіабетичні засоби привертають увагу як потенційні препарати для лікування раку молочної залози. Епідеміологічні дослідження свідчать, що метформін знижує частоту виникнення раку та смертність від нього у хворих на діабет 2-го типу. Доклінічні дослідження *in vivo* та *in vitro* відкривають нові перспективи щодо розуміння внутрішньоклітинних механізмів, які обумовлюють онкостатичний ефект метформіну. Огляд присвячений аналізу цих механізмів та можливостям застосування метформіну як ад'ювантного засобу в лікуванні раку молочної залози.

Ключові слова: рак молочної залози, метформін, цукровий діабет, інсулін.