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Article

The effects of muscle factors irisin on lipid metabolism in breast cancer: A possible mechanism anti-tumor mechanism of physical activity

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Abstract: Breast cancer is the most prevalent cancer in the female population and is a significant cause of global cancer deaths in this group. Obesity increases a woman's risk of developing breast cancer and has a negative impact on prognosis. Metabolic alterations are an important part of the process of cancer migration; invasion and proliferation, with lipids being a major metabolic substrate for rapid cancer progression, capable of influencing the metabolic crosstalk between tumor cells and other cells in the tumor microenvironment. Physical activity-induced irisin affects the progression of obesity-associated breast cancer and is a new indicator for breast cancer diagnosis. Existing evidence suggests a potential inhibitory effect of physical activity-induced irisin on the progression of breast cancer. A strong association exists between obesity and breast cancer progression and outcomes. This paper discusses how physical activity-induced irisin may achieve cancer suppression by affecting lipid metabolic processes between breast cancer cells and cancer-associated adipocytes, and elucidates the molecular pathways involved in the effects of irisin on cancer lipid reprogramming, thereby helping to prevent the metastatic progression of breast cancer, and ultimately improving the survival rate of this patient group.

Keywords: irisin; adipocyte; cancer-associated adipocytes; breast cancer; cancer

1. Introduction

Breast cancer is a global concern with high mortality and morbidity rates worldwide. The latest data indicate that breast cancer has overtaken lung cancer as the most commonly diagnosed cancer globally, posing a significant threat to women's health [1]. Triple-negative breast cancer (TNBC) is a specific subtype of breast cancer in which the cancer tissue is negative for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2). It is characterized by high aggressiveness, high metastatic potential, high propensity for recurrence and bad prognosis [2]. The obese is a recognized hazard element for the incidence and recurrence of breast cancer, and the burden of obesity increasingly increases the aggressiveness and morbidity of TNBC. Obesity with breast cancer have lower disease-free and overall survival rates compared to nonobese women with breast cancer, even when obese patients are appropriately treated [3]. Studies have shown that excessive adipocyte accumulation results in the secreting of inflammatory factors, chemokines and adipokines, which subsequently leads to abnormal metabolism of the cancer microenvironment (TME), ultimately stimulating breast cancer invasion, progression and progression of metastasis, and impeding anticancer agent reactions [4]. Breast cancer cells contribute to lipolysis and phenotypic changes in adipocytes in the tumor microenvironment (TME), forming aberrant cancer-associated adipocytes

(CAA) at the frontiers of cancer invasion [5]. Together, these two types of cells are involved in breast cancer progression and metastasis through cancer lipid reprogramming. Therefore, maintaining a normal weight range is important for TNBC patients to prevent further cancer development and progression.

Physical activity as a non-pharmacologic intervention strategy can have a positive impact on the lives of breast cancer survivors who are overweight or obese, with the advantages of being less invasive, psychologically acceptable and feasible to mitigate the associated negative impacts resulting from cancer treatment while improving overall quality of life, cardiorespiratory fitness, and muscle strength of breast cancer survivors [6]. During physical activity, skeletal muscle can release various types of exercise factors from tissues into the bloodstream via endocrine, autocrine, and paracrine systems to stimulate skeletal muscle growth, increase body energy metabolism, influence lipid, carbohydrate, and protein metabolism, regulate inflammation, and influence inter-organ messaging. The newly discovered cytokine irisin, which is secreted by motility-induced secretion, has been shown to inhibit a number of cancers associated with women, and many studies have shown that it has an important effect on the migration, aggression and proliferation of cancer cells. Several studies have shown that serum irisin levels are significantly lower in breast cancer patients than in healthy women, suggesting that irisin may be associated with the risk of breast cancer [7,8]. Irisin, as an exercise-induced release of muscle factor, can regulate the metabolic state of fat cells, “browning” white fat, thus increasing energy expenditure and reducing fat accumulation [9–11]. This process can help reduce the metabolic burden triggered by obesity and reduce the risk of breast cancer at its source. Irisin has a positive effect on glucose metabolism and insulin sensitivity. Studies have shown that irisin can improve cellular glucose uptake and insulin sensitivity by activating the AMPK (adenylate-activated protein kinase) signaling pathway, which is potentially therapeutic for the prevention or treatment of obesity-related metabolic diseases [12]. Irisin may also fight breast cancer by modulating the immune system. Obesity usually leads to immune system dysfunction, which manifests as a pro-inflammatory state and immunosuppression. Irisin helps to inhibit the spread of breast cancer cells through its ability to reduce the secretion of pro-inflammatory cytokines (such as TNF-alpha and IL-6), which reduces the chronic inflammatory response, modulates the function of immune cells, and reduces chronic inflammation, thus improving the tumor microenvironment [13–15].

Modulation of irisin levels by exercise or drugs may be a potential strategy to improve the prognosis of obesity-related breast cancer. Studies have shown that regular aerobic exercise can significantly increase the levels of irisin in the body, thus indirectly reducing the incidence and recurrence of breast cancer [16]. Although corresponding clinical evidence exists regarding the positive impacts of physical activity-induced irisin on breast cancer [17,18], the mechanisms of how physical activity-induced irisin inhibits or delays the development of obesity-associated breast cancer have not yet been clearly established. To this aim, this paper builds on the collation of previous studies to illustrate how physical activity-induced irisin can inhibit the development of triple-negative breast cancer by modulating the mechanism of crosstalk between adipose and cancer. The regulatory mechanisms and triggered signaling pathways involved in these processes are being sorted out with a view to

better explaining the crosstalk between them and providing new ideas for future breast cancer treatments.

2. Current status of breast cancer and the relationship between obesity and the development of breast cancer

Breast cancer is the highest incidence of malignant tumors among women globally and the most frequently occurring cause of cancer death among women in our country [19]. The ageing population has put more women in the breast cancer-prone age group, and poor lifestyles, such as lack of exercise, unhealthy eating habits and high-stress environments, further exacerbate the incidence and mortality rates of breast cancer. According to the latest global cancer incidence and mortality estimates from the internationally relevant organizations on cancer, female breast cancer has overtaken lung cancer as one of the most common types of cancer worldwide, with an estimated 2.3 million new cases (11.7%) and more than 685,000 new deaths (6.9%) being breast cancer, its incidence and lethality are the highest in most countries [1].

The etiology of breast cancer is a complex multifactorial process and are related to age, reproduction, environment, genetics, smoking, radiation, alcohol consumption, work and rest, physical activity, and hormone levels [20–29]. In recent decades, with changes in modern people's eating habits and lifestyles, the global obese population has been growing rapidly, the proportion of women who are overweight and obese has been increasing, and more and more research is beginning to focus on the impact of obesity on breast cancer rates. Evidence suggests that physical obesity has a significant impact on the progression of breast cancer, with women who are obese having a higher incidence of breast cancer than nonobese individuals, and that obesity increases the risks of poor outcomes, risk of disease recurrence and increased mortality [30,31]. In recent years, a growing number of epidemiologic studies have focused on the relationship between breast cancer and obesity. These studies have found that the impact of obesity on breast cancer varies by menopausal status and breast cancer subtype. Most studies have shown that obesity is positively associated with breast cancer risk among postmenopausal women, meaning that obese women are more likely to develop breast cancer [32–34]. While relatively few studies have been conducted on premenopausal women and the findings are inconsistent, and further research is needed to validate the effect of obesity on breast cancer risk in premenopausal women [35–37]. However, in the case of triple-negative breast cancer (TNBC), an overwhelming majority of studies have confirmed that obesity is strongly correlated with the risk of breast cancer in premenopausal TNBC patients [38,39]. Some studies have shown that obesity has no effect on premenopausal women and even decreases their disease incidence, but it still has an important impact on the prognosis of breast cancer patients, with obesity increasing the risks of mortality by 30% compared with breast cancer patients with a normal body mass index (BMI) [20] [22]. Although the malignant association of obesity on breast cancer is well established, we do not yet have a complete understanding of the biomolecular mechanisms that promote carcinogenesis because of the diverse pathways through which obesity affects breast cancer development and progression.

3. Relationship between cancer-associated adipocytes and breast cancer

Anatomically, breast tissue consists primarily of glandular and adipose tissue. In the normal breast, mammary adipocytes and mammary ductal cells are divided by a basement membrane that acts as a barrier, limiting direct interaction between mature adipocytes and epithelial cells. However, when tumor cells break has crossed the basement membrane, they are directly infiltrated in the tumor microenvironment (TME) containing adipocytes, which allows the possibility of adipocyte-tumor cell interactions [40]. The progression of breast cancer depends not only on the properties of the cancer cells themselves, but also on the support and regulation of the tumor microenvironment in which they are located. TME is a complex and diverse ecosystem composed of infiltrating immune cells, migratory support cells and stroma, which can provide necessary nutrients and support for cancer cells, as well as angiogenesis and suppression of immune response through various mechanisms [41]. In the TME, activities such as metabolism, secretion, and immunity are no longer subject to the body's normal regulation as they are in normal tissues, and are characterized by hypoxia, chronic inflammation and immunosuppression. Adipocytes, as a class of stromal cells, are one of the important components that make up the TME of breast cancer, and adipocytes promote cancer progression by interacting with cancer cells. Specifically, in the pre-cancer phase of breast carcinogenesis, cancer cells invade the surrounding adipose tissue. During this process, the cancer cells undergo continuous dynamic interactions with the adipocytes inducing intracellular metabolic reprogramming of the adipocytes, accompanied by phenotypic alterations such as lipid reduction, alteration toward fibroblast-like changes, and upregulation of inflammatory marker expression, thereby transforming normal adipocytes into a special type of adipocyte, i.e., BC cancer-associated adipocytes (CAAs) [42–44]. These experimental results have shown that CAAs play an important role in promoting the proliferation of BC, stimulating neo-angiogenesis to supply tumors, helping cancer cells to spread, invade surrounding tissues, and metastasize further to distant organs [45,46].

Sustained interactions between tumor cells and adipocytes lead to metabolic competition and symbiosis, driving metabolic reprogramming of breast cancer cells and CAAs. TNBC utilizes metabolic reprogramming to meet bioenergetic and biosynthetic demands, maintain redox balance and further promote oncogenic signaling, cell proliferation and metastasis [47]. CAAs store lipids as triglycerides (TGs), which are released as free fatty acids (FFAs) through a lipolytic process of triglycerides (TGs) mediated by lipases such as hormone-sensitive triglyceride lipase (HSL), adipose triglyceride lipase (ATGL), and monoacylglycerol lipase (MAGL) and the subsequent uptake of FFAs into tumor cells in a fatty acid-binding protein 4 (FABP4)-dependent manner [48]. Once free fatty acids (FFAs) are stored in lipid droplets after being transferred to tumor cells, they are lipolyzed by the action of enzymes (ATGL, HSL, and MAGL) to form fatty acids (FAs). These fatty acids are further metabolized in the cytoplasm and mitochondria of tumor cells. In the cytoplasm, fatty acids are oxidized by β-oxidation to produce guttate adenine dinucleotide (NADH), flavin adenine dinucleotide (FADH1), and acetyl-coenzyme A (Acetyl-CoA). In mitochondria, fatty acids are β-oxidized via the fatty acid oxidation

(FAO) pathway regulated by the rate-limiting enzyme carnitine palmitoyl transferase 1 (CPT1) [49,50]. These metabolic processes generate energy and metabolites that provide breast cancer cells with a source of energy required for growth and invasion. CAAs enhance the energy production efficiency of breast cancer cells by increasing the rate of FAO in BC cells and promoting CPT1 expression, which in turn promotes tumor growth and progression. Adipocytes are an important component of breast tissue, and obesity is closely related to the role of adipocytes in regulating the behavior of breast cancer cells. Obesity, defined as excessive accumulation of adipose tissue, causes a noticeable increase in the amount and volume of adipocytes and elevated levels of TGs, leading to an increased release of fatty acids (FAs), which provide more anabolic substrates for tumor cells. Balaban et al. [51] observed the transfer of adipocyte-derived FFAs into breast cancer cells through adipocyte-breast cancer cell coculture, and it is noteworthy that "obese" adipocytes have an enhanced ability to transfer FFAs to breast cancer cells. This further validates that CAAs in TME promote the lipolytic process of TGs, leading to an increased release of FAs and more anabolic substrates for tumor cells.

4. The motility factor irisin is a key molecule in the regulation of breast cancer development

The inducible cytokine of physical activity, irisin, is produced by cleavage of the transmembrane protein FNDC-5 (Fibronectin type III repeat sequence protein 5), a protein that contains multiple structural domains of fibronectin III. In response to exercise stimulation, levels of PPARγ coactivator-1α (PGC-1α) rise in skeleton muscle cells, which drives the elevated expression of FNDC5, which is subsequently sheared into irisin and released into the circulatory system [52]. Irisin is mainly derived from muscle and adipose tissue and plays a key function to induce fat browning as well as regulating energetic expenditure [9–11]. Currently, studies have focused on changes in serum irisin level of breast cancer survivors, and irisin may serve as a cancer biomarker. Pravatopoulou et al. [7] showed that serum irisin levels were lower in breast cancer patients than in healthy controls, and it has been theorized that each 1 unit increase in irisin levels decreases the probability of developing breast cancer by nearly 90%. Another observational study found, that among breast cancer patients with spinal metastases, serum sample irisin levels were lower in those with spinal metastases than in those without spinal metastases, i.e., higher irisin levels may be associated with a lower risk of spinal metastases [8]. Serum irisin may be a new target for the prevention and treatment of spinal metastases in breast cancer. Gannon et al. [53] found by in vitro cellular assays that irisin significantly inhibited the growth and migration of malignant breast cancer cells, while producing no side effects on normal cells. Specifically, irisin remarkably reduces the number, migration ability and survival of malignant MDA-MB-231 cells, while it has no effect on non-malignant MCF-10a cells. In addition, irisin enhanced tumor sensitivity to common antitumor drugs by potentiating the cytotoxic effects of doxorubicin and reduced malignant cell viability by stimulating cysteine asparaginase activity, which leads to apoptotic cell death. Immunohistochemical staining of tissue samples from breast cancer patients with antibodies to irisin by Kuloglu et al. [54] observed a noticeable increase in irisin

staining in breast cancer tissues compared to normal breast tissues. This suggests that the high expression of irisin may be closely related to the proliferation, survival and migration of breast cancer cells, which suggests that irisin is not only important in the development of breast cancer, but may also influence its progression and deterioration. Panagiotou et al. [55] conducted an evaluation of irisin levels in women with benign/malignant breast tumors versus healthy controls. It was found that irisin levels were higher in patients with benign/malignant breast tumors compared to healthy controls, and that irisin levels were comparable between tumor types. This suggests that irisin levels may play some role in the development of benign/malignant breast tumors and that different types of tumors may be similarly affected. Cebulski et al. [56] compared the expression and ultrastructural localization of FNDC5/Ir in breast cancer cell types and regular breast cancer cell lines. They found that FNDC5/Ir was present in the cytoplasm of breast cancer cells and tumor fibroblasts, and that breast cancer cell lines had higher levels of FNDC5/Ir expression compared to normal breast cancer cell lines. In addition, it was found that serum levels of irisin were not associated with the expression levels of FNDC5/Ir in breast cancer tissues, however, irisin levels were associated with lymph node metastasis and histologic grading. This finding suggests that the expression of FNDC5/Ir in breast cancer cells is associated with breast cancer progression, but serum irisin levels may be more reflective of metastasis and malignancy of breast cancer. In addition to this, a study measuring FNDC5/irisin expression in tumor tissue included 150 postmenopausal women diagnosed with breast cancer. The results showed that women with breast cancer and obesity exhibited higher levels of irisin expression compared to women with breast cancer and normal body mass index. This finding suggests that irisin may be involved in the regulation of the tumor microenvironment in obese breast cancer patients [57].

Cancer oncogenesis, progression and metastasis are inextricably linked to the TME. Adipose tissue accounts for 90% of the histological composition of the breast and is an essential part of the breast cancer TME. There are two main types of adipose tissue, white adipose tissue (WAT) and brown adipose tissue (BAT), based on their structure and function. White adipocytes have more lipid droplets which are mainly composed of TGs and their main function is to store energy for the body's needs. In contrast, brown adipocytes contain a large number of mitochondria that are rich in brown lipids associated with energy metabolism and whose main function is to convert energy from food into heat, thus producing thermoregulatory effects. In brown adipocytes, uncoupling protein 1 (UCP1) exists in the mitochondria, which enables the energy generated from the breakdown of FAs not to be converted into ATP for direct energy supply to the organism, but rather through mediated uncoupling of oxidative phosphorylation to generate heat and dissipate energy, thus maintaining the energy balance in the body [58–60]. The activity-inducible cytokine irisin, derived primarily from muscle and adipose tissue, plays an essential role in inducing fat browning and regulating energy expenditure, and promotes the transformation of white adipocytes to brown adipocytes, increasing brown fat quantity and metabolic activity in the body [61–63]. Earlier studies demonstrated that irisin upregulates UCP1 expression by mediating phosphorylation of the p38 mitogen-activated protein kinase and extracellular signaling-associated kinase signaling pathways to enhance energy expenditure and promotes the browning of white adipocytes to brown adipocytes in

mice [64,65]. Relevant follow up studies found that muscle-derived irisin induced enhanced expression of UCP1 in white adipocytes of obese mice, significantly reduced WAT volume and fat fraction, and promoted adipose tissue browning [66]. Meanwhile, an increase in white adipocyte volume and a decrease in the extent of exercise-induced conversion of white adipose tissue to brown fat were observed in FNDC5 knockout mice [67,68]. These findings emphasize the critical role of irisin as an important regulator in the regulation of energy metabolism and obesity. In addition to inducing fat browning, irisin also promotes adipocyte breakdown. Xiong et al. [69] found that overexpression of FNDC5 mediated by lentivirus could reduce obesity symptoms in obese mice by increasing the expression of HSL and promoted FAO, a result that suggests that overexpression of FNDC5 may contribute to the increase of lipolysis and energy metabolism in adipocytes. The same study also showed that irisin upregulated the expression of key lipolytic enzymes such as ATGL and HSL, while increasing the mRNA levels of FABP4. Together, these regulatory effects promoted glycerol secretion and reduced lipid accumulation in adipocytes, ultimately leading to a reduction in adipocyte size. These findings further support the important role of irisin in lipid metabolism and energy homeostasis [70].

5. Irisin may affect breast cancer lipid metabolism by acting on cancer-associated adipocytes

When irisin acts in breast cancer TMEs, binding to CAAs may promote their browning and activate thermogenesis. Brown adipose tissue (BAT), which consists of traditional brown adipocytes present in specific anatomical locations such as the scapular region, and beige adipocytes distributed in white adipose tissue, produces heat through metabolic activity (rather than muscle shivering). This non-shivering heat production not only plays an important role in cold acclimatization, but also plays a key role in energy metabolism and body weight regulation [71]. UCP1 causes the electrochemical gradient on both sides of the inner mitochondrial membrane to decrease by lowering the proton gradient, at which point the protons no longer synthesize ATP from ADP and inorganic phosphate via ATP synthase, but instead return to the mitochondrial matrix via UCP1. This process dissipates the energy transferred through the respiratory chain, resulting in the release of energy in the form of heat rather than for ATP synthesis. In addition, in some cases, UCP1 activity can be stimulated by hormonal signals that increase cyclic adenosine monophosphate (cAMP) levels via β3-adrenergic receptors, which in turn further promotes UCP1 expression and activity through activation of protein kinase A, thereby enhancing adaptive thermogenesis [52] [72–74]. Irisin plays an essential role in promoting the transformation of white adipose tissue to brown adipose tissue by enhancing the expression of UCP1 on the inner mitochondrial membrane. In the breast cancer TME, irisin may produce localized hyperthermia by increasing UCP1 expression in CAAs. This process involves FA as a substrate for BAT thermogenesis, which is produced by cAMP-induced lipolysis, and subsequently used as an FFA for FAO processes in brown adipocytes [65,67]. Based on this, it can be speculated that in the breast cancer TME, irisin may regulate thermogenesis by acting on CAAs and activating their thermogenic function, so that more FFAs in CAAs are utilized by mitochondria to

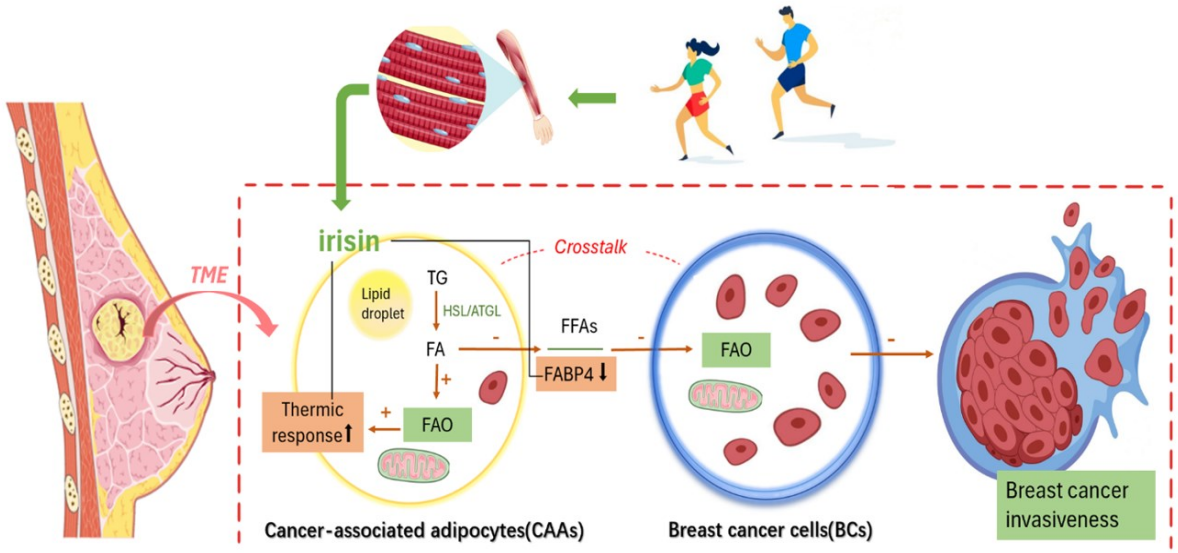
participate in FAO processes in adipocytes. This causes a decrease in FFAs in the TME, which has conversely minimized the amount of FFAs entering cancer cells, thus affecting the cancer development process.

In addition, serum irisin has an antagonistic effect on FABP 4 [75,76]. FABPs play important roles in lipid metabolism, signaling, and regulation of gene expression. FABP 4 (also known as aP2), a member of the FABP family, is expressed mainly in adipocytes and macrophages, and is a core protein in the mechanism of lipid metabolism, which promotes the dissolution and translocation of FFA in adipocytes [77,78]. In vitro data from one study showed that co-incubation of adipocytes with tumor cells caused an increase in FABP4 expression in the breast cancer TME and was highest in the TNBC type. FABP4 plays a key role in the metabolic interactions between adipocytes and breast cancer cells, especially in the TME of TNBC. Inhibition of FABP4 effectively reduces lipolysis in adipocytes and β-oxidation in breast cancer cells, limiting the energy supply to breast cancer cells and thus inhibiting tumor growth [79]. Notably, FABP4 was highly expressed in the adipose tissue of obese patients, and serum FABP4 levels were positively correlated with body mass index (BMI), suggesting that FABP4 plays an important regulatory role in obesity and related metabolic disorders, which has been found to be reflected in both mouse models and human studies [80–82]. When irisin acts on the breast cancer TME, it can exert its inhibitory effect to reduce the expression of FABP4. The reduction of FABP4, which is an FFA transport protein, then lipid transfer between CAAs and tumor cells as well as β-oxidation in breast cancer cells are also reduced.

6. Conclusion

Currently, there are no targeted or specific therapeutic options for women with TNBC, and several epidemiological studies have investigated the effect of post diagnostic obese status upon the prognosis for breast cancer, with the majority of studies finding that obesity is not only linked to the development of breast cancer, but also affects the course and prognosis of breast cancer patients, making them more likely to recur and leading to higher mortality rates [83–85]. Based on studies related to obesity and breast cancer progression, increasing evidence suggests that breast cancer development is significantly influenced by xenobiotic interactions between cancer cells and CAAs in the TME. Several mechanisms by which CAA drives cancer progression have been postulated, including adipokine regulation, metabolic reprogramming, extracellular matrix remodeling, and immune cell regulation [86,87]. Here, we found that physical activity-induced irisin can act directly on critical function cells involved in energetic metabolism and homeostasis in vivo, affecting metabolic changes in adipose tissue and leading to increased thermogenesis. Based on this, there is a new research idea about the effect of irisin binding to CAAs on the reprogramming of lipid metabolism of obesity-associated breast cancer, illustrated in **Figure 1**: in the breast cancer TME, irisin may promote browning and activate the thermogenic function of CAAs by acting on CAAs and increasing the expression of UCP1 on their inner membranes of mitochondria. During this process, we speculate that more FAs produced by TG hydrolysis in CAAs are utilized by mitochondria to participate FAO processes in adipocytes to regulate thermogenesis, and a smaller portion enters the

TME in the form of FFAs. The FFAs entering the TME need to be assimilated and exploited by tumor cells with the help of the transporter function of FABP4, but due to the intervention of irisin, the expression of FABP4 is inhibited. We hypothesize that the reduced of FABP4 leads to a reduction of lipid transfer between CAAs and breast cancer cells, which subsequently would affect the FAO processes in breast cancer cells. In summary, we suggest that physical activity-induced irisin inhibits the development of TNBC by activating the thermogenic function in CAAs and affecting the reprogramming of tumor lipid metabolism.



TG: triglyceride; FA: fatty acid; HSL: hormone-sensitive triglyceride lipase; ATGL: adipose triglyceride lipase; FFA: free fatty acid; FABP4: fatty acid binding protein 4; FAO: fatty acid oxidation; TME: tumor microenvironment

Figure 1. Mechanism of action of exercise-induced irisin affecting lipid metabolism in obese individuals with breast cancer.

Discovering irisin offers a new potential basis for physical activity therapy, and has received widespread attention being a promising therapy target for its action in cancer development and prevention. Going forward, we would combine clinical specimens and in vivo and ex vivo experiments to determine the function of irisin in lipid metabolism and its effect on the adipose tissue surrounding breast cancer tumors, to comprehensively elucidate the process and intrinsic mechanism of physical activity-mediated irisin's involvement in the regulation of heat production in CAAs and reprogramming of lipid metabolism in tumors, and to provide a detailed Experiment to the study of the pathological mechanism of TNBC and the design of potential target drugs. to study the pathological mechanism of TNBC and potential target drug design, and thus to develop more effective clinical treatment protocols.

Author contributions: Conceptualization, MD and JZ; methodology, MD; validation, MD, JZ and CL; investigation, MD; writing—original draft preparation, JZ; writing—review and editing, JZ, CL and ST. All authors have read and agreed to the published version of the manuscript.

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