The interaction of obesity and inflammation in breast cancer.

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Abstract

Obesity and overweight have closely considered with several chronic diseases. Evidence of this field has demonstrated that significantly impact on the multiple cancers progression, such as breast cancer, prostate cancer, hepatocellular carcinoma, pancreatic cancer and cervical cancer. Epidemiological studies have shown that there is about 20% of cancer related to obesity, which were affected by lifestyle including dietary behavior and physical activity. Based on these findings, obesity is considered as one of most harmful factors for the breast cancer in women, especially after menopause. Many hypotheses have been proposed to explain how obesity contributes to breast cancer development. The inflammatory cytokines produced from adipocytes is one of main reason triggers tumor microenvironment and tumor progression. Better understanding the association between adipocytes and inflammation implanting breast tumor development could apply to develop new alternative methods for prevention/cure. In this review, we summarize the concept and evidence associated to interaction of obesity-driven changes and inflammation in breast cancer microenvironment.

Introduction

Obesity is a critical epidemiological issue, with excess adipocytes accumulation, causing physiological and even pathological complications impacted to the health [1]. The prevalence of obesity has rapidly increased in the past decades worldwide [2]. In 2014, global statistics has been done by World Health Organization, more than 1.9 billion adults are overweight and over 600 million people are obesity [3]. In US, there are more than 35% of adult are obesity [4], suggesting that obesity is a critical problem to be prevented and cured in the future. Obesity has demonstrated that are associated with other metabolic diseases and several kinds of cancer. In addition, obesity fertilizes inflammatory microenvironment, which is favorable to tumorigenesis. The interaction between obesity and inflammation in breast cancer was summarized in this article.

Obesity Accompanies Low-Grade Inflammation

Adipocytes, as fat-storage depots, locate in adipose tissue that is an active endocrine system and associated with immunological functions as well as secretion of several kinds of adipokine [5,6]. Adipose tissue is an important energy and endocrine organ while its dysfunction strongly triggers the initiate course of several diseases [7]. The most frequent prevalence of disorders in obesity-related complication such as type II DM, insulin resistance, atherosclerosis and several cancers [8]. It is well established that a systemic metabolic disorder like obesity creates a supportive environment for tumor cell proliferation. This environment continually produced insulin, endogenous hormones and various adipokines. In addition, obesity induced hypoxia, immune modulation and inflammatory cytokines accompanied to fertility angiogenesis of cancer [9].

In thin subject, some immune cells infiltrated into adipose tissue secreting the anti-inflammatory cytokines such as interleukin-4 (IL-4), IL-10 and IL-13 to support a normal metabolic function [10]. On the contrary, obesity has more immune cells infiltration, excessive fat accumulation, causes low-grade and chronic inflammatory environment. These immune cells such as macrophages trend to secret pro-inflammatory cytokines such as monocyte chemotactic protein-1 (MCP-1), IL-6, and tumor necrosis factor-α (TNF-α). Moreover, other tumor-infiltrating lymphocytes present in breast tissue resulting in escape from immune control, which is known as cancer immunoediting [11]. The possible processes of immunoediting in malignant cells is including elimination of immunosurveillance, equilibrium of surrounding cells, and transformed cells escape immune system [11], suggesting the malignant cells easily develop to breast cancer.

Approving evidence has shown that the obesity-related inflammation is associated with the cancer development through multiple mechanisms [12]. The local hypoxia around adipocytes in the microenvironment was proposed that contributes to this kind of low-grade inflammation. During adiposity, the group of adipocytes enlarges and accompanies surrounding vasculature forming, made the cells without sufficient oxygen, resulting in the hypoxia [13]. Adipose tissue triggers this local hypoxia is considered as one of important factors stimulating inflammatory response [14]. Subsequently, the hypoxia-inducible factor-1α (HIF-1α) is activated, involving in regulating both the innate and adaptive immunity [15]. HIF-1α promotes pro-inflammatory cytokines production such as TNF-α, MCP-1 and IL-6 mediated M1 macrophage infiltration in the adipose tissue. Nowadays, the obesity-associated low-grade inflammation is widely accepted as an important concept in cancer pathogenesis. Nevertheless, other factors such as adipokines and hormones in obese state that relate to breast tumor microenvironment were discussed in the following section.

Breast Cancer and Its Microenvironment

The intricate interaction between tumorigenesis and the immune regulation is a critical issue attracted scientist's interest recently. On the basis of researches, the possible mechanisms have been proposed. Tumor-associated macrophages (TAM) activate tumor proliferation, matrix remodeling, metastasis, and angiogenesis as well as blunting of adaptive immunity [16]. Innate and adaptive immunity play an important role with the dynamic interaction resulting in tumor progression or inhibition [17]. In normal physiology, macrophages play an important role in host defense and in proper tissue development [18]. These cells, product several cytokines, directly act on the inflammatory developmental processes in the innate immune system, and these mediators also bridge to the adaptive immune system, contributing to pathogens clearance, sensors of tissue damage and maintaining tissues homeostasis [18]. In tumor microenvironment, neoplastic cells secret tumor-derived chemotactic factors like MCP-1, vascular endothelial growth factor (VEGF) and macrophage colony stimulating factor (M-CSF) recruiting circulating monocytes, and then trigger the monocytes differentiation toward TAM. Experimental animal and human studies were demonstrated these mediators linked to poor prognosis in ovarian, breast and endometrial cancers [19].

Macrophages are polarized and divided to two phenotypes, the M1 and M2 macrophage with different characteristics [20]. M1 macrophage is promoted by T helper type I (Th1) cytokines such as IL-1 and TNF-α and Toll-like receptor (TLR) ligands to produce inflammatory cytokines, thereby, brings of the adaptive immune response as well as defend the viral and microbial infections in host. Regard to the M2 macrophage, is promoted by Th2 cytokines like IL-4 and IL-13, exerts angiogenesis, wound healing, injured tissues cleaning, and blunts the adaptive immune response [21]. The imbalance of population between M1 and M2 macrophages linked to pathological development. For example, uncontrolled counts polarization of M1 macrophage induces chronic inflammatory diseases while excessive M2 macrophage

promotes immune suppression [22]. Furthermore, TAM seems like M2 macrophage, which executes the tumorigenesis properties in the microenvironment [23]. The murine tumor models have demonstrated that TAM executes tumor promotion via nuclear transcription factor (NF-κB) signaling pathway [24]. Otherwise, the local hypoxia activates the HIF-1α around TAM of tumors was also showed through the activation of NF-κB. Moreover, TAM alternately produces cytokines and chemokine's sustaining and amplifying the neoplastic favor environment [25]. The variation of immune system during malignance procession highlights that diverse immune regulations in the tumor microenvironment play an important role connected with inflammation and cancer.

Obesity and Breast Cancer

On the basis of epidemiological and experimental studies, the obesity development links with metabolic diseases and several kinds of cancer. The excess adipose tissue causes neoplastic status developed to cancer such as endometrium, breast, esophagus, liver, colon and ovary [7]. Especially, some study was showed the close relationship between abnormal obesity and breast cancer [1]. Obesity is associated with a worse breast cancer prognosis and increases the expression of cyclooxygenase-2 (COX-2) and the infiltration of macrophages in the adipose tissue. Eicosanoid prostaglandin E2 (PGE2) is the pro-inflammatory mediator, which is a down-stream factor of COX-2, stimulates aromatase expression and estrogen production in adipose tissue, thereby, promotes breast cancer development [26].

Factors Involved in Obesity-Associated Breast Cancer

Several kinds of cell, extracellular matrix, soluble factors and signaling molecules are components in the tumor microenvironment, which stimulate tumorigenesis and escape the immune response. In addition, accumulating obese tissue diminishes the oxygen level leading to hypoxia, resulting in modification the genes expression related to angiogenesis, cell proliferation and apoptosis, and ultimately increases the risk of cancer development in this kind of microenvironment [14]. A growing body of obesity-related inflammatory state is associated with promoting cancer development. Nevertheless, other factors such as estrogen, insulin-like growth factor-1 (IGF-1) and leptin involving in obesity-associated breast cancer were summarized below.

An increase of estrogen synthesis from adipocytes as well as raises the levels of insulin and IGF-1 secretions were accompanied with obesity [27]. In premenopausal women, estrogen is usually synthesized by ovaries, however, in obese postmenopausal women, estrogen is major produced from excessive adipose tissue and this kind of estrogen promotes the breast cancer development [28]. In addition, over expressed Insulin, IGF-1 and IGF-1 receptor (IGF-1R) are present in many kinds of cancer such as obesity-associated breast cancer [29].

Leptin and adiponectin are two major adipokines secreted by adipocytes associated with breast cancer development. Leptin, a hormone peptide, exerts satiety and energy homeostasis, has also been found that obese subjects have higher level of leptin in serum compared to the lean individuals. The possible actions of leptin are involving in cell survival, proliferation,

angiogenesis, immune regulation and inflammatory response, which contribute to tumor progression [30]. Furthermore, leptin has been showed to crosstalk with the estrogen pathway by enhancing the expression of aromatase, thereby, increase estrogen synthesis. Some study has demonstrated that leptin induced reactive oxygen species (ROS) production and caused COX-2 expression and NF-κB pathway activation and then increased several pro-inflammatory mediators' secretion [31]. On the contrary, adiponectin is another adipokine that inversely correlates with adiposity. Several clinical evidences were reported that adiponectin acted a protective effect on the procession of breast cancer [32]. Therefore, the contrary roles between leptin and adiponectin were indicated in cancer development as leptin affects tumor development and progression, while adiponectin involves in tumor suppression.

In summary, accumulating evidence related to obesity and breast cancer has been proposed continually. To explore advance and effective treatments for prevention and/or cure in obesity-related breast tumorigenesis could be applied to increase the life quality of patients with this kind of cancer. Therefore, a comprehensive cooperation among the relevant epidemiologists and statisticians, researchers and clinicians is critical needed to approach this goal.

Acknowledgement

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