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Mini Review

Obesity and Cancer Progression

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Abstract

Obesity, which is a state of excess of nutrients, chronically activates cellular growth factor and metabolic signalling pathways and stimulates neoplastic transformation. Excess of adiposity has been identified as a risk factor for recurrence, reduced effectiveness and complications of the treatment, development of second primary tumor and mortality. Obesity is associated with the progression of various cancers and it is an important predictor of poor outcome of the disease.

Several mechanisms have been proposed to link obesity with cancer. Quantity and quality of surrounding adipose tissue affect biological and secretory nature of adipocytes. Fatty acid metabolism plays significant role in the biology of cancer. Obesity causes alterations in adipose tissue microenvironment along with endocrinal imbalance that favors tumor initiation as well as progression. Tumor-promoting consequences of obesity occur via insulin resistance, dyslipedemia and inflamed adipose tissue that release local and systemic inflammatory mediators,

Obesity worsens the progression of the disease affecting clinical course not only in relation to cancer outcome, but also other comorbid conditions. Improvement in the health of adipose tissue to reduce inflammatory state would be a novel therapeutic approach to minimize burden of cancer-related mortality. Hence in future, studies bridging the gap to connect preclinical experimental studies with human observations to evaluate impact of obesity on progression of different cancers are needed.

Keywords: Obesity; Adipose Tissue; Inflammation; Progression of Cancer

Background

Obesity is defined as increased adipose mass arising from energy imbalance. Currently all over the world, obesity is an epidemic associated with altered whole-body physiology and hormonal balance that promote risk of developing number of cancers with poor survival outcome. Adipose tissue is a dynamic endocrine organ that maintains energy homeostasis. Obesity has been identified as a significant risk factor for the development of various cancers. Obesity, which is a state of excess of nutrients, chronically activates cellular growth factor and metabolic signalling pathways and stimulates neoplastic transformation [1]. Pathophysiological effects of hyperadiposity have been found to be associated with development and progression of tumor predominantly in metabolically and hormonally driven cancers [2]. Obesity at the time of diagnosis of the cancer is associated with advanced state of the disease affecting progression of the disease, response to the therapeutic agents and disease-free survival [3]. Researchers also observed strong association between increased body mass index and cancer-related mortality, but no exact consensus linking obesity with the pathogenesis of cancer [4]. Among breast cancer women with BMI more than 40Kg/m^2, mortality rate is three times more than lean women suggesting obesity as a poor prognostic factor [5]. Goodwin et al observed significant association of higher BMI with increased risk of early (within first 5 years) and late (after 5 years) distant recurrences and death in breast cancer women [6]. Excess of adiposity has been identified as a risk factor for recurrence, reduced effectiveness and complications of the treatment, development of second primary tumor and mortality [7].

Potential Link between Obesity and Cancer Progression

Obesity is associated with the progression of various cancers and it is an important predictor of poor outcome of the disease. Also it has been observed to be associated with higher grade nature of tumor in prostate and breast cancers. Other cancers associated with poor outcome with obesity are tumors of kidney, pancreas, esophagus, thyroid and endometrium [8]. Several mechanisms have been proposed to link obesity with cancer. Adipocytes form tuor microenvironment in various cancers especially at the sites surrounded by adipose tissue. Quantity and quality of surrounding adipose tissue affect biological and secretory nature of adipocytes. Fatty acid metabolism plays significant role in the biology of cancer. Cancer cells which are metabolically flexible, get benefited from high lipid storage to fulfill increased demand of energy and prevent lipotoxic effects of high concentration of fatty acids. Role of fatty acid binding protein (FABP) has been implicated in cancer biology and it is emerging as an important factor in cancer cell lipid metabolism [9]. Altered lipid metabolism like increased lipogenesis occur in cancer cells due to the disturbances in signalling pathways. Hence enzymes of lipogenesis pathway can be targeted in anti-cancer treatment [10]. Adipose tissue dysfunction is supportive for tumor microenvironment through local and systemic effects that fuel local tumor growth as well as metastasis [11]. Abnormal adipocytes adjacent to tumor cells are termed as cancer-associated adipocytes that form reciprocal signaling

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pathways with the tumor cells. Such adipocytes are found to be resistant to chemotherapy and radiotherapy leading to unfavorable clinical course.

Several mechanisms have been proposed to explore link between adverse effects of obesity with prognsis of cancer. Obesity causes alterations in adipose tissue microenvironment along with endocrinal imbalance that favors tumor initiation as well as progression [12]. Obesity is a state of chronic low-grade systemic inflammation through which it promots the cancer risk as well as progression of cancer. Obese individuals harbor inflamed adipose tissue with immune cell infiltration leading to altered local environment. Tumor-promoting consequences of obesity occur via insulin resistance, dyslipedemia and inflamed adipose tissue that release local and systemic inflammatory mediators. Inflammation in adipose tissue is associated with poor prognosis in breast and tongue cancer.

Interventions for Weight Loss to Halt Progression of Caner

Rising prevalence of obesity and cancer emphasizes the significance of elucidation of the mechanism through which obesity may impact aggressiveness of tumor. Obesity among cancer survivors is a growing public health burden that needs an urgent attention. It can be a result of specific cancer treatment including chemotherapy, hormonal therapy and steroid medications [13]. Obesity worsens the progression of the disease affecting clinical course not only in relation to cancer outcome, but also other comorbid conditions. It can also have impact on other medical conditions like hypertension, diabetes mellitus, cardiovascular disease and dyslipedemia that can affect overall survival. Thus obesity increases 5-year all-cause and cancer-specific mortality and morbidity [14].

Improvement in the health of adipose tissue to reduce inflammatory state would be a novel therapeutic approach to minimize burden of cancer-related mortality. Weight reduction by diet and exercise management, an economical and modifiable option, help to improve quality of life among cancer survivors. Also it makes favorable alterations in tumor microenvironment and further tumor behavior through modifiable relation of adipocytes with dietary intake [15]. Calorie restriction might be an effective therapeutic intervention to improve outcome of cancer patients. In one of randomized controlled trial, it has been observed to reduce cancer related mortality among postmenopausal women with breast cancer [16]. There is scarcity of data regarding effect of weight loss on outcome of cancer. In case of breast cancer survivors, Pierce et al reported favorable effects of weight reduction on the recurrence [17]. But there are no direct evidences from the studies suggesting weight loss intervention conferring survival advantage. Orlistat, an inhibitor of lipase that prevents absorption of fat, also inhibits intra-cellular lipase and triglycerides/free fatty acid cycling and fatty acid synthase. Hence its anti-cancer efficacy is also recognized [18]. Reggiani et al reviewed role of adipose tissue-related inflammation, adipose metabolic alterations, genomic instability and dysregulation of immune system, angiogenesis and stiffness of extracellular matrix in the causation and progression of breast cancer. They suggested some innoative therapeutic strategies like caloric restriction, immune checkpoint inhibition, modulation of microbiota and immune cell metabolism and browning of white adipose tissue [19].

Conclusion

Pharmacological interventions with weight reducing and anti-inflammatory medications could be beneficial. But efficacy of these drugs has not been investigated for halting progression of cancer. Hence in future, studies bridging the gap to connect preclinical experimental studies with human observations to evaluate impact of obesity on progression of different cancers must be carried out. Overall the biological mechanisms that link association of obesity with progression of cancer are metabolic factors, endoctrinal imbalance and chronic loe-grade systemic inflammation. Potential of these therapeutic interventions need to be studied in depth to implement their use in clinical practice.

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