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Diet and Cancer Metabolic Reprogramming

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Abstract

Cancer is a complex disease with different types arising from different tissues. Different therapies are being addressed to treat the cancer patients. Environmental factor like diet is a risk factor for many cancer suggesting the need for adequate nutrition and diet for cancer patients. Dietary intake is related to the energy intake via food for a person. Diet influences metabolism which in turn can regulate the process of cancer and metabolic reprogramming. Breast cancer has been used in the work as an exemplarity cancer to be influenced by diet and nutrition. Diet based strategies is a suggestive for cancer treatment based on Warburg effect. It may be also possible to limit the reverse Warburg effect by metabolic coupling. The review work discusses about the metabolic syndrome and cancer and hypothesizes metabolic reprogramming can be used to regulate cancer as well as epithelial mesenchymal transition.

Introduction

Cells as the building block of life in a living organism need energy which comes from dietary intake of foods. A well balanced diet provides not only carbohydrates, fats and proteins but also vitamins, minerals and other essential requirements for organismal functioning. However excess intake of food can lead to storage in the human body and development of health problems [1]. However, cancer patients are suggested to maintain a healthy body weight and consume nutritious foods. Instances in cancer treatment are there, wherein side effects can make a person to opt for less amount of food consumption and lose weight leading to malnourishment, or else subject the person to a weight gain [2]. It is difficult to treat a person in first line of treatment without sustaining the person's adequate nutritional and healthy state [3]. Although diet and nutrition affect health of any cancer patient, herein discussion has been emphasized on breast cancer as an exemplarily type of cancer.

Breast cancer patients (BCP) are suggested to go for a nutritional assessment immediately after their diagnosis [4]. Interestingly, energy restriction to control weight can be a potential strategy for breast cancer prevention [5]. The statistics of breast cancer and other forms of cancer speaks about a rise in the incidences, and which might not decline easily with increase in incidences of breast cancer for males [6]. Predictions are speaking about cancer to be the leading cause of death in every country [7].

Diet and nutrition for cancer patients

Healthful eating for a person demands consumption of a balanced diet including a variety of unrefined carbohydrates, proteins, fats, vitamins and minerals [8]. This is apart from sustaining a healthy lifestyle. However, consumption of extra quantities of individual nutrients will not provide a person with more energy. Certain foods, like whole grains and healthy unsaturated fats can supply with the food reserves, but intake of excess refined sugar and white starches can leave a person depleted and carve for more sweets [9,10]. Complex carbohydrates can provide a person's health with sustained energy because of their digestion at a consistent and slow rate. This also helps to stabilize one's sugar levels due to less insulin production from the pancreas, giving a feeling of satiety [11]. A breast cancer patient is suggested to maintain a healthy and balanced diet that might not only help in healing the body heal from cancer treatment, but also overcome numerous side effects of the treatment procedures [12]. Researchers have substantiated that cancer is correlated with dietary factors, like high intake of meat has more probability for high rate of colorectal cancer development and restricting energy intake can cause a general reduction in cancer development [13-15]. Inspite of the fact that dietary factors are important in determining the risk of cancer development, establishing the exact effect of diet on cancer development is still a research problem [16].

Cancer patients have varied nutritional requirements and it varies from person to person. The determination of diet will not only help to build up one's strength, but also withstand effects of cancer and its treatment. The workers can help to identify one's specific nutrition goals and plan methods to meet them. This will take in consideration a patient's type of cancer, treatment and any associated side effects [17]. Factors like body weight, diet and exercise plays role in breast cancer recurrence and survival. Lifestyle choices can also have the greatest impact on reducing the risk of breast cancer recurrence and improve overall survival. At Canada, women with breast cancer are suggested to maintain a body mass index (BMI) between 18.5-24.9; intake a diet lower in fat and high in vegetables, fruits and grains; and maintain a state of physical activeness [18].

Dietary energy density (ED), a measure of diet quality which helps in estimating the amount of energy per unit of food (Kcal per gram) being consumed is seen to be positively associated with BMI, as well as with many risk factors for postmenopausal breast cancer. The value of dietary patterns incorporating fruits and vegetables and other low ED foods can lead to weight management and reduce the risk of

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post menopausal breast cancer [19]. Thus, nutritional intervention in breast cancer patients must be considered as an integral part of the total therapeutic approach. However, additional research inputs from dietary interventions in large clinical trials are a necessity to improve the long-term survival with a better quality of life [20].

Cytoskeleton and cancer

Cancer is a disease that occurs when the normal cellular processes that regulate cell behaviour fails and functional abnormalities in a cell not being killed by the cellular process survives and leads to a generation of cells with functional abnormalities [21]. The development of a cancerous cell can be traced to not only the endogenous factors but also to multiple environmental factors, which includes diet as a component. A cancerous cell also possesses the same cytoskeletal build-up of a normal cell. Imbalanced diet can lead to adiposity, and multiple cellular and molecular pathways are implicated as a link between degrees of adiposity and cancer. Cytoskeleton not only plays role in cancer cell migration and invasion but also in epithelial mesenchymal transition (EMT). EMT is a process characterized not only in the developmental stages, but also in cancerous states. [22].

Cytoskeletal remodelling as well as the cell cycle regulation are of essential requirement in nutritional programming of the embryonic development [23] with the involvement of a few numbers of gatekeeper processes. Thus, there are involvement of gatekeeper genes and proteins whose expression changes due to nutritional deficiency [24]. Nutritional insults of protein and iron deficiency in rats were observed to be associated with a common phenotype of raised blood pressure [23]. Nutritional stress can result in metabolic syndrome (MetS) and MetS is associated with risk of cancer development [25,26].

Metabolic syndrome

Metabolic syndrome leads to an increase in the risk of diseases and enhances tumour progression apart from leading to side effects from treatments responses. Biochemical reactions directed by the imbalance of the metabolic components can adverse state of the host and organ-specific tumour microenvironment leading to an accelerated rate of recurrence and mortality [27].

The link between type 2 diabetes, metabolic syndrome (MetS) and breast cancer has been studied well. Fasting insulin levels, abdominal obesity can be linked well to the postmenopausal breast cancer [26]. Peroxisome proliferator activated receptors (PPAR) are linked to metabolic disorders and PPAR modulators can acts as chemopreventive agents [28-30]. Insulin resistance and insulin like growth factor system 1 plays a key role in the association between metabolic syndrome and cancer. The effects of MetS can be additive or synergistic in cancer development, and MetS has been linked to colorectal, breast, endometrial, pancreas, liver and may be prostrate cancer [31]. However, MetS has been seen to reduce the risk of breast cancer development in premenopausal women [32], whereas increased risk of breast cancer is seen in postmenopausal women with MetS association [33,34]. Additionally, Li et al., 2020 suggests MetS to be a predictor for the risk of cancer recurrence and mortality in women with breast cancer, particularly in Caucasians [35]. Inflammation and hypoxia are also suggested to be the potential factors involved in the link between MetS and cancer [36].

Metabolic stress is known to regulate cytoskeletal dynamics and oncogenesis. Caino et al., 2013 reported that mitochondrial HSP90 chaperones can overcome metabolic stress as well as promote tumour cell metastasis [37]. The cellular cytoskeleton along with its components is involved in tumour cell migration and metastasis and is a part of epithelial mesenchymal transition [22,38]. Many factors, like MYC amplification and oxidative stress can lead to the occurrence of metabolic reprogramming phenotypes in breast cancer metastasis [39]. Furthermore, cancer cells showing resistance towards chemotherapy can also be sensitized to metabolic therapies [40]. Researchers have established the role of nutrition in the management of metabolic stress [41].

Metabolic therapy along with alternative diets is a suggestive for cancer treatment because of their ability to target cancer cell metabolic processes [42]. The practise involves usage of special diets, enzymes, nutritional supplements as well as other practices [43]. Additionally, modifications in the diet can limit tumour-specific nutritional requirements and enhance cytotoxicity of anti-cancer drugs [44].

Metabolic reprogramming

Cancer metabolic reprogramming recognized as one of the ten cancer hallmarks is characterized by many functions like elevated glycolysis, pentose phosphate pathway, lipid metabolism, glutaminolysis, mitochondrial biogenesis, etc. These characteristics have been used for diagnosis, disease staging, monitoring tumour response to therapies, detecting cancer recurrence. Metabolic reprogramming leads to the immune cell dysfunctioning [45]. The information obtained by imaging of the cancer cells helps in detection, prevention and treatment process [46]. The process of change of tumour cellular bioenergetics or metabolic reprogramming [47] can be changed by drugs or therapeutic strategies which includes a healthy and nutritious diet for a cancer patient and the latter can be put forth for a conventional anti-cancer agent. Drugs are of help to change or arrest the metabolic reprogramming in cancer cells, and maintaining adequate nutritious state can act a second line of therapy [3,48]. Nutrient sharing and metabolic symbiosis are common in many type of tumours which involves significantly lactate [42]. The metabolic reprogramming in cancer cells not only involves cancer cells but also host cell populations. Symbiotic metabolism is observed in many types of cancer, like lung cancer, breast cancer, colon cancer, etc. [49-51]. However, treatment with a ketogenic diet can destroy the metabolism of cancer cells, lead to cancer cell starvation and cell death [52] and restore immune function [42]. The ketogenic diet also leads to the production of ketone bodied and that cannot be metabolized by the cancer cells, leading to survival and enrichment of the host cells but not the cancer cells [52,53].

Conclusion

Lifestyle changes and nutritional modifications with a healthy diet can decrease cancer risk and alleviate MetS [26]. However more studies are a necessity to unravel the link between MetS and its components with cancer [54]. Dietary guidelines can help to improve BCPs nutritional status and improve their overall health and prognosis [55]. Expression of the cytoskeleton proteins can be related to the degree of malignancy and inturn knowledge of these proteins can help in cancer prognosis and treatment [56]. Troubles in functioning of cytoskeleton has shown linkage to cancer development and progression, as well with incidences of epithelial mesenchymal transition [22], and problems in cytoskeleton functions can be related to MetS [57,58]. Energy restriction (ER) is also known to be a potential strategy to prevent breast cancer [5,59]. Nutritious diet is not only important for the cancerous cells, but also the non-cancer cells, as well as for the host cells (Figure 1). Metabolic reprogramming can provide therapeutic targets for the treatment of triple negative breast cancer [60]. Metabolic reprogramming has been linked to epithelial-mesenchymal plasticity [61]. Metabolic reprogramming has been observed in neuronal differentiation also [62]. Additionally, energy demanding processes,

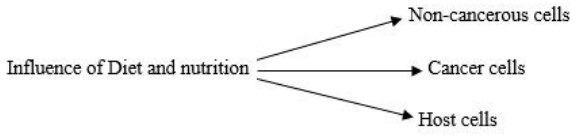

Figure 1. Schematic illustration of diet on tumour environment

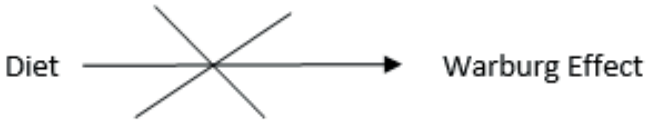

Figure 2. Schematic illustration to show that diet can limit Warburg effect

like cell growth and cell differentiation are tension modulated processes [63]. Metabolic heterogeneity in tumour cells can be coupled to the reverse Warburg effect [64], wherein timorous cells produce and meet their ATP requirement via aerobic glycolysis [65]. Diet based strategies has been suggested for cancer treatment based on Warburg effect [66] (Figure 2) and may be the same diet-based strategy can be used for novel biomarker and anticancer agent development. These suggest hypothesizing that epithelial mesenchymal transition can be linked to MetS and nutritional modifications, and ER might influence the process of epithelial mesenchymal transition and will help to target metastatic and refractory cancers.

Conflict of interest

The author declares no conflict of interest.

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