Obesity and Cancer: Evidence, Postulated Mechanisms and Prospectives

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Abstract

Obesity is a major health problem tremendously increasing worldwide, obesity has been accompanied by a state of metabolic dysregulation, characterized by insulin resistance and may be associated with many comorbidities such as metabolic syndrome, type 2 diabetes and cardiovascular complications. Lately a great attention has been gained toward the association of obesity with certain cancers. Numerous studies and meta-analysis reported that, obesity is associated with increased risk of esophageal adenocarcinoma, postmenopausal breast cancer, and endometrial, renal, pancreatic, prostate and colorectal cancers. In spite of, the evidence of such association that link obesity with risk and recurrence or death from cancer, however the linking mechanisms has not been yet fully explained. Obesity may promote cancer by: 1) alteration of adipocytokines: Leptin, adiponectin, resistin and visfatin with promotion of angiogenesis and interactions with other mediators and cytokines. 2) Hypoxia and angiogenesis due to expansion of adipose tissue with release of certain mediators that stimulate angiogenesis. 3) Metaflammation state of low grade and chronic inflammation that merely stimulate release of cytokines as (TNFα) and (IL-6) and the activation of pro-inflammatory signaling. 4) Insulin resistance with hyperinsulinemia and increased levels of insulin and growth factors as IGFs and IGF binding proteins. 5) Increased levels of sex steroids, including estradiol and Dehydroepiandrosterone (DHEA) particularly in cases of endometrial and postmenopausal breast cancers. 6) oxidative stress and reduction of antioxidants with possibility of oxidative damage or mutation of DNA. 7) epigenetic mechanisms, including DNA methylation , histones and chromatin remodeling factors . In fact, it remains unclear how the convergence of these mechanisms may drive obesity-associated cancer, considering the complex and multi-factorial characterization of cancer as well as the variation of genetics background of obese subjects. Prospective studies is worth pursuing especially towards therapeutic implications to prevent or treat obesity- associated cancer. Our aim is providing updated and comprehensive review about postulated and prospective links and molecular mechanisms between obesity and cancer, focusing upon mechanistic mediators that may drive obesity- associated cancers and may be targeted molecules for prospectives therapies

Key words: Cancer; Obesity; Adipokines; Insulin resistance; Proteomics

Introduction

The pandemic of obesity is alarming and expanding all over the world [1]. It was estimated that, 2.2 billion adults are overweight or obese worldwide. Moreover, estimations based on regression analysis , suggested that , by 2030 ,more than 20%of adults will be obese in addition to 38% will be overweight as well, if the current trends continue in the same manner[2,3]. Obesity as a chronic disease , is strongly associated with an increase in mortality and morbidity. Obesity is merely linked to metabolic dysregulations as insulin resistance, and associated with comorbidities as diabetes mellitus type 2, hypertension, cardiovascular complications and certain types of cancers [4]. Many reports has focused on the association of obesity with some types of cancers as adenocarcinoma of the esophagus, post-menopausal breast, ovarian, endometrium, liver, colorectal, gallbladder, pancreas, kidney, gastric cardia, as well as non-Hodgkin lymphoma, multiple myeloma, metastatic prostate cancer, and unfortunately the list of cancer types is increasing [5-11]. Even more, obesity has been linked to increase the risk of recurrence, and deaths among cancer patients, thereby, better exploration and comprehensive understanding of the linking mechanisms between obesity and occurrence or aggressiveness of certain cancers, will allow the development of recent strategies against cancer [12-14]. While obesity is associated with an increased risk of several malignancies, other types of cancer as squamous cell carcinoma of esophagus, lung and premenopausal breast cancer may exhibit inverse association with obesity [15-17]. The concept of association of metabolic dysregulation encountered in obesity and carcinogenesis was firstly enunciated by Otto Warburg [18]. Fifty years later, the International Agency for Research on Cancer (IARC) reported that, avoiding weight gain could be protective against some cancers [19]. Substantial observational studies and supporting evidences has suggested the positive association between obesity with risk increase of many cancers, and with increased risk of cancer mortality [20,21]. Indeed, such associations were well established by

several epidemiological and large prospective studies; however, the linking mechanism has not been fully understood. Previously, IARC, American Institute for Cancer Research (AICR) and World Cancer Research Fund (WCRF) reported the convincing evidence for the association of obesity with certain types such as, endometrial, esophageal adenocarcinoma, colorectal, postmenopausal breast, prostate, and renal carcinoma [1,21-25]. To Lesser extent, other malignancies may be associated with obesity as malignant melanoma, thyroid cancers, leukemia, non-Hodgkin's lymphoma, and multiple myeloma [26,27]. Other few studies have investigated the association of obesity with stomach and cervical cancer but less data and evidences were reported [28,29]. Other reports suggested a probable evidence for association of obesity with gallbladder cancer and aggressiveness of prostate cancer [30].Types of cancers that has been linked to obesity with their associated findings are summarized in Table 1. In this review, we will focus upon the proposed linking mechanisms and suggested mediators of obesity-associated cancers.

Mechanisms linking obesity with cancer

It was estimated that about 20% of all cancers may be influenced by obesity and approximately the half of cancer cases can be attributed to obesity in postmenopausal women [54], additionally substantial recent evidences has supported the cause-and-effect relationship in-between obesity or overweight at one side and the onset of these cancers on the other side [34]. Association and influence of obesity and cancer risk is merely gender and type of cancer specific, however the higher risk for different types of cancer is pivotally due to life style, dietary factors and anthropometric parameters as BMI or waist circumference, these factors activate several molecular or biological mechanisms [55]. It seems likely that obesity attributes to cancer through many mechanisms and various mechanisms could work differently in different people; substantially the etiology of cancers is different in different types and sites of cancer. For example, insulin and growth factors may drive prostate and colon cancer [56], whereas sex steroids may drive breast and

Table 1: Types and evidences for association of obesity and cancer

Type of cancer	Findings for association of obesity with cancer	References
Post-menopausal breast cancer	Obesity increases breast cancer risk by 50%, in postmenopausal women with increased serum concentrations of free estradiol	[31, 32]
	Obesity increases breast cancer risk among non-hormone replacement therapy users of postmenopausal women	[33]
	For increasing BMI by 5 kg/m2 , the risk of postmenopausal breast cancer by 31%	[34]
Colorectal cancer	Obesity is related to a higher risk of colorectal cancer	[22, 35]
	waist circumference and the waist/hip ratio are also strongly associated with colorectal cancer	[36]
Esophageal adenocarcinoma	Obesity is associated with a 3-fold increase in risk for adenocarcinoma of the esophagus	[24, 37, 38]
	High BMI is associated with gastroesophageal reflux is very strongly associated with esophageal adenocarcinoma	[39]
Endometrial cancer	Obesity is associated with 2 to 3-fold increase in risk for developing endometrial in obese women than in lean women	[21, 40]
	40% of endometrial cancer incidence has been estimated to be attributable to excess body weight	[22]
Hepatocellular carcinoma (HCC)	the relative risk of mortality from liver cancer was 1.68 times higher in obese women and 4.52 times higher in obese men	[21]
	Obesity is a risk factor for the development of HCC	[41, 42]
Prostate cancer	Obesity significant positive association with an estimated increase in prostate cancer risk (5% excess risk per 5 unit increment of BMI)	[43, 44]
	high BMI at time of prostate cancer diagnosis was associated with increased overall mortality	[45-47]
Pancreatic cancer	High BMI is associated with doubling of risk for pancreatic cancer in men and women	[24]
	Positive association of Pancreatic cancer with waist circumference in men not in women	[48]
Renal cell carcinoma	Obesity is associated with high risk for renal cell carcinoma	[23, 49]
	Obesity has inverse relationship with prognosis in renal cell carcinoma, associated with post-operative complications.	[50-52]
Ovarian cancer	Obesity may affect survival by negative impact on surgical and chemotherapeutic intervention	[53]

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endometrial cancer. On the other hand, chronic inflammation may drive other types of cancers, in fact all of the previous mechanisms may contribute to carcinogenic effect of obesity in site specific or in universal and direct way [57]. Universally acting mechanisms could promote carcinogenesis for all or majority of malignancies, simply because those mechanisms are consequences of hormonal and metabolic alterations prevalent in obesity. Otherwise, site-specific mechanisms could particularly promote tumors whenever complications of obesity heightens the risk for one type of cancer at specific site as for example risk of adenocarcinoma of esophagus as an assumed effect of aggravated gastro-esophageal reflux or for liver cancer can be a consequence of nonalcoholic steatohepatitis being comorbid effects of obesity [58]. Obesity occurs when caloric intake exceeds energy expenditure causing excess accumulation of adipose tissue. White Adipose Tissue (WAT) has been considered as an endocrine organ beside its main primary role as a fuel reservoir organ. WAT secretes adipokines, sex steroids, and cytokines that, are involved in regulation of fuel storage, metabolism, food intake, insulin sensitivity, and immunological function [59]. Most of the obesity linked diseases or morbidity changes, such as diabetes mellitus, insulin resistance, coronary heart diseases and cancers are mostly caused by alteration or dysfunction of WAT leading to a state of chronic inflammation with alteration of excretion of adipokines and cytokines [60]. Adipokines, cytokines secreted from adipose tissue together with the state of low grade inflammation (Metaflammation) and expanded hypoxic adipose tissue are among the proposed mechanisms that may promote carcinogenesis in obese subjects. Proposed linking mechanisms of obesity and cancer are illustrated in Figure 1; linking mediators are summarized in Figure 2.
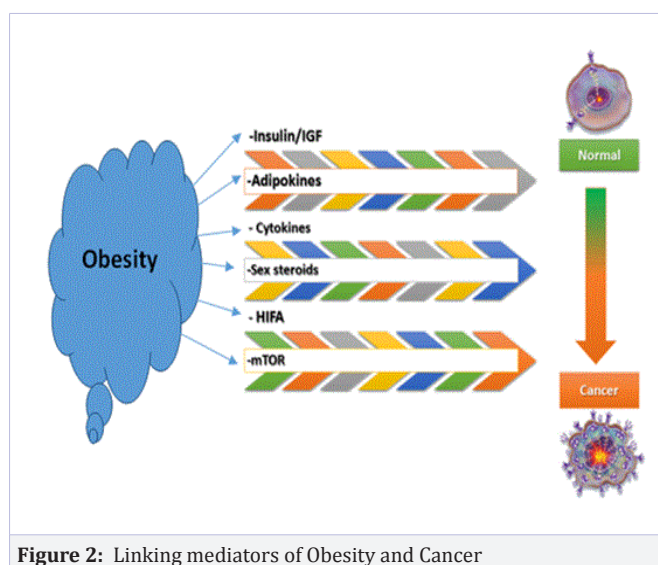

Figure 2: Linking mediators of Obesity and Cancer

Adipokines

WAT is a dynamically active endocrinal organ; it is not, as previously thought, such a fuel reservoir. It is capable of synthesizing and secreting a panel of hormones namely termed "adipokines" [59]. Adipokines are regulatory hormones for caloric intake and metabolism, as well as having a pivotal role in angiogenesis and cell growth. Through their subtypes, leptin, visfatin, resistin and adiponectin, they seem to play important roles in the pathophysiology of development of cancer and its progression [61-63].

Leptin is considered as central mediator of a feedback loop, which regulates appetite and energy homeostasis [64]. The central nervous system is the major physiological site of leptin action; however, expression of leptin receptor (OBR; also known as LEPR) is also observed at lower levels of leptin in peripheral tissues in case of obesity [65]. Chronic over expression of leptin enhances leptin resistance, resulting in increased circulating leptin levels, in a similar way to insulin resistance that is associated with raised adiposity [66]. The close correlation between adiposity, leptin levels and expression of OBR may propose a role for this neuroendocrine hormone in promoting cancer development and progression. Several studies have displayed an over expression of leptin OBR in various cancers, including breast, prostate and colon cancer [67,68]. Furthermore, high level of circulating leptin in obese females has been documented to increase the risk of breast cancer in post-menopausal females [69,70,71]. Increased leptin levels in obese subjects is reported to have mitogenic and anti-apoptotic effects and differential roles in regulation of cell migration in certain cancers included within the list of obesity linked cancers, such as breast, ovarian, prostate, endometrium, colon and thyroid cancers [72-75]. Contribution of leptin in tumor development and progression has been displayed by various signaling mechanisms. Leptin signals via a trans membrane receptor (LRb) control STAT3 and ERK activation [76]. Leptin induces STAT3 phosphorylation in the human breast cancer line, MCF7and blocking phosphorylation with the specific inhibitor

Figure 1: Mechanisms linking Obesity with Cancer

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AG490 abolished leptin-induced proliferation [77]. Furthermore, leptin increases HER2 protein levels through a STAT3 mediated upregulation of Hsp90 in breast cancer cells. Inhibition of the STAT3 signaling cascade by AG490 abrogated leptin induced HER2 expression [78]. Activation of leptin receptors leads to phosphorylation of MAPK and increased proliferation in MCF7 breast cancer cells [79]. Chronic elevation of leptin also causes ERK1/2 activation in human breast cancer cells additionally, Akt phosphorylation in human prostate cancer cells [72,80].

Adiponectin is the most abundant adipokine, secreted only by mature adipocytes and has anti-inflammatory activity [81], it regulate carbohydrate and lipid metabolism, enhancing insulin sensitivity [82]. Adiponectin serum levels were thought to have an inverse association with BMI. Epidemiologic and preclinical data propose a protective effect for increased adiponectin levels on obesity-related cancer risk [83].Thus, adiponectin was proposed to have anti-tumor effect and levels of adiponectin were inversely related to risk for several cancers such as, postmenopausal breast cancer, renal cell carcinoma, prostate, endometrial and colorectal cancer [70,84 -87]. Adiponectin promotes apoptosis, induce expression of p53, inhibits expression of Bcl-2, additionally it activates AMPK pathway but inactivates ERK1 and ERK2 [88]. Mechanisms mediate anti-carcinogenic and anti-proliferative effects of adiponectin were impaired experimentally via blocking of its receptors AdipoR1 [89]. Adiponectin antagonizes carcinogenic effect of leptin on hepatocellular carcinoma cells through increase of phosphorylation of JNK, stimulation of apoptotic mediators and inhibition of mTOR phosphorylation mechanisms [90]. Another report claimed that pleiotropic effects of adiponectin are arbitrated to altered ceramide to sphingosine ratio with rise of ceramidase levels and activity [91].

Several adipokines have been identified and are suggested to be involved in obesity-related cancers, for example; resistin, visfatin, thrombopoietin and growth-related oncogene factor α. Their levels were found to be increased in obese subjects and are anticipated to promote carcinogenesis, progression and metastasis via enhancing angiogenesis, proliferative and anti-apoptotic activity [92-94].

Hypoxia and angiogenesis

Obesity modifies physiological functions of WAT, resulting in a state of low-grade inflammation and leading to expansion of adipocytes and their vasculature, with decrease of oxygen perfusion and subsequently localized hypoxia [95]. Nevertheless, there is no increase in cardiac output or blood flow to the adipose tissue, particularly to WAT [96-98]. Previous studies on animal models revealed lower levels of oxygen in WAT in obese mice when compared with lean mice [99]. Lack of oxygen results in activation of hypoxia induced factor 1-alpha (HIF-1α) , that is a heterodimeric transcriptional factor that mainly targets and controls certain angiogenesis promoting genes such as vascular endothelial growth factor A (VEGF-A), fibroblast growth factor (FGF), Thrombospodin-1 (TSP-1) and angiogenesis prohibiting genes as plasminogen activator inhibitor, matrix metalloproteinases MMP-2 and MMP-9. Once

HIF-1α transcription factor is secreted by hypoxic adipocytes, it will stimulate pro-angiogenesis process [100]. HIF-1α mediates cellular responses to hypoxia via regulation of glucose uptake and stimulation of anaerobic oxidation [101]. Expression of HIF-1α is reported to be increased in adipose tissue of obese individuals, and over-expression of it is reported in certain cancers and positively correlated with mortality and unresponsiveness to therapy [102,103]. Thus, it is possible that hypoxia through an angiogenic role, may interconnect obesity with cancer, HIF-1α as a mediator of hypoxia, has another crucial role in controlling genes involved in cell survival and increased metastatic potential as well [104]. Hyperplasia of hypoxic adipose tissue, that are merely occurring in obesity, resulting in proliferation of vascular stromal cells and angiogenesis, is well confirmed as an early mechanism for cancer development and metastasis [105]. Thus, it may be the missing link between the adipose tissue progenitors of vascular stromal cells that could promote cancer development and progression through angiogenesis, endocrine or paracrine signaling to malignant cells [106].In fact, hypoxia of adipose tissue in obese subjects and the released mediator; HIF-1α may be a well-recognized explanation of obesity- associated cancers.

Metaflammation

Obesity stimulates an inflammatory status that is called "Metaflammation", which is characterized by being a low-grade, metabolically linked and chronically acting inflammatory process [107]. Despite of it is unclear, how this inflammatory state is started? One suggested mechanism is hypoxia. Through weight gain and expansion of adipose tissue, cells are too distant from the organ's vasculature causing them to become poorly oxygenated and resulting in hypoxia in the area of this event [108]. Such inflammatory condition occurs due to release HIF-1α, that mediates the infiltration of macrophages and monocytes into adipose tissue, and stimulates secretion of tumor necrosis factor-α (TNF-α) from WAT [60]. TNF-α was found to mediate endotoxin-induced tumor necrosis, cancer angiogenesis additionally it has been involved in metastasis [109-111]. Therefore, increasing levels of TNFα in the bloodstream of obese subjects is one of potential mechanism of TNF-α-induced carcinogenesis [112]. Obesity-induced inflammation involves the activation of the nuclear transcription factor NF-κB by inactivating the inhibitor of NF-κB (IκB) thus, inhibiting apoptosis and allowing cell survival [113].This pathway has been shown to be implicated in the development and progression of cancer [114]. Moreover, stimulation of NF-κB in cancer cells is able to activate cell cycling through c-Myc and cyclin D1, resulting of increased cell growth and proliferation, association between obesity-induced inflammation and the stimulation of NF-κB by TNF-α are well-established, however, other roles of NF-κB in obesity-associated cancers is still unknown. Interleukin-6 (IL-6) is another cytokine shown to be raised in obesity and IL-6 levels are positively associated with BMI [112,115]. IL-6 induce JAK-STAT3 signal transduction cascade and stimulate cell proliferation, that has been suggested to act through The Mitogen-Activated Protein Kinase (MAPK) pathway, thus, pointing to the integral role of IL-6 in cell proliferation, differentiation and metastases, associated

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with inflammation in obesity–linked cancers [116,117]. Metaflammation state is correlated to abnormally high levels of cytokines and concomitant activation of pro-inflammatory mediators which might be important inducers for progression of cancer cells [23].

Insulin resistance and growth Factors

One of the proposed mechanisms that explain association between obesity and cancer is insulin resistance or low sensitivity for insulin hormone. Increased adiposity and body weight are directly correlated with insulin resistance that is compensated by over stimulation of insulin secretion, resulting in hyperinsulinemia. High serum levels of insulin is potentially promoting aggressiveness of certain cancers such as postmenopausal breast and endometrial cancer [7,118]. Insulin hormone when excreted within normal values under physiological conditions has an anabolic and anti-mitotic effect, however only when excreted in excess or higher values, as in obesity associated with hyperinsulinemia or insulin resistance, it has an obvious mitogenic effect [55]. Binding of insulin to its own Insulin Receptor (IR) triggers both phosphatidylinositol-3 kinase and Extracellular-signal Regulated Kinase (ERK), IR is highly expressed in adipose tissue and interestingly, over expressed in breast cancer cells and most of haematopoietic cancer cells [119,120]. Receptor for IGF-I (IGF-IR) has shown more than fifty percentage homology with IR and sequence similarity of about 85% for their tyrosine kinase domain, therefore both hormones could interact with any one of both receptors [118]. Binding and activation of IGF-IR results in phosphorylation of IRS proteins, which stimulate the oncogenic Ras-MAPK and PI3K-Akt signaling pathways, Signaling pathway of the PI3K-Akt induces cell proliferation and is frequently activated in cancers [121,122]. Another downstream signaling molecule of Akt is mTOR, which stimulates protein translation and cancer growth [68]. Furthermore, tumors with constitutive stimulation of the PI3K pathway are insensitive to dietary restrictions, which can normally delay the incidence and decrease growth of various tumor types by decreasing the levels of circulating insulin and IGF-1, suggesting an association between obesity and cancer [123]. Insulin resistance and consequent hyperinsulinemia that accompany obesity, diabetes type 2 and metabolic syndrome serve to facilitate glucose uptake by muscle, fat, and liver mediated by insulin receptors. Elevated levels of insulin may also stimulate mitogenesis and growth in a number of tissues and may also increase IGF-1 and decrease IGF binding proteins, thereby providing higher levels of biologically active IGF-1 proteins, which further interact with cell-surface receptors to stimulate tumor growth and may induce carcinogenesis.

Sex steroids

Post-menopausal breast cancer risk was reported to be increased in women with high serum levels of sex hormones, such as, Dehydroepiandrosterone (DHEA), testosterone, estrone, and estradiol [124,125]. Sex hormones may directly mediate the effect of obesity on cancer through activating growth and progression of tumor cells , in particular breast, and endometrial

tumors [126,127]. Mechanisms meditating carcinogenic effects of estrogen may be related to induction of DNA damage, regulation of expression of insulin receptor IRS-1 in the breast or/and genetic instability [128]. In addition, estrogen stimulates cellular proliferation and angiogenesis [129].Several studies have documented a positive correlation between heightened circulating estrogen levels and the risk of postmenopausal breast cancer [124,130]. Production of estrogens after menopause, mostly takes place in the peripheral adipose tissues, catalyzed by cytochrome P450 dependent enzyme; aromatase enzyme, that converts androgen precursors into estrogens. CYP19 is the gene encoding aromatase and it is thought to be induced in postmenopausal women and not in premenopausal females [16,131]. Therefore, the greater risk of hormone receptor positive breast cancer in a post menopause period of overweight/obese women has been referred, in particular, to elevated estrogen production in adipose tissue by aromatase enzyme as a consequence of hyper adiposity [132].

To date, the specific mechanism by which post-menopausal women, but not pre-menopausal women, have an obesity-related risk of breast cancer has not been fully clarified. Production of estrogen differs significantly between pre-menopausal and post-menopausal women. The main source of estrogen production in pre-menopausal women is the ovaries; whereas, for post-menopausal women, it is from peripheral aromatization in adipose tissue [32]. In post-menopausal women, fat cells aromatize ovarian and adrenal androgens into estrogen. It has been demonstrated that elevated circulating levels of free estrogen, as well as estrone and androgens, are associated with breast cancer [31]. Therefore, Increased BMI has been associated with increased the risk of postmenopausal breast cancer not premenopausal breast cancer [16,34,131].

Similarly, heightened concentrations of plasma estradiol and estrone observed in endometrial cancer are associated with increased cancer risk in postmenopausal obese women due to activation of aromatase enzyme, in expanded adipose tissue due to obesity , converting androgens into estradiol and estrone [40]. Elevated levels of estradiol induces endometrial cell proliferation, blocks apoptosis and at the same time encourages IGF-I synthesis within endometrial tissue [23]. In a reverse manner, elevated BMI in premenopausal women, decreases breast cancer risk [126]. While , EPIC study and other epidemiological studies have reported that elevated plasma levels of androgens are correlated with increased risk of breast cancer in both pre- and postmenopausal women, therefore proposing that androgens may also be considered as links between obesity and breast cancer [20,125].

Oxidative stress

As disused before, obese patients usually exhibited lower levels of antioxidant enzymes and increased concentrations of oxidative stress byproducts. Obesity causes elevation of the sizes and activities of adipocytes, which in turn leads to liberation of inflammatory molecules as Interleukins and. Monocyte Chemoattractant Protein-1 (MCP-1), causing tissue necrosis

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and subsequent accumulation of activated macrophages. This pro-inflammatory status stimulates, in turn, insulin resistance development, over production of Reactive Oxygen Species (ROS) and induction of oxidative stress and modification of critical macromolecules and, finally, carcinogenesis. Heightened levels of ROS proceed to increased susceptibility to mutagenic factors leading to mutations with DNA damage and carcinogenesis [133-135]. Increased ROS are also contributed to enhancement of proliferation by transactivation of the tyrosine kinase receptor through ligand-independent mechanism, and finally, promoting spread of cancer cells and metastasis into distant organs [136,137]. Besides, ROS may contribute to stabilization of HIF1α that promote tumor angiogenesis allowing potentiation of carcinogenic effect of ROS [138-140]. Elevation of circulating levels or local ROS present within the tumor environment that were derived from increased adiposity and obesity accelerate oxidative stress within tumor cells and contribute to increased risk for cancer progression in patients with obesity [141]. Interaction of chronic inflammatory status; metaflammation in obese subjects with hypoxia of WAT may be one of the proposed mechanisms for increasing systemic oxidative stress, thus antioxidant activities may be independently decreased with subsequent increased oxidative damage to DNA, which may heighten cancer risk.

Epigenetic changes

Epigenetics are dealing with mechanisms beyond genomic or DNA-based alteration at genome such as genetic mutation and transcription factor targeting. Casual factors for epigenetic changes include disparity in DNA or environmental factors such as diet, and dietary supplements, stress, exercise, and exposure to chemicals. Interestingly epigenetic changes could affect susceptibility or risk for diseases, representing a common linking mechanism between disease and environment [142].Recently, epigenetic modifications has been proposed as a linking mechanism between obesity and cancer. However, lack of detailed interpretation of the epigenetic regulatory pathways perturbed by environmental and causal factors may be an obstacle for comprehensive understanding of that mechanism [143]. Epigenetic mechanisms regulate gene expression by coordinating and controlling the levels and activities of the so called highly conserved genomic processing, they include DNA methylation, post-translation histone covalent amendments, chromatin remodeling factors, and noncoding, micro RNAs or regulatory RNAs [144]. Previous reports demonstrated that BMI was associated to immunological alterations related to IGF signaling pathway and involvement of inflammation and angiogenesis as possible carcinogenic events in obesity, one study documented an association of increased BMI with positive expression IGF-IR mRNA only in postmenopausal breast cancer but not among premenopausal patients [145,146]. Recently positive association of BMI with multiple epigenetic modifications was demonstrated in Estrogen Receptor (ER) positive breast cancer patients, they identified such association between BMI with methylation of the genes involved in immunological response, insulin like growth factor pathway and DNA repair process. In addition, they

identified particle sites; SH3BP2, IGFBP6, DNMT3, and ERCC6 as being most significantly associated with BMI in ER positive breast cancer patients [147]. In Epigenome Wide Association Study (EWAS), a positive association has been demonstrated between BMI and methylation of DNA within HIF3A intron, that was proposed to be involved in hypoxia, low grade inflammatory state and carcinogenesis in obesity [148]. Representing a complexity and interactions between DNA methylation, genotype, age and disease. Increased BMI in European adults was found to be associated in a positive manner with increased methylation at HIF3A1 locus, providing supporting evidence of the crucial role of HIF signaling in mediating comorbidities associated with obesity and increased BMI [148].

In spite of the huge development of recent technologies for assessment of epigenetic mechanisms, however the interpretation of such of epigenetic findings or the confirmation of their biological relevance remains a significant challenge. This is in part may point to the complexity of epigenetic mechanisms or the gaps in our understanding of how several epigenetic mechanisms may interact all together to regulate gene expression or induce molecular events as carcinogenesis in obesity-associated cancers .

Conclusion

The pandemic of obesity is expanding all over the world and raising prevalence of obesity has significantly increased the risk of certain types of cancer. There is growing evidences supporting that obesity is associated with an increased risk of certain cancers such as postmenopausal, endometrial, esophageal, liver, gall bladder, prostate, colorectal and pancreatic cancer. Although some of these associations can be due to changes in hormones, dietary or environmental factors associated with obesity, however varieties of tumor types, suggesting that other crucial mechanisms may trigger that association. It has been postulated that the mechanisms by which obesity may promote cancer include: adipokines secreted by the adipocyte, for example, increased levels of leptin, resistin, visfatin and inflammatory cytokine and decreased adiponectin. Hypoxia and angiogenesis commenced due to expansion with hypo perfusion of enlarged adipocytes could be another triggering mechanism for carcinogenesis. Hyperinsulinemia and increase levels of IGF may potentiate the proliferation process. Recently, epigenetic modifications has been proposed as a linking mechanism between obesity and cancer, including DNA methylation, histone modification and chromatin remodeling factors. It is likely that many of these mechanisms cooperate with each other and with other environmental factors to result in multiple 'knockouts' which are needed for carcinogenesis. However, it remains uncertain how the merging of these events drives obesity-linked cancer. Thus, it is still a matter of controversial, whether targeting therapies for these mechanisms could prevent effects of obesity on cancer or carcinogenic effect of obesity.

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