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‘Micro’-management of Obesity and Cancer

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ABSTRACT

Recent decades have witnessed the emergence of diseases that tend to occur simultaneously and are often inter-related in more than one ways. Metabolic syndrome has come to be a dominant concern primarily in the developed countries and the incidence rate under this umbrella of disorders is constantly increasing. Another life-changing disease, cancer is also on the rise and the National Cancer Institute (NCI) estimates that as of January1, 2012, approximately 13.7 million Americans living have had a history of cancer. Extensive research has been done at the clinical, translational and molecular level and numerous inter-connections have been established and proposed between the two morbid conditions, metabolic syndrome and cancer. MicroRNAs (miRNAs) have more recently emerged on the research front and present a whole new area of possible approaches and mechanisms that could potentially provide answers to numerous questions at the molecular level. This review focuses on the links between obesity, the most common manifestations of metabolic syndrome and cancer, exploring the role of miRNAs as therapeutic targets for these co-morbid conditions.

INTRODUCTION

Metabolic Syndrome and obesity

A ‘syndrome’ is an association of many patho-physiological conditions and symptoms that often occur concurrently, and detection of one abnormality, indicates the likely presence of other risks in the system. Modern unhealthy lifestyle accompanied with genetic predisposition in certain cases leads to increased incidence of disorders such as visceral obesity, insulin resistance, diabetes, dyslipidemia, hypertension, pro-inflammatory state and pro-thrombotic state, collectively known as ‘metabolic syndrome’ [1]. According to the American Heart Association/ National Heart, Lung and Blood Institute/ American Dental Association and other related studies, comparing various age groups and populations, the incidence of metabolic syndrome increases with age and body mass index (BMI) [2]. The National Health Statistics Reports, 2009 estimates 34% of the US population to have met the criteria for metabolic syndrome and further emphasizes that its prevalence increases with age and BMI [3].

Progressive and chronic in nature, obesity is one of the most commonly seen forms of metabolic syndrome. The World Health Organization (WHO) defines individuals with a BMI greater than or equal to 30 as obese and according to Centers for Disease Control and Prevention (CDC), more than one third of the US population is obese [4, 5]. The death rate in the US among men and women has increased by 52% and 66% respectively due to obesity [6]. Body

fat distribution is primarily of two kinds: subcutaneous and visceral. Subcutaneous fat and visceral fat show anatomical, molecular and cellular differences. Subcutaneous fat constitutes almost 80% of the body fat, whereas visceral fat range between 5-20%. Visceral, intra-abdominal fat increases with age in both males and females and has been shown to be a risk indicator for metabolic disorders and a precursor for conditions such as type 2 diabetes and cardiovascular diseases [7]. Visceral fat consists of large adipocytes that are insulin resistant, hyperlypolytic and characterized by rich vasculature [8]. Adipocytes are considered to be active endocrine organs that significantly contribute to the pro-inflammatory state in obesity. Increased levels of leptin, C-reactive protein (CRP), tumor necrosis factor- α (TNF-α), Interleukin-6 (IL-6) and reduced adiponectin are the most common markers that are associated with obesity [9].

Though evidence suggests that obesity and metabolic syndrome go hand in hand, there are individuals who are metabolically obese and have metabolic disorders that are usually seen in obese people, but maintain a normal weight and BMI [10, 11]. On the other hand, there are metabolically healthy obese individuals who have a BMI>30, but do not show metabolic disorders. This discrepancy can probably be attributed to the degree of visceral obesity in the two groups of people [12].

Cancer

The other interest of this review article is cancer which is a significant health issue globally. In the United States, one in every four deaths is due to cancer and in 2013; there is a projection of a total of 1,660,290 new cancer cases and 580,350 cancer deaths [13, 14]. The World Cancer Research Fund (WCRF) estimated that one-fourth to one-third of the cancers in countries like US are due to modifiable, preventable factors such as lack of physical activity, excess weight and unhealthy dietary habits [15]. These factors are as important as other established cancer risk factors such as tobacco and alcohol consumption. At the cellular level, some of the known hallmarks of cancer include continued maintenance of proliferation and replication, abnormal functioning of tumor suppressors, drug resistance, angiogenesis, invasion and metastasis [16]. However, more recently energy metabolism has started to emerge as a potential key player in the risk, incidence, treatment and prognosis of cancer.

Interrelationship between obesity and cancer

Enormous research has been done to understand correlations and identify common links between obesity and cancer. Based on the IARC and the WRCF reports, cancers that are associated with increased BMI are endometrial cancer, esophageal adenocarcinoma, colorectal, postmenopausal breast, prostate, renal cancer, leukemia, non-Hodgkin's lymphoma, multiple myeloma, malignant melanoma, and thyroid cancer [17, 18].

Obesity in women is a public concern as 70% of post-menopausal women in the US are either overweight or obese [19]. A meta-analysis of studies of women diagnosed with breast cancer determined that obesity may increase the risk for breast cancer specific death as well as mortality due to other causes by atleast 33% [20, 21] and one of the reasons for this increase in mortality may be due to increasing blood levels of estradiol [22]. Research suggests that weight loss primarily reduces breast cancer risk by decreasing the levels of biomarkers and inflammatory factors [23, 24]. Multiple studies have suggested a

positive correlation between high BMI, body fatness and increased risk, early onset and reduced survival of pancreatic cancer [18, 25, 26] and a prospective study also suggests that one fourth of the pancreatic cases could be attributed to obesity [27]. Obese women with ovarian cancer seem to have a slightly worse survival than women who are non-obese [28]. Obesity could also increase the incidence of kidney cancer indirectly due to hypertension or thyroid cancer due to excess uptake of iodine [29, 30]. A substantial proportion of the bone marrow of obese individuals consists of fat cells and this renders cancer cells in leukemia patients to be resistant to the effects of chemotherapy [31]. Therefore, correlation between obesity and cancer has been observed and studied in various cancers.

Cytokines, secreted by adipose tissue called adipokines play a significant role in the development of cancer, cell migration, and angiogenesis and in maintaining a state of chronic low grade inflammation, all of which are established promoters of cancer development and progression [32]. A positive correlation has been observed between increase in white adipose tissue and adipose stromal and endothelial cell recruitment favoring tumor growth [33]. Accumulation of visceral adipose tissue also results in poor response to chemotherapy treatment [34]. The above mentioned studies emphasize the fact that obesity does play multiple roles in different aspects of cancer progression.

LINKS BETWEEN OBESITY AND CANCER

Pathways

Various mechanisms have been investigated to determine the potential link between obesity and cancer. Some of the explored pathways include PI3K/Akt/mTOR (Phosphatidylinositide 3- kinases/ Protein kinase B/ mammalian target of rapamycin) pathway, MAPK (mitogen activated protein kinase) pathway and STAT3 (Signal transducer and activator of transcription 3) signaling, the pro-inflammatory pathways JNK (c-Jun N-terminal kinases), NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and the IGF (Insulin-like growth factor) pathway [35].

PI3K pathway: The PI3K/Akt pathway plays a role in obesity and insulin resistance and is required for insulin dependent regulation of metabolism. Studies in mice have shown that, diet induced obesity result in activation of Akt and mTOR [36]. The retinal tissue from rats that had retinal degeneration due to being fed high fat diet had lower levels of Akt [37]. A study in patients showed that mutations of PTEN, a tumor suppressor increases insulin sensitivity through the PI3K-Akt pathway by increasing Akt phosphorylation but on the contrary lead to an increased risk of obesity as patients with the PTEN haploinsufficiency showed increased body mass [38]. In an obesity-induced mouse model of colon cancer, phosphorylation of Akt was detected suggesting activation of the PI3K/Akt pathway [39, 40]. There is a high frequency of alterations in the PI3K pathway in cancers and many important players such as receptor tyrosine kinases, Akt and PTEN are frequently mutated [41].

IGF pathway: Obesity leads to an increase in the circulating levels of insulin, IGF-I and IGF-II. Growth hormone stimulates IGF-I in most tissues and both of them together play an important role on fat, protein and glucose metabolism. When IGF-I, IGF-II and insulin bind to receptors, it results in the phosphorylation of the insulin receptor substrate (IRS) protein, which further activates the ERK pathway downstream resulting in increased cell proliferation [42]. The insulin and the IGF-I

pathway are linked to cancer as they inhibit apoptosis and favor cell proliferation [27]. It has been shown that when cells overexpressing IGF-IRs where transplanted into nude mice they often turned tumorigenic. The IGF-I axis is associated with angiogenesis as IGF-I synergizes with the transcription factor hypoxia inducible factor-1 (HIF-1α) in promoting replication of tumor cells [43, 44]. HIF-1α is associated with increased metastasis and poor prognosis [45]. Increased expression of IGF-I or the IGF-IR is directly linked to human cancers in breast, lung, thyroid, gastrointestinal tract, prostate, glioblastoma, neuroblastoma, meningioma and rhabdomyosarcoma [46, 47].

Insulin-like growth factor binding protein (IGFBP)-3, a major binding protein of IGFs in circulation, is known to modulate the actions of circulating IGFs [48, 49]. A study in obese adolescents showed reduced levels of intact IGFBP-3 in circulation compared to the normal counterparts suggesting a positive correlation between proteolyzed IGFBP-3 and adiposity [50]. Studies from various groups have shown that the anti-proliferative functions of IGFBP-3 are mainly through the attenuation of the IGF/IGF-IR interaction, but IGF/IGF-IR –independent functions are through interaction with various signaling molecules or proteins that are essential for apoptotic functions in various cancers [51-53]. IGFBP-3 has been shown to be necessary for DNA-PKcs autophosphorylation and the DNA repair response, but it also favors apoptosis of tumor cells after DNA-damaging therapy in estrogen receptor-negative breast cancer cells [54]. Another member of the IGFBP family, IGFBP-5 is known to play a role in the regulation of angiogenesis and prevention of tumor growth in in a model of human ovarian cancer [55]. On the other hand, studies also show that overexpression of IGFBP-5 acts as a poor prognostic marker in patients with urothelial carcinomas [56]. Therefore, the IGFs, the IGF binding proteins and the IGF pathway in general seem to be an important link that could be exploited to address both obesity and cancer.

Therefore multiple pathways seem to be intermingled in obesity and cancer making it increasingly challenging to determine the ideal junction to target, but more detailed research in understanding the common players in these pathways will help us address this interconnected problem in the most efficient way.

Biological Factors

Some of the biological factors and conditions that are common to both obesity and cancer are discussed below.

Inflammation

Inflammatory cytokines in circulation are elevated in obesity resulting in a state of low grade inflammation, which is also a characteristic hallmark of most cancers [57-59]. Almost all tumor micro-environments show presence of inflammatory cells and biomarkers such as cytokines, chemokines and adipokines and this is reflected in biopsied samples from tumors. The most abundantly found and commonly studied adipokines in the context of cancer and obesity are leptin, a potent pro-inflammatory agent and adiponectin, an important insulin-sensitizing agent. Studies suggest that leptin deficient *ob/ob* mice become hyperinsulinemic and that systemic concentrations of leptin are relative to the body fat composition [60]. On the cancer front, leptin works synergistically with vascular endothelial growth factor (VEGF) and fibroblast growth factor -2 (FGF-2) to promote angiogenesis. Leptin also increases the expression of genes involved in cell migration such as matrix metalloproteinases

[61, 62]. Increase in the production of leptin inversely correlates with the levels of adiponectin secretion in obese individuals. An inverse correlation has been established between circulating levels of adiponectin and the occurrence of breast cancer in pre-menopausal and post-menopausal women and prostate cancer [63, 64]. Lower adiponectin levels have been demonstrated in colorectal cancer, endometrial cancer and esophageal cancer [65-67]. The two possible mechanisms by which adiponectin plays a role in oncogenesis is possibly via its receptor mediated signaling or indirectly by influencing insulin sensitivity thereby modulating inflammation and angiogenesis [68]. In general, obesity leads to a state of low grade steady inflammation, due to chronic over-nutrition which sets an ideal platform for an increased risk of cancer incidence and progression.

Cancer stem cells: Adipose tissue is the primary producer of leptin and in cancer cells both leptin and its receptor are overexpressed. It has been demonstrated that the selective expression of the leptin receptor is a characteristic feature of cancer stem cells [69]. Cancer stem cells promote initiation and differentiation of carcinogenesis by deregulation of the cell renewal process. Therefore these cancer stem cells are a significant risk factor in oncogenesis and resistance to conventional anti-cancer treatment is attributed to the presence of the stem cell population in cancer cells [70, 71]. Another relatively less explored mechanism is the possibility that mesenchymal stromal cells can become cancer associated fibroblasts that could act as a potential source of precursor cells for neovascularization which is critical for tumor formation and metastasis [72].

Hormones

Synthesis and bioavailability of estrogen, androgen and progestins are influenced by obesity. In obesity, sex hormones advance cancer by mechanisms such as promoting the formation of estrogens from androgenic precursors, increased insulin concentrations that reduce the concentration of sex-hormone binding globulin and increased androgen synthesis in the ovaries [73]. Estrogens and androgens directly and indirectly increase breast cancer risk by accelerating cellular growth and transformation [74]. Early age at menarche and late menopausal age correlate with increased risk of breast cancer [75]. Gender based differences in regional body fat distribution may be attributed to the function of sex hormones [76]. Also, increased estradiol is associated with increased endometrial cancer in post-menopausal women [77]. So far, data shows CRP, estradiol and fasting insulin as the biomarkers of breast cancer risk that independently show a two-fold increased risk [78-80].

MICRO-RNAs

More recently in the past decade, a more evolutionary conserved category of post-transcriptional regulators of gene expression called miRNAs came to the forefront [81]. miRNAs are 18-25 nucleotides long, non-coding RNA, that base pair to sites within the target mRNA and either block translation or degrade mRNA or both, based on the level of complementarity [82]. In the nucleus, miRNAs are transcribed by polymerase II or III, to pri-miRNAs, The stem-loop structure of pri-miRNA is further cut by Drosha, an endonuclease and its cofactor DiGeorge syndrome critical region gene 8 (DGCR8) to form pre-miRNAs, which is then exported to the cytoplasm by exportin-5 and a dicer generates the ~ 22 nucleotide miRNA duplex [81, 83]. Approximately 400 mRNAs are targeted by each miRNA and almost 50% of the

mammalian cell mRNA are targeted by a single or multiple miRNAs [81]. miRNAs are known to be involved in numerous biological processes such a cell differentiation, apoptosis in cancers, cardiovascular diseases, lipid metabolism and glucose homeostasis [84-87]. They are usually tissue-specific and specific to developmental stages [88]. Differences in the role of miRNA have been shown in obese conditions versus normal, lean metabolic conditions, therefore showing the potential to be involved in obesity associated complications [89].

Role of miRNA in obesity and cancer

miRNA expression differ in subcutaneous and visceral fat suggesting that miRNAs could be tapped as a potential therapeutic target to address obesity [90, 91]. miRNAs can either accelerate or inhibit the adipocyte differentiation process and regulate the pathways involved in adipogenesis [92]. miRNA expression profile in leptin deficient *ob/ob* mice and diet induced obese mice show that miRNA are either upregulated or downregulated in the two different models of obesity providing a global pattern of miRNA in normal and obese states. miRNAs such as let7, miR-27 and miR-143 have been shown to be deregulated in the pathogenesis of metabolic disorders. Studies in obese mice show that miR-103 and miR-143 in pre-adipocytes accelerated adipogenesis but were downregulated in obesity [90]. High throughput sequencing of miRNA expression biomarkers in obesity have identified miR-935 and miR-4772 as biomarkers that could predict a response to weight loss due to hypocaloric diet in peripheral blood mononuclear cells [93].

miRNAs have been more elaborately studied in cancer progression [94]. They either serve as tumor suppressors (miR-15, miR-16, let-7) or as oncogenes (miR-17-92) depending on the target genes [95]. Aberrant miRNA expression profiles have been studied in clinical tumor specimens and in cancer cell lines *in vitro*. miRNAs are known to target genes that are involved in cellular functions such as apoptosis, invasion, metastasis and cell proliferation [96]. miR-34a is a miRNA that is induced by the tumor suppressor p53, and suppresses cyclinD1 and CDK6 expression [97]. miR-192 and miR-215 enhances p21 expression in colon cancer cells and induces cell cycle arrest [98]. The oncogene Myc plays a role in cell proliferation and is regulated by miR-154 and miR-34 [99, 100]. miR-200 family enhances metastasis and contributes towards tumor progression [101]. miRNAs clearly play a significant role in obesity as well as cancer, making it worthwhile to pursue further studies in these areas.

miRNA common to cancer and obesity

Some miRNAs have identical targets in diabetes and cancer; and obesity and cancer, thereby indicating an increased possibility of potential miRNAs that link obesity and cancer [32].

miR-143 has been linked with adipogenesis as well as human cancers [102, 103]. miR-143 is upregulated in the liver of obese models of mice, both genetic and dietary. Its overexpression impairs glucose homeostasis stimulated by insulin but on the other hand, mice that are deficient in miR-143 protect the mice from developing obesity related insulin resistance [104]. Low levels of miR-143 have been reported in several cancers such as colorectal cancer, non-small cell lung cancer and osteosarcoma and it is involved in processes such as metastasis, apoptosis, p53 regulation and chemo-sensitization [32]. Overexpression of miR-143 inhibits cell proliferation, angiogenesis, and tumor growth and

increases chemosensitivity to oxaliplatin treatment in an IGF-IR-dependent manner in colorectal cancer. miR-143 levels in these patients correlate with the degree of metastasis and lymph node involvement [105]. miR-143 is upregulated during the differentiation of prostate cancer stem cells and promotes metastasis by inhibiting the expression of fibronectin type III domain containing 3B (FNDC3B) [106]. Prostate cancer recurrence has shown associations with miR-21 and also has been shown to be differentially expressed in obese and non-obese patients diagnosed with prostate cancer [107].

miR-93 and miR-335 are other examples of miRNAs that are involved in metastasis, angiogenesis and cell proliferation in addition to their role in insulin production, trafficking and secretion [108-112]. miR-335 is upregulated in the liver and white adipose tissue of obese mice (*ob/ob,db/db* and KKAy). This increase in miRNA335 levels is associated with expression levels of adipocyte differentiation markers such as PPAR-γ and FAS in 3T3 adipocytes [113]. miR-335 regulates the BRCA regulatory cascade that mainly impacts proliferation and apoptosis in breast cancer [114].

miR-93 is considered to be a characteristic marker for hyperglycemic conditions [115, 116] and is overexpressed in the adipose tissue of Polycystic Ovary Syndrome (PCOS). It plays a role in the function of insulin sensitive glucose transporter, GLUT-4, which is also a highly predicted target for miR-93 [92]. miR-93 targets integrin-β8 and enhances cell survival and tumor growth in cancers [117]. It also acts as a negative regulator of FUS1, a tumor suppressor in non-small cell lung cancer [118]. These studies motivate researchers to continue the pursuit for identifying such common miRNAs that may synergistically help address obesity and cancer.

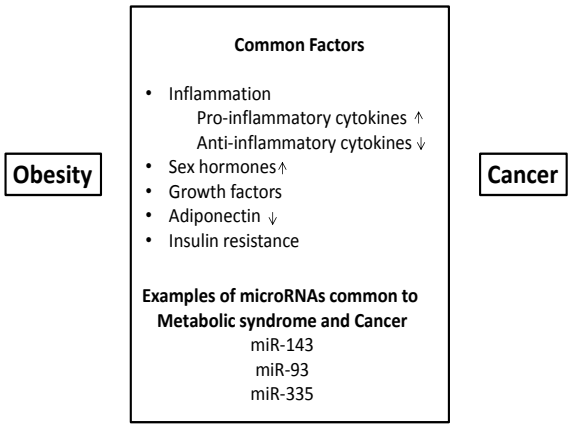

Figure 1: Link between obesity and cancer

CONCLUSIONS AND FUTURE PERSPECTIVES

This review discusses two co-morbid conditions that are extensively studied, cancer and obesity and summarizes the possible relationships and common mechanisms that could potentially connect these two diseases. Due to the overlapping nature of molecular pathways it seems logical to understand and identify mechanisms that would enable addressing both the conditions simultaneously. Articulately designed research studies and clinical trials are of prime importance to elucidate the manner and the extent to which obesity; diet; physical activity and chronic inflammation are interrelated and influence cancer control and prevention.

In the past decade molecular research has profoundly expanded by the discovery of miRNAs. miRNAs have been identified and studied in various contexts including cancers, insulin resistance and obesity amongst others. It would be interesting to decipher the interconnections between these co-occurring abnormalities on the basis of miRNAs. miRNAs present themselves as a promising diagnostic tool

for the early detection of diseases. Studies show that miRNAs can be detected and characterized in serum, thereby positioning them as a unique set of biomarkers for diagnosis of various diseases and to assess risk of certain diseases [119]. More research to identify novel techniques and methodologies to overexpress or silence miRNAs to design patient-tailored therapy would be extremely beneficial and critical in exploring miRNAs as a therapeutic tool in the near future. Anti-nucleotides against miRNAs are not very stable and therefore to increase stability some of the modifications that can be incorporated are 2′-O-methyl (2′-O-Me) and 2′-O-methoxyethyl (2′-O-MOE) oligonucleotides [120]. Another important asset would be development of conditional knockout mice for miRNA or miRNA clusters that would serve as a powerful tool to assess the role of miRNAs in obesity and cancer. The library of knockouts in the mouse genome started by the Sanger Institute in Cambridge is a step in this direction [121].

In conclusion, it can be stated that miRNAs have great potential in establishing themselves as beneficial tools and hopefully more research in this direction would enable the scientific community address multiple conditions and help move towards a better and healthier community.

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