Signalling Pathways Implicated in Obesity Associated Cancers

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Abstract: Intensive research over recent years has provided irrefutable evidence of links between obesity and the risk of an increasing number of human cancers. The predicted economic burden is causing significant concern. This has prompted investigation of the underlying mechanisms with a focus on deregulated metabolic pathways. A number of metabolic processes and associated signalling pathways are associated with the development of obesity. These include a number of interlinking pathways regulating endocrine, redox, inflammation, immunity and lipogenic processes. The identification of deregulated metabolic pathways in obesity with promotion of carcinogenesis has targeted research on the signalling molecules involved. Consequently this mini review is focused on aberrant signalling of deregulated pathways provoked by diets that lead to obesity and their role in carcinogenesis. Knowledge of the signalling molecules involved will assist in directing and establishing dietary manipulation strategies to restore metabolic health in obese individuals. Importantly the identified diversity of signalling pathways linked to obesity related cancers will permit design of more effective combinatorial and multi-targeted cancer therapies in the future.

Keywords: Obesity related cancer, metabolic signalling, signalling pathways

INTRODUCTION

The 2007 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) report [1] unequivocally endorsed links between obesity and increased risk of cancer. The global scale of the current obesity epidemic is causing significant concern as the projected rise in co-morbidities such as cancer are accompanied by increased economic and social burdens [2-4]. This has prompted intense research efforts to establish the determinants of increased cancer risk associated with obesity. Consequently substantial evidence has emerged establishing links between obesity and colorectal, kidney, liver/gall bladder, pancreatic, oesophageal, stomach, prostate, postmenopausal breast, endometrial, uterine and ovarian cancers, summarised in update reports from WCRF/AICR [5-7]. Accumulating evidence indicates that dietary factors such as consumption of excess calories, fat and sugars, together with sedentary behaviour and associated low energy expenditure are associated with increased cancer risk [1] (Fig. 1). Conversely, reduced calorie intake and increased fruit, vegetable and fibre intake have been linked to reduced cancer risk [1] (Fig. 1). Research on the physiological changes caused by the dietary and lifestyle trends leading to obesity has directed close scrutiny of associated deregulated signalling pathways to identify links with carcinogenesis [8-13]. Obesity is characterised by profound metabolic deregulation of signalling pathways that are essential to maintain homeostatic control of biological processes in cells and tissues [14-18]. Homeostatic control is fundamental in preventing the aberrant signalling that is a distinguishing characteristic of cancer cells. This review will examine the evidence linking signalling of the endocrine system [14, 15, 17]; redox regulation [19-21]; inflammatory and immune responses [16, 22-25] and lipogenesis [26] that are deregulated in obesity and linked to increased cancer risk (Fig. 2). The identification of signalling pathways linking obesity with cancer present novel targets and strategies to break the obesity cancer link.

ADIPOKINE SIGNALLING PATHWAYS IMPLICATED IN CANCER

Adipose tissue, the body’s largest endocrine organ [27, 28], demonstrates significant deregulation of homeostatic control in response to consumption of high energy diets and obesity. Levels of adipose derived hormones and cytokines are altered [14, 29-31]. Two of the most abundant adipose hormones, leptin and adiponectin, regulate energy homeostasis [32]. Obesity is characterised by increased leptin and decreased adiponectin in serum with implications for a role as potential mediators in carcinogenesis linked to obesity [33-36]. The intracellular signalling leptin receptor, ObRb, is expressed in several tissues (colon, oesophageal, breast) associated with increased cancer risk linked to obesity [33-38] and altered levels in tumours have been reported to have clinical implications [33, 35, 36, 38-41]. Roles in stimulation of cell proliferation, anti-apoptotic activity and inflammation have been demonstrated [11, 13, 42, 43]. Leptin regulates...
several signalling pathways, JAK/STAT3 (Janus kinase/signal transducer and activator of transcription 3), PI3K/Akt (phosphatidylinositol-4,5-bisphosphate 3-kinase/v-akt murine thymoma viral oncogene homolog), mTOR (mammalian target of rapamycin) and MAPK (mitogen-activated protein kinase), that present targets for modulation of carcinogenesis. Leptin is also linked to inflammatory and immune responses [13,36,44], activating a number of inflammatory cytokines associated with cancer. Leptin induced cytokines such as CXCL1 (chemokine CXC motif ligand 1) [13,41] and vascular perturbations leading to elevated VEGF (vascular endothelial growth factor) may be important in angiogenesis required for tumour growth [45].

Adiponectin is an abundant adipokine that is decreased with increased visceral obesity [15, 17]. There are two adiponectin receptors, ADIPO R1 and ADIPO R2, mediating signalling of full-length adiponectin and the truncated
globular portion of adiponectin [46]. These receptors are located in tissues prone to obesity related carcinogenesis and are expressed by colon and breast cancers [34, 35, 41, 42, 48]. Adiponectin stimulates phosphorylation of AMPK (5'-adenosine monophosphate-activated protein kinase) to regulate cellular energy metabolism and protein synthesis [34]. Adiponectin has been demonstrated in vitro to counter leptin induced IL-6 (interleukin-6), NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells) and STAT3 to reduce cell proliferation [12, 47]. Adiponectin is also reported to be associated with improved insulin regulation, blood glucose and triglyceride levels [48, 49].

**INSULIN AND INSULIN LIKE GROWTH FACTORS**

Inappropriate glycaemic control is a feature of obesity with consequences for development of diabetes and risk of developing cancer [50]. Hyperglycaemia in response to obesity is associated with hyperinsulinaemia and the promotion of uncontrolled cell growth associated with tumorigenesis [51, 52]. Insulin signalling is initiated via transmembrane receptors, insulin (INSR) and insulin growth factor (IGF) receptor hybrids (IGF/INSR) to activate intracellular signalling cascades that ultimately influence gene transcription and cellular processes regulating growth and differentiation [53]. Insulin receptors are expressed by cells linked to obesity related carcinogenesis and in cancer [37, 41]. INSRs activate PI3K/Akt and downstream activation of mTOR and, or MAPK to regulate cell growth and mitogenesis [52]. Similarly, increased circulating insulin-like growth factor-I (IGF-1) in obese individuals activates PI3/Akt and MAPK [52]. IGF-I is also linked to increased risk and poor prognosis for several human obesity related cancers [54]. Bioavailable IGF-I is increased by hyperinsulinaemia in obese individuals as a consequence of insulin induced decreases in IGF binding proteins [52]. Notably, VEGF is also induced by elevated insulin and IGF-1 levels associated with obesity [55] and aggressive cancers [56, 57].

**STEROID HORMONES**

Elevated levels of both total and free oestrogens produced by adipose tissue are linked with obesity related breast cancer [58]. Aromatase, responsible for oestrogen biosynthesis, is also elevated with obesity and can further influence the impact of oestrogens on carcinogenesis [24]. Activation of oestrogen receptors (ER) leads to canonical oestrogen response element (ERE)-dependent signalling. Oestrogen bound receptors activate EREs in promoter regions of target genes inducing transcription of genes regulating proliferation and angiogenesis [59]. Non-genomic effects following complex of ER with other receptors, such as EGFR (epidermal growth factor receptor) and IGR, leads to induction of MAPK and PI3K/Akt pathways [60]. In addition to oestrogen signalling effects on regulation of cell proliferation, mammalian cell metabolism of oestrogen generates DNA-reactive metabolites that cause DNA mutations associated with carcinogenesis [61].

Links between obesity related cancers and the androgen hormones are more equivocal. However, there are links between obesity and aggressive prostate cancer [62]. This is attributed to promiscuous androgen receptor activity between androgens and circulating cytokines (IL-6), growth factors (IGF, epidermal growth factor) and stimulation of JAK/STAT and PI3K/Akt/mTOR promoting cell survival and proliferation [63].

There has also been some interest in the extensive metabolic effects of glucocorticoids. These hormones are increased during calorie restriction and weight reduction [64] both factors associated with reduced cancer risk. Glucocorticoids activate glucocorticoid receptors to regulate transcription of genes intimately involved in regulation of apoptosis [15, 65-67]. Cell regulation of apoptosis is crucial in preventing carcinogenesis. Another aspect of glucocorticoid function is as an anti-inflammatory [68]. The role of glucocorticoids in limiting and resolving inflammation [69] could potentially be an important pathway linked to obesity related cancer.

**OXIDATIVE STRESS, IMMUNITY AND INFLAMMATORY FACTORS**

The cascade of deregulated metabolic pathways deriving from over consumption of nutrients and the development of obesity ultimately overwhelm redox defences [70]. The transcription factor Nrf2 (nuclear factor (erythroid-derived 2)-like 2) has been identified as a key regulator of redox balance [71] and is deregulated in obesity [49]. Deregulation of Nrf2 regulated gene transcription has implications for a host of signaling pathways that are involved in detoxifying metabolites and damaged proteins, maintenance of redox balance and DNA repair [72]. This has implications for carcinogenesis since regulation of these processes is crucial to maintaining homeostasis, DNA integrity and cell regulation.

Deregulation of metabolic pathways and the resultant oxidative stress in obesity is associated with activation of inflammatory and immune responses [73]. Immune and inflammatory responses are intimately linked with carcinogenesis [74]. This is characterised by increased NFκB activity, inappropriate production of pro-inflammatory cytokines, immune cell infiltration and disrupted tissue homeostasis [16, 22, 24, 75, 76]. Increases in circulating CRP (C-reactive protein), TNFα (tumour necrosis factor alpha), IL6, IL1β (interleukin-1 beta) and macrophage attractants, such as MCP-1 (monocyte chemotactic protein-1) are generated as a consequence of the production of pro-inflammatory cytokines from excess adipose tissue [77]. This exacerbates the deregulated inflammatory and immune responses [77]. Cross-talk between insulin, leptin and adiponectin pathways are linked to activation of inflammatory cytokines associated with carcinogenesis [13, 78]. Mediation of these responses involves recruitment of NFκB, STAT3, c-jun-NH2 terminal protein kinase (JNK) pathways [77]. NFκB is recognised as an active player in tumour associated aberrant expression of genes involved in cell proliferation, apoptosis, angiogenesis and inflammation.

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LIPOGENIC PATHWAYS

Obesity is associated with activation of lipogenic pathways characterised by elevated levels of fatty acid synthase (FASN) [18]. Over expression of FASN is a common event in malignancies [26]. Elevated FASN has been identified as a prognostic indicator and is linked to therapy resistant tumours [83]. Increased lipogenesis via the AKT-mTORC1 (mechanistic target of rapamycin complex 1) pathway has also been linked to hepatocellular carcinoma [84]. While mTORC1, a nutrient and insulin sensor, is also emerging as a regulator of lipid homeostasis that may be implicated in carcinogenesis [85]. This may be relevant to obesity associated liver cancer. Further research in this area may also reveal other lipogenic pathways implicated in obesity related cancer.

CONCLUSION

The metabolic deregulation associated with obesity presents a number of interconnected pathways that have implications for carcinogenesis. This knowledge can inform on potential strategies to reduce cancer risk and also direct investigation of the potential of therapies that restore metabolic regulation to improve outcomes for cancer patients. A number of studies have demonstrated that reducing dietary energy consumption can restore homeostatic regulation of metabolic pathways and reduce obesity related cancers [54,86-88]. Investigation of the presence of receptors for the various signalling molecules and hormones deregulated in obesity in tissues prone to obesity related cancers may inform about the potential to manipulate these signalling pathways to prevent cancer. There has been limited study of the potential to influence outcomes for cancer patients using therapeutics directed at alleviating the disorders associated with the metabolic syndrome [89-91]. Diabetic therapies have been linked to reduction of some cancers, but not others [90]. Greater understanding of the interplay of deregulated metabolic pathways in carcinogenesis will be essential in directing appropriate and more effective therapeutic strategies for individuals and contribute to producing multi-targeted approaches to reduce therapy resistance. Thus further studies are warranted to determine appropriate strategies to combat obesity related cancer and develop novel combination therapies and multi-targeted approaches to provide more effective treatment of cancer patients.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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