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Obesity, cancer, and acetyl-CoA metabolism

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Abstract

As rates of obesity soar in the United States and around the world, cancer attributed to obesity has emerged as major threat to public health. The link between obesity and cancer can be attributed in part to the state of chronic inflammation that develops in obesity. Acetyl-CoA production and protein acetylation patterns are highly sensitive to metabolic state and are significantly altered in obesity. In this article, we explore the potential role of nutrient-sensitive lysine acetylation in regulating inflammatory processes in obesity-linked cancer.

Obesity promotes cancer development

Obesity dramatically increases an individual's risk of developing and dying from cancer. As much as 20% of the cancer burden may be attributable to obesity [1, 2]. High body mass index (BMI) is associated with increased relative risk of developing multiple types of cancer, including those of the esophagus, pancreas, colon, breast, uterus, ovaries, kidney, thyroid, liver and gallbladder. The risk of dying from liver cancer, for example, is 4.52 fold greater in men with a BMI over 35 than in those with a normal BMI (18.5–24.9). Women with a BMI over 40 exhibit a remarkable 6.35 fold higher risk of death by uterine cancer [2]. It is projected that by 2030, obesity will directly contribute to another 500,000 cases of cancer in the United States, and a drop of just 2.2 pounds in the average adult could prevent approximately 100,000 of these cases [3]. Nevertheless, incidence of overweight and obesity has risen continuously over the past twenty years [4], indicating that there is a great need to develop novel strategies to prevent and treat obesity-linked cancers. Two primary mechanisms have been implicated in promoting cancer in obesity: 1) elevated levels of insulin and insulin-like growth factors (IGFs) and 2) chronic inflammation.

Insulin and insulin-like growth factors in obesity mediated cancer

Insulin resistance and type II diabetes are closely linked to obesity and result in elevated circulating levels of insulin and IGF-1. In healthy individuals, the beta cells of the pancreas release insulin after feeding in response to elevated blood glucose levels to stimulate the uptake of glucose from blood into peripheral tissues such as adipose and muscle. Insulin resistance frequently develops in these tissues in obese individuals, and to compensate for this, the pancreas secretes increasing amounts of insulin. Insulin also promotes hepatic production of IGF-1 and inhibits production of insulin-like growth factor binding proteins (IGFBPs), which bind circulating IGF, reducing its bioavailability [5, 6]. Thus, insulin

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resistance results in increased availability of insulin and IGF-1 to bind to receptors on peripheral tissues, resulting in aberrant activation of pro-growth signaling pathways, such as the phosphoinositide 3-kinase (PI3K)-Akt and mitogen activated protein kinase (MAPK) pathways [6–8]. Reciprocally, calorie restriction reduces circulating IGF levels and can impair tumor growth in certain contexts [9,10]. In particular, the ability of calorie restriction to suppress PI3K-Akt pathway activity appears to be critical for its anticancer effects, since xenograft tumors with constitutive PI3K-Akt pathway activation were resistant to the tumor-suppressive effects of calorie restriction [11].

Inflammation and the link between obesity and carcinogenesis

A second major contributor to increased carcinogenesis in obesity is inflammation [1,12]. An inflammatory microenvironment can promote tumor growth through multiple mechanisms, from stimulating pro-growth signaling pathways and enhancing cell survival to promoting angiogenesis, invasion, and metastasis [13]. Obesity is frequently associated with the development of a chronic state of low-grade inflammation, characterized by infiltration of adipose tissue by immune cells such as macrophages and elevated production of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF α) and interleukin-6 (IL-6) [14,15].

In liver, several factors may contribute to the development of a cancer-promoting inflammatory microenvironment. Obesity causes endoplasmic reticulum (ER) stress and activation of the unfolded protein response (UPR) in the liver, and components of the UPR can directly activate the JNK and IKK-NF- κ B inflammatory signaling pathways [16,17]. The ER also plays a key role in lipid synthesis and metabolism [18], and ER stress may contribute to development of hepatosteatosis. Treatment of obese mice with chemical chaperones reduces liver lipid accumulation and improves insulin action and metabolic homeostasis [19]. Interestingly, altered lipid profiles in the ER were also recently implicated as a cause of ER stress in obesity, via disruption of SERCA function and the ER's capacity to regulate calcium metabolism [20]. Inappropriate deposition of lipids in hepatocytes is associated with inflammation, and the progression from hepatosteatosis to steatohepatitis is considered to be a major factor leading to the initiation of hepatocellular carcinoma (HCC) [12, 21]. Hence, a close relationship exists between ER stress, altered lipid metabolism, and inflammation in the liver. Adipose tissue-derived cytokines may also help to initiate inflammatory processes in the liver, provoking activation of inflammatory signaling pathways in hepatocytes and resident Kupffer cells [12]. The transcription factor NF- κ B is a major transcriptional mediator of inflammatory gene expression and participates in inflammation-linked cancers such as HCC both by promoting cell survival and by stimulating production of cytokines such as IL-6 and TNF α [22–24]. In addition to further activating NF- κ B, IL-6 can stimulate Jak-dependent activation of STAT3, which stimulates transcription of cell cycle and other growth and survival-related genes [1,12]. Of note, NF- κ B can also suppress tumor growth in certain conditions; loss of NF- κ B activity in the hepatocytes can promote HCC development due to liver damage and cell death, resulting in compensatory proliferation [22, 25].

Recent development of mouse models of cancer that are perpetuated by obesity have both confirmed a carcinogenic role for obesity-linked inflammation and enabled dissection of the molecular mechanisms underlying this link. Hepatocellular carcinoma (HCC) caused by the liver-specific carcinogen diethyl nitrosamine (DEN) was recently shown to be potentiated by obesity [26, 27]. DEN elicits HCC development at a high frequency when administered to juvenile mice. When given to adult mice, however, cancer does not develop unless mice are also given an additional tumor-promoting agent. Remarkably, high fat feeding could serve as a tumor-promoter, and over 80% of mice fed a high-fat diet developed HCC when

administered DEN as adults [26]. Increased production of IL-6 and TNF α was required for the tumor-promoting effects of obesity, since mice deficient in IL-6 or TNF receptor 1 (TNFR1) were protected against the effects of HFD in potentiating tumor growth [26].

As describe above, some of the key pathways and players that link obesity with cancer have begun to emerge, although many of the details and levels of regulation have yet to be uncovered. In this review article, we explore the hypothesis that changes in acetyl-CoA availability and protein acetylation might contribute to the link between obesity and cancer by promoting both lipid accumulation and inflammation.

Acetyl-CoA and the regulation of acetylation

The ability of an organism to modify use of cellular fuels in response to changes in nutrient availability is critical for sustaining metabolic homeostasis, and impairment in ability to mediate these adaptive responses is characteristic of metabolic diseases such as type II diabetes. The importance of cellular capacity to gauge intracellular metabolic resources is highlighted by the key roles of metabolic sensors such as AMPK, which responds to cellular energy levels, and mTOR, which serves as a key point of integration for signal transduction and nutrient availability cues, in maintaining metabolic homeostasis and in contributing to diseases such as diabetes and cancer [28–31]. Acetylation, a post-translational modification that occurs on lysine residues and at protein N-termini, is emerging as another mechanism for intracellular detection of nutrient availability.

Lysine acetylation of proteins is accomplished by lysine acetyltransferases (KATs) and reversed by lysine deacetylases (KDACs). Many protein-modifying enzymes rely on metabolites as co-factors [32], and in some cases, the activities of these enzymes can be regulated by availability of their metabolite co-factors. This is true in the case of sirtuin deacetylases (class III KDACs), which utilize NAD⁺ as a co-factor and are activated as the NAD⁺/NADH ratio rises, as occurs during nutrient deprivation [33]. As will be elaborated, acetyl-CoA availability may also regulate KAT-dependent acetylation reactions; hence, acetylation may be unique among protein modifications for its ability to be regulated in a nutrient-sensitive manner by both the “on” and “off” reactions (Figure 1).

Acetyl-CoA is compartmentalized into mitochondrial and nuclear-cytoplasmic pools in eukaryotic cells, and these pools are functionally distinct [34]. The nuclear-cytoplasmic level of acetyl-CoA in mammalian cells is established primarily by the combined actions of two enzymes: ATP-citrate lyase (ACL), which converts nutrient-derived citrate into acetyl-CoA and oxaloacetate, and acetyl-CoA synthetase (AceCS1), which utilizes acetate as a substrate for acetyl-CoA synthesis [35]. Acetyl-CoA is positioned at the metabolic crossroads of glycolysis, fatty acid oxidation, ketogenesis, amino acid metabolism, the TCA cycle, and lipid synthesis, suggesting that acetyl-CoA may be an ideal metabolite for the cells to sense their nutrient status. Indeed, glucose-dependent production of acetyl-CoA has been shown to regulate global levels of histone lysine acetylation in both yeast and mammals [36, 37]. Levels of lysine acetylation on a number of metabolic enzymes, such as PEPCK, PKM2, and MDH, have also been shown to be glucose-regulated [38, 39]. N-terminal acetylation, which occurs on a high percentage of mammalian proteins, is also sensitive to acetyl-CoA availability [40]. Studies in yeast have provided evidence that acetyl-CoA levels may fluctuate within a range to limit the activity of the KAT Gcn5 [41], based on its K_d for acetyl-CoA (8.5 μ M) [42]. While it is not yet clear whether this is also true in mammalian cells (in which Gcn5 K_d for acetyl-CoA is 0.56 μ M) [42], it is noteworthy that many KATs, including Gcn5, are subject to product inhibition by free coenzyme A (CoASH), indicating that the acetyl-CoA/CoASH ratio might be the relevant regulator of KAT activity instead of absolute levels of acetyl-CoA [43].

Nuclear-cytoplasmic acetyl-CoA production is impacted by metabolic state in a complex manner. ACL is generally more active in nutrient-replete conditions. ACL transcript and protein levels are increased by insulin and caloric intake and decreased in glucose deprivation, starvation, and diabetes [44–46]. ACL is overexpressed in several cancers, including those of the lung, prostate, bladder, breast, liver, stomach, and colon [47]. ACL is also subject to allosteric activation by sugar phosphates, and ACL phosphorylation at Ser455, a site regulated by Akt and protein kinase A, enhances its activity *in vitro* assays [48]. Hence, ACL may serve as an integration point for signaling and metabolic cues when metabolic conditions are favorable (Figure 2). Reciprocally, AceCS1 may become more active when nutrients are scarce, since it is deacetylated and activated by SIRT1 [49].

Acetylation patterns changes with feeding and fasting and with dietary changes in the liver, and major roles have been identified for SIRT1 and SIRT3 in orchestrating these responses [50]. Under caloric restricted conditions, dozens of mitochondrial proteins are differentially acetylated in comparison to mice on *ad libitum* diets [51]. In fasted conditions, SIRT3 is activated and mitochondrial proteins such as the long chain acyl-CoA dehydrogenase (LCAD) become deacetylated, thus promoting fatty acid oxidation [52]. Conversely, mice on high-fat diet (HFD) display hyperacetylation of hepatic mitochondrial and cytoplasmic proteins, as well as reduced NAD⁺ levels and downregulation of SIRT3 [53, 54]. Within the nucleus, SIRT1 plays an important role in the fasting response, by deacetylating the coactivator PGC-1 α and promoting PPAR α -dependent transcription of genes involved in fatty acid oxidation. Mice lacking SIRT1 exhibit exacerbated liver inflammation, lipid accumulation, and ER stress when fed a high fat diet [55]. A recent proteomics study characterized mitochondrial and cytoplasmic acetyl-proteins regulated by feeding and fasting finding that multiple tissues exhibit changes in acetylation patterns in response to nutrient availability [56]. Current evidence clearly implicates sirtuins in mediating feeding and diet-induced changes in acetylation, and it will be of great interest to determine the contribution of acetyl-CoA-dependent regulation of KATs.

The role of metabolism in modulating acetylation in the context of inflammatory responses is not yet clear. However, NF- κ B activity is regulated by acetylation at multiple levels, detailed below, suggesting that altered regulation of acetylation in obesity could plausibly contribute to obesity-linked cancers. In support of this possibility, SIRT1 overexpression was shown to suppress obesity-linked HCC [27]. Interestingly, SIRT6, also known to modulate NF- κ B action [57], was also recently shown to be a tumor suppressor with a key role in the regulation of cancer cell metabolism [58]. It is plausible that acetyl-CoA might play a key role in HCC development or progression, given its dual roles in the regulation of acetylation events and as a precursor for *de novo* lipogenesis.

Role of acetylation in NF- κ B activation

NF- κ B is a key transcriptional mediator of inflammatory responses, and has been shown to contribute to obesity-linked inflammation and associated metabolic dysfunction [14, 15]. NF- κ B transcription factors—most commonly heterodimers consisting of p50 and p65 subunits—are, under basal conditions, held in an inactive state in the cytoplasm bound to I κ B proteins. Upon receipt of activating signals such as inflammatory cytokines, I κ B kinase (IKK) phosphorylates I κ Bs, stimulating their ubiquitination and degradation, thereby freeing NF- κ B to translocate into the nucleus and promote transcription of its target genes. NF- κ B activates a large repertoire of genes involved in inflammation and cell survival [1]. While increased activity of NF- κ B and enhanced production of inflammatory cytokines can promote tumorigenesis, loss of NF- κ B activity in hepatocytes can conversely promote tumor development, due to liver damage and compensatory proliferation [22–25, 59, 60]. Hence, it

may be desirable to suppress inflammatory responses in obesity without complete ablation of NF- κ B function.

Notably, the duration and magnitude of NF- κ B-dependent transcription are regulated by acetylation [61, 62]. Several KATs and KDACs associate with NF- κ B and influence its activities by directly regulating the acetylation of NF- κ B subunits and by modulating histone acetylation at NF- κ B target genes to promote or repress gene expression. p300/CBP acetylates several lysines on the p65 and p50 subunits of NF- κ B. Acetylation of Lys 221 of p65 promotes DNA binding and impairs binding to I κ B [63]; conversely, deacetylation by HDAC3 promotes I κ B binding nuclear export, and termination of NF- κ B activity [64]. Lys310 acetylation, a target of the deacetylase SIRT1, also promotes NF- κ B activity by providing a binding site for the bromodomain-containing coactivator Brd4 and impairing methylation of Lys314 and Lys315, which destabilizes NF- κ B [65]. Hence, p65 acetylation plays an important role in modulating the potency and duration of NF- κ B activity. Acetylation of p50 by p300 also promotes NF- κ B activity, by increasing its ability to bind DNA [66]. Interestingly, acetylation of p65 Lys122 and Lys123 conversely inhibits binding to DNA, suggesting that regulation by acetylation is complex and could potentially mediate different outcomes depending on context. In addition to direct acetylation of NF- κ B, p300/CBP and PCAF play key roles as coactivators of NF- κ B-dependent transcription by acetylating histones at the promoters of target genes [67, 68]. Recruitment of deacetylases HDAC1, HDAC2, SIRT1 and SIRT6 to the NF- κ B transcriptional complex appears to play a balancing role in restraining the amplitude of NF- κ B responses. Upon inhibition of HDACs or deletion of SIRT1 or SIRT6, NF- κ B transactivates gene expression more potently [57, 65, 69]. As described above, SIRT1 acts directly on NF- κ B itself, whereas SIRT6 activity is directed towards histone H3 Lys9 at NF- κ B target genes [57, 65]. Thus, increased activity of acetyltransferases can promote or extend NF- κ B activation, whereas deacetylases contribute to suppression or termination of NF- κ B activity. Of note, STAT3 acetylation is also required for its dimerization and activation, and its acetylation can be metabolically regulated by SIRT1 [70, 71].

A key regulator of fatty acid oxidation, PGC-1 α , is also regulated by acetylation. PGC-1 α is acetylated and turned off by GCN5, and deacetylated and activated by SIRT1; SIRT1-dependent deacetylation occurs during fasting and it has been proposed that Gcn5-mediated acetylation of PGC-1 α may also be responsive to metabolic state [72, 73]. SIRT6 was also recently shown to regulate PGC-1 α acetylation, although surprisingly its effects oppose those of SIRT1. SIRT6 activates GCN5, promoting acetylation of PGC-1 α [74]. Of course acetyl-CoA is also a precursor for lipid synthesis, and increased acetyl-CoA availability could also directly support increased lipid accumulation. Hence, in response to organismal metabolic state, changes in acetyl-CoA availability might alter acetylation of targets such as PGC- α , STAT3, NF- κ B, and histones at NF- κ B target genes, thereby contributing to inflammation and lipid accumulation in obesity and fostering cancer development (Figure 3).

Is acetylation a target for obesity-linked cancers?

What are the effects of modulation of acetylation on obesity-linked diseases such as diabetes and cancer? SIRT1 has been implicated in several studies in the development of obesity-linked insulin resistance. For example, in the absence of SIRT1 in myeloid cells, NF- κ B is hyperacetylated, NF- κ B target gene expression is elevated, and mice are predisposed to the development of insulin resistance [65]. Lack of SIRT1 in the liver increases steatosis upon high fat feeding due to inability to activate PPAR α -dependent fatty acid oxidation [55]. SIRT1 transgenic overexpression conversely protected against high fat diet-induced inflammation, reducing NF- κ B activation and target gene expression. Since both

inflammation and hepatosteatosis are linked with cancer development, nodes that impact both of these processes, such as SIRT1 activation, may have significant promise in suppressing obesity-linked liver cancer. SIRT1 overexpression in liver was indeed able to suppress the effects of obesity on potentiating DEN-induced hepatocellular carcinoma [27].

Inhibition of HAT activity can also reduce NF- κ B activation, and targeting acetyltransferases can reduce obesity-linked inflammation. For example, the natural compound curcumin, which can inhibit the KATs p300 and CBP, has been described in several studies to reduce obesity and obesity-linked diabetes [75]. Supplementation of curcumin to mice on high fat diet reversed the detrimental effects of high fat diet on blood glucose levels, fat accumulation and insulin resistance [76]. Curcumin treatment curtailed adipose tissue inflammation, reduced hepatosteatosis and lipogenic gene expression, and suppressed NF- κ B levels and activity [76, 77]

Hence, promotion of SIRT1-dependent deacetylation or inhibition of KAT-mediated acetylation reduces liver inflammation and lipid accumulation. Whether the modulation of acetyl-CoA production- for example through targeting of ACL- would have similar beneficial effects remains to be seen. Silencing ACL in the liver has been shown to reduce high-fat diet-induced lipid accumulation [78, 79]. Considering the available evidence, further exploration of the potential to target acetylation or acetyl-CoA metabolism in obesity-related cancers may be fruitful.

Conclusion

Developing successful strategies to prevent or treat cancer associated with obesity could save many thousands of lives in the coming decades. Much has yet to be learned about the molecular mechanisms linking obesity and cancer, although key players have been identified. Acetyl-CoA metabolism and regulation of protein acetylation could represent a promising angle to explore therapeutically, with the goal of suppressing inflammatory pathway activity in obesity.

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Figure 1. Nutrient availability may regulate acetylation levels through both acetyl-CoA-dependent regulation of KATs and NAD⁺-dependent regulation of sirtuins

During nutrient deprivation, nuclear-cytoplasmic acetylation of proteins may decrease as a consequence of both reduced availability of acetyl-CoA to promote KAT activation and rising levels of NAD⁺ or NAD⁺/NADH to promote sirtuin deacetylase activity.

Reciprocally, in high nutrient conditions, metabolic conditions inhibit sirtuins and high availability of acetyl-CoA could facilitate KAT activity.

Figure 2. ACL integrates information from metabolic processes and signaling pathways
 ACL cleaves citrate into acetyl-CoA and oxaloacetate in an ATP-dependent manner, and serves as a key source of extra-mitochondrial acetyl-CoA. ACL is generally more active in nutrient-replete states and may be allosterically activated by sugar phosphates, as well as by Akt-dependent phosphorylation.

Figure 3. Acetyl-CoA could impact processes involved in tumor growth through regulation of lipid synthesis and transcription factor acetylation

Acetyl-CoA has important roles both as a precursor for de novo lipogenesis and as an acetyl-group donor for acetylation reactions. Acetylation regulates multiple transcription factors with key roles in liver cancer. For example, PPARα-dependent activation of fatty acid oxidation is inhibited when the coactivator PGC-1α is acetylation. Reciprocally, the activities of NF-κB and STAT3 activity are promoted by acetylation. It is not yet clear whether acetyl-CoA availability is regulatory for these acetylation events.