OPINION

Molecular mechanisms of cancer development in obesity

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Abstract | The increasing incidence of obesity and its co-morbid conditions poses a great challenge to global health. In addition to cardiovascular disease and diabetes, epidemiological data demonstrate a link between obesity and multiple types of cancer. The molecular mechanisms underlying how obesity causes an increased risk of cancer are poorly understood. Obesity disrupts the dynamic role of the adipocyte in energy homeostasis, resulting in inflammation and alteration of adipokine (for example, leptin and adiponectin) signalling. Additionally, obesity causes secondary changes that are related to insulin signalling and lipid deregulation that may also foster cancer development. Understanding these molecular links may provide an avenue for preventive and therapeutic strategies to reduce cancer risk and mortality in an increasingly obese population.

Obesity is defined as an excess accumulation of adipose tissue. It occurs in mammalian species when calorific intake exceeds energy expenditure. The ability to store excess calories as adipose tissue was a useful adaptation that allowed our ancestors to survive periods of nutritional deprivation. Unfortunately, obesity is now at epidemic proportions in the developed world[1], as well as in many developing countries[2].

The links between obesity, type 2 diabetes and cardiovascular diseases have long been appreciated. However, it has recently become clear that obesity is associated with an increased frequency of many cancers[3]. Epidemiological data suggest a significant association between increased body mass index (BMI) and several haematological cancers[4], pancreatic cancer[5], prostate cancer[6], postmenopausal breast cancer[7] and other cancers[4–8] (TABLE 1). These associations are particularly distressing given the rise in childhood obesity, which portends an increased incidence of cancer as obese children reach adulthood[9].

Adipose tissue is a heterogeneous organ consisting of multiple cell types. Classically, adipose tissue is subdivided into white and brown adipose tissues, which have different functions. White adipose tissue, which is present in the subcutaneous layer, omentum and retroperitoneum, stores excess energy as lipid and is greatly increased in obesity. Brown adipose tissue in the cervical and supraclavicular areas dissipates energy through thermogenesis. Both types of adipose tissue can be divided into an adipocyte fraction, which contains lipid-laden adipocytes, and a stromal-vascular fraction, which includes preadipocytes, endothelial cells, macrophages and other immune cells (FIG. 1). Cell types in both fractions of adipose tissue can change the metabolic homeostasis of the organism. Thus, the increased risk of cancer in obesity may be due to changes in adipocyte biology or in the non-adipose cells in the stromal-vascular fraction. The relative contribution of cells in these two fractions to carcinogenesis remains elusive.

Human obesity is a complex phenotype that results from a combination of elevated calorific intake and a relative lack of physical activity. Increased adipose tissue mass is associated with metabolic changes that are described as metabolic syndrome, which is characterized by abdominal obesity, reduced high-density lipoprotein (HDL) cholesterol levels, increased levels of triglycerides, hypertension and insulin resistance. Because obesity alters whole-organism physiology, animal models are required to study the effects of increased adiposity. Genetic models such as leptin-deficient (*ob/ob*) mice, or leptin receptor-deficient (*db/db*) mice or rats (*fa/fa*) are often used, but these models have many limitations. Although these models gain weight as adipose tissues, they also suffer from immune deficiencies, reproductive hormone abnormalities and changes in bone homeostasis that complicate the analysis of the effects of obesity on neoplasia. Mice that are fed a high-fat, high-carbohydrate diet develop diet-induced obesity (DIO), which closely mirrors human obesity. However, mouse models of cancer may cause decreased appetite and cachexia, which results in rapid weight loss. This weight loss may confound the examination of the effects of obesity on later stages of tumour promotion or metastasis. Thus, there are many challenges to studying the effects of obesity on cancer development.

Although ample epidemiological data suggest links between cancer and obesity, there is no definitive evidence regarding the mechanisms that are responsible for this increased risk. For some cancers (for example, oesophageal adenocarcinoma) the secondary effects of changes in body habitus may have a key role[8]. Other cancers, such as breast cancer and endometrial cancer, probably occur secondarily to the hormonal changes that are associated with obesity[10]. These mechanisms may explain some of the increase in cancer incidence in obese individuals. However, the breadth of the associations between multiple cancer types and obesity suggests that more general mechanisms are involved.

In this Opinion article, we critically discuss the potential mechanisms for the increased tumorigenesis that is seen in obesity. We delineate the hypotheses regarding the effects of increased adipose tissue per se versus the effect of secondary consequences of obesity such as insulin resistance and type 2 diabetes. We also discuss the potential therapeutic ramifications of the links between obesity and cancer.

Effects of increased adipose tissue

In addition to storing excess calories in the form of lipid, adipose tissue has an active role in endocrine signalling to the rest of the body. Extensive data have shown that adipose tissue secretes molecules into the bloodstream, which signal to other metabolic organs or to the brain to coordinate responses to altered metabolic demands. These molecules, known as adipokines, can be secreted both from the adipocyte fraction and from the stromal-vascular fraction. As discussed below, it is likely that some of these adipokines have a role in modulating the risk of cancer development. The most likely contributors from the adipose tissue itself are the adipokines leptin, adiponectin and pro-inflammatory molecules.

Inflammatory cytokines. The first functional polypeptides that were shown to be secreted from fat tissue and to have a systemic role in metabolic homeostasis were the inflammatory cytokines. Originally observed as an increase in tumour necrosis

factor-α (TNFα) expression from fat in rodent obesity[11], this response has also been shown to occur in humans[12] and to involve the secretion of other cytokines, including interleukin-6 (IL-6)[13] and plasminogen activator inhibitor 1 (PAI1; also known as SERPINE1)[14]. The secretion of these cytokines contributes to the insulin resistance that is associated with obesity. Subsequent work has shown that much of the production of these cytokines from adipose tissues is actually from monocytes[15] and other immune cells that infiltrate adipose tissues in obesity[16]. Why obesity triggers immune cell infiltration of the adipose tissue remains under investigation. However, it is clear that this increased secretion of cytokines causes chronic inflammation that affects the function of other tissues in the body. Indeed, a growing body of evidence suggests that the inflammatory milieu of the obese state is intimately linked to the development of cancer through various mechanisms[17].

TNFα, a cytokine that was originally identified as mediating endotoxin-induced tumour necrosis[18], has been shown to be involved in the development of a number of cancers through the promotion of angiogenesis[19] and metastasis[20]. For example, TNFα is required for azoxymethane-induced colon carcinogenesis[21], and TNF receptors are required for chemically induced skin[22] and liver[23] carcinogenesis. It is clear that there are increasing levels of TNFα in the bloodstream of both obese rodents[24] and obese humans[25], suggesting one possible link between obesity and tumorigenesis.

TNFα has been implicated in the development of obesity-induced cancer in mice. The elimination of TNFα signalling by the deletion of the TNF receptor gene *Tnfrsf1a* (also known as *Tnfr1*) abrogates the ability of a high-fat diet to promote liver carcinogenesis that is induced by the chemical carcinogen diethyl-nitrosamine (DEN)[26]. Interestingly, the deletion of *Tnfrsf1a* has no effect on the development of liver cancer in lean mice in response to DEN[27]. These data argue that TNFα has a more prominent role in liver tumorigenesis in obesity than it has in the lean state. It remains unclear whether TNFα produced from the adipose tissue itself contributes to this effect, as circulating inflammatory cells that arose or that were activated in the adipose tissues might also contribute at distant sites.

A potential mechanism of tumour promotion by obesity-induced inflammation is the activation of the transcription factor nuclear factor-κB (NF-κB) by inflammatory pathways. NF-κB is activated by a variety of signals, including TNFα, Toll-like receptors and other inflammatory cytokines (FIG. 2). The activation of NF-κB has been shown to be important in the development of cancers, including glioblastoma[28], lymphoma[29] and pancreatic cancer[30]. Activated NF-κB is required for cholestasis-induced liver cancer, which is a model of TNFα-induced cancer[31]. However, the role of NF-κB in tumorigenesis in DIO models remains controversial. Liver-specific inactivation of NF-κB signalling by conditional deletion of inhibitor of κB kinase-γ (*Ikbkg*) surprisingly resulted in increased tumorigenesis in animals on a high-fat diet[32]. This effect may be due to increased apoptosis in the liver, resulting in the compensatory proliferation of hepatocytes, as well as in the activation of other cytokine-induced inflammatory pathways. Thus, further experiments are needed to refine our understanding of the role of NF-κB in obesity-associated carcinogenesis.

Another major pro-inflammatory molecule that is produced in adipose tissue is the cytokine IL-6. Circulating IL-6 levels are correlated with BMI[25], and adipose tissue is thought to account for up to 35% of circulating IL-6 in healthy subjects[33]. IL-6 signals to the nucleus through signal transducer and activator of transcription 3 (STAT3), an oncoprotein that is activated in a wide variety of cancers[34]. In genetic and dietary models of obesity, the activation of STAT3 is increased in tumours that are grown in obese animals[26]. Interestingly, STAT3 is activated by leptin[35], and may have a role in the pro-tumorigenic effects of this adipokine. Furthermore, the tumour-promoting effect of obesity on chemically induced hepatocellular carcinoma is eliminated in mice that lack endogenous IL-6 (REF. 26). It remains unclear whether IL-6 that is secreted from the adipose tissue itself is crucial for this process or whether it is secondary to signalling within the liver or circulating inflammatory cells.

Other inflammatory cytokines such as PAI1 may also contribute to the increased risk of cancer in obesity. PAI1 is the primary inhibitor of the plasminogen activators urokinase and tissue plasminogen activator, and is produced at high levels in adipose tissue. Plasminogen is the precursor of the extracellular protease plasmin, and is a key component for metastasis[36] and angiogenesis[37]. Activation of plasminogen may result in increased extracellular remodelling, which is a key process in cancer development[38]. High PAI1 levels are associated with poor outcomes in breast cancer in humans[39]. PAI1 inhibitors can reduce the risk of polyp formation in adenomatous polyposis coli (*Apc*)^{min} mice, a common genetic model of colorectal cancer[40], suggesting that PAI1 is involved in tumorigenesis. The role of PAI1 in cancer has also been explored in genetic models of *Serpine1* deletion, which lack PAI1. Tumours explanted into *Serpine1*$^{-/-}$ mice were unable to grow and invade owing to deficient vascularization[41]. This effect on tumour vasculature may depend on the prevention of endothelial cell apoptosis[42]. Thus, increased expression of PAI1 in obesity may increase the vascularization and invasiveness of tumours, although this has not been formally demonstrated.

Table 1 | **Summary of increased relative risk* of different cancers in obesity**

Cancer type	Men (95% CI)	Women (95% CI)
Breast	ND	1.12 (1.08–1.16)
Colon	1.24 (1.20–1.28)	1.09 (1.05–1.13)
Endometrial	NA	1.59 (1.50–1.68)
Oesophageal	1.52 (1.33–1.74)	1.51 (1.31–1.74)
Kidney	1.24 (1.15–1.34)	1.34 (1.25–1.43)
Leukaemia	1.08 (1.02–1.14)	1.17 (1.04–1.32)
Melanoma	1.17 (1.05–1.30)	0.96 (0.92–1.01)
Myeloma	1.11 (1.05–1.18)	1.11 (1.07–1.15)
Non-Hodgkin's lymphoma	1.06 (1.03–1.09)	1.07 (1.00–1.14)
Pancreatic	1.07 (0.93–1.23)	1.12 (1.02–1.22)
Prostate	1.03 (1.00–1.07)	NA
Rectal	1.09 (1.06–1.12)	1.02 (1.00–1.05)
Thyroid	1.33 (1.04–1.70)	1.14 (1.06–1.23)

CI, confidence interval; NA, not applicable; ND, not determined. *Relative risks are taken from a meta-analysis of data as reported in Renehan *et al.*[3] and Roberts *et al.*[172]. The relative risk per 5 kg per m^2 increase in body mass index is reported for each site and sex.

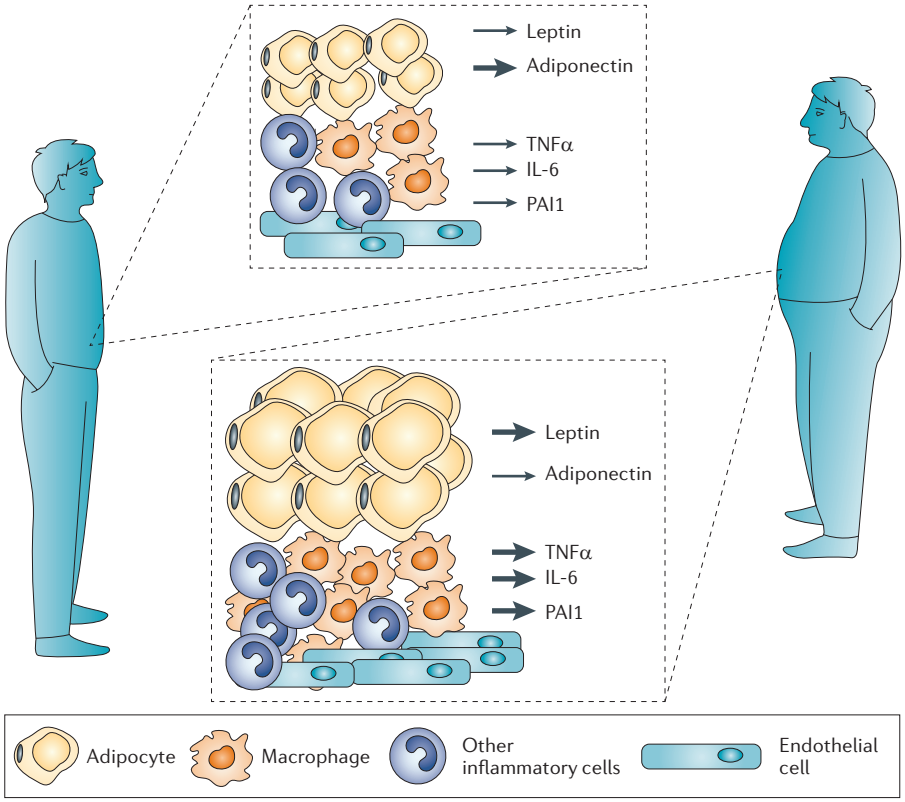

Figure 1 | **Changes in adipose tissue in obesity.** Adipose tissue can be fractionated into lipid-containing adipocytes and into the stromal-vascular fraction, which contains pre-adipocytes, macrophages, other inflammatory cells and endothelial cells. In the obese state, there is an increase in the size and number of adipocytes, as well as increases in the inflammatory and endothelial compartments of the stromal-vascular fraction. This change in the composition of the adipose tissue results in the increased secretion of leptin and inflammatory cytokines, with a decrease in the secretion of adiponectin. IL-6, interleukin-6; PAI1, plasminogen activator inhibitor 1; TNFα, tumour necrosis factor-α.

Leptin. Leptin is an adipocyte-derived hormone that is the central mediator of a feedback loop that regulates appetite and energy homeostasis[43]. The major physiological site of leptin action is in the central nervous system, but the leptin receptor (OBR; also known as LEPR) is also expressed at lower levels in peripheral tissues[44]. Several studies have documented OBR expression in multiple cancers, including those of the breast, prostate and colon[45–47].

Leptin levels are closely correlated with adiposity in humans[48], and subsequent studies have suggested that this hormone may be linked to the increased incidence of cancer in obesity. A number of epidemiological studies have examined the association of leptin levels with cancer, with differing results. In an analysis of Greek men, after adjustment for BMI, leptin levels were not correlated with prostate cancer incidence[49]. A larger study in Scandinavian men showed an association between leptin levels and prostate cancer risk, although this was true for intermediate, but not for the highest, leptin levels[50]. A regression analysis of women in Massachusetts, USA, found that leptin was not associated with increased carcinoma *in situ* of the breast[51]. By contrast, an analysis of Japanese women with colorectal cancer indicated that leptin was associated with increased risk, independently of BMI[52].

Leptin signals through a transmembrane receptor (OBR) that contains intracellular tyrosines, which mediate downstream signalling via the ERK and STAT3 pathways[53]. These and other signalling pathways may allow leptin to function as a growth factor, contributing to the initiation and/or progression of cancer[46]. Leptin stimulates the growth of colonic epithelial cells and cancer cells from the breast, prostate and ovary[54–57]. Interestingly, co-culture experiments found that mature adipocytes from wild-type, but not from leptin-deficient, *ob/ob* mice, increased the proliferation of colon cancer cells[58].

Several studies have suggested mechanisms by which leptin might contribute to carcinogenesis. The effect of leptin on cancer cell proliferation has been shown to involve activation of MAPK[54,57] (FIG. 2). In androgen-independent prostate cancer cells, leptin activated JUN N-terminal kinase (JNK), and inhibition of JNK activation blocked the effects of leptin on cellular proliferation[56]. Leptin stimulates the expression and activity of aromatase and the transactivation of oestrogen receptor-α in breast cancer cells, both of which stimulate tumour growth[59].

Studies in animal models also indicate a role for leptin in carcinogenesis, although some of the data are contradictory. Obese mice with increased leptin levels show an increased susceptibility to azoxymethane-induced colorectal carcinogenesis[60]. However, leptin administration to azoxymethane-treated rats inhibited the development of precancerous lesions[61]. In another study, mice that had intact central leptin signalling, but that were deficient in peripheral OBR, had decreased progression and metastasis of mammary tumours. These effects seemed to be cell autonomous, as transplantation of tumours that were deficient in OBR into wild-type animals resulted in tumours that grew more slowly than tumours that expressed OBR[62]. Thus, leptin signalling may have an important role in the promotion of tumour growth *in vivo*.

Adiponectin. Adiponectin is another adipokine that may have a role in cancer. Adiponectin levels are reduced in obesity, and adiponectin acts on a number of tissues to regulate glucose and lipid metabolism[63,64]. Several basic and epidemiological studies have suggested that adiponectin has antitumour effects. As with leptin, it is difficult to distinguish whether these actions are secondary to effects on systemic metabolism or are due to direct actions on tumour tissues[65].

Epidemiological studies have pointed to a link between adiponectin and carcinogenesis. In a prospective analysis, adiponectin levels were inversely associated with breast cancer risk in postmenopausal women[66]. Adiponectin levels were also inversely correlated with the risk of endometrial and renal cell carcinoma[67,68]. However, in a later prospective study, adiponectin levels were not predictive of endometrial cancer risk[69]. Using a case–control design, a single nucleotide polymorphism (SNP) in the 5′ region of adiponectin was found to be associated with decreased colorectal cancer risk[70].

The mechanisms by which adiponectin inhibits tumorigenesis have been examined in several studies. Adiponectin inhibits prostate and colon cancer cell growth[71,72].

Haploinsufficiency of adiponectin is associated with mammary tumour development in mice, by downregulating PTEN and upregulating PI3K–AKT signalling[73]. In colon cancer cells, adiponectin blocked cell cycle progression, and its anti-proliferative effects were impaired by knockdown of the adiponectin receptors[72]. Furthermore, adiponectin increased AMP-activated kinase (AMPK) activity, which is a key regulator of proliferation in response to nutrient status[74]. In response to adiponectin, hepatocellular carcinoma cells had increased JNK phosphorylation, decreased mTOR phosphorylation and increased apoptosis[75]. Tumours implanted in adiponectin-deficient mice showed increased growth relative to controls, which was found to be due to reduced macrophage infiltration[76]. Recently, it has been shown that many of the effects of adiponectin are mediated by increased ceramidase activity, resulting in an alteration of the ratio of ceramide to sphingosine-1-phosphate[77]. Although alterations of sphingolipid metabolism may modulate tumorigenesis[78], whether the effects of adiponectin on cancer are mediated by ceramidase activity remains unexplored.

Although the above data are not conclusive, in aggregate they suggest that leptin might stimulate, and that adiponectin might inhibit, carcinogenesis. A prostate cancer cell model showed reduced proliferation in response to adiponectin, which was blocked by treatment with leptin[79]. In hepatocellular carcinoma cells, the proliferative effects of leptin were blocked by adiponectin. Moreover, when tumours were implanted into nude mice, leptin increased tumour burden, and these effects were impaired when animals were co-treated with adiponectin[75]. Thus, adiponectin and leptin seem to have opposing roles in cancer development, similar to their functions in metabolic disease[80] and other diseases[81].

Contribution of adipose progenitors. Obesity results in hyperplasia and hypertrophy of adipose tissue. This process results in the proliferation of adipocyte progenitors in the stromal-vascular fraction and increases angiogenesis to oxygenate an increasingly hypoxic tissue[82]. Many of these processes are also active in the early steps of cancer development. These similarities have led some to hypothesize that adipose tissue progenitors in the stromal-vascular fraction may contribute to tumorigenesis by increasing tumour angiogenesis, or by paracrine or endocrine signalling to malignant cells[83].

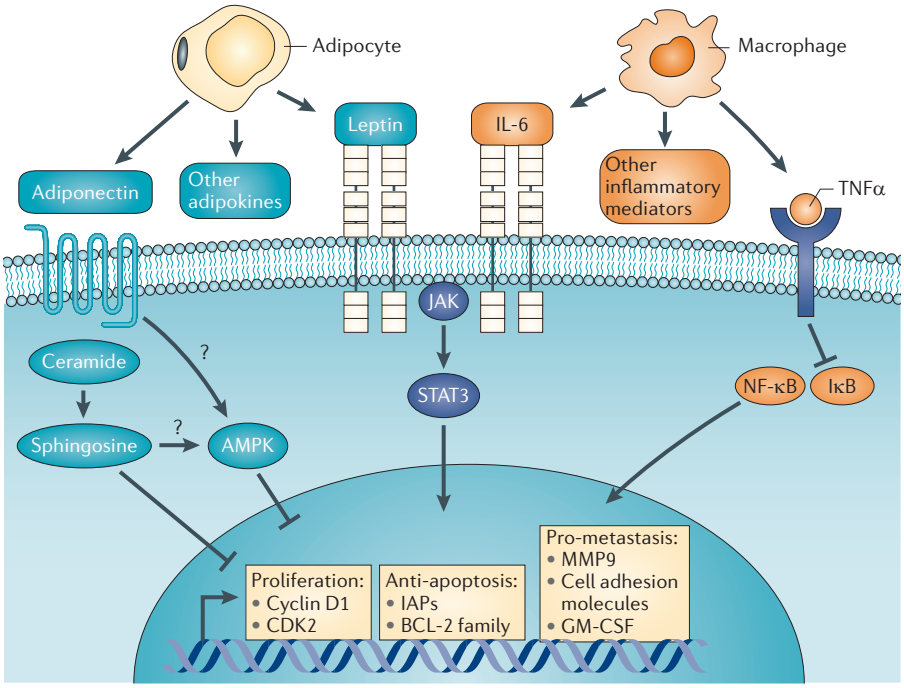

Figure 2 | **Adipokine and inflammatory signalling in obesity.** Adiponectin secreted from adipocytes binds to its own receptors (ADIPOR1 and ADIPOR2), and inhibits proliferation and metastasis. Adiponectin increases the conversion of ceramide to sphingosine-1-phosphate, which has a variety of effects on apoptosis and insulin resistance, possibly via AMP-activated kinase (AMPK). Circulating leptin produced from adipocytes can bind to the leptin receptor (OBR), or the interleukin-6 (IL-6) receptor, and can activate JAK–signal transducer and activator of transcription (STAT) signalling through STAT3. STAT3 is known to function as an oncogenic transcription factor. Other adipokines may also play an important part in promoting cancer development. Inflammatory cells in the adipose tissue produce IL-6 and tumour necrosis factor-α (TNFα), as well as multiple other cytokines. IL-6 activates JAK–STAT signalling to promote proliferation and metastasis. TNFα binds to the TNF receptors, and activates nuclear factor-κB (NF-κB) through the degradation of inhibitor of κB kinase (IκB). NF-κB is now free to translocate to the nucleus, where it inhibits apoptosis and promotes proliferation and metastasis. These pathways can activate proliferation via cell cycle regulators, including cyclin D1 and cyclin-dependent kinase 2 (CDK2). Inflammatory signalling can trigger pro-apoptotic or anti-apoptotic signalling, depending on context. In cancer, the activation of inhibitors of apoptosis (IAPs) and members of the BCL-2 family can prevent apoptosis. Metastasis can be enhanced by increased expression of cell adhesion molecules such as E-selectin (ELAM1) or vascular cell adhesion molecule 1 (VCAM1). Furthermore, the expression of growth factors such as granulocyte-macrophage colony stimulating factor (GM-CSF) or vascular endothelial growth factor (VEGF) can stimulate metastasis. The expression of matrix metalloproteinases (such as MMP9) can also increase the remodelling of the microenvironment, resulting in metastasis. In this way, inflammatory cytokines that are produced from adipose tissue can promote tumorigenesis.

Data to support this hypothesis arise from experiments using green fluorescent protein (GFP)-labelled stromal-vascular precursors that are injected into nude mice bearing xenograft tumours[84]. Interestingly, pre-adipocytes (identified by cell surface marker staining) that were injected intravenously or subcutaneously engrafted into the tumour stroma and vasculature. Similarly, in nude mice bearing GFP-labelled orthotopic fat transplants, GFP-positive cells were identified in tumour tissue xenografts. These data suggest that adipose tissue progenitors can spontaneously mobilize and home to sites of tumours, possibly through binding to specific molecules that are present on the tumour endothelium[85]. Importantly, the injection of adipose progenitors into mice with tumours promoted tumour growth compared with mice injected with lung stromal cells or 3T3 fibroblasts.

Together, these data raise a provocative hypothesis that adipose tissue progenitors may contribute to tumour development. Given the close relationship between the vasculature and adipose tissue[86,87], one can speculate that pre-adipocytes create a pro-angiogenic niche that facilitates tumour development. A growing body of work suggests that tumour-associated fibroblasts may enhance tumour growth[88] or metastasis[89], and it is possible that pre-adipocytes can

also contribute to this effect. Further work is needed to explore whether endogenous adipocyte progenitors engraft to tumours in obese models, and to delineate their functional importance *in vivo*.

Secondary consequences of obesity

The obese phenotype is associated with a number of secondary physiological changes that may also have roles in the development of cancer. The cytokines that are secreted by adipose tissue can activate tissue-resident macrophages and other inflammatory cells that can promote cancer. Furthermore, most obese individuals develop insulin resistance in key metabolic tissues: skeletal muscle, adipose tissue and the heart. Insulin levels subsequently rise as pancreatic β-cells secrete more insulin to compensate for the resulting hyperglycaemia. Obesity is also associated with alterations in circulating lipids, specifically increases in low density lipoprotein (LDL) cholesterol, triglycerides and free fatty acids. All of these factors may have tumorigenic roles and contribute to the primary effects of increased adipose tissue (described above).

Inflammatory cells. The cytokines that are secreted by adipose tissue can activate macrophages and other inflammatory cells in many tissues. Extensive data have demonstrated that, during obesity, the adipose tissue becomes infiltrated with macrophages[15,90]. Although some data suggest that macrophage infiltration can have beneficial roles in adipose homeostasis[91], obesity can cause the activation of macrophages to a pro-inflammatory state under some conditions[92]. Interestingly, there is evidence that obesity increases macrophage infiltration in other tissues such as pancreatic islets[93] and muscle[94].

The increase in macrophage infiltration raises the hypothesis that obesity-associated increased macrophage infiltration contributes to tumorigenesis. It has recently been demonstrated that tumour-associated macrophages (TAMs) have a key role in the tumour microenvironment[95]. TAMs are believed to contribute to tissue invasion[96], angiogenesis[97] and metastasis[98]. Increased macrophage chemoattractant protein 1 (MCP1; also known as CCL2) in breast tumour extracts is a predictor of early relapse[99] and metastasis[98]. Furthermore, proliferating macrophages in breast tumours are associated with high tumour grade and poor prognosis[100]. Intriguingly, obesity is associated with increased macrophage infiltration in breast tumours[101]. Thus, it is possible that the activation of macrophages or other inflammatory cells in the setting of obesity may result in increased tumorigenesis or may result in poorer outcomes in obese cancer patients. Further experiments are needed to demonstrate the causal role of TAMs in obesity.

Increased insulin–IGF signalling. Most obese people have some degree of insulin resistance[102] and this is often associated with elevated levels of circulating insulin. Epidemiological data link type 2 diabetes with an increased incidence of multiple types of cancer, including breast[103], colorectal[104], hepatocellular[105], endometrial[105] and pancreatic malignancies[106]. Furthermore, in retrospective studies, patients with type 2 diabetes have a worse prognosis than matched patients with the same malignancy without diabetes[107,108]. These data suggest that the diabetic state may promote a more aggressive cancer phenotype or a poorer response to treatment. The increased incidence of cancer in patients with type 2 diabetes has led many to speculate that the derangement of the insulin axis is a major contributor to the increased risk of cancer that is seen in obesity (FIG. 3).

Although the obese state generates peripheral insulin resistance in many tissues, not all insulin signalling is impaired. In the diabetic liver, the gluconeogenic pathway becomes insulin resistant, and insulin-stimulated lipogenesis remains sensitive[109]. Thus, in diabetes, specific tissues and signalling pathways can remain insulin-sensitive and are exposed to higher than normal levels of insulin signalling. Initial experiments demonstrated that insulin promoted DNA synthesis in human breast cancer cell lines[110], suggesting a mitogenic effect. Furthermore, explants of breast cancer cells that are genetically deficient in insulin receptor substrate 2 (*IRS2*), which encodes a downstream mediator of the insulin receptor (INSR), are unable to metastasize[111]. The combined effects of insulin on proliferation and metastasis may increase tumorigenesis in the hyperinsulinaemic state.

In addition to insulin, the insulin-like growth factors (IGFs) may have roles in cancer development. IGF1 and IGF2 are hormones that are primarily produced in the liver and they share sequence homology with insulin[112]. Hyperinsulinaemia increases the production of IGF1 in the liver[113]. IGF1 and IGF2 are primarily expressed in the liver, but may also be expressed in neoplastic tissue. In fact, *IGF2* mRNA is the most highly upregulated transcript in colorectal cancer compared with normal colonic mucosa[114].

Whether obesity is associated with increased IGF levels is controversial. Some studies have demonstrated that obese patients with type 2 diabetes have higher circulating levels of IGF1 and IGF2 (REF. 115). This was also demonstrated in rodent models of obesity[116]. However, obesity results in a reduction in growth hormone levels, which controls IGF1 secretion, blunting effects on total IGF1 levels[117]. Thus, obesity has a complex association with IGF1 serum levels.

Further adding to the complexity of this pathway is the fact that elevated insulin levels result in altered levels of IGF-binding proteins (IGFBPs). These proteins, a family of six members, modulate the bioavailablility of IGFs by sequestering them from clearance pathways and by affecting their binding to cognate receptors. Hyperinsulinaemia can reduce the amount of IGFBPs in the circulation[118], and the modulation of IGFBPs may contribute to tumorigenesis, as they modify IGF1 and IGF2 levels *in vivo*. For example, the tumour suppressor p53 increases the transcription of *IGFBP3*, which reduces IGF1 signalling[119]. Furthermore, reduced levels of IGFBP1 are associated with an increased risk of colorectal cancer[120] and with reduced overall survival in patients with resected colorectal cancer[121]. However, the role of IGFBPs is controversial, as overexpression of IGFBPs may contribute to cancer development in some settings, possibly by maintaining high local concentrations of insulin and IGFs and by promoting tumour cell proliferation[122]. Thus, the effect of obesity on the local bioactive concentrations of IGFs is difficult to determine.

IGF1 and IGF2 bind to the IGF1 receptor (IGF1R), which can heterodimerize with INSR. Increased expression of INSR and IGF1R occurs in multiple different types of solid tumours[123–126]. Activation of these receptors results in the phosphorylation of the IRS proteins, which activate the oncogenic RAS–MAPK and PI3K–AKT pathways[127,128] (FIG. 3). Furthermore, the AKT pathway activates mTOR, which promotes protein translation and cancer cell growth[129]. Interestingly, tumours with constitutive activation of the PI3K pathway are insensitive to dietary restriction[130], suggesting that this pathway is important in linking nutritional status and cancer.

The effects of IGFs seem to be important in a wide variety of cancers, as transgenic expression of *Igf1* or *Igf1r* in mice drives the development of skin cancer[131], prostate cancer[132], pancreatic neuroendocrine carcinoma[133] and breast cancer[134], whereas the expression of IGF2 drives lung cancer[135] and breast cancer[136]. Transgenic overexpression of IGF1R in mammary ductal epithelium in an inducible mouse mammary tumour virus (MMTV) system promotes tumorigenesis in mice[137]. This suggests that even in the presence of physiological levels of insulin or IGFs, increased signalling through the IGF1R pathway can drive cancer development. In humans, elevated levels of IGF1 or IGF2 may contribute to the risk of cancer, as higher levels of IGFs have been linked to an increased risk of prostate cancer[138].

The role of IGF1 in cancer promotion in the obese state has been explored in genetic models of either germline or inducible liver-specific deletion of *Igf1*, in which mice have a 75% reduction in circulating levels of IGF1. Tumours implanted into DIO mice with germline IGF1 deficiency are much smaller than tumours implanted into control DIO mice. Furthermore, genetic deletion of *Igf1* in the liver reduces liver metastases of a colorectal cancer cell line injected into the venous circulation. Interestingly, acute deletion of *Igf1* did not have the same effect of decreasing tumour size or colorectal metastasis[139]. These data argue that the effects of chronic IGF1 signalling, as typically seen in obesity and type 2 diabetes, may be more important than acute changes in IGF1 levels.

Elevated lipid levels. Obesity, especially increased abdominal adiposity, is associated with decreased HDL cholesterol levels, increased triglyceride levels and other lipid abnormalities. Many have speculated that the increases in circulating lipid levels and other nutrients in obesity may be commandeered by cancer cells. These metabolic building blocks can be used to produce new membrane structures, as well as carbon intermediates that can be repurposed for the generation of nucleic acids and amino acids for cellular replication. This concept is supported by data showing the hyperactivation of a number of lipid synthesis pathways in human cancers. For example, the upregulation of fatty acid synthase (FASN) correlates with poor prognosis for human prostate cancer[140]. This study showed an interaction between FASN expression and BMI, as overweight men with a variant *FASN* allele had increased prostate cancer-specific mortality. This association raises the hypothesis that the upregulation of FASN expression may provide a selective advantage for cancer cell proliferation or survival in obesity. FASN in cancer cells is thought to promote the production of phospholipids that are involved in membrane production[141], and chemical inhibitors of FASN result in tumour cell death *in vitro* and *in vivo*[142,143]. However, the mechanisms through which FASN affects tumour cell growth and survival remain largely unexplored.

Intriguingly, FASN is crucial for the activation of the peroxisome proliferator-activated receptor-α (PPARα), possibly through the generation of an endogenous ligand for PPARα activation in the liver[144]. PPARα

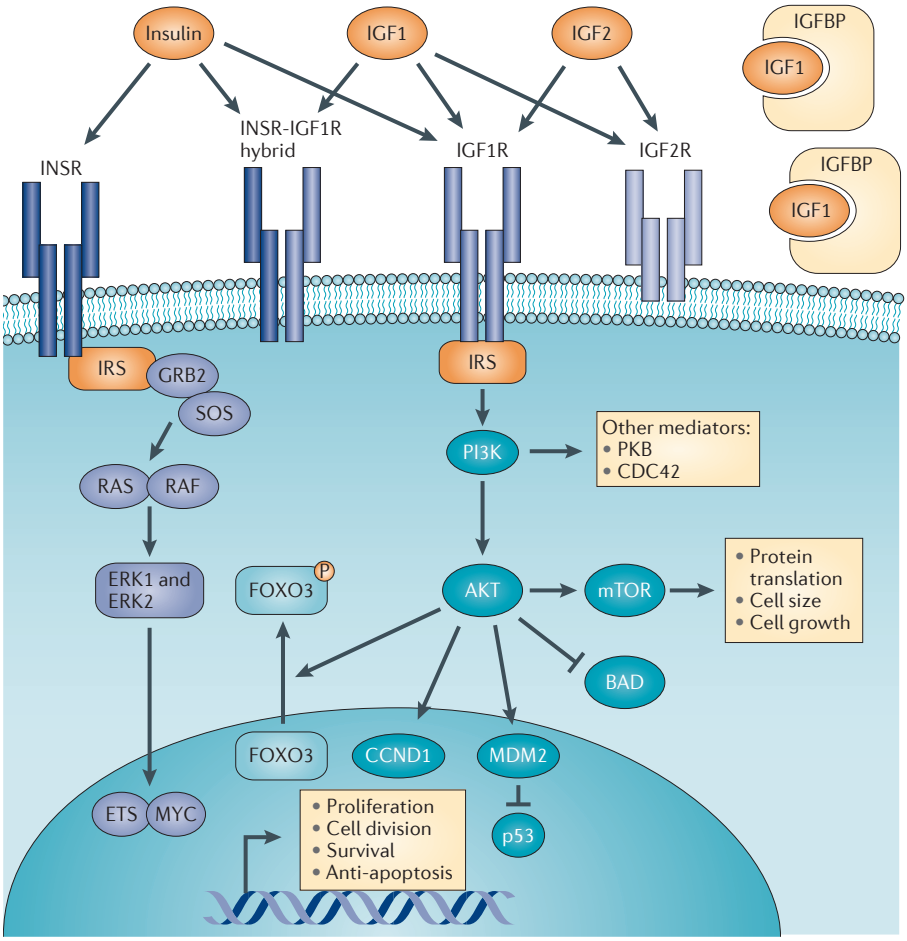

Figure 3 | **Insulin signalling in obesity.** Obesity results in increases in the circulating concentrations of insulin, and possibly insulin-like growth factor 1 (IGF1) and IGF2. IGF-binding proteins (IGFBPs) may sequester these molecules, which thus changes the amount of bioactive insulin or IGFs in the microenvironment. Insulin receptor (INSR) and IGF1 receptor (IGF1R) form homodimers or heterodimers, which can bind insulin, IGF1 and IGF2. IGF2R is a truncated receptor that is thought to lack signalling capacity. Binding of insulin, IGF1 or IGF2 results in the phosphorylation of the insulin receptor substrate (IRS) proteins, which can activate downstream signalling. IRS proteins signal through growth factor receptor-bound protein 2 (GRB2) and SOS to activate downstream signalling cascades through ERK pathways, which results in increased cell proliferation. ERK can activate oncogenic pathways through phosphorylation of MYC and members of the ETS family such as ETS1 and ETS-like transcription factor 1 (ELK1). Activation of the PI3K pathway results in AKT phosphorylation and mTOR activation. PI3K can also activate other mediators of transformation, including phosphorylation of cell division control protein 42 (CDC42), which regulates the cytoskeletal changes that are needed for invasion and cytokinesis. Furthermore, activation of PI3K can activate protein kinase B (PKB), which inhibits negative regulators of the cell cycle such as p27 (also known as KIP1) and p21 (also known as CIP1) through several mechanisms. Activation of mTOR can promote protein synthesis and influence cell growth. AKT inhibits BCL-2 antagonist of cell death (BAD), an anti-apoptotic protein, and activates cyclin D1. Phosphorylation of forkhead box O (FOXO) proteins (such as FOXO3A) by AKT results in FOXO nuclear exclusion, which promotes cell survival and cell division. AKT also activates MDM2, which degrades p53 and thus prevents the activation of cell cycle checkpoints and apoptosis.

mediates the effects of many non-genotoxic chemical carcinogens, which cause increases in peroxisome-mediated fatty acid oxidation. This oxidative process results in increased levels of reactive oxygen species (ROS), which drive mutagenesis and carcinogenesis[145,146]. Furthermore, synthetic ligands for the related PPARβ and PPARδ have also been shown to increase the risk of colonic polyps[147], although some other ligands did not show this effect[148]. These data add support to the hypothesis that chronically elevated levels of fatty acids or other lipids may have a role in tumour promotion. Clearly, more studies are required to probe this hypothesis.

The increased activity of FASN seen in cancer cells is matched to an increase in enzymes that release fatty acids, namely the monoacylglycerol lipase (MAGL) pathway. This pathway is upregulated in certain aggressive cancers[149], and controls the production of free fatty acids (FFAs) within cells. These FFAs are then used either as macromolecular building blocks or for signalling within the cell. Tumour explants with reduced MAGL activity grew significantly slower than tumour explants with high MAGL activity. Interestingly, this growth defect could be rescued with the supplementation of a high-fat diet[149]. Thus, the alterations in lipids seen in obesity may promote a more aggressive tumorigenic phenotype by increasing levels of FFAs within tumour cells. Taken together, these data suggest that increased levels of FFAs, whether generated in tumours via increased MAGL activity or in the host through a high-fat diet, increase the growth of tumours. However, it remains to be seen whether these pathways have important roles in tumour initiation and metastasis.

Another potential consequence of elevated levels of circulating lipids is the lipotoxic effects of FFAs. In type 2 diabetes, one hypothesis suggests that the pathological effects of obesity result from excess lipid storage in non-adipose tissue. In this scenario, the adipose tissue is unable to store all of the excess lipid that is produced (whether from adipocyte dysfunction, exhaustion of adipocyte precursors or other processes). The excess lipid is deposited in other tissues, resulting in adverse effects on tissues such as muscle, heart, liver or pancreatic β-cells[150], possibly through the generation of ROS[151]. Although no formal proof exists, one hypothesis is that excess lipid may result in the generation of ROS in multiple tissues, which may increase the risk of DNA mutation and cancer[151].

Primary and secondary effects of obesity

It is difficult to assess whether increased adipose tissue per se or whether the secondary consequences of obesity are most important in increasing the likelihood of carcinogenesis. A few studies address this question by examining the risk of cancer in mouse models where there is a disassociation between fat mass and insulin sensitivity. A-ZIP/fatless mice[152], which express a dominant-negative protein for B-ZIP proteins (such as those of the CCAAT/enhancer-binding protein (C/EBP) family) have no mature fat cells. These mice are lean, but have insulin resistance, hyperinsulinaemia and increased serum levels of inflammatory cytokines. In these mice, the formation of skin tumours on exposure to DMBA and TPA was increased relative to wild-type controls[153]. Similarly, the incidence and weight of tumours in a transgenic model of breast cancer were also increased in this model. Serum analysis showed a lack of leptin or adiponectin, but increased levels of inflammatory cytokines, insulin and IGF1. These data suggest that inflammation and hyperinsulinaema without increased adipose mass can increase cancer formation. However, it is difficult to extrapolate this artificial model to more relevant physiological situations.

Other work addressing the relative contribution of insulin resistance comes from the MKR mouse model. These mice express a kinase-dead version of IGF1R in skeletal muscle[154]. Female animals are lean, but have hyperinsulinaemia and mild glucose intolerance. MKR mice have an increased incidence of tumours in a model of breast cancer that expresses polyoma middle T antigen in the mammary epithelium[155]. Furthermore, explants of tumours derived from wild-type animals have an increased growth rate in these animals. This suggests that circulating factors, rather than cell-autonomous factors, are most important for increasing tumour formation. These data imply that increased insulin signalling itself can drive tumour promotion in the absence of increased levels of adipokines. However, the relative role of insulin versus IGF1 signalling in these experiments was not addressed. These experiments begin to dissect the relative contributions of increased adiposity and the secondary consequences of obesity, but more work is needed to fully elucidate the importance of all of these pathways in cancer.

Therapeutic implications

The association between cancer and obesity may be due to the convergence of pathways involving adipokines, inflammation and insulin resistance (FIG. 4). However, it remains unclear whether therapeutic intervention can prevent the effect of obesity on cancer. Data from bariatric surgery (for example, gastric bypass for weight loss) studies suggest that weight loss after surgery is associated with a reduced incidence of cancer[156,157] and a decreased incidence of metastatic disease[157]. However, other studies examining the incidence of a select group of cancers in a cohort of patients undergoing bariatric surgery do not support these findings[158]. Whether weight loss after a prolonged period of obesity, as in the bariatric surgery studies, is sufficient to reduce the risk of obesity-associated cancers is not yet clear, and more years of follow-up will be required to assess its true effect.

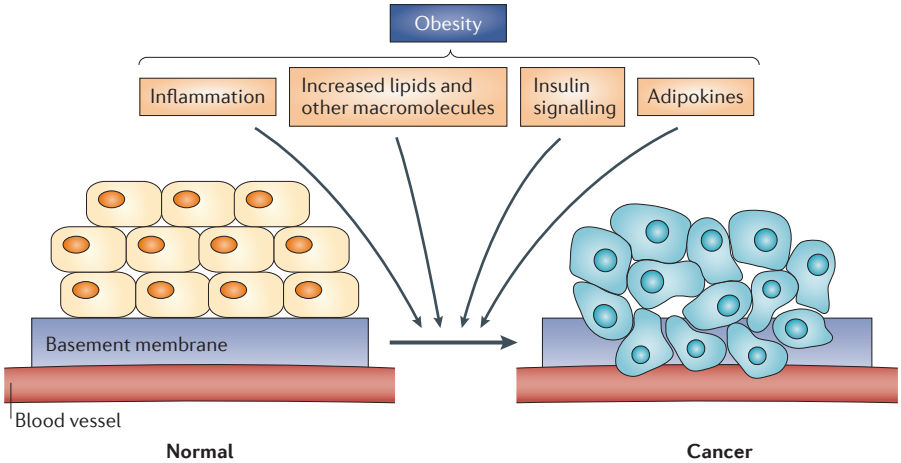

Figure 4 | **Summary of pathways that may link obesity to cancer development.** A convergence of increased inflammation, insulin signalling, increased availability of lipids and other macromolecules, and changes in adipokine signalling may contribute to the conversion of normal epithelial cells to an invasive tumour. Although all of these pathways can contribute to cancer in certain circumstances, it remains unclear whether these pathways are predominantly required for cancer in obese humans.

Another potential therapeutic implication of the association between obesity, insulin resistance and cancer lies in the choices of therapy for patients with obesity and type 2 diabetes. Accumulating data suggest that patients who are taking insulin or drugs that increase insulin secretion (for example, sulphonylureas) may have higher risks of cancer than patients taking oral insulin-sensitizing agents such as metformin or thiazolidinediones (TZDs)[159,160]. Additionally, cancer patients taking insulin or insulin secretagogues may have worse cancer outcomes than those taking metformin or TZDs[161,162]. However, these data are retrospective, and patients who are taking insulin typically have more advanced diabetes. Furthermore, not all data sets have shown this association[163]. However, the avoidance of supplementary insulin in individuals who are at a particularly high risk of cancer may be prudent.

A growing body of data demonstrates that metformin and TZDs may have antitumorigenic effects in many model systems, either as single agents or in combination with conventional chemotherapy[164–166]. These effects may be due to a reduction in circulating insulin owing to increased insulin sensitivity, or owing to the modulation of intracellular targets of these drugs[167–169]. Epidemiological data suggest that taking metformin or TZDs may be associated with lower cancer incidence[170]. Whether metformin or TZDs might have additional efficacy in obese patients with cancer compared with the general population of cancer patients is not clear.

Another potential therapeutic implication of the role of obesity in cancer promotion is the modulation of inflammatory pathways as chemoprevention. Epidemiological data from the Aspirin/Folate Polyp Prevention study showed that the risk reduction in incidence of colorectal adenomas with a daily dose of 325 mg of aspirin was greater among subjects with higher BMI, although this effect was not seen at lower doses[171]. Prospective studies of cancer incidence in the obese population taking aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) are needed to shed further light on the therapeutic potential of modulating inflammation in obesity.

Conclusions

Clinical and epidemiological data suggest that obesity is associated with an increased risk of cancer. Although some of these associations can be explained by changes in body habitus or hormones associated with obesity, there are increases in a large variety of tumour types, suggesting that fundamental biological mechanisms may underlie these links.

Currently, there are many theories that could explain the increased incidence of cancer in obesity. The preponderance of the evidence suggests that a combination of factors secreted by the adipocyte, such as increased leptin, decreased adiponectin and increased inflammatory cytokine secretion, along with contributions from the secondary effects of obesity, especially hyperinsulinaemia and hyperlipidemia, result in the increased incidence of cancer (FIG. 4). The effect of adipocyte progenitors and lipotoxicity on carcinogenesis remains to be determined. It is likely that many of these factors collaborate with other environmental factors to result in multiple 'hits' that are needed for tumorigenesis. However, there are still many unanswered questions as to the precise role of each of these influences. More work will be needed to explore the relative importance of these processes in promoting tumorigenesis. Because obesity modifies whole-organism physiology, it has been difficult to find suitable model systems that can be used to dissect these effects.

The molecular pathways that evolved to efficiently store energy during periods of nutrient deprivation, which characterized most of human evolutionary time, now have a maladaptive role in the modern era of sedentary lifestyle and calorific excess. Attempts to promote reduced adiposity and increased insulin sensitivity may also have beneficial effects in reducing the incidence of cancer. For people with obesity, it remains unclear whether weight loss will be sufficient to prevent the development of cancers, although there is encouraging data that it may do so. However, the growing incidence of obesity in children and young adults suggests that lifestyle changes and therapeutics that may reduce or prevent adiposity could offer the additional benefit of reducing the incidence and mortality from cancer.

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