CHAPTER 12.

Molecular and metabolic mechanisms underlying the obesity–cancer link

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During the past 50 years in the USA, the prevalence of obesity, defined as having a body mass index (BMI) of 30 kg/m^2 or greater, has tripled. Today, nearly 40% of adults and 20% of children in the USA are obese [1]. Worldwide, more than 600 million adults are obese and 2.1 billion are overweight [2]. Obesity increases the risk of several chronic diseases and comorbidities [3], including type 2 diabetes, cardiovascular disease, hypertension, chronic inflammation, and, as discussed in this chapter, cancer.

In the USA, obesity has recently surpassed tobacco use as the leading preventable cause of cancer-related death [4]. As illustrated in Fig. 12.1, obese individuals are at a higher risk of developing several different cancer types, including breast (in postmenopausal women), ovarian, liver, kidney, colon, pancreatic, gastric, oesophageal, and endometrial cancers [5]. An estimated 13% of incident cancer cases worldwide, and approximately 20% of incident cases in Europe and North America, are attributable to obesity [6]. More than 40 000 new cancer diagnoses in the USA each year are attributed to obesity. In addition to having a higher risk of developing cancer, obese individuals are more likely to have reduced response to anticancer therapies [7], and obesity is implicated in about 20% of all cancer-related mortalities [8]. This includes prostate cancer, for which obesity is associated with progression but not incidence [9].

This chapter characterizes the many ways in which obesity can influence normal epithelial tissue homeostasis, cancer development, and/or cancer progression, including metabolic perturbations involving hormonal, growth factor, and inflammatory alterations as well as interactions with the stroma and vasculature.

Obesity affects each hallmark of cancer

Hanahan and Weinberg identified the essential biological capabilities acquired by all cancer cells during the multistep development of a tumour in their classic article "The hallmarks of cancer", published in 2000 [10], and updated these in their 2011 article "Hallmarks of cancer: the next generation" [11]. These essential aberrations of cancer cells, summarized in Fig. 12.2, include sustaining proliferative signalling, increased chronic inflammation, evading growth suppressors, resisting cell death, genome instability, enabling replicative immortality, inducing angiogenesis, and activating processes related to invasion and metastasis. Conceptual progress in the decade between

Fig. 12.1. Obesity-related cancers. Based on recent systematic reviews and meta-analyses (www.aicr.org/continuous-update-project/), obesity is associated with an increased risk of developing and dying from the following cancers: breast (in postmenopausal women), ovarian, endometrial, liver, pancreatic, kidney, colon, oesophageal (adenocarcinoma subtype), and gallbladder. In addition, obesity is associated with progression (but not incidence) of prostate cancer. Reprinted with permission from Hursting SD, O'Flanagan CH, Bowers LW (2015). Breaking the cancer-obesity link. The Scientist. 1 November 2015. Available from: http://www.the-scientist.com/?articles.view/articleNo/44280/title/Breaking-the-Cancer-Obesity-Link/.

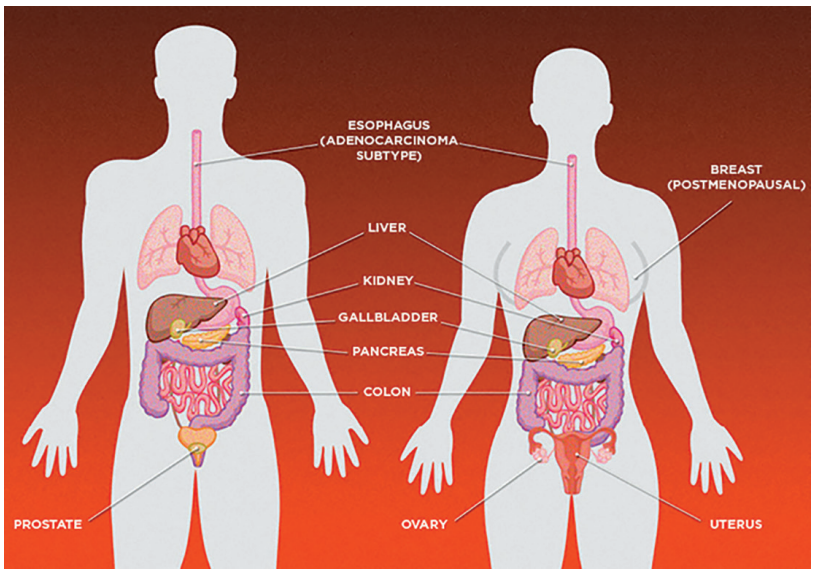
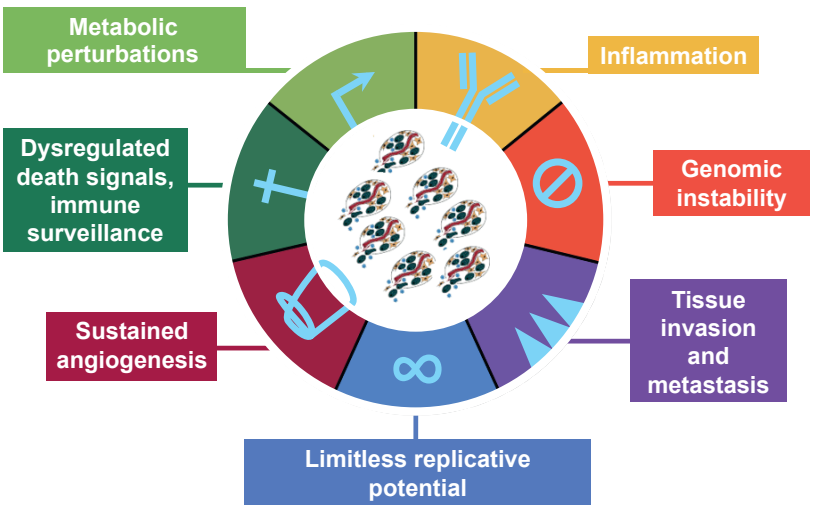


Fig. 12.2. Obesity affects each of the well-established hallmarks of cancer, including reprogrammed energy metabolism, sustained proliferative signalling, increased chronic inflammation, increased genome instability, enabled replicative immortality, enhanced angiogenesis, activated processes related to invasion and metastasis, and resistance to growth suppressors, cell death inducers, and immunoregulators. Reprinted from Hanahan and Weinberg (2011) [11], copyright 2011, with permission from Elsevier.



these two articles led to the identification of additional hallmarks, including reprogramming of energy metabolism, evading immune destruction, and the creation of the tumour microenvironment through the recruitment of various non-cancerous cells. Emerging evidence supports the concept that metabolic reprogramming, inflammation, and genome instability (including epigenetic changes) underlie many of the other hallmarks and foster multiple hallmark functions.

In the case of cancer-associated metabolic reprogramming, cancer cells preferentially metabolize glucose through glycolysis rather than oxidative phosphorylation, even in the presence of oxygen [11–13]. Thus, citric acid cycle intermediates are not used for adenosine triphosphate (ATP) production and are shuttled out of the mitochondria, providing precursors for nucleotide, amino acid, and lipid synthesis pathways for the dividing cell [13]. In this way, cancer cells readily take up and metabolize glucose to provide substrate for production of daughter cells, and levels of glucose uptake transporters (GLUT) and glycolytic enzymes (e.g. hexokinase II) are elevated in most cancers [14].

Metabolic syndrome and systemic metabolic perturbations

The interactions between cellular energetics in cancer cells and the systemic metabolic changes associated with obesity are emerging as critical drivers of obesity-related cancer. Intrinsically linked with obesity is metabolic syndrome, which is characterized by insulin resistance, hyperglycaemia, hypertension, and dyslipidaemia and is associated with alterations in several cancer-related host factors. In both obesity and metabolic syndrome, alterations occur in circulating levels of insulin and

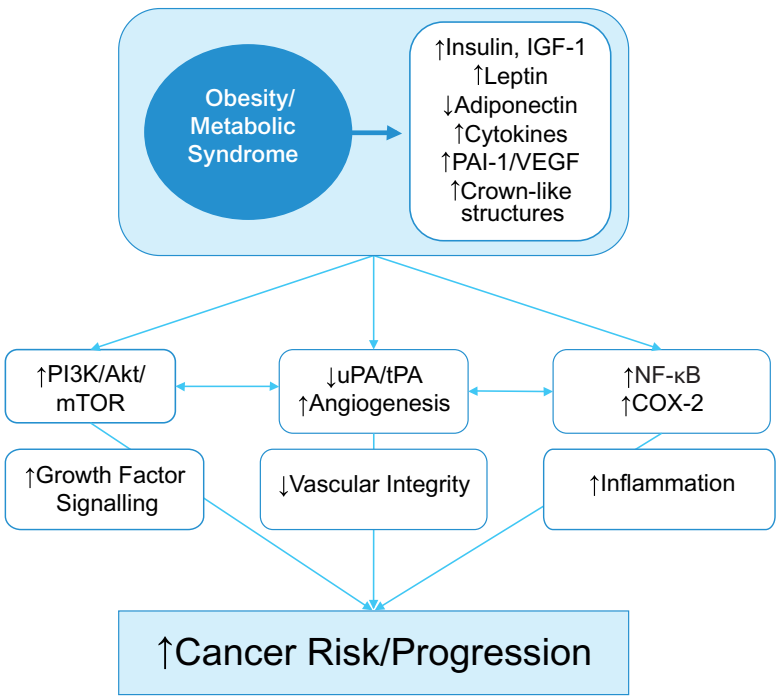
insulin-like growth factor-1 (IGF-1); adipokines, such as leptin, adiponectin, resistin, and monocyte chemotactic factors; inflammatory factors, such as interleukin-6 (IL-6), IL-10, and IL-17; interferon-γ and tumour necrosis factor-α (TNF-α); several chemokines; lipid mediators, such as prostaglandin E2 (PGE2); and vascular-associated factors, such as vascular endothelial growth factor (VEGF) and plasminogen activator inhibitor-1 (PAI-1) [15, 16]. Each of these factors has a putative role in the development and progression of cancer as well as several other chronic diseases [15, 16], including cardiovascular disease and type 2 diabetes. These factors are explored in more detail below.

Insulin, IGF-1, and growth factor signalling

As shown in Fig. 12.3, insulin, a peptide hormone produced by pancreatic β-cells, is released in response to elevated blood glucose. Hyperglycaemia is a hallmark of metabolic syndrome and is associated with insulin resistance, aberrant glucose metabolism, chronic inflammation, and the production of other metabolic hormones, such as IGF-1 [17]. IGF-1 is a peptide growth factor produced primarily by the liver after stimulation by growth hormone. IGF-1 regulates the growth and development of many tissues, particularly during embryonic development [18]. IGF-1 in circulation is typically bound to IGF-binding proteins (IGFBPs), which regulate the amount of free IGF-1 bioavailable to bind to the IGF-1 receptor (IGF-1R) to induce growth or survival signalling [19]. In metabolic syndrome, the amount of bioavailable IGF-1 is increased via hyperglycaemia-induced suppression of IGFBP synthesis and/or hyperinsulinaemia-induced promotion of hepatic growth hormone receptor expression and IGF-1 synthesis [17]. Elevated circulating IGF-1 is an established risk factor for many cancer types [19].

Downstream of both the insulin receptor and IGF-1R is the phosphatidylinositol-3 kinase (PI3K)/Akt pathway (Fig. 12.3), one of the most commonly altered pathways in epithelial cancers [20]. This pathway integrates intracellular and extracellular signals, such as growth factor concentrations and nutrient availability, to regulate cell survival and proliferation, protein translation, and metabolism. Activation of receptor tyrosine kinases, such as the insulin receptor or IGF-1R, stimulates PI3K to produce lipid messengers that facilitate activation of the Akt cascade [20]. Akt regulates the mammalian target of rapamycin (mTOR) [21], which controls cell growth, proliferation, and survival through downstream mediators. mTOR activation is inhibited by increased

Fig. 12.3. Obesity causes many metabolic disturbances (often characterized as metabolic syndrome), including insulin resistance, hyperinsulinaemia, and elevated bioavailable insulin-like growth factor-1 (IGF-1), which can activate receptor tyrosine kinase signalling through the phosphatidylinositol-3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway. An increase in steady-state signalling through this pathway can drive increases in cellular proliferation and protein translation, and reinforce cancer-associated metabolic reprogramming. Obesity is also associated with adipose remodelling, including the formation of crown-like structures and pro-inflammatory changes in the adipose secretome, including increased leptin and cytokines and decreased adiponectin. This typically results in increased inflammatory signalling through the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway and increased cyclooxygenase-2 (COX-2) activity. In addition, obesity often increases circulating levels of plasminogen activator inhibitor-1 (PAI-1) and vascular endothelial growth factor (VEGF), which can result in increased angiogenesis and decreased vascular integrity regulators, such as tissue plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA).



adenosine monophosphate (AMP)-activated protein kinase (AMPK) under low-nutrient conditions [22]. Increased activation of mTOR is common in tumours and many normal tissues from obese and/or diabetic mice [23], and specific mTOR inhibitors block the tumour-enhancing effects of obesity in mouse models [24–26]. Furthermore, both rapamycin (an mTOR inhibitor) and metformin (an AMPK activator) have been shown to block tumour formation in multiple animal models [27–31]. Interestingly, in some model systems rapamycin has also been shown to block inflammation associated with tumour formation [32].

Chronic inflammation: the role of adipose tissue

White adipose tissue (WAT) consists mainly of adipocytes, which serve to store neutralized triacylglycerides for use during periods of energy deficit. This is in contrast to brown adipose tissue, which generates body heat, particularly in neonate infants [33]. The secretome of white versus brown adipocytes differs markedly (Fig. 12.4). WAT is characterized by secretion of leptin, resistin, PAI-1, inflammatory cytokines, and free fatty acids, whereas brown adipose tissue is characterized by secretion of bone morphogenetic proteins, lactate (which induces uncoupling proteins), retinaldehyde, triiodothyronine (T3), and other factors associated with response to cold stress and/or increased energy expenditure [33]. Moreover, brown adipocytes produce adiponectin (but not leptin) and fibroblast growth factor-21, which can be anti-inflammatory and insulin-sensitizing [33]. Also contained in WAT are several types of stromal cells, including pre-adipocytes, vascular cells, fibroblasts, and a host of immune cells, such as adipose tissue macrophages [34].

The increase in adipose tissue mass associated with obesity drives chronic inflammation in at least three ways, depicted in Figs. 12.3 and 12.4 and summarized below.

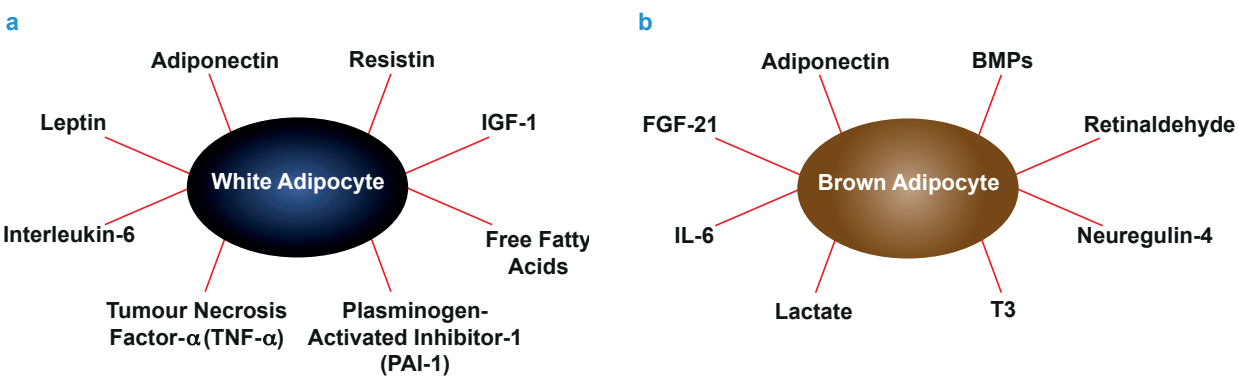
Altered adipose secretome

Leptin

Levels of leptin, a peptide hormone produced by adipocytes, are positively correlated with adipose storage and nutritional status, and leptin functions as an energy sensor. Leptin release from adipocytes signals to the brain to reduce appetite. In an obese state, WAT overproduces leptin and the brain becomes desensitized to the signal [35]. Leptin release is stimulated by several hormones and signalling factors, including insulin, glucocorticoids, TNF-α, and estrogen [36]. Leptin interacts directly with peripheral tissues, interacts indirectly with hypothalamic pathways, and modulates immune function, cytokine production, angiogenesis, carcinogenesis, and many other biological processes [36].

The leptin receptor is structurally and functionally similar to class I cytokine receptors, including in their ability to signal through the signal transducer and activator of transcription (STAT) family of transcription factors. STATs induce transcription programmes for several cellular processes, including cell growth, proliferation, survival, migration, and differentiation, and the activity of STATs is commonly deregulated in cancer [37].

Fig. 12.4. The secretomes of white versus brown adipocytes. (a) White adipocytes, when they accumulate triglyceride, produce more cancer-associated factors, such as leptin, resistin, insulin-like growth factor-1 (IGF-1), free fatty acids, tumour necrosis factor-α (TNF-α), and interleukin-6 (IL-6). They also decrease their production of adiponectin. (b) The secretome of brown adipocytes includes several factors involved in thermogenesis, decreased inflammation, normalized insulin sensitivity, and/or increased energy expenditure, such as adiponectin, bone morphogenetic proteins (BMPs), neuregulin-4, lactate, triiodothyronine (T3), retinaldehyde, and fibroblast growth factor-21 (FGF-21).



Adiponectin

Adiponectin is the most abundant hormone secreted from WAT. In contrast with leptin, levels of adiponectin are negatively correlated with adiposity. Adiponectin functions to counter the metabolic alterations associated with obesity and hyperleptinaemia by modulating glucose metabolism, increasing fatty acid oxidation and insulin sensitivity [38], and reducing IGF-1/mTOR signalling through AMPK activation. Adiponectin can also reduce pro-inflammatory cytokine expression and induce anti-inflammatory cytokine expression via inhibition of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [39]. Due to the anti-tumorigenic function of adiponectin, drugs mimicking its action are now coming to the fore as anticancer drugs and may pave the way in helping to treat obesity-related cancers [40]. Although leptin levels correlate with poor cancer prognosis and adiponectin levels correlate with favourable prognosis, it is the ratio of these two adipokines that may be important in cancer, rather than their absolute concentrations [41].

Sex hormones

Sex hormones have long been associated with obesity [42]. BMI is positively correlated with levels of estrone, estradiol, and free estradiol in postmenopausal women who are not taking hormone replacement therapy [43]. Increased estrogen levels are also observed in obese men [42, 44], whereas testosterone levels are significantly decreased [45]. Changes in sex hormones can have profound effects on the body, including menstrual disturbances, hirsutism, hypertension, erectile dysfunction, gynaecomastia, and increased adiposity [42]. Moreover, high estrogen levels are associated with a significantly increased risk of postmenopausal breast cancer [42, 43, 46], ovarian cancer [47], and endometrial cancer [48].

In premenopausal women, estrogen is synthesized mainly in the ovaries, whereas in postmenopausal women, endogenous estrogen is produced at peripheral sites. In obese postmenopausal women, adipose tissue is the main source of estrogen biosynthesis [43]. Circulating estrogens bind to either of the cytoplasmic estrogen receptors, ERα and ERβ, resulting in receptor dimerization and recruitment to the nucleus. ERα and ERβ can bind directly to DNA or to other transcription factors to induce expression of genes involved in a variety of cellular processes, including growth, proliferation, and differentiation [49]. The two receptors have opposite roles in cancer: ERα is mitogenic and ERβ is tumour-suppressive [50]. Obese postmenopausal cohorts are more consistently associated with increased risk of hormone receptor-positive than hormone receptor-negative breast cancers [51]. The increase in circulating estrogens and a greater risk of ER-positive breast cancer in obese women has led to several trials investigating the effectiveness of adjuvant therapy with aromatase inhibitors and ER antagonists (e.g. tamoxifen) in obese breast cancer patients [52]. Obesity may also play a role in development of male breast cancer, because aromatase in adipocytes converts androgens to estrogens. More than 90% of male breast cancer is ER-positive, and tamoxifen forms part of the standard of care [53].

Crown-like structures

Obesity further drives subclinical inflammation in visceral and subcutaneous WAT, characterized by rings of activated macrophages surrounding engorged or necrotic adipocytes and referred to as crown-like structures. This adipocyte–macrophage interaction results in a pro-inflammatory secretome from both cell types that activates the cellular transcription factor NF-κB, leading to increased levels of cytokines and other inflammatory factors, and triggers inflammation [54].

Adipose remodelling and lipid infiltration in other tissues

Stored triacylglycerides undergo lipolysis within the cytoplasm of adipocytes and are released into the bloodstream as free fatty acids during times of low substrate availability or heightened energy requirements [55]. Once in the circulation, free fatty acids can be used for β-oxidation by peripheral tissues to provide intermediates for both the citric acid cycle and oxidative phosphorylation to generate energy. In a diseased state such as metabolic syndrome or type 2 diabetes, WAT does not respond appropriately to changes in energy requirements, resulting in altered metabolic signalling characterized by elevated adipokine and cytokine production [56]. As stated above, cancer cells undergo a massive metabolic reprogramming to adapt to changing energy needs associated with the generation of daughter cells [11, 13]. In particular, there is a high demand for fatty acids for the formation of lipid bilayers in dividing cells. Excess WAT therefore promotes tumour cell proliferation through the provision of circulating fatty acids [57].

When lipid storage capacity in adipose tissue is exceeded, surplus lipids often accumulate within muscle, liver, and pancreatic tissue [58]. As a consequence, muscle dysfunction and hepatic and pancreatic steatosis can develop; each has been positively associated with insulin resistance and ultimately leads

to impairment of lipid processing and clearance within these tissues [58]. As a result of lipotoxic and inflammation-mediated adipocyte dysfunction, the liver and pancreas are unable to cope with the overflow of lipids and lipotoxic effects of free fatty acids [59]. Consequently, lipid intermediates impair the function of cellular organelles and cause further release of cytokines, which foster insulin resistance by activating intracellular kinases, thus impairing the cell's ability to respond to insulin.

Obesity is the most common cause of non-alcoholic fatty liver disease (NAFLD), a spectrum of diseases including variable degrees of simple steatosis, non-alcoholic steatohepatitis (NASH), and cirrhosis [60]. Simple steatosis is benign, whereas NASH is characterized by hepatocyte injury, inflammation, and/or fibrosis, which can lead to cirrhosis, liver failure, and hepatocellular carcinoma [61]. NAFLD is diagnosed when liver fat content is greater than 5–10% by weight in the absence of alcohol use or other liver disease [62]. About 80% of cases of cryptogenic cirrhosis present with NASH, and 0.5% of these patients will progress to hepatocellular carcinoma, a percentage that increases significantly with hepatitis C-associated cirrhosis [63].

NAFLD is one of the most common chronic diseases [64, 65], and the incidence in both adults and children is rising rapidly [65, 66]. Furthermore, the prevalence of fatty liver disease has increased concomitantly with the increase in childhood obesity during the past 30 years [66]. NAFLD is a multifactorial disorder linked to components of metabolic syndrome, including hypertriglyceridaemia, obesity, and insulin resistance [62]. Ultimately, hepatic steatosis leads to impairment of lipid processing and clearance in the liver. Lipotoxic and inflammation-mediated mechanisms have been suggested to be responsible for adipocyte dysfunction and remodelling of peripheral lipid storage capacities, resulting in release of free fatty acids and increased hepatic lipid burden [67]. In NAFLD, the liver is overwhelmed with excess lipids. The lipotoxic effects of free fatty acids and lipid intermediates impair the function of liver cell organelles by mechanisms that involve production of reactive oxygen species, endoplasmic reticular stress, activation of pro-inflammatory programmes, and eventually death of hepatic cells [68]. The accumulation of toxic lipids and the release of pro-inflammatory cytokines cause insulin resistance by activating JNK, PKC, and other kinases, thereby impairing insulin signalling [69]. Disturbed insulin signalling contributes to diminished fatty acid oxidation and assembly and secretion of very-low-density lipoprotein (VLDL) through inadequate regulation of peroxisome proliferator-activated receptor (PPARα and PPARγ) [70]. Activation of cellular defence programmes, specifically activation of NF-κB, is an important determinant for disease progression from steatosis to NASH [71]. Although those at risk of hepatocellular carcinoma currently make up a small proportion of the population, as the prevalence of obesity and type 2 diabetes continues to rise, this will become a more significant public health concern.

Pancreatic adipocyte infiltration and fat accumulation appears to be an early event in obesity-associated pancreatic endocrine dysfunction and can trigger pancreatic steatosis, non-alcoholic fatty pancreatic disease (NAFPD), and pancreatitis [72, 73]. In addition, "fatty pancreas" has been positively associated with visceral WAT mass and systemic insulin resistance [72, 73]. Together, pancreatic steatosis and NAFPD contribute to the already complex metabolic and inflammatory perturbations associated with obesity and metabolic syndrome.

Angiogenesis

As adipose tissue grows, so too does the need for new blood vessels. Angiogenesis is the outgrowth of new blood vessels from existing blood vessels and is mediated by factors such as VEGF, which can be produced and secreted by both adipocytes and tumour cells. VEGF is angiogenic, is mitogenic, and has vascular permeability-enhancing activities specific for endothelial cells [74]. Circulating levels of VEGF are increased in obese individuals, and expression of VEGF is associated with poor prognosis in several obesity-related cancer types [75]. Secretion of angiogenic factors induces local blood vessel development through interactions with proximal endothelial cells; release of VEGF into the circulation can interact with peripheral tissues and may also facilitate angiogenesis at tumour sites. In addition to providing adequate oxygen and nutrients to cells within the primary tumour mass, newly forming blood vessels presumably provide a route into the circulation for cells to metastasize to distal sites in the body. Excess VEGF may complicate treatment options for obese patients, because anti-VEGF therapies (e.g. bevacizumab) have reduced efficacy in obese colon cancer patients compared with non-obese individuals [76].

Another angiogenic factor, PAI-1, is a serine protease inhibitor produced by endothelial cells, stromal cells, and adipocytes in visceral WAT [77]. Increased circulating PAI-1 levels, frequently found in obese subjects, are associated with an increased risk of atherosclerosis and cardiovascular disease, diabetes, and several cancer types [77]. PAI-1, through its inhibition of plasminogen activators, regulates fibrinolysis and the integrity of the extracellular matrix [78]. Remodelling of the extracellular matrix is a key feature of invasive cancers

and is involved in the development of metastatic disease [79]. Therefore, PAI-1 is a potential anti-angiogenic target in some obese populations. However, caution should also be exercised when administering such treatments in obese patients, because the application of an anti-angiogenic therapy will induce hypoxia in the primary tumour and may encourage cells to metastasize, which is already a concern in obese patients.

Emerging mechanism linking obesity and cancer: the microbiome

An emerging field of research is the influence of the microbiome, the community of commensal, symbiotic, and pathogenic microorganisms that inhabit an individual, on obesity and related chronic diseases. In both humans and mice, two divisions of bacteria, the Bacteroidetes and Firmicutes, represent more than 90% of all phylogenetic types in the gut, although there are large differences between individuals at the species level [80]. The relative ratio of these two divisions is significantly altered with obesity, with a decrease in Bacteroidetes and a corresponding increase in Firmicutes, resulting in a microbiome with an enhanced ability to harvest dietary energy. This increased metabolic potential is transmissible between subjects: colonization of a germ-free mouse with the microbiota of an obese (versus lean) mouse leads to a significantly greater gain of fat mass, independent of energy intake [81].

Obesity is also associated with an overall reduction in gut bacterial diversity [82], and decreased bacterial richness has been linked to elevated systemic inflammation, measured by plasma C-reactive protein and white blood cell counts [83]. Furthermore, weight loss does not significantly improve C-reactive protein levels in obese subjects with low microbiome richness [84], suggesting that resistance to the inflammation-reducing effects of weight loss may be mediated by differences in microbiome richness. Other studies have demonstrated that high-fat feeding is accompanied by impairments in gut barrier function, including decreased gene expression for tight junction proteins and higher plasma levels of lipopolysaccharide, a component of the outer membrane of gram-negative bacteria [85]. Lipopolysaccharide has previously been shown to induce metabolic endotoxaemia, characterized in part by elevated infiltration of macrophages into adipose tissue and expression of pro-inflammatory cytokines [86]. Increased systemic inflammation is also apparent in mice fed high-fat diets, and these diet-related effects can be completely prevented by treatment with a broad-spectrum antibiotic [85]. Therefore, gut microbial dysbiosis and impaired barrier function associated with obesity can induce chronic systemic and adipose tissue inflammation. Given the known role of this type of inflammation in the progression of many cancer types [87], it is highly probable that obesity-induced perturbations of the gut microbiota are a contributing factor in the obesity–cancer link.

Key points

- Obesity is an established risk factor for many cancers.
- Obese cancer patients, relative to non-obese patients, often have poorer prognosis, are resistant to chemotherapies, and are more prone to developing distant metastases.
- Multiple mechanisms underlie the obesity–cancer link, and each hallmark of cancer is affected by obesity.
- Perturbations in systemic metabolism and inflammation, and the effects of these perturbations on cancer-prone cells, are a current research focus.
- Obesity-induced changes in the microbiome, and their impact on pro-tumorigenic metabolic and inflammatory signals, are an emerging research area.

Research needs

The association between obesity and many cancers is well established, but with the number of obese adults in the world rising towards 700 million, many important questions remain to be answered, including the following.

- Can the effects of chronic obesity on cancer risk or progression be reversed with weight loss? If so, what are the optimal weight-loss approaches to prevent obesity-related cancers? If not, can weight loss be combined with other interventions (anti-inflammatory agents or targeted interventions to normalize metabolism) to decrease the obesity-associated cancer burden?
- Can we eavesdrop on the cross-talk between adipocytes, macrophages, the microbiota, and epithelial cells to identify ways to disrupt the pro-tumorigenic signals coming from these interactions? This will require a transdisciplinary, systems approach to uncover new targets and intervention strategies.
- How does obesity increase cancer metastases, and what can be done about this?
- How does obesity impair the response to many cancer chemotherapeutic agents, and what can be done about this?

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