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Obesity and cancer: inflammation bridges the two

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Obesity is a growing public health problem and affects 35% US adults. Obesity increases the risk of many cancer types and is associated with poor outcomes. Clinical management of cancer patients has been essentially the same between normal weight and obese individuals. Understanding causal mechanisms by which obesity drives cancer initiation and progression is essential for the development of novel precision therapy for obese cancer patients. One caveat is that various mechanisms have been proposed for different cancer types for their progression under obesity. Since obesity is known to have global impact on inflammation, here we will summarize recent literature and discuss the potential of inflammation being the common causal mechanism to promote cancer promotion across cancer types.

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Introduction: obesity, inflammation, and immune alterations

Obesity, as defined in adults by a body mass index (BMI) of greater than or equal to 30, is a growing public health problem worldwide, particularly in Western countries. The world health organization has reported that 13% of adults over the age of 18 are clinically obese, totaling more than 600 million people. In the US 34.9% of adults (age >20) are obese [1]. It has been estimated that nearly 20% of deaths in US adults between 1986 and 2006 were related to obesity [2]. The health risks from obesity arise from its association with the increased risk of several diseases including hypertension, type 2 diabetes, cardiovascular disease, osteoarthritis, kidney failure, liver disease and several types of cancer [3,4]. The link between obesity and increased cancer incidence and cancer-related deaths has been well established over the last two decades and it has been estimated that 14% of cancer deaths in men and 20% in woman are attributable to obesity [5]. As a common factor for many chronic diseases, different mechanisms have been used to explain how obesity drives their progression. Interestingly, chronic inflammation, a phenotype associated with obesity, has been known to be major factor that contributes to the disease progression of the above chronic conditions.

Obesity-associated inflammation is first triggered by excess nutrients, and is primarily localized in specialized metabolic tissues such as white adipose tissue [6•], which acts as a major source of energy and is primarily composed of adipocytes. Adipocytes are endocrine cells that secrete a large range of cytokines, hormones and growth factors, referred to as adipokines, and specialize in the storage of energy as triglycerides in cytoplasmic lipid droplets [7•]. Excess nutrients leads to activation of metabolic signaling pathways including c-Jun N-terminal kinase (JNK), nuclear factor κ B (NFκB), and protein kinase R [8,9]. Activation of these pathways leads to an induction of low-level of inflammatory cytokines resulting in a low-grade inflammatory response [6•]. Excess nutrients and obesity also lead to the hyperplasia and hypertrophy of white adipose tissue adipocytes, as well as the extensive tissue remodeling and an increase in free fatty acids resulting in changes in adipokine production and a low-grade inflammatory response [10•,11]. Obesity also leads to increased endoplasmic reticulum stress resulting in activation of the unfolded protein response, which leads to activation of NFκB, JNK and increased oxidative stress, and in turn the upregulation of inflammatory cytokines [12]. These pathways all contribute to the initiation of obesity associated inflammation. While obesity associated inflammation is primarily localized in white adipose tissue, other tissues have been shown to have increased inflammation under obesity, including the liver, pancreas, and brain [13].

This low-grade inflammatory response associated with obesity leads to changes in immune cell infiltration and polarization in white adipose tissue [14]. In particular, macrophages are the major innate immune cells that are recruited to white adipose tissue under obesity and are one of the major sources of inflammatory cytokines in obese white adipose tissue [15]. The recruitment of

macrophages into obese white adipose tissue is mediated by a few different mechanisms [11]: Firstly, adipose tissue macrophages and adipocytes secrete a milieu of elevated levels of chemokines, including CCL2, CCL3 and RANTES/CCL5, which promote the recruitment of macrophages into obese white adipose tissue; secondly, obesity-induced adipocyte hypertrophy leads to increased adipocyte cell death, in turn recruiting macrophages to phagocytize the dead adipocytes; and finally, adipocyte hypertrophy and cell death leads to increased levels of free fatty acids (FFAs), which act as TLR4 agonists and likely ligands for nod-like receptors to induce an inflammatory response and recruitment of macrophages in white adipose tissue. These mechanisms work in concert to induce a large increase in adipose tissue macrophages in obese white adipose tissue.

In addition to the increased adipose tissue macrophages in white adipose tissue from obese individuals, white adipose tissue can also shift the polarization of macrophages, from an anti-inflammatory M2-like phenotype in lean white adipose tissue, to a more pro-inflammatory M1-like phenotype in obese white adipose tissue [16•]. This is partly due to the imbalance of obesity-related adipokines, that is, the change in leptin and adiponectin ratio. Obese white adipose tissue tends to have an increase in the production of leptin, which is pro-inflammatory, proangiogenic, and pro-proliferative, and a decrease in adiponectin, which is anti-inflammatory, antiangiogenic and anti-proliferative [17,18]. The increased leptin level leads to monocyte differentiation into macrophages and repolarization of adipose tissue macrophages. Recent studies have suggested that adipose tissue macrophages in obese white adipose tissue may not be classically activated M1 macrophages. Using proteomic and other techniques, Kratz *et al.* has recently shown that adipose tissue macrophages from obese humans and animals have a distinct phenotype that express inflammatory cytokines associated with M1 macrophages but lacked other characteristics of M1 macrophages [19••]. The pro-inflammatory adipose tissue macrophages in obese white adipose tissue recruit other immune cells, and along with adipocytes secrete more than 50 different cytokines, hormones and chemokines, all of which contributing to the chronic inflammation associated with obesity [10•,11].

The impact of obesity on immunity is not limited to macrophages. Recent literature have identified a panel of immune alterations, including those from both adaptive and innate immunity, that are impacted by obesity, including the increased Th1 cell response [20], CD8 cytotoxic T cell response [21], natural killer (NK) cells [22], etc. as well as the decreased number of regulatory T cells [23]. The interaction between these cells in adipose tissues is very complex. For example, CD8 T cells have been shown to be the early event showing up in adipose tissue of diet-induced obesity, which plays an important role in further recruiting M1 macrophages and subsequent inflammation [21]. Th1 cytokines are also the known activator of M1 macrophages in general and this axis has been established in adipose tissue of obese individual and contributes to insulin resistance [24•].

Among all the immune alterations, obesity-associated inflammation is of particular interest because the pathophysiology of many of the major human diseases associated with obesity, including type 2 diabetes, cardiovascular disease, and cancer, have been linked to inflammation [17,25,26]. Here we will discuss the effect of obesity on, and the role of obesity-associated inflammation in the carcinogenesis and disease progression of several major types of cancer.

Obesity and cancer

Breast cancer

Breast cancer is the second leading cause of cancer-related death among women in the US (NCI SEER data) [27]. On the basis of the expression of estrogen receptor (ER), progesterone receptor (PR), and HER2, invasive breast cancer can be further classified as luminal type, HER2-positive, and triple negative breast cancer. There is a well-established increased risk of developing ER+ luminal breast cancer in postmenopausal obese women [28,29]. A recent meta-analysis of 25 studies found that obesity increased the risk of developing breast cancer in a nonlinear dose–response in postmenopausal breast cancer [30••]. Two recent meta-analysis have shown that obesity is associated with a worse clinical outcome in both premenopausal and postmenopausal women with a higher relative risk of total mortality in obese premenopausal patients than postmenopausal patients [31••,32••]. In addition, a retrospective review has shown that obesity is linked to the advanced TMN stage at time of diagnosis and a worse clinical outcome in both premenopausal and postmenopausal women [33]. Recent studies have also shown that obesity is associated with an increased prevalence of triple negative breast cancer, the most aggressive subtype of breast cancer; and it may serve, along with menopausal status, as a predictor for the sensitivity to neoadjuvant chemotherapy in triple negative breast cancer [34,35••]. A recent prospective study has shown a link between obesity and the development of metastasis in breast cancer patients. This report also indicated that non-obese patients responded better to first-line metastatic chemotherapy treatment than obese patients [36••]. Even though there are some other studies that have concluded differently on prognosis using smaller number of patients [28,37], it is a general recognition that obesity is associated with bad prognosis in breast cancer patients.

There have been several hypotheses to explain how obesity promotes breast cancer development and progression. However, there have been no studies showing a mechanistic link between obesity and breast cancer development or progression. One of the reasons for this is

possibly the lack of good models for studying the effect of obesity on breast cancer. While FVB/N and Balb/C mice are permissive to breast cancer, they are relatively resistant to obesity. In contrast, C57BL/6 mice are susceptible to diet-induced obesity, but have very few breast cancer models available [38].

Adipose tissue derived estrogens

One possible link between obesity and the increased incidence of ER+ breast cancer in postmenopausal women is the elevated level of circulating estrogens from increased aromatization of androgens in adipose tissue [39]. This hypothesis, however, fails to fully explain the relationship between body mass and breast cancer incidence and poor clinical outcome, as the relationship is present in ER-negative breast cancers [34,36••]. Also, some recent studies have indicated that circulating estrogens may protect against the development of breast cancer in obese women [40].

Metabolic syndrome, insulin and IGF-1

Another hypothesis is that obesity-associated metabolic syndrome results in elevated levels of insulin and insulin-like growth factor 1 (IGF-1) [41•]. Studies have shown that obesity-associated metabolic syndrome and type 2 diabetes, is associated with an increased risk of breast cancer [42]. Epidemiological studies have shown a correlation between circulating levels of IGF-1 and the development of ER+ breast cancer [43]. IGF-1 is known to act as a mitogen in breast epithelial cells and is important in mammary gland development. Binding of IGF-1 to its receptor, IGF-1R, leads to activation of PI3K/AKT/mTOR and mitogen activated protein kinases (MAPKs) signaling [44]. IGF-1 signaling also induces activation of ERα, via activation S6 kinase down stream of mTOR, leading to enhanced estrogen signaling and the promotion of breast cancer [45]. However, the genetic evidence supporting insulin/IGF-1 signaling being the causal factors for obesity-driven cancer progression is lacking. It is known that the development of obesity-associated metabolic syndrome and insulin resistance is caused by obesity-associated inflammation [25], underscoring the potential importance of inflammation as the critical factor for obesity-driven cancer progression.

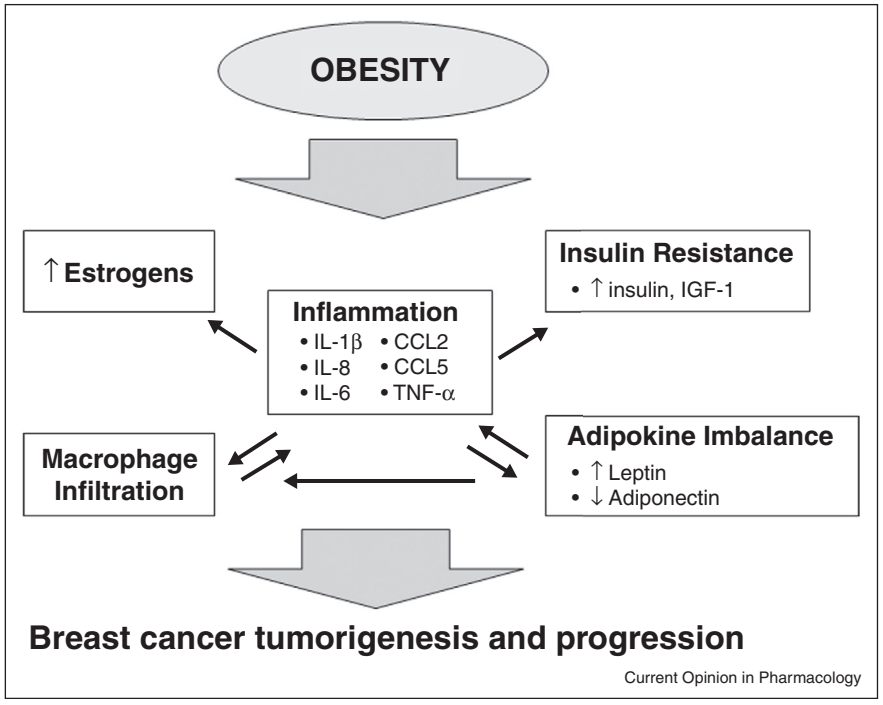
Balance between leptin and adiponectin

Other studies have looked at the role of elevated levels of leptin and decreased levels of adiponectin in obese patients. Leptin is known to be pro-tumorigenic and to act directly on breast epithelial cells to promote proliferation, by promoting estrogen signaling, activation of MAPKs and STAT3 signaling, and inhibition of apoptosis by activation of AKT signaling [46]. Leptin is also pro-angiogenic and has been shown to promote epithelial–mesenchymal transition (EMT) in breast cancer and to promote the self-renewal of mammary stem cells and breast cancer stem cells [47•,48•,49•]. Adiponectin has been shown to be anti-tumorigenic in the breast, as systemically low level of adiponectin is associated with increased lymph node metastasis and more aggressive tumors [50]. Adiponectin can inhibit the proliferation of breast cancer cells by inhibiting MAPK and AKT signaling, promoting apoptosis, and downregulation of metastatic properties by inhibiting mTOR signaling via activation of AMPK [51]. Thus the shift in leptin and adiponectin balance is thought to play a role in obesity-associated breast cancer development and progression. Interestingly, leptin signaling is also involved in eliciting a pro-inflammatory circuit to promote cancer progression. Crosstalk between IL-1, leptin and notch has shown to promote proliferation, migration and upregulation of vascular endothelial growth factor and receptor 2 in breast cancer [52••]. The genetic evidence of leptin signaling in obesity-driven breast cancer progression is established using animal models lacking either leptin or its receptor, but conclusions drawn from these results are debatable due to the impact of leptin signaling on normal mammary gland development and tumorigenesis in non-obese mice [53].

Inflammation

A growing amount of evidence supports a link between obesity-associated inflammation and breast cancer incidence and progression. Adipose tissue in the breast has been shown to be involved in obesity-associated inflammation, with increased adipocyte hyperplasia and cell death, cytokine production and macrophage infiltration [54]. Transcriptomic and Gene Set Enrichment analysis of data from luminal breast cancer patients has shown that obesity is associated with the enrichment in genes and pathways associated with inflammation and immune cell trafficking in obese patients compared to non-obese patients [55••]. These pathways were also enriched in obese *MMTV-TGFα/α* mice, a model for luminal breast cancer in which obesity promotes tumor progression. A recent report has shown that interaction between adipocytes and breast cancer cells leads to the production of inflammatory cytokines and increase the number of cancer cells with tumor-forming capabilities [56••]. The other hypotheses for the link between obesity and breast cancer as discussed above have also been linked with inflammation (Figure 1). IL-6, TNF-α, and prostaglandin E2, which are all elevated in obese patients, have been shown to increase the expression of aromatase and the production of estrogens in both adipose tissue and breast tissue [57,58]. As mentioned above, obesity-associated metabolic syndrome and elevated insulin levels are tightly linked with inflammation [25]. Leptin is also known to induce the expression of pro-inflammatory, pro-tumorigenic cytokines in macrophages, including IL-1, IL-6 and TNF-α [59]. Other studies have shown the concomitant elevation of IL-1β and leptin with increased body mass in rats that drives the growth of mammary epithelium [60]

Figure 1



Obesity promotes breast cancer. Obesity leads to macrophage infiltration and inflammation in white adipose tissue in the breast. This is associated with the upregulation of several pro-inflammatory and pro-tumorigenic cytokines. Inflammatory cytokines can promote the upregulation of aromatase and increased production of estrogens in stromal cells of the breast. Obesity-associated inflammation is also involved in the development of insulin resistance and increased IGF-1, which is a mitogen for breast epithelial cells. Obesity also leads to an increase in leptin and a decrease in adiponectin. Leptin expression is induced by inflammatory cytokines and can induce expression of inflammatory cytokines leading to increased inflammation. Leptin can promote breast cancer through increased proliferation, survival and angiogenesis. All of these factors likely contribute to a pro-tumorigenic microenvironment that promotes breast cancer.

and that leptin expression in pre-adipocytes can be induced by IL-1 and TNF-α secreted from ATM [61].

Many studies have demonstrated that elevated levels of inflammatory cytokines including IL-6 [62], TNF-α{To, 2013 #218}, IL-8 [63] are associated with increased breast cancer tumor growth and poor patient outcomes. These same cytokines have all been shown to be upregulated in obese white adipose tissue [10•,64]. While there is no direct evidence linking high levels of cytokines in obese patients to increased breast cancer incidence and poor outcome, there is plenty of correlative evidence suggesting a link. Gene ontology analysis of normal breast tissue has shown that pathways involving IL-6, IL-8 are enriched in obese patients, and that IL-6 from adipose stromal cells can promote breast cancer cell proliferation and migration [54,65•]. Obese ovariectomized mice, in which there was increased breast cancer tumor growth in a syngeneic transplant model of Py230 breast cancer cells, had elevated levels of TNF-α in the mammary gland and TNF-α could induce Py230 growth *in vitro* [66]. However, while there is correlative evidence to suggest a possible role of elevated cytokines in obesity associated breast cancer incidence and progression, a recent study found no correlation between circulating levels of IL-6 and TNF-α and breast cancer risk in postmenopausal women [67]. While there is a potential connection between obesity-associated inflammation and breast cancer, it is yet to be determined the causal mechanism of how inflammation contributes to obesity-driven breast cancer progression. Future studies using genetically modified mice deficient in these cytokine pathways and immune cell types will need to be done to further define the requirement of inflammation in obesity-driven breast cancer progression.

Colorectal cancer

The association between BMI and colorectal cancer incidence has been evaluated in several epidemiological studies, and it has been shown that the risk and incidence of colorectal cancer increase with BMI [4,68]. A meta-analysis of 30 prospective studies found an increased risk of colorectal cancer in obese men and women, though the association was higher in men [69••]. While the relative risk of colorectal cancer with obesity is moderate, due to the high prevalence of obesity it is estimated that 35.4% of colorectal cancer cases in men and 20.8% in women in the U.S. are attributable to obesity [70]. The relationship between body mass and colorectal cancer development

has also been studied in animal models, where both APC^{min} mice, a model for spontaneous colorectal cancer, and mice treated with azoxymethane, a carcinogen used to induce colorectal cancer, fed a high-fat diet had increased colon polyp formation [71,72••].

The dysregulation of leptin and adiponectin during obesity may also play a role in obesity-associated colorectal cancer. A few epidemiological studies have examined the relationship between levels of circulating leptin and colorectal cancer risk, finding that high levels of leptin are associated with an increased risk of colon cancer, but not rectal cancer, in men and no association in women [73,74]. Leptin has also been shown to promote proliferation, survival and invasiveness of colon cancer cells through activation of MAPKs, PI3K, NF-κB and STAT3 signaling [75–77]. Inflammation and inflammatory cytokines are known to play a critical role in the development of both colitis-associated and sporadic colorectal cancer [78,79]. Colonic TNF-α expression is elevated in HFD-fed mice [80], and TNF-α is potent inducer of IL-6 which is known to play a role in promoting colorectal cancer [81]. A recent study found that leptin stimulated the production of IL-6 and TNF-α and promoted proliferation in colon epithelial cells in an mTOR-dependent manner [82••]. Adiponectin can inhibit colorectal cancer cell growth through activation of AMPK [83], and loss of adiponectin enhances development of both colitis-associated colorectal cancer and in APC^{min} mice [84]. Furthermore, epidemiological studies have found that circulating levels of adiponectin is inversely correlated with risk of colorectal cancer [85]. However, other studies have found no significant correlation between adiponectin levels and colorectal cancer risk [86].

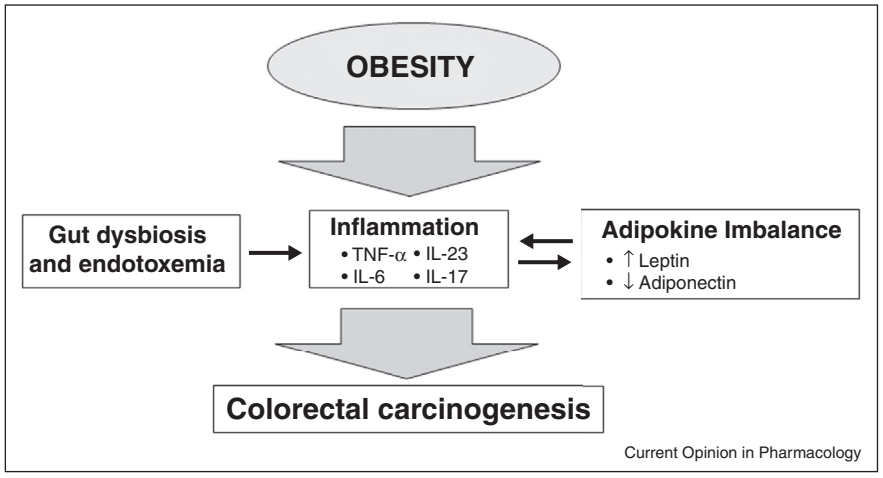
A growing amount of evidence has linked colorectal cancer to intestinal microbiota and dysfunction of the intestinal barrier [87,88•]. Studies have also shown that altered gut microbiota is present in patients with adenomas of the colon, suggesting a role for dysbiosis in the early stages of colorectal cancer development [89,90]. The development of colorectal cancer in animal models has been shown to be linked to leakage of the intestinal barrier and activation of pro-inflammatory tumor promoting IL-23/IL-17 signaling [91]. A previous study also supported a role for intestinal barrier dysfunction and subsequent endotoxemia in the development and progression of colorectal cancer in APC^{min} mice [92]. Obesity is also associated with changes in the gut microbiome and dysfunction of intestinal barrier [93]. Pfalzer *et al.* recently reported that genetically obese or diet-induced obese (mice fed a HFD) APC^{1638N} colon tumor-bearing obese mice had altered gut microbiome compared to non-obese mice [94••]. They identified a depletion of *Parabecteroides distasonis*, which has been shown to be anti-inflammatory in the gut and to reduce dextran sodium sulfate-induced inflammatory cytokines and colitis in mice [95]. HFD-fed mice have also been shown to have increased levels of circulating lipopolysaccharide (LPS), a marker of intestinal barrier dysfunction and endotoxemia, which has been shown to promote colorectal cancer development [96]. Another study has suggested that HFD-fed mice have increased colorectal cancer development primarily due to gut dysbiosis associated with obesity. They showed that fecal transfer from obese Kras (G12Dint) mice to normal-weight mice was sufficient to increase colorectal cancer development and progression [97••]. These studies indicate that inflammation due to obesity-mediated gut dysbiosis and intestinal barrier dysfunction, along with changes in the balance between leptin and adiponectin, plays a role in the increased risk of colorectal cancer in obese individuals (Figure 2).

Liver cancer

Liver cancer is the fifth most common type of cancer in men and the ninth most common in women worldwide, and is the second most common cause of cancer related death due to a yearly fatality ratio that is close to 1 and a 5 year-survival of less than 10% [98]. Hepatocellular carcinoma accounts for 75-90% of liver cancer, and usually arises in the context of chronic liver disease [98]. Globally, hepatitis B or C viral (HBV and HCV) infections are the most common cause of chronic liver disease and HCC [99]; however, in western countries non-alcoholic fatty liver disease (NAFLD) is the most common type of chronic liver disease and NAFLD-related cirrhosis is predicted to be the most common reason for liver transplantation within a decade [100]. NAFLD encompasses a range of progressive liver disease from hepatic steatosis to non-alcoholic steatohepatitis (NASH) which ultimately leads to cirrhosis [98,101]. NAFLD, NASH and NASH-related cirrhosis are associated with increased risk of HCC and studies have shown that about 2.6% of people with NASH-related cirrhosis develop HCC [102]. While cirrhosis is a major risk factor for HCC, a growing amount of evidence has shown that HCC can develop from individuals with NAFLD without the presence of cirrhosis [103]. The development of HCC in patients with non-cirrhotic NAFLD is problematic because non-cirrhotic NAFLD is often asymptomatic. As a result, these patients are not monitored for the development of HCC and HCC are commonly presented symptomatically with a larger tumor burden. Such patients had a median survival of just 7.2 months [104••].

The development of NAFLD is closely correlated with obesity, obesity-associated metabolic syndrome and type 2 diabetes [105•]. About one-fourth of the population in the US have NAFLD, 8% of which progress into NASH which progresses into cirrhosis with 25% frequency [106]. The rate of NAFLD is much higher in obese individuals and type 2 diabetics. One study in Europe found that 94% of obese individuals had NAFLD, with 25% presenting some form of NASH [107]. As a major risk factor for the

Figure 2



Obesity and colorectal cancer. Obesity is associated with changes in the intestinal microbiome and dysfunction of the intestinal barrier. Gut dysbiosis and endotoxemia promotes inflammation through the upregulation inflammatory cytokines, particularly IL-6, TNF-α, IL-17 and IL-23, which promote CRC carcinogenesis. Obesity-associated changes in leptin and adiponectin also leads to increased inflammation and CRC carcinogenesis.

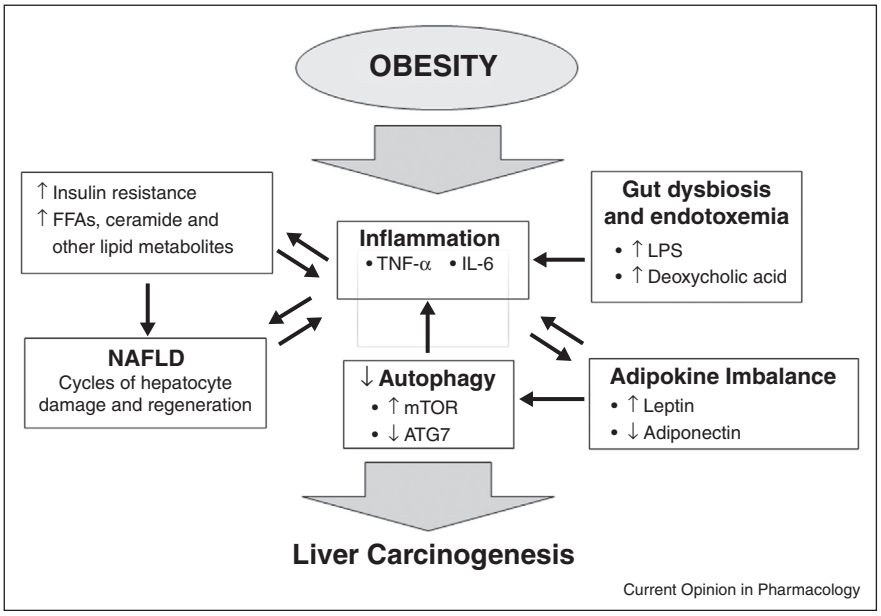
development of NAFLD and NASH, obesity is associated with an increased risk of developing HCC [4]. A meta-analysis of 11 cohort studies found that obesity was associated with increased HCC, with a relative risk of 1.89 [108••]. One study found that the risk of death from liver cancer was 4.5 times higher in men with a BMI of greater than 35 compared to men with a normal BMI [4]. Given its prevalence, obesity, at least in the US and other western countries, is likely to become the leading risk factor for HCC [109].

Excess caloric intake can result in increased triglyceride production in the liver that is greater than the ability of the liver to export, leading to accumulation of triglycerides in the form of lipid droplets in parenchymal hepatocytes and hepatic steatosis (the beginning stages of NAFLD) [105•]. Obesity and lipid accumulation in liver leads to an increase in the levels of free fatty acids and other lipid metabolites, such as diacylglyceride and ceramide, which results in hepatocyte injury, endoplasmic reticulum (ER) stress and inflammation [105•,110••]. These factors all contribute to a cycle of hepatocyte cell death and compensatory proliferation and inflammation that result in the progression of hepatic steatosis to NASH and eventually NASH-related cirrhosis [109,110••]. Increased levels of IL-6 and TNF-α have been shown to be major drivers of cell proliferation in NAFLD and NASH, and play important roles in the development of obesity-associated HCC [111,112]. These cycles of cell death and regeneration and the associated cell proliferation and inflammation create a pro-tumorigenic microenvironment that promotes the development of HCC (Figure 3) [98].

Another mechanism involved in the progression of NAFLD to HCC in obese individuals is again the imbalance between leptin and adiponectin. Apart from its involvement in obesity-associated insulin resistance and inflammation, leptin can induce pro-tumorigenic signaling in the liver, including STAT3 and PI3K/Akt [113]. Of particular importance in HCC, is activation of PI3K/Akt and its downstream target mTOR, which has been shown to be active in about 40% of HCC patients [114]. The activation of mTOR by leptin and other factors in NAFLD leads not only to the proliferation and pro-survival signaling, but also to the inhibition of autophagy [115]. Autophagy is important for preventing oxidative stress by removing damaged organelles, including mitochondria, and the resolution of inflammation [116]. Thus the inhibition of autophagy leads to increased oxidative stress and inflammation resulting in liver damage [115,117]. Obesity also suppresses autophagy through the downregulation of autophagy related gene 7 (ATG7), which is associated with insulin resistance and liver damage [118]. Adiponectin has an antagonistic effect to leptin. It can inhibit the development of HCC by reducing activation of STAT3 and PI3K through activation of AMPK and upregulation of SOCS3 [119,120].

As mentioned previously obesity is associated with dysbiosis of the gut and increased intestinal permeability and endotoxemia. Bacterial products such as LPS can promote liver inflammation via the upregulation of inflammatory cytokines from Kupffer cells and liver-infiltrating macrophages which can promote the development of HCC [121]. A recent report by Kumar *et al.* indicated that obesity promoted hepatocarcinogenesis in the HCV

Figure 3



Obesity and liver cancer. The development of liver cancer in obese patients is associated with chronic liver damage and NAFLD. Obesity leads to an accumulation of triglycerides in the liver (hepatic steatosis), which leads to increased free fatty acids and other lipid metabolites and in turn to hepatocyte cell death and regeneration. This process is associated with liver inflammation. Upregulation of leptin and down regulation of ATG7 result in decreased autophagy that leads to increased inflammation and oxidative stress. Gut dysbiosis and endotoxemia leads to increased inflammation. Cycles of liver damage and regeneration and the associated inflammation creates a microenvironment that promotes the development liver cancer.

oncogene NS5A-transgenic mice via the activation of TLR4 by LPS [122]. Activation of TLR4 by LPS led to activation of Nanog which cooperates with leptin-induced STAT3 to upregulate TWIST in $CD133^+$/$CD49f^+$/$Nanog^+$ cells, thought to be tumor-initiating cells in alcohol-associated HCC [123]. Obesity-associated dysbiosis also contributes to the elevated level of deoxycholic acid, which can promote the secretion of inflammatory cytokines in hepatic stellate cells and promote the development of carcinogen-induced HCC [124].

Other cancers

Obesity is also associated with increased risk and progression of several other types of cancer. Obesity is associated with an increased risk of pancreatitis [125] and pancreatic cancer [126], as well as the increased mortality in pancreatic cancer patients [127]. The mechanisms by which obesity promotes pancreatic cancer is not completely known; however, they likely involve obesity-associated inflammation, insulin resistance, increased infiltration of macrophages and immunosuppressive cells, and dysregulation of autophagy [128–130]. Obesity is also associated with the incidence and mortality of endometrial and ovarian cancer [131,132]. Obesity likely promotes endothelial cancer through increased insulin/IGF signaling, increased estrogens, chronic inflammation and increased leptin mediated activation of PI3k/Akt/mTOR signaling [133,134]. Obesity is also associated with esophageal cancers, through due to a lack of good animal models, more studies will need to be done to verify a link between obesity and esophageal cancer and to identify a mechanism [135].

Obesity, inflammasome activation and cancer

One major source of inflammation in obese white adipose tissue is inflammasome activation in ATM. Inflammasomes are multiprotein complexes that activate IL-1β and IL-18 via Caspase 1 (Casp-1)-mediated cleavage in response to pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). Inflammasomes consist of a NOD-like receptor, NLRP1, NLRP3 or NLRC4, or Pyrin family protein AIM2, the adapter protein ASC and Casp1 [136,137]. NLRP3 inflammasome activation and IL-1β have been shown to be involved in obesity associated adipose tissue inflammation, insulin resistance and type 2 diabetes [138,139]. Inflammasomes have also been shown to play a complex and tissue specific role in cancer [136,140]. IL-1β has been shown to promote proliferation and invasion of colon cancer cells [141]. Polymorphisms in the *IL1B* gene is associated with breast cancer progression and prognosis [142], and IL-1β is also upregulated in stromal cells in IDC of the breast compared to DCIS and is associated with a more aggressive phenotype [143,144].

Although there is no evidence for the role of inflammasome activation in obesity-associated cancer, there is evidence that IL-1β may play a role. Studies have shown that the inflammatory effect of leptin is dependent of IL-1β, as they do not occur in IL-1β$^{-/-}$ mice [145]. Furthermore, as mentioned earlier, IL-1β is elevated with increased body weight in obese rats and can promote expansion of mammary epithelium [60]. In a recent study, Arendt *et al.* found that interactions between adipocytes and macrophages via an IL-1β/CCL2/CXCL12 signaling nexus, promotes breast cancer angiogenesis and progression under obesity [146••]. Inflammasome activation and IL-1β has been shown to be a driver of obesity-associated insulin resistance and type II diabetes, which is an independent risk factor for the development of obesity-associated cancer including breast, liver, and pancreatic [42,104••,147]. Inflammasomes have also been shown to play a role in the development of pancreatitis, an important risk factor in the development of pancreatic cancer [148,149]. As such, an examination of the role of inflammasomes in obesity-associated cancer is warranted.

Perspective

Emerging evidence indicates that obesity-associated chronic inflammation is a cancer-promoting event, which is largely attributable to the innate immune cells especially macrophages. A potential paradox here is here that obesity-associated adipose tissue tends to accumulate M1-like polarized macrophages, the classic type of anti-tumor macrophages regularly described in the cancer literature. The pro-inflammatory microenvironment in the obesity-associated adipose tissue also accumulates the classic anti-tumor Th1 and CD8 T cells. Recent studies have shown that macrophage polarization is complex existing of a spectrum of polarization, with most tissue macrophages being somewhere between the extremes of an M1 and M2 polarization [150••]. Data also suggest that individual macrophages within a tissue vary widely and that polarization changes based on signaling from the tumor microenvironment [150••]. Therefore, one potential explanation could be that changes in the microenvironment during tumor development change adipose tissue macrophages from a more M1-like phenotype, to a more tumor-promoting M2-like like stage under obesity. It is likely that there are significant difference between the microenvironments from obese adipose tissues and obese tumor tissues. A side-by-side profiling of immune cell composition, cytokine production profile, and effector immune cell function within adipose tissues versus tumor tissues should be performed in order to draw some meaning information.

Nevertheless, obesity increases the risk of developing several different types of cancer and is associated with a worse clinical outcome. The mechanisms by which obesity promotes caner have been proposed in a tissue-specific manner in most of the studies and involve the interplay between different signaling events. However, the underlying theme is the obesity-associated inflammation, which is known to promote the progression of several types of cancer described above and likely in some other cancer types as well. More studies need to be de done to identify causal mechanisms of obesity-associated cancers and to identify therapeutic targets to better treat obese cancer patients. Given the role of inflammation in obesity-associated cancers, a likely place to start would be anti-inflammatory therapies in obese patient populations.

Conflict of interest statement

Nothing declared.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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