Biological Mechanisms for the Effect of Obesity on Cancer Risk: Experimental Evidence

Mauricio Berriel Diaz, Stephan Herzig and Tobias Schafmeier

Abstract

Multiple epidemiological studies demonstrated that overweight and obesity significantly increase the risk of several types of cancer. As the prevalence of obesity is dramatically rising, it is expected that it will represent one of the major lifestyle-associated risk factors for cancer development in the near future. Numerous recent studies expanded knowledge about key players and pathways, which are deregulated in the obese state and potentially promote cancer initiation, progression and aggressiveness via remote and local effects. These players include (but are not limited to) insulin/IGF, adipokines and inflammatory signaling molecules as well as metabolites. Nevertheless, the detailed mechanisms linking obesity and malignant transformation at the systemic, cellular and molecular level still demand further investigation. Additionally, dysfunctional molecular metabolic pathways appear to be specific for distinct cancer entities, thereby yet precluding definition of a common principle. This chapter will present an overview of the current knowledge of molecular nodes linking obesity and cancer and will briefly touch upon potential therapy options addressing metabolic cancer etiologies.

M. Berriel Diaz, S. Herzig and T. Schafmeier contributed equally to this chapter.

M. Berriel Diaz · S. Herzig (✉) · T. Schafmeier
Institute for Diabetes and Cancer, Helmholtz Center Munich, Neuherberg, Germany
e-mail: stephan.herzig@helmholtz-muenchen.de

M. Berriel Diaz · S. Herzig · T. Schafmeier
Joint Heidelberg-IDC Translational Diabetes Program, Inner Medicine I,
University Hospital Heidelberg, Heidelberg, Germany

S. Herzig
Chair Molecular Metabolic Control, Medical Faculty,
Technical University Munich, Munich, Germany

T. Pischon and K. Nimptsch (eds.), *Obesity and Cancer*, Recent Results
in Cancer Research 208, DOI 10.1007/978-3-319-42542-9_12

Keywords
Inter-tissue crosstalk · Adipokines · Hormone signaling · Metabolic inflammation · Cancer metabolism

1 Introduction

The worldwide prevalence of overweight and its severe form obesity has reached pandemic dimensions with nowadays 500 million people being obese. In addition to its negative impact on quality of life and physical fitness, obesity commonly progresses into deleterious and often fatal pathologies, including type 2 diabetes, cardiovascular diseases and several types of cancer [1–3].

A causal connection between adiposity and increased cancer risk has been hypothesized based on obvious evidence from multiple epidemiological studies [4]. Notably, the tumor-promoting effects of excess body weight vary between distinct cancer entities and genders [4]. Additionally, several components of obesity might be independent risk factors, including elevated body weight per se as indicated by the BMI, but also weight gain and body fat distribution [5–8]. Thus, multiple mechanisms appear to be involved in obesity-associated cancer development.

Already in the early 1950s, first experimental evidence for an obesity-driven promotion of breast cancer appearance resulted from animal studies [9]. Numerous studies have since then been performed, which contributed significantly to understanding the risk connection between increased body weight and tumor development. However, a universal concept mechanistically defining the metabolic etiology of cancer still seems to be far from being achieved. As numerous players have been identified to date, it is questionable that a general mechanism exists which can explain the interconnection of obesity and cancer. It is rather very likely that the collective of pathophysiological changes in body homeostasis that occur during obesity cumulatively increase cancer risk. In essence, these changes can be grouped into altered inter-tissue cross talk on the one and generation of a tumor-promoting metabolic profile on the other hand. As a consequence, several hormones and metabolites display abnormal levels in the circulation and in the tumor microenvironment during obesity, eventually promoting tumor cell growth and invasiveness.

In this chapter, we will review the current state of the art, concerning the pathophysiological alterations caused by adiposity, which are potential molecular mediators of metabolic tumor promotion.

2 Tissue Communication

Communication between tissues and cells in our bodies occurs via hormones, cytokines and metabolites that are sensed through a variety of cellular mechanisms. Inter-tissue cross talk is vital for proper function of a biological system. As a consequence, dysfunction of tissue communication precipitates into various diseases.

Obesity primarily affects the white adipose tissue, which faces the challenge of dealing with a constant energy surplus and thus lipid overload of the adipocytes and eventually pathological expansion and cell death. Beside the adipocyte fraction, the tissue consists of several cell types with distinctive functions, as a whole summarized as stromal vascular fraction (SVF). The SVF, which contains, e.g., progenitor cells as well as cells of the immune system, has specific functions for adipose tissue integrity and thus is crucial for energy homeostasis. Dysfunctional adipocytes exert effects on cells of the SVF, such that the function of both adipose tissue fractions is compromised during obesity. The pathological consequences of adipose tissue dysfunction and their implications for cancer are outlined below.

2.1 Adipose Tissue

2.1.1 Endocrine Effects of Adipose Tissue

Adipose tissue is not considered being solely a calorie-storing depot. Nowadays it is seen as a huge endocrine organ that secretes a multitude of bioactive factors (adipokines), thereby locally and remotely regulating energy homeostasis on multiple levels [10]. In an obese setting, the body fat mass is not only markedly increased, but adipose tissue becomes also functionally impaired upon overloading of adipocytes with lipids and massive invasion of immune cells. As a result, adipose tissue dysfunction manifests in an altered signature of adipokines, particularly in visceral adipose tissue. Changes in the adipokine profile during obesity are exemplified by elevated release of leptin, resistin and pro-inflammatory cytokines, as well as reduced secretion of adiponectin [11]. Strikingly, certain cancer cells express adipokine receptors in high amounts and are therefore particularly responsive to an altered adipose secretome. The molecular pathways affected by adipokine signaling and their implications for tumor development, progression and metastasis thus required further discussion.

Leptin

Leptin is a 167 amino acid peptide hormone that activates anorexigenic and inhibits orexigenic neurons in the hypothalamus, and increases the sympathetic tone, thereby controlling food intake and energy expenditure, respectively [12]. Loss-of-function of one of the genes encoding either leptin (*OB*) or its receptor (*LEPR, OB-R*) results in severe hyperphagia in mice and men, and consequently leads to development of extreme obesity [13]. Leptin levels in the blood are

proportional to the amount of (visceral) adipose tissue. As a consequence of leptin resistance during obesity, the production and secretion of leptin are disproportionately increased, thereby precipitating in a vicious circle of progressively aggravating hyperleptinemia.

The leptin receptor is abundant in a number of peripheral tissues. Notably, malignant cells frequently express particularly high levels of OB-R. In line with this, specific SNPs in the leptin receptor gene were linked to an enlarged risk of certain cancers [14], altogether highlighting the significance of leptin signaling for tumor development. Despite being obese, leptin-deficient *ob/ob* mice were protected from developing specific types of cancer, whereas other tumors occurred more frequently, indicating that leptin has a role in a specific subset of obesity-associated cancer entities [15].

Epidemiologic studies indicate a connection between elevated circulating leptin levels and occurrence of (postmenopausal) breast cancer [16]. Furthermore, plasma leptin concentration is significantly correlated with poor clinical outcome in breast cancer [17]. Importantly, leptin plays a role in development of the mammary gland and the leptin receptor is thus highly expressed in mammary epithelia [18]. In the majority of human mammary tumors, leptin as well as leptin receptors is overexpressed, which provides an explanation for the increased breast cancer risk in obese women [18, 19]. Concordantly, ablation of leptin signaling suppressed tumor development in murine breast cancer models [20–22]. Given that obesity is a risk factor mainly for postmenopausal breast cancer, whereas obese young women seem rather to be protected from malignancies of the breast, increased leptin signaling is unlikely to be the sole reason for risk enhancement. At least in specific subtypes of mammary tumors in elderly women, leptin might work in synergy with estrogen, which is produced in high amounts by adipose tissue after menopause (see below). Notably, leptin potentially induces adipose tissue aromatase activity, resulting in an increased production of estrogen [17].

A connection between leptin and cancers of the gastrointestinal tract has been proposed based on several studies involving human samples. Specifically, leptin receptor expression has been observed in human colon cancer cell lines as well as colon biopsies and resected colonic adenocarcinomas [23, 24]. Besides promoting proliferation and migration/invasion, leptin-induced metabolic reprogramming by inhibition of mitochondrial respiration has been observed in human colon cancer cell lines [25], which is in accordance with observations that have been made earlier in a breast cancer mouse model [26]. Notably, whereas circulating leptin levels were found to be decreased in colon cancer patients, they were negatively correlated with tumor aggressiveness [27]. It is unclear though if decreased serum leptin levels in patients with aggressive colon cancer were secondary effects caused by the tumor disease, e.g., upon cancer-associated weight loss.

More recently, leptin signaling has been shown to be involved in pancreatic cancer by in vitro and in vivo studies. While pancreatic tumor cells were shown to express distinct isoforms of the leptin receptor, leptin accordingly stimulated tumor growth, migration and metastasis formation [28, 29]. Clinical relevance of these observations still needs to be demonstrated.

Evidence exists that leptin also promotes growth and invasiveness of cholangiocarcinomas, gliomas and thyroid tumors [30–32]. However, epidemiological data supporting an association between obesity and these tumor entities are yet lacking.

Leptin signaling has been recently reported to be centrally involved in the development of chemotherapy resistance in glioblastoma, gastrointestinal- and breast cancer [33–35], thereby worsening the clinical outcome of anticancer therapies in obese subjects. Importantly though, a present study provides evidence for an increased response of colon cancer patients with high circulating leptin to treatment with Vascular Endothelial Growth Factor (VEGF) inhibitors [36]. Altogether, these data indicate that leptin levels might be an indicator for therapeutic responsiveness, thereby representing a potential biomarker for patient stratification.

Leptin acts via a group of signal transduction pathways that have been shown previously to have tumor-promoting effects [32, 37]. Upon binding by its ligand, OB-R induces several intracellular signaling pathways through interaction with the cytoplasmic kinase janus kinase (JAK) 2. Whereas the short receptor isoforms activate PI3K-Akt signaling via phosphorylation of insulin receptor substrates (IRS), the long isoform (OB-Rb) induces phosphorylation of the mitogenic transcription factor signal transducer and activator of transcription (STAT) 3. In addition, leptin induces MAP kinase signaling pathways and promotes neovascularization through activation of angiogenetic factors. In colonic epithelial cells, leptin treatment resulted in p42/44 MAP kinase activation, thereby inducing their proliferation in vitro and in vivo [23]. Furthermore, migration and invasiveness of colon cancer cell lines derived from particularly aggressive human tumors were potentiated by leptin-dependent stimulation of PI3K and Src signaling pathways, which subsequently activated Rho GTPases, Cdc42 and Rac1 [24]. In pancreatic cancer cells, leptin was able to promote proliferation and migration through activation of PI3K-AKT signaling and enhanced expression of matrix metalloproteinase-13 [28, 29].

Altogether, clinical and experimental evidence exists that leptin signaling affects a large number of distinct tumor entities, thus being one of the foremost links between obesity and cancer risk. On a cellular level, leptin promotes signaling pathways involved in proliferation, survival, migration and angiogenesis, as well as inhibition of apoptosis, all of which are key determinants of tumor development and progression.

Adiponectin

Adiponectin is a 244 amino acid peptide secreted by adipocytes. It exists in several multimeric forms and induces signaling via its two receptor isoforms [38]. By augmenting the insulin response, adiponectin contributes to coordination of glucose and lipid metabolism [39]. Adiponectin secretion is induced by oxidation of fatty acids. In line with this, obese adipose tissue usually displays a markedly reduced adiponectin production [40]. Given its beneficial effects on insulin sensitivity and its inverse correlation with body weight, adiponectin is considered the “good guy” among the adipokines.

Several epidemiological studies provide evidence for a tumor-suppressing action of adiponectin, since its levels inversely correlate with cancers of the colon, mammary gland, endometrium and kidneys [41–43]. Accordingly, a high leptin/adiponectin ratio has been associated with poor survival in colorectal cancer patients [44]. Kaklamani et al. [45] found specific SNPs in the adiponectin and adiponectin receptor gene loci to be associated with either increased or decreased colorectal cancer risk in Caucasians. A recent meta-analysis provided evidence for an association of three SNP in the adiponectin gene with colorectal cancer in Asians, whereas there was no evidence for a significant correlation in the white ethnicity [46]. Overall, efforts to identify adiponectin SNPs associated with increases colorectal cancer risk provided inconsistent results to some degree [47]. Thus, significance of the proposed association remains a matter of debate.

Epidemiological evidence is supported by in vitro studies, demonstrating that adiponectin has anti-proliferative effects on distinct cancer cell lines [48, 49]. These data were confirmed by observations obtained in vivo using tumor mouse models. Growth of various subcutaneous and chemically induced tumors was promoted in adiponectin knockout mice, which particularly was observed under high-fat diet feeding [50, 51]. In line with this finding, adiponectin administration inhibited epithelial proliferation and development of neoplastic foci in colons of obese adiponectin-deficient mice [51]. In breast cancer mouse models, adiponectin haploinsufficiency resulted in early onset of mammary tumors as well as faster progression and enhanced metastasis formation compared to control animals [52].

Although the exact mechanisms underlying its protective function are still a matter of investigation, several mechanisms of anti-carcinogenic action of adiponectin have been convincingly demonstrated, including but not limited to restriction of macrophage recruitment [50], AMPK and LKB1 activation [49, 53], as well as inhibition of mTOR, STAT3 and AKT pathways [51, 52, 54]. Overall, the biological functions of adiponectin antagonize specific aspects of leptin action.

Others

The *VEGF* family controls development of the vascular system during embryogenesis and induces angiogenesis in response to hypoxia. In solid cancers, VEGF is frequently highly expressed to promote vascularization, thereby ensuring nutrient and oxygen supply, which is vital for tumor growth. Consequently, the VEGF pathway is one of the most promising therapeutic targets in oncology. VEGF- and VEGF-receptor-directed therapies are available on the market and approved for treatment of renal, prostate, pancreatic and gastrointestinal tumors. Treatment of further cancer entities is currently being tested in phase II and III studies [55].

Adipose tissue is an important source for circulating VEGF, and leptin activates VEGF expression (see above). As hypoxia occurs in obese adipose tissue, neovascularization is required, resulting in enhanced VEGF expression [56]. In consistency with this, circulating VEGF levels were twofold elevated in centrally obese versus normal weight subjects and VEGF expression was significantly upregulated in visceral compared to subcutaneous adipose tissue in the obese group [6]. Furthermore, VEGF serum levels were elevated in a mouse model of postmenopausal

obesity concomitant with enhanced growth of orthotopically implanted breast tumors compared to lean controls. Notably, in this study, VEGF expression in the subcutaneous adipose tissue was found to be higher than in visceral fat [57]. Conditioned media from visceral adipose tissue obtained from obese donors significantly promoted proliferation of esophageal adenocarcinoma and colorectal carcinoma cell lines, which was rescued by neutralization of VEGF using a specific antibody [6]. In genetically obese mice, VEGF signaling is involved in adipose tissue inflammation, which has additional implications for obesity-linked tumor promotion [58]. Altogether, these data suggest tumor-promoting actions of adipose tissue-derived VEGF through angiogenesis induction and beyond.

In summary, adipose tissue secretes a pattern of bioactive molecules, with implications for tumor development and/or progression as they control signaling pathways involved in cell proliferation, angiogenesis and migration. The composition of the adipose tissue secretome depends on the metabolic health of the adipose organ. A considerable number of studies have revealed potential molecular mechanisms that could explain how alterations in leptin and/or adiponectin levels might increase cancer risk in an obese setting. As these adipokines have basically antagonistic functions, not only their absolute levels might be of relevance for tumor development, but also their ratio should be taken into account. It should be noted that adipose tissue secretes a number of further molecules (e.g., resistin, visfatin, nesfatin, lipocalin-2 and others). Although they have not yet been as intensively investigated with respect to cancer as the above described factors, changes in their serum levels have been associated with cancer development. For example, high levels of resistin have been observed to correlate with tumor and inflammatory markers, but not with anthropometric variables in a breast cancer cohort [59]. Moreover, adipocytes secrete pro-inflammatory cytokines, which are discussed in detail below. Altogether, it might be worth considering the entire adipokine signature of an individual as prognostic factor to assess cancer risk and the clinical outcome [60]. In addition, obesity and insulin resistance are associated with increased circulating levels of adipose tissue-derived fatty acids and other lipid species, which can serve as substrates for enhanced tumor growth (see below).

2.1.2 Cancer-Associated Adipocytes (CAAs)

Besides the role of adipose tissue as an endocrine organ exerting systemic effects, adipocytes are increasingly recognized as important component of the tumor microenvironment, particularly in tumors growing in close proximity to adipocytes [61]. For instance, human and murine breast cancer cells showed increased invasive capacity when co-cultivated with mature adipocytes [62]. Conversely, the adipocytes exposed to the tumor cells exhibited a modified phenotype favoring delipidation and overexpression of proteases, including matrix metalloproteinases 11 and proinflammatory cytokines such as interleukin (IL)-1beta and IL-6, the latter of which was shown to contribute to the proinvasive effects in tumor cells. Importantly, the presence of such modified adipocytes was shown in human breast tumors and tumor size was associated with increased IL-6 expression in the surrounding adipocytes [62]. In a recent study, the secretion of the chemokine CCL7 by

periprostatic adipose tissue was found to be enhanced during obesity. Elevated CCL7 levels stimulated directed migration of CCR3-positive prostate cancer cells. As a result, obese individuals are at higher risk of particularly aggressive forms of prostate cancer [63]. Notably, CCR3 expression was associated with poor prognosis in human patients [63]. Thus, even in tumor entities without an obvious correlation between obesity and tumor risk, exemplified by prostate cancer, adipocytes in the tumor microenvironment potentially affect disease progression by secretion of pro-inflammatory mediators.

2.2 Other Tissues

2.2.1 Insulin and IGF Signaling

Constantly elevated levels of circulating insulin as a consequence of the development of insulin resistance, which can be observed in the majority of obese individuals, are associated with progression and aggressiveness of several types of cancer [64, 65]. This relationship has been validated in a vast number of studies using animal models of hyperinsulinemia and insulin resistance [66]. Likewise, levels of the insulin-related peptide hormone insulin-like growth factor (IGF) 1 were interpreted as biomarkers for cancer development [67]. Notably, insulin induces hepatic IGF1 expression in a growth hormone-dependent manner, and enhances IGF1 bioavailability by repression of IGF binding proteins [4, 64]. Thus, hyperinsulinemia goes hand in hand with elevated circulating IGF1 levels.

Insulin and IGFs activate heterotetrameric tyrosine kinase receptor complexes, namely insulin receptor (IR) and IGF1 receptor (IGF1R), respectively. Whereas IGF1R is ubiquitously expressed and activates proliferative and anti-apoptotic pathways, IR expression is mainly found in rapidly dividing cells (isoform A) as well as metabolically active tissues, including liver, muscle and adipose tissues (isoform B). Thus, IR-B mediates the metabolic functions of insulin. Importantly, the mitogenic IR-A and IGF1R were found to be highly expressed in tumor cells [68]. Due to their high homology, IR and IGF1R potently form hybrid receptors. Notably, IGFs have a substantially higher affinity to IR/IGF1R hybrids than insulin, resulting in IGF1 occupation and consequently enhanced proliferation of cells expressing both receptors. Consistently, accumulation of hybrid receptors is characteristic for several cancer types [64, 68].

The major downstream effectors of IR/IGF1R are the PI3K/AKT and MAPK signaling pathways. Whereas PI3K mediates metabolic functions of insulin in liver, muscle and adipose tissue, both pathways have been linked to proliferation in various cancers [64]. As these pathways can be targeted with small molecule inhibitors, they became attractive for specific anticancer therapies. Inhibiting the PI3K/AKT/mTOR axis resulted in reduced growth of mammary tumors in hyperinsulinemic mice in a similar way as previously demonstrated for tyrosine kinase inhibitors blocking IR/IGF1R activity [69–71]. Of note, the anti-diabetic drug metformin, which among other effects activates AMPK and inhibits mTOR, and

eventually attenuates hyperinsulinemia, has been shown to suppress tumor activity [72].

2.2.2 Signaling via Sex Hormones

Sex hormones are involved in specific cancer entities, exemplified by the implications of estrogen and androgen signaling in breast and endometrial, as well as prostate cancer, respectively. Obesity increases the risk of development of postmenopausal breast cancer, whereas the risk of premenopausal breast cancer appears to be reduced [73]. It is evident that the adipokine leptin, which correlates with the grade of obesity, is involved in breast cancer development and progression. However, an exclusive role of leptin is unlikely, given the apparent protective function of obesity in the context of premenopausal breast cancer. After menopause, adipose tissue is the main source for estrogen production. Thus, circulating levels of estrogens directly correlate with the amount of body fat. Moreover, in obese adipose tissue, expression of aromatase, the enzyme that converts androgens to estrogens is further induced by excess of pro-inflammatory cytokines, thereby further promoting hyperestrogenemia [74]. Notably, obese women are at higher risk of developing mammary tumors derived from cells that express the estrogen receptor (ER-positive breast cancer), which applies to a high number of postmenopausal breast cancers [75]. Estrogens have many modes of action, which could contribute to tumor promotion, including mitogenic effects, mediation of genetic instability and inhibition of apoptosis [76].

Androgens play a key role in prostate cancer development and progression. According to epidemiological studies, there is no significant increase in relative prostate cancer risk in obese men [4]. This is in line with the observation that obesity correlates with low testosterone and sex hormone-binding globulin levels [77]. However, disease progression and mortality are significantly enhanced in obese patients [4]. In this context, a recent study has demonstrated that periprostatic adipose tissue-derived inflammatory signals might determine aggressiveness and invasiveness of prostate tumors under obese conditions (see above and [63]).

2.2.3 Immune Cells and Pro-inflammatory Signaling

Whereas the immune system has significant tumor-suppressing functions, cancer often develops in local environments where persistent inflammation occurs [78]. Chronic inflammatory states generally have pro-tumorigenic potential as they promote proliferation and cell survival by inducing mitotic and anti-apoptotic pathways [79]. Moreover, tumors frequently exhibit characteristics that are typically associated with inflammatory processes including activation of pro-inflammatory signaling pathways, angiogenesis and tissue remodeling [79].

Obese adipose tissue undergoes a substantial remodeling process. In this context, massive infiltration of adipose tissue by cells of the innate immune system takes place. Indeed, formation of distinctive “crown-like structures” by macrophages surrounding dying adipocytes is a hallmark of adipose tissue inflammation during obesity [80, 81]. Moreover, whereas adipose tissue-resident macrophages predominantly exhibit an anti-inflammatory M2 phenotype under lean conditions,

pro-inflammatory M1 polarized macrophages become more abundant during obesity. Macrophage reprogramming might be driven by free fatty acids and inflammatory mediators released from dysfunctional adipocytes [82]. Enhanced secretion of an array of pro-inflammatory cytokines by immune cells and adipocytes can be observed in an obese setting. Specifically, release of tumor necrosis factor (TNF) α, interleukin (IL)-1beta and IL-6, as well as CC-chemokine ligands (CCL), is markedly increased during obesity, thereby aggravating adipocyte dysfunction and promoting systemic insulin resistance [82–84]. Altogether, under obese conditions, infiltration of adipose tissue by macrophages, mast cells and lymphocytes, as well as alterations in the adipose tissue secretome, precipitates into a persistent local and systemic subclinical inflammatory state.

Pro-inflammatory cytokines have been shown to be involved in tumor development and/or progression, thus providing a possible direct link between adipose tissue inflammation and cancer. Notably, they also induce expression of chemokines and prostaglandins, resulting in recruitment and activation of immune cells, ultimately establishing an inflammatory feed-forward mechanism [78]. TNFα promotes tumor progression through activation of transcription factors controlling proliferative and anti-apoptotic pathways, particularly NF-κB and AP-1 [78, 85]. It has been also shown to be involved in mutagenesis and epithelial to mesenchymal transition, the latter of which is a critical event in metastasis formation [86]. IL-6 promotes expression of genes involved in oncogenic pathways, mainly via Jak-STAT activation [85]. In this context, the Karin laboratory demonstrated that TNFα and IL-6 directly promote tumor growth in a STAT3-dependent manner in a carcinogen-induced liver cancer mouse model. Notably, the tumor-promoting effect of pro-inflammatory signaling was amplified in obese animals. Accordingly, loss of either the IL-6 receptor or TNF receptor 1 largely prevented tumor development even under obese conditions [87]. A more recent study demonstrated that under obese conditions, HCC was promoted through stabilization of the E3 ligase Mcl-1. Of note, IL-6 regulates Mcl-1 turnover, which was disrupted during obesity, resulting in an IL-6 independent HCC promotion in obese mice [88]. TNFα signaling was found to be central for progression of PanIN lesions toward pancreatic cancer in obese mice, supporting a general role of pro-inflammatory signaling in obesity-associated tumor development [89].

Specific tumor-suppressing immune cells are quantitatively reduced during obesity, which has implications for cancer risk. In mice and men, obesity is associated with dysfunction of the innate and adaptive immune system, which manifests for instance in reduced numbers of natural killer (NK) and cytotoxic $CD8^+$ T cells [86]. These cells have direct antitumor effects as they mediate cytotoxicity to cancer cells [78]. In line with this, exercise was shown to induce infiltration of distinct tumors by NK cells, thereby inhibiting tumor growth [90]. Additionally, a reduction in regulatory T (Treg) cells could be observed in the abdominal fat of obese mice and humans [91]. Whereas Treg cells play a role in immune evasion of tumor cells, they probably have antitumor function as well as suppressive effects on chronic inflammatory states.

Several other types of immune cells have tumor-promoting or tumor-suppressing activities, including neutrophils, B-lymphocytes and T-helper cells [78]. It still needs to be shown in detail if and how these cells are affected by obesity and may link metabolic dysfunction to cancer manifestation.

3 The Gut Microbiome

Microorganisms have been threatening human health at all times. While bacteria-associated infectious diseases have mostly lost their terror due to the discovery of vaccination and antibiotics, microbes have gained attention as pathogens also in non-communicable diseases. In this context, a number of bacterial species have been designated as carcinogenic [92].

The vast majority of the human microbiota resides in the digestive tract, which provides optimal growth conditions for various bacterial species, e.g., constant temperature and availability of nutrients. Actually, the gastrointestinal tract of an average healthy adult contains more than 1 kg of bacterial mass [93]. Metagenomic analyses based on 16S rRNA sequences have revealed an unexpectedly high complexity of gut bacterial communities and that their composition depends on several parameters [94]. The symbiotic relationship between the intestinal microflora and its host results in mutual benefits for both organisms.

As gut-resident bacteria are involved in digestion and absorption of macronutrients, they have a key function in regulating metabolism of their host. However, despite being generally advantageous and health promoting for the host, the gut microbiota might as well contribute to several pathologies. In the other direction, metabolic status and diet composition potentially have significant impact on the composition of the intestinal microflora [95–97]. While Firmicutes and Bacteroidetes are the most abundant bacterial phylae under healthy conditions, Enterobacteriaceae were found to be enriched in the intestinal tracts of obese humans and rodents [98]. This family of Proteobacteria, which is hardly detectable in healthy microbiomes, is known to release large amounts of lipopolysaccharide (LPS), thereby locally and systemically leading to a pro-inflammatory milieu [99]. Accordingly, circulating LPS levels were found to be 2–3 times elevated in obese mice compared to lean controls [100]. Thus, by constantly triggering an innate immune response, a modified gut microbial community potentially might contribute to the low-grade chronic inflammatory state that is observed under obese conditions.

Obesogenic diets that contain high amounts of fat while being poor in fiber were reported to cause lowering of microbial diversity (dysbiosis) in the gut, which has been linked to cancer [101, 102]. In line with this, transfer of wild-type microbiota to dysbiotic mice reduced tumor burden in a colorectal cancer model [102]. Notably, eradication of the microbiota through germ-free housing or antibiotic treatment resulted in tumor reduction in various rodent models of colorectal cancer, leading to the assumption that no microflora at all might be better than dysbiosis

[101]. As inhibitory effects of gut microbiota elimination could be observed on tumors of the liver, the lung and the mammary gland, it is plausible that intestinal bacteria also potentially promote remote oncogenesis [101].

Specific gut-resident microbes break down dietary fiber into bioactive short-chain fatty acids (SCFA), mainly acetic, propionic and butyric acid. Whereas butyrate can be used by colonocytes as an energy substrate, SFCA are generally known to have anti-inflammatory effects [103, 104]. Moreover, butyrate was shown to have tumor-suppressing functions in neoplastic colon cells under defined dietary and microbial conditions [105]. By contrast, in colonocytes with mutations in the *Msh2* and *Apc* genes, butyrate production by microbes resulted in enhanced proliferation [106]. Furthermore, gut bacteria have important functions in bile acid metabolism. It has been recently demonstrated that mice fed a high-fat diet exhibited elevated levels of the secondary bile acid deoxycholic acid (DCA), concomitant with significant alterations of the gut microbiota [107]. It has been shown in the same study that DCA promotes development of hepatocellular carcinomas through induction of DNA damage, which could be prevented by antibiotic elimination of gut bacteria [107]. The carcinogenic effect of DCA can be at least partially explained by its cytotoxic and genotoxic potential [108]. Thus, disrupted bile acid homeostasis provides another connection between obesity, gut microbiota and cancer.

It is accepted that the connection between dysbiosis and cancer is caused not only by toxic actions of specific pathogens, but also by an impaired host–microbe interaction. However, the underlying molecular mechanisms are only partially resolved. Dysbiosis potentially results in barrier failure of the intestinal mucosa and subsequent inflammatory response. It has been hypothesized that a healthy microflora (eubiosis) might at a low-level activate receptors of the innate immune system, which are presently in the focus of tumor-suppressing immune therapies [109]. It is questionable though, if the degree of activation of the innate immune response is sufficient to induce anti-tumor effects [101]. Also, this is somewhat counterintuitive and contradictory to the tumor-promoting effects of LPS, which acts through stimulation of the innate immune system. Also, in disagreement with the hypothesis that induction of a (low level) innate immune system response could exert anti-tumorigenic effects, activation of Toll-like receptors resulted in pancreatic inflammation and subsequent carcinogenesis [110].

There is consensus that the gut microbiota contributes to health and disease in many respects. By mediating inflammatory responses, accumulation of toxic compounds, and/or provoking barrier failure, a dysbalanced microbiota might link obesity to certain cancers. Regardless of whether alterations of the microbiota are cause or consequence of obesity, promoting a healthy microbiome composition in the gut might not only help to maintain general wellbeing, but also could provide to a certain degree protection from cancer. Thus, diets rich in fiber as well as pre- and probiotic nutritional supplementation should always be taken into account when we think about lifestyle modifications aiming toward cancer prevention.

4 Tumor Cell Metabolism

Already in the 1920s, the German biochemist Otto Warburg hypothesized that a metabolic switch from respiration to increased glucose consumption for lactic acid fermentation (a process termed aerobic glycolysis or the Warburg effect) represents a main event in the transformation of a normal to a tumor cell and that cancer cells could be defeated by targeting their energetic requirements [111]. Although widely neglected for a long period of time, the field of cancer metabolism achieved enormous attention by researchers in the past decade. Consequently, Warburg's concept mainly focused on increased glucose consumption has been extended by the definition of a plethora of specific changes referred to as the metabolic reprogramming of cancer cells [112]. As both direct and indirect consequence of oncogenic mutations, cancer cell metabolism is considered a prerequisite for maintaining viability and fulfilling the biosynthetic demands associated with cell proliferation. However, the precise metabolic program of cancer cells might depend on their specific oncogenic mutations, the tissue context and other factors, including macro- and microenvironmental components. Nevertheless, most cancer cells display several of the six hallmarks of cancer metabolism, which have been defined in a recent review based on known cancer-associated metabolic changes [112]. Some of the metabolic features of cancer cells might contribute to the risk association between obesity and cancer. These include (1) the increased uptake of glucose, which might be favored by hyperglycemia under diabetic conditions, (2) the opportunistic modes of nutrient acquisition enabling tumor cells to benefit from increased lipid availability under obesity conditions and, at least in part related to the latter, (3) the metabolic interactions with the environment, e.g., neighboring adipocytes.

4.1 Hyperglycemia

As a central component of metabolic reprogramming, cancer cells take up high amounts of glucose, which is utilized for ATP production by aerobic glycolysis and generation of building blocks for nucleotide, amino acid and lipid biosynthesis. This suggests that increased concentrations of glucose in the circulation (hyperglycemia), as a hallmark of type 1 and type 2 diabetes mellitus (DM) could contribute to tumorigenesis. Indeed, a number of epidemiological studies suggest that DM is associated with higher prevalence as well as increased mortality for certain types of cancer, including liver, pancreas, colorectal, kidney, bladder, endometrial and breast cancers [113, 114]. Notably, type 2 diabetes represents approximately 90 % of total diabetes cases and arises from insulin resistance under obesity conditions. Therefore, given that cancer occurs preferentially in the older population, in which type 1 diabetes is less frequent, it can be assumed that the increased cancer risk associated with DM refers to mainly to type 2 diabetes [114]. Like for obesity, the risk connection between DM and cancer is complex and might be based on

various mechanisms including increased levels of pro-inflammatory cytokines as well as oncogenic effects of hyperglycemia which are not directly linked to glucose as an energy substrate, e.g., anti-apoptosis, induced cell migration and invasion as well as hyperglycemic memory effects [115]. However, hyperglycemic conditions in vitro have been shown to trigger increased glucose uptake in choriocarcinoma cells by inducing expression of the glucose transporter isoforms GLUT1 and GLUT3 [116]. Also, hyperglycemia has been shown to contribute to hypoxia-inducible factor (HIF)-1 alpha stabilization [117], which in turn can induce the expression of glycolytic enzymes further enhancing glucose utilization. However, the direct effects of hyperglycemia on cancer development are widely unexplored, also due to technical difficulties in studying the effects of high glucose levels on cancer in vivo without interfering with the effects of absence or induction of insulin signaling.

4.2 Lipid Metabolism

As part of the metabolic reprogramming of cancer cells, fatty acids are generally considered to serve as building blocks for biosynthesis of membranes and signaling molecules, as well as to support other aspects of the transformed phenotype of rapidly proliferating cells [118]. Consequently, there are numerous examples showing that oncogenic pathways re-activate de novo lipid synthesis, in part through increased expression and activation of the required metabolic enzymes, including fatty acid synthase (FASN) [118, 119]. Along this line, inhibition of fatty acid availability by different modes could offer novel opportunities in cancer therapy [120].

Despite the observation that cancer cells acquired increased capacity for de novo lipid synthesis to enable proliferation, it is conceivable that under obesity conditions, the increased availability of exogenous lipids from the circulation and from cancer-associated adipocytes could promote tumor development. In support of this idea, Nomura et al. showed that inactivation of the lipolytic enzyme monoacylglycerol lipase (MAGL) markedly impaired the tumorigenic capacity of different aggressive human cancer cell lines representing melanoma, breast and ovarian cancer. They identified MAGL in a proteomic analysis in which this lipase was consistently elevated in the aggressive cell lines compared with their non-aggressive counterparts from the same cancer entity. Knockdown of MAGL in the aggressive or overexpression in the non-aggressive cell lines impaired or induced oncogenic features, respectively, including migration, invasion and in vivo growth. Strikingly, the reduced in vivo growth of xenograft tumors upon knockdown of MAGL in the implanted cells could be rescued by feeding the mice a HFD, suggesting a pro-tumorigenic effect of the availability of exogenous fatty acids [121]. Another study showed that the proliferation of breast cancer and sarcoma cells expressing Lipoprotein Lipase (LPL) and CD36 is accelerated upon treatment with triglyceride-rich lipoproteins. Since LPL and CD36 are involved in lipoprotein-associated triglyceride lipolysis and fatty acid uptake, respectively, this

suggests that these cells are capable to acquire fatty acids from the circulation or other sources to fuel their growth [122]. In addition, providing prostate cancer cells, which are characterized by high lipogenic capacity, with LPL and TG-rich lipoproteins prevented the growth inhibitory effects of fatty acid synthesis inhibition [122]. Interestingly, there is also evidence that under hypoxic conditions or Ras activation, certain cancer cells can switch from de novo lipogenesis to scavenging of serum fatty acids to meet their lipid requirements [123]. Similarly, another study demonstrated in a panel of cell lines and in tumors that exogenous palmitate could be incorporated into both structural and oncogenic signaling lipids [124]. Furthermore, dietary lipids potentially also act as ligands for nuclear receptor transcription factors. In this context, a recent study showed that high-fat diet promotes stemness and induced the capacity for tumor initiation of intestinal progenitor cells via activation of PPARδ and subsequent induction of WNT/β-catenin signaling [125].

Also, more direct interactions between adipocytes and cancer cells might contribute to metabolic adaptations promoting tumor growth and aggressiveness. For instance, co-culturing of primary adipocytes with ovarian cancer cells led to the direct transfer of lipids by induced lipolysis in the adipocytes and beta oxidation in the cancer cells, suggesting that adipocytes can act as an energy source to promote tumor growth [126]. Interestingly, ovarian cancer metastasis to the omentum, an organ primarily composed of adipocytes, was induced by adipokines characterized by induced fatty acid binding protein (FABP) 4 expression, indicating a modified lipid metabolism phenotype.

Although further research is required to elucidate the interaction between cancer cell metabolism and the altered metabolic macro and microenvironment in metabolic diseases, the described examples might point to the implication of such mechanisms in the connection between obesity and cancer and guide further studies in this direction in the future.

5 Outlook and Open Questions

Obesity increases the risk of several cancer entities by triggering multiple (patho-) physiological alterations in local and remote fashions. Given its pandemic prevalence, obesity is expected to become one of the main lifestyle-associated risk factors for cancer development in the near future. Knowledge of the underlying molecular principles will be crucial, as it will open new opportunities for "metabolocentric" cancer treatment and prevention. Such options would include targeted therapies affecting deregulated pathways under obese conditions, exemplified by inhibition of inflammatory and growth factor signaling. Importantly, interventions targeting obesity and metabolic dysfunction in a more general way might have (immediate) effects on cancer risk independent of actual weight loss: Exercise triggers the release of potentially tumor-suppressing myokines, such as oncostatin and SPARC [127, 128]. Bariatric surgery instantly results in metabolic improvements

independent of body weight loss, including elevated adiponectin levels and alleviation of hyperinsulinemia [129–131]. Pre- and probiotics could be an option for supporting a healthier intestinal microflora [132]. Noteworthy, transplantation of healthy microbiota showed antitumor effects at least in murine cancer models [102]. Major future challenges will include the tumor entity-specific definition of metabolic complications and/or obesity-associated comorbidities, including type 2 diabetes, insulin resistance and dyslipidemia that determine increased tumor progression and/or aggressiveness in affected patients. Of particular interest will be the question to which extend metabolic dysfunction cannot only trigger tumor promotion but might also serve as an initiating event in the malignant transformation of a normal to a cancer cell, independent of classical gene mutations in oncogenes or tumor suppressors. Clinical and experimental studies in this direction can be anticipated to shed light onto this exciting field of biomedicine to overcome metabolism-driven tumorigenesis in the future.

References

1. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, Singh GM, Gutierrez HR, Lu Y, Bahalim AN, Farzadfar F, Riley LM, Ezzati M, Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating G (2011) National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet 377(9765):557–567. doi:10.1016/S0140-6736(10)62037-5
2. Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie ML, Gortmaker SL (2011) The global obesity pandemic: shaped by global drivers and local environments. Lancet 378(9793):804–814. doi:10.1016/S0140-6736(11)60813-1
3. Malik VS, Willett WC, Hu FB (2013) Global obesity: trends, risk factors and policy implications. Nat Rev Endocrinol 9(1):13–27. doi:10.1038/nrendo.2012.199
4. Calle EE, Kaaks R (2004) Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 4(8):579–591. doi:10.1038/nrc1408
5. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M (2008) Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 371(9612):569–578. doi:10.1016/S0140-6736(08)60269-X
6. Lysaght J, van der Stok EP, Allott EH, Casey R, Donohoe CL, Howard JM, McGarrigle SA, Ravi N, Reynolds JV, Pidgeon GP (2011) Pro-inflammatory and tumour proliferative properties of excess visceral adipose tissue. Cancer Lett 312(1):62–72. doi:10.1016/j.canlet.2011.07.034
7. Hosono S, Matsuo K, Hirose K, Ito H, Suzuki T, Kawase T, Watanabe M, Nakanishi T, Tajima K, Tanaka H (2011) Weight gain during adulthood and body weight at age 20 are associated with the risk of endometrial cancer in Japanese women. J Epidemiol 21(6):466–473
8. Zhao J, Lawless MW (2013) Stop feeding cancer: pro-inflammatory role of visceral adiposity in liver cancer. Cytokine 64(3):626–637. doi:10.1016/j.cyto.2013.09.009
9. Waxler SH, Tabar P, Melcher LR (1953) Obesity and the time of appearance of spontaneous mammary carcinoma in C3H mice. Cancer Res 13(3):276–278
10. Trayhurn P (2005) Endocrine and signalling role of adipose tissue: new perspectives on fat. Acta Physiol Scand 184(4):285–293. doi:10.1111/j.1365-201X.2005.01468.x
11. Bulcao C, Ferreira SR, Giuffrida FM, Ribeiro-Filho FF (2006) The new adipose tissue and adipocytokines. Curr Diabetes Rev 2(1):19–28

12. Cowley MA, Smart JL, Rubinstein M, Cerdan MG, Diano S, Horvath TL, Cone RD, Low MJ (2001) Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. Nature 411(6836):480–484. doi:10.1038/35078085
13. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM (1994) Positional cloning of the mouse obese gene and its human homologue. Nature 372(6505):425–432. doi:10.1038/372425a0
14. Nyante SJ, Gammon MD, Kaufman JS, Bensen JT, Lin DY, Barnholtz-Sloan JS, Hu Y, He Q, Luo J, Millikan RC (2011) Common genetic variation in adiponectin, leptin, and leptin receptor and association with breast cancer subtypes. Breast Cancer Res Treat 129 (2):593–606. doi:10.1007/s10549-011-1517-z
15. Heston WE, Vlahakis G (1962) Genetic obesity and neoplasia. J Natl Cancer Inst 29:197–209
16. Gross AL, Newschaffer CJ, Hoffman-Bolton J, Rifai N, Visvanathan K (2013) Adipocytokines, inflammation, and breast cancer risk in postmenopausal women: a prospective study. Cancer Epidemiol Biomark Prev 22(7):1319–1324. doi:10.1158/1055-9965.EPI-12-1444
17. Rose DP, Gilhooly EM, Nixon DW (2002) Adverse effects of obesity on breast cancer prognosis, and the biological actions of leptin (review). Int J Oncol 21(6):1285–1292
18. Hu X, Juneja SC, Maihle NJ, Cleary MP (2002) Leptin–a growth factor in normal and malignant breast cells and for normal mammary gland development. J Natl Cancer Inst 94 (22):1704–1711
19. Ishikawa M, Kitayama J, Nagawa H (2004) Enhanced expression of leptin and leptin receptor (OB-R) in human breast cancer. Clin Cancer Res 10(13):4325–4331. doi:10.1158/1078-0432.CCR-03-0749
20. Xue RQ, Gu JC, Du ST, Yu W, Wang Y, Zhang ZT, Bai ZG, Ma XM (2012) Lentivirus-mediated RNA interference targeting the ObR gene in human breast cancer MCF-7 cells in a nude mouse xenograft model. Chin Med J (Engl) 125(9):1563–1570
21. Cleary MP, Phillips FC, Getzin SC, Jacobson TL, Jacobson MK, Christensen TA, Juneja SC, Grande JP, Maihle NJ (2003) Genetically obese MMTV-TGF-alpha/Lep(ob)Lep (ob) female mice do not develop mammary tumors. Breast Cancer Res Treat 77(3):205–215
22. Cleary MP, Juneja SC, Phillips FC, Hu X, Grande JP, Maihle NJ (2004) Leptin receptor-deficient MMTV-TGF-alpha/Lepr(db)Lepr(db) female mice do not develop oncogene-induced mammary tumors. Exp Biol Med (Maywood) 229(2):182–193
23. Hardwick JC, Van Den Brink GR, Offerhaus GJ, Van Deventer SJ, Peppelenbosch MP (2001) Leptin is a growth factor for colonic epithelial cells. Gastroenterology 121(1):79–90
24. Jaffe T, Schwartz B (2008) Leptin promotes motility and invasiveness in human colon cancer cells by activating multiple signal-transduction pathways. Int J Cancer 123(11):2543–2556. doi:10.1002/ijc.23821
25. Yehuda-Shnaidman E, Nimri L, Tarnovscki T, Kirshtein B, Rudich A, Schwartz B (2013) Secreted human adipose leptin decreases mitochondrial respiration in HCT116 colon cancer cells. PLoS ONE 8(9):e74843. doi:10.1371/journal.pone.0074843
26. Park J, Kusminski CM, Chua SC, Scherer PE (2010) Leptin receptor signaling supports cancer cell metabolism through suppression of mitochondrial respiration in vivo. Am J Pathol 177(6):3133–3144. doi:10.2353/ajpath.2010.100595
27. Salageanu A, Tucureanu C, Lerescu L, Caras I, Pitica R, Gangura G, Costea R, Neagu S (2010) Serum levels of adipokines resistin and leptin in patients with colon cancer. J Med Life 3(4):416–420
28. Mendonsa AM, Chalfant MC, Gorden LD, VanSaun MN (2015) Modulation of the leptin receptor mediates tumor growth and migration of pancreatic cancer cells. PLoS ONE 10(4): e0126686. doi:10.1371/journal.pone.0126686
29. Fan Y, Gan Y, Shen Y, Cai X, Song Y, Zhao F, Yao M, Gu J, Tu H (2015) Leptin signaling enhances cell invasion and promotes the metastasis of human pancreatic cancer via

increasing MMP-13 production. Oncotarget 6(18):16120–16134. doi:10.18632/oncotarget.3878
30. Fava G, Alpini G, Rychlicki C, Saccomanno S, DeMorrow S, Trozzi L, Candelaresi C, Venter J, Di Sario A, Marzioni M, Bearzi I, Glaser S, Alvaro D, Marucci L, Francis H, Svegliati-Baroni G, Benedetti A (2008) Leptin enhances cholangiocarcinoma cell growth. Cancer Res 68(16):6752–6761. doi:10.1158/0008-5472.CAN-07-6682
31. Yeh WL, Lu DY, Lee MJ, Fu WM (2009) Leptin induces migration and invasion of glioma cells through MMP-13 production. Glia 57(4):454–464. doi:10.1002/glia.20773
32. Uddin S, Hussain AR, Siraj AK, Khan OS, Bavi PP, Al-Kuraya KS (2011) Role of leptin and its receptors in the pathogenesis of thyroid cancer. Int J Clin Exp Pathol 4(7):637–643
33. Han G, Wang L, Zhao W, Yue Z, Zhao R, Li Y, Zhou X, Hu X, Liu J (2013) High expression of leptin receptor leads to temozolomide resistance with exhibiting stem/progenitor cell features in gliobalastoma. Cell Cycle 12(24):3833–3840. doi:10.4161/cc.26809
34. Bain GH, Collie-Duguid E, Murray GI, Gilbert FJ, Denison A, McKiddie F, Ahearn T, Fleming I, Leeds J, Phull P, Park K, Nanthakumaran S, Grabsch HI, Tan P, Welch A, Schweiger L, Dahle-Smith A, Urquhart G, Finegan M, Petty RD (2014) Tumour expression of leptin is associated with chemotherapy resistance and therapy-independent prognosis in gastro-oesophageal adenocarcinomas. Br J Cancer 110(6):1525–1534. doi:10.1038/bjc.2014.45
35. Nadal-Serrano M, Sastre-Serra J, Valle A, Roca P, Oliver J (2015) Chronic-leptin attenuates Cisplatin cytotoxicity in MCF-7 breast cancer cell line. Cell Physiol Biochem 36(1):221–232. doi:10.1159/000374066
36. Pommier AJ, Farren M, Patel B, Wappett M, Michopoulos F, Smith NR, Kendrew J, Frith J, Huby R, Eberlein C, Campbell H, Womack C, Smith PD, Robertson J, Morgan S, Critchlow SE, Barry ST (2016) Leptin, BMI, and a metabolic gene expression signature associated with clinical outcome to VEGF inhibition in colorectal cancer. Cell Metab 23(1):77–93. doi:10.1016/j.cmet.2015.10.015
37. Garofalo C, Surmacz E (2006) Leptin and cancer. J Cell Physiol 207(1):12–22. doi:10.1002/jcp.20472
38. Yamauchi T, Kadowaki T (2013) Adiponectin receptor as a key player in healthy longevity and obesity-related diseases. Cell Metab 17(2):185–196. doi:10.1016/j.cmet.2013.01.001
39. Yamauchi T, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M, Okada-Iwabu M, Kawamoto S, Kubota N, Kubota T, Ito Y, Kamon J, Tsuchida A, Kumagai K, Kozono H, Hada Y, Ogata H, Tokuyama K, Tsunoda M, Ide T, Murakami K, Awazawa M, Takamoto I, Froguel P, Hara K, Tobe K, Nagai R, Ueki K, Kadowaki T (2007) Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. Nat Med 13(3):332–339. doi:10.1038/nm1557
40. Diez JJ, Iglesias P (2003) The role of the novel adipocyte-derived hormone adiponectin in human disease. Eur J Endocrinol 148(3):293–300
41. Riondino S, Roselli M, Palmirotta R, Della-Morte D, Ferroni P, Guadagni F (2014) Obesity and colorectal cancer: role of adipokines in tumor initiation and progression. World J Gastroenterol 20(18):5177–5190. doi:10.3748/wjg.v20.i18.5177
42. Mantzoros C, Petridou E, Dessypris N, Chavelas C, Dalamaga M, Alexe DM, Papadiamantis Y, Markopoulos C, Spanos E, Chrousos G, Trichopoulos D (2004) Adiponectin and breast cancer risk. J Clin Endocrinol Metab 89(3):1102–1107. doi:10.1210/jc.2003-031804
43. Cust AE, Kaaks R, Friedenreich C, Bonnet F, Laville M, Lukanova A, Rinaldi S, Dossus L, Slimani N, Lundin E, Tjonneland A, Olsen A, Overvad K, Clavel-Chapelon F, Mesrine S, Joulin V, Linseisen J, Rohrmann S, Pischon T, Boeing H, Trichopoulos D, Trichopoulou A, Benetou V, Palli D, Berrino F, Tumino R, Sacerdote C, Mattiello A, Quiros JR, Mendez MA, Sanchez MJ, Larranaga N, Tormo MJ, Ardanaz E, Bueno-de-Mesquita HB, Peeters PH, van Gils CH, Khaw KT, Bingham S, Allen N, Key T, Jenab M, Riboli E (2007)

Plasma adiponectin levels and endometrial cancer risk in pre- and postmenopausal women. J Clin Endocrinol Metab 92(1):255–263. doi:10.1210/jc.2006-1371
44. Guadagni F, Roselli M, Martini F, Spila A, Riondino S, D'Alessandro R, Del Monte G, Formica V, Laudisi A, Portarena I, Palmirotta R, Ferroni P (2009) Prognostic significance of serum adipokine levels in colorectal cancer patients. Anticancer Res 29(8):3321–3327
45. Kaklamani VG, Wisinski KB, Sadim M, Gulden C, Do A, Offit K, Baron JA, Ahsan H, Mantzoros C, Pasche B (2008) Variants of the adiponectin (ADIPOQ) and adiponectin receptor 1 (ADIPOR1) genes and colorectal cancer risk. JAMA 300(13):1523–1531. doi:10.1001/jama.300.13.1523
46. Yang X, Li J, Cai W, Yang Q, Lu Z, Yu J, Yu H, Zhang N, Sun D, Qu Y, Guo H, Wen F, Ji Y (2015) Adiponectin gene polymorphisms are associated with increased risk of colorectal cancer. Med Sci Monit 21:2595–2606. doi:10.12659/MSM.893472
47. Ye C, Wang J, Tan S, Zhang J, Li M, Sun P (2013) Meta-analysis of adiponectin polymorphisms and colorectal cancer risk. Int J Med Sci 10(9):1113–1120. doi:10.7150/ijms.6843
48. Bub JD, Miyazaki T, Iwamoto Y (2006) Adiponectin as a growth inhibitor in prostate cancer cells. Biochem Biophys Res Commun 340(4):1158–1166. doi:10.1016/j.bbrc.2005.12.103
49. Kim AY, Lee YS, Kim KH, Lee JH, Lee HK, Jang SH, Kim SE, Lee GY, Lee JW, Jung SA, Chung HY, Jeong S, Kim JB (2010) Adiponectin represses colon cancer cell proliferation via AdipoR1- and -R2-mediated AMPK activation. Mol Endocrinol 24(7):1441–1452. doi:10.1210/me.2009-0498
50. Sun Y, Lodish HF (2010) Adiponectin deficiency promotes tumor growth in mice by reducing macrophage infiltration. PLoS ONE 5(8):e11987. doi:10.1371/journal.pone.0011987
51. Fujisawa T, Endo H, Tomimoto A, Sugiyama M, Takahashi H, Saito S, Inamori M, Nakajima N, Watanabe M, Kubota N, Yamauchi T, Kadowaki T, Wada K, Nakagama H, Nakajima A (2008) Adiponectin suppresses colorectal carcinogenesis under the high-fat diet condition. Gut 57(11):1531–1538. doi:10.1136/gut.2008.159293
52. Lam JB, Chow KH, Xu A, Lam KS, Liu J, Wong NS, Moon RT, Shepherd PR, Cooper GJ, Wang Y (2009) Adiponectin haploinsufficiency promotes mammary tumor development in MMTV-PyVT mice by modulation of phosphatase and tensin homolog activities. PLoS ONE 4(3):e4968. doi:10.1371/journal.pone.0004968
53. Taliaferro-Smith L, Nagalingam A, Zhong D, Zhou W, Saxena NK, Sharma D (2009) LKB1 is required for adiponectin-mediated modulation of AMPK-S6K axis and inhibition of migration and invasion of breast cancer cells. Oncogene 28(29):2621–2633. doi:10.1038/onc.2009.129
54. Sharma D, Wang J, Fu PP, Sharma S, Nagalingam A, Mells J, Handy J, Page AJ, Cohen C, Anania FA, Saxena NK (2010) Adiponectin antagonizes the oncogenic actions of leptin in hepatocellular carcinogenesis. Hepatology 52(5):1713–1722. doi:10.1002/hep.23892
55. Dowlati A (2010) Hunting and trapping the vascular endothelial growth factor. J Clin Oncol 28(2):185–187. doi:10.1200/JCO.2009.25.4359
56. Cao Y (2007) Angiogenesis modulates adipogenesis and obesity. J Clin Invest 117(9):2362–2368. doi:10.1172/JCI32239
57. Gu JW, Young E, Patterson SG, Makey KL, Wells J, Huang M, Tucker KB, Miele L (2011) Postmenopausal obesity promotes tumor angiogenesis and breast cancer progression in mice. Cancer Biol Ther 11(10):910–917
58. Karaman S, Hollmen M, Robciuc MR, Alitalo A, Nurmi H, Morf B, Buschle D, Alkan HF, Ochsenbein AM, Alitalo K, Wolfrum C, Detmar M (2015) Blockade of VEGF-C and VEGF-D modulates adipose tissue inflammation and improves metabolic parameters under high-fat diet. Mol Metab 4(2):93–105. doi:10.1016/j.molmet.2014.11.006
59. Dalamaga M, Karmaniolas K, Papadavid E, Pelekanos N, Sotiropoulos G, Lekka A (2013) Hyperresistinemia is associated with postmenopausal breast cancer. Menopause 20(8):845–851. doi:10.1097/GME.0b013e31827f06dc

60. Assiri AM, Kamel HF, Hassanien MF (2015) Resistin, visfatin, adiponectin, and leptin: risk of breast cancer in pre- and postmenopausal saudi females and their possible diagnostic and predictive implications as novel biomarkers. Dis Markers 2015:253519. doi:10.1155/2015/253519
61. Nieman KM, Romero IL, Van Houten B, Lengyel E (2013) Adipose tissue and adipocytes support tumorigenesis and metastasis. Biochim Biophys Acta 1831(10):1533–1541. doi:10.1016/j.bbalip.2013.02.010
62. Dirat B, Bochet L, Dabek M, Daviaud D, Dauvillier S, Majed B, Wang YY, Meulle A, Salles B, Le Gonidec S, Garrido I, Escourrou G, Valet P, Muller C (2011) Cancer-associated adipocytes exhibit an activated phenotype and contribute to breast cancer invasion. Cancer Res 71(7):2455–2465. doi:10.1158/0008-5472.CAN-10-3323
63. Laurent V, Guerard A, Mazerolles C, Le Gonidec S, Toulet A, Nieto L, Zaidi F, Majed B, Garandeau D, Socrier Y, Golzio M, Cadoudal T, Chaoui K, Dray C, Monsarrat B, Schiltz O, Wang YY, Couderc B, Valet P, Malavaud B, Muller C (2016) Periprostatic adipocytes act as a driving force for prostate cancer progression in obesity. Nat Commun 7:10230. doi:10.1038/ncomms10230
64. Cohen DH, LeRoith D (2012) Obesity, type 2 diabetes, and cancer: the insulin and IGF connection. Endocr Relat Cancer 19(5):F27–F45. doi:10.1530/ERC-11-0374
65. Tsugane S, Inoue M (2010) Insulin resistance and cancer: epidemiological evidence. Cancer Sci 101(5):1073–1079. doi:10.1111/j.1349-7006.2010.01521.x
66. Gallagher EJ, LeRoith D (2015) Obesity and diabetes: the increased risk of cancer and cancer-related mortality. Physiol Rev 95(3):727–748. doi:10.1152/physrev.00030.2014
67. Chen W, Wang S, Tian T, Bai J, Hu Z, Xu Y, Dong J, Chen F, Wang X, Shen H (2009) Phenotypes and genotypes of insulin-like growth factor 1, IGF-binding protein-3 and cancer risk: evidence from 96 studies. Eur J Hum Genet 17(12):1668–1675. doi:10.1038/ejhg.2009.86
68. Belfiore A, Frasca F, Pandini G, Sciacca L, Vigneri R (2009) Insulin receptor isoforms and insulin receptor/insulin-like growth factor receptor hybrids in physiology and disease. Endocr Rev 30(6):586–623. doi:10.1210/er.2008-0047
69. Fierz Y, Novosyadlyy R, Vijayakumar A, Yakar S, LeRoith D (2010) Mammalian target of rapamycin inhibition abrogates insulin-mediated mammary tumor progression in type 2 diabetes. Endocr Relat Cancer 17(4):941–951. doi:10.1677/ERC-10-0091
70. Gallagher EJ, Fierz Y, Vijayakumar A, Haddad N, Yakar S, LeRoith D (2012) Inhibiting PI3K reduces mammary tumor growth and induces hyperglycemia in a mouse model of insulin resistance and hyperinsulinemia. Oncogene 31(27):3213–3222. doi:10.1038/onc.2011.495
71. Novosyadlyy R, Lann DE, Vijayakumar A, Rowzee A, Lazzarino DA, Fierz Y, Carboni JM, Gottardis MM, Pennisi PA, Molinolo AA, Kurshan N, Mejia W, Santopietro S, Yakar S, Wood TL, LeRoith D (2010) Insulin-mediated acceleration of breast cancer development and progression in a nonobese model of type 2 diabetes. Cancer Res 70(2):741–751. doi:10.1158/0008-5472.CAN-09-2141
72. Malek M, Aghili R, Emami Z, Khamseh ME (2013) Risk of cancer in diabetes: the effect of metformin. ISRN Endocrinol 2013:636927. doi:10.1155/2013/636927
73. Carmichael AR, Bates T (2004) Obesity and breast cancer: a review of the literature. Breast 13(2):85–92. doi:10.1016/j.breast.2003.03.001
74. Wang X, Simpson ER, Brown KA (2015) Aromatase overexpression in dysfunctional adipose tissue links obesity to postmenopausal breast cancer. J Steroid Biochem Mol Biol 153:35–44. doi:10.1016/j.jsbmb.2015.07.008
75. Colditz GA, Rosner BA, Chen WY, Holmes MD, Hankinson SE (2004) Risk factors for breast cancer according to estrogen and progesterone receptor status. J Natl Cancer Inst 96(3):218–228
76. Ungefroren H, Gieseler F, Lehnert H (2015) Obesity and cancer. Internist (Berl) 56(2):127–128, 130–126. doi:10.1007/s00108-014-3536-4

77. Allan CA, McLachlan RI (2010) Androgens and obesity. Curr Opin Endocrinol Diab Obes 17(3):224–232. doi:10.1097/MED.0b013e3283398ee2
78. Grivennikov SI, Greten FR, Karin M (2010) Immunity, inflammation, and cancer. Cell 140 (6):883–899. doi:10.1016/j.cell.2010.01.025
79. Mantovani A, Allavena P, Sica A, Balkwill F (2008) Cancer-related inflammation. Nature 454(7203):436–444. doi:10.1038/nature07205
80. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr (2003) Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 112 (12):1796–1808. doi:10.1172/JCI19246
81. Murano I, Barbatelli G, Parisani V, Latini C, Muzzonigro G, Castellucci M, Cinti S (2008) Dead adipocytes, detected as crown-like structures, are prevalent in visceral fat depots of genetically obese mice. J Lipid Res 49(7):1562–1568. doi:10.1194/jlr.M800019-JLR200
82. McNelis JC, Olefsky JM (2014) Macrophages, immunity, and metabolic disease. Immunity 41(1):36–48. doi:10.1016/j.immuni.2014.05.010
83. Gregor MF, Hotamisligil GS (2011) Inflammatory mechanisms in obesity. Annu Rev Immunol 29:415–445. doi:10.1146/annurev-immunol-031210-101322
84. Chen L, Chen R, Wang H, Liang F (2015) Mechanisms linking inflammation to insulin resistance. Int J Endocrinol 2015:508409. doi:10.1155/2015/508409
85. Lin WW, Karin M (2007) A cytokine-mediated link between innate immunity, inflammation, and cancer. J Clin Invest 117(5):1175–1183. doi:10.1172/JCI31537
86. Font-Burgada J, Sun B, Karin M (2016) Obesity and cancer: the oil that feeds the flame. Cell Metab 23(1):48–62. doi:10.1016/j.cmet.2015.12.015
87. Park EJ, Lee JH, Yu GY, He G, Ali SR, Holzer RG, Osterreicher CH, Takahashi H, Karin M (2010) Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. Cell 140(2):197–208. doi:10.1016/j.cell.2009.12.052
88. Gruber S, Straub BK, Ackermann PJ, Wunderlich CM, Mauer J, Seeger JM, Buning H, Heukamp L, Kashkar H, Schirmacher P, Bruning JC, Wunderlich FT (2013) Obesity promotes liver carcinogenesis via Mcl-1 stabilization independent of IL-6Ralpha signaling. Cell Rep 4(4):669–680. doi:10.1016/j.celrep.2013.07.023
89. Khasawneh J, Schulz MD, Walch A, Rozman J, Hrabe de Angelis M, Klingenspor M, Buck A, Schwaiger M, Saur D, Schmid RM, Kloppel G, Sipos B, Greten FR, Arkan MC (2009) Inflammation and mitochondrial fatty acid beta-oxidation link obesity to early tumor promotion. Proc Natl Acad Sci USA 106(9):3354–3359. doi:10.1073/pnas.0802864106
90. Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, Johannesen HH, Becker JC, Pedersen KS, Dethlefsen C, Nielsen J, Gehl J, Pedersen BK, Thor Straten P, Hojman P (2016) Voluntary running suppresses tumor growth through epinephrine- and IL-6-dependent NK cell mobilization and redistribution. Cell Metab. doi:10.1016/j.cmet.2016.01.011
91. Feuerer M, Herrero L, Cipolletta D, Naaz A, Wong J, Nayer A, Lee J, Goldfine AB, Benoist C, Shoelson S, Mathis D (2009) Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. Nat Med 15(8):930–939. doi:10.1038/nm.2002
92. Garrett WS (2015) Cancer and the microbiota. Science 348(6230):80–86. doi:10.1126/science.aaa4972
93. Nicholson JK, Holmes E, Wilson ID (2005) Gut microorganisms, mammalian metabolism and personalized health care. Nat Rev Microbiol 3(5):431–438. doi:10.1038/nrmicro1152
94. Claesson MJ, O'Toole PW (2010) Evaluating the latest high-throughput molecular techniques for the exploration of microbial gut communities. Gut Microbes 1(4):277–278. doi:10.4161/gmic.1.4.12306
95. Zhang C, Zhang M, Wang S, Han R, Cao Y, Hua W, Mao Y, Zhang X, Pang X, Wei C, Zhao G, Chen Y, Zhao L (2010) Interactions between gut microbiota, host genetics and diet relevant to development of metabolic syndromes in mice. ISME J 4(2):232–241. doi:10.1038/ismej.2009.112

96. Carmody RN, Gerber GK, Luevano JM Jr, Gatti DM, Somes L, Svenson KL, Turnbaugh PJ (2015) Diet dominates host genotype in shaping the murine gut microbiota. Cell Host Microbe 17(1):72–84. doi:10.1016/j.chom.2014.11.010
97. Hartstra AV, Bouter KE, Backhed F, Nieuwdorp M (2015) Insights into the role of the microbiome in obesity and type 2 diabetes. Diabetes Care 38(1):159–165. doi:10.2337/dc14-0769
98. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, Gill SR, Nelson KE, Relman DA (2005) Diversity of the human intestinal microbial flora. Science 308(5728):1635–1638. doi:10.1126/science.1110591
99. Zhao L (2013) The gut microbiota and obesity: from correlation to causality. Nat Rev Microbiol 11(9):639–647. doi:10.1038/nrmicro3089
100. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C, Waget A, Delmee E, Cousin B, Sulpice T, Chamontin B, Ferrieres J, Tanti JF, Gibson GR, Casteilla L, Delzenne NM, Alessi MC, Burcelin R (2007) Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 56(7):1761–1772. doi:10.2337/db06-1491
101. Schwabe RF, Jobin C (2013) The microbiome and cancer. Nat Rev Cancer 13(11):800–812. doi:10.1038/nrc3610
102. Couturier-Maillard A, Secher T, Rehman A, Normand S, De Arcangelis A, Haesler R, Huot L, Grandjean T, Bressenot A, Delanoye-Crespin A, Gaillot O, Schreiber S, Lemoine Y, Ryffel B, Hot D, Nunez G, Chen G, Rosenstiel P, Chamaillard M (2013) NOD2-mediated dysbiosis predisposes mice to transmissible colitis and colorectal cancer. J Clin Invest 123(2):700–711. doi:10.1172/JCI62236
103. Maslowski KM, Vieira AT, Ng A, Kranich J, Sierro F, Yu D, Schilter HC, Rolph MS, Mackay F, Artis D, Xavier RJ, Teixeira MM, Mackay CR (2009) Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. Nature 461(7268):1282–1286. doi:10.1038/nature08530
104. Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly YM, Glickman JN, Garrett WS (2013) The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science 341(6145):569–573. doi:10.1126/science.1241165
105. Donohoe DR, Holley D, Collins LB, Montgomery SA, Whitmore AC, Hillhouse A, Curry KP, Renner SW, Greenwalt A, Ryan EP, Godfrey V, Heise MT, Threadgill DS, Han A, Swenberg JA, Threadgill DW, Bultman SJ (2014) A gnotobiotic mouse model demonstrates that dietary fiber protects against colorectal tumorigenesis in a microbiota- and butyrate-dependent manner. Cancer Discov 4(12):1387–1397. doi:10.1158/2159-8290.CD-14-0501
106. Belcheva A, Irrazabal T, Robertson SJ, Streutker C, Maughan H, Rubino S, Moriyama EH, Copeland JK, Kumar S, Green B, Geddes K, Pezo RC, Navarre WW, Milosevic M, Wilson BC, Girardin SE, Wolever TM, Edelmann W, Guttman DS, Philpott DJ, Martin A (2014) Gut microbial metabolism drives transformation of MSH2-deficient colon epithelial cells. Cell 158(2):288–299. doi:10.1016/j.cell.2014.04.051
107. Yoshimoto S, Loo TM, Atarashi K, Kanda H, Sato S, Oyadomari S, Iwakura Y, Oshima K, Morita H, Hattori M, Honda K, Ishikawa Y, Hara E, Ohtani N (2013) Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. Nature 499(7456):97–101. doi:10.1038/nature12347
108. Pearson JR, Gill CI, Rowland IR (2009) Diet, fecal water, and colon cancer–development of a biomarker. Nutr Rev 67(9):509–526. doi:10.1111/j.1753-4887.2009.00224.x
109. Garaude J, Kent A, van Rooijen N, Blander JM (2012) Simultaneous targeting of toll- and nod-like receptors induces effective tumor-specific immune responses. Sci Transl Med 4(120):120ra116. doi:10.1126/scitranslmed.3002868
110. Ochi A, Nguyen AH, Bedrosian AS, Mushlin HM, Zarbakhsh S, Barilla R, Zambirinis CP, Fallon NC, Rehman A, Pylayeva-Gupta Y, Badar S, Hajdu CH, Frey AB, Bar-Sagi D,

Miller G (2012) MyD88 inhibition amplifies dendritic cell capacity to promote pancreatic carcinogenesis via Th2 cells. J Exp Med 209(9):1671–1687. doi:10.1084/jem.20111706
111. Warburg O, Wind F, Negelein E (1927) The metabolism of tumors in the body. J Gen Physiol 8(6):519–530
112. Pavlova NN, Thompson CB (2016) The emerging hallmarks of cancer metabolism. Cell Metab 23(1):27–47. doi:10.1016/j.cmet.2015.12.006
113. Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ (2004) Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol 159(12):1160–1167. doi:10.1093/aje/kwh161
114. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R (2009) Diabetes and cancer. Endocr Relat Cancer 16(4):1103–1123. doi:10.1677/ERC-09-0087
115. Ryu TY, Park J, Scherer PE (2014) Hyperglycemia as a risk factor for cancer progression. Diabetes Metab J 38(5):330–336. doi:10.4093/dmj.2014.38.5.330
116. Hahn T, Barth S, Hofmann W, Reich O, Lang I, Desoye G (1998) Hyperglycemia regulates the glucose-transport system of clonal choriocarcinoma cells in vitro. A potential molecular mechanism contributing to the adjunct effect of glucose in tumor therapy. Int J Cancer 78 (3):353–360. doi:10.1002/(SICI)1097-0215(19981029)78:3<353:AID-IJC16>3.0.CO;2-7
117. Catrina SB, Okamoto K, Pereira T, Brismar K, Poellinger L (2004) Hyperglycemia regulates hypoxia-inducible factor-1alpha protein stability and function. Diabetes 53(12):3226–3232
118. Santos CR, Schulze A (2012) Lipid metabolism in cancer. FEBS J 279(15):2610–2623. doi:10.1111/j.1742-4658.2012.08644.x
119. Menendez JA, Lupu R (2007) Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis. Nat Rev Cancer 7(10):763–777. doi:10.1038/nrc2222
120. Currie E, Schulze A, Zechner R, Walther TC, Farese RV Jr (2013) Cellular fatty acid metabolism and cancer. Cell Metab 18(2):153–161. doi:10.1016/j.cmet.2013.05.017
121. Nomura DK, Long JZ, Niessen S, Hoover HS, Ng SW, Cravatt BF (2010) Monoacylglycerol lipase regulates a fatty acid network that promotes cancer pathogenesis. Cell 140(1):49–61. doi:10.1016/j.cell.2009.11.027
122. Kuemmerle NB, Rysman E, Lombardo PS, Flanagan AJ, Lipe BC, Wells WA, Pettus JR, Froehlich HM, Memoli VA, Morganelli PM, Swinnen JV, Timmerman LA, Chaychi L, Fricano CJ, Eisenberg BL, Coleman WB, Kinlaw WB (2011) Lipoprotein lipase links dietary fat to solid tumor cell proliferation. Mol Cancer Ther 10(3):427–436. doi:10.1158/1535-7163.MCT-10-0802
123. Kamphorst JJ, Cross JR, Fan J, de Stanchina E, Mathew R, White EP, Thompson CB, Rabinowitz JD (2013) Hypoxic and Ras-transformed cells support growth by scavenging unsaturated fatty acids from lysophospholipids. Proc Natl Acad Sci USA 110(22):8882–8887. doi:10.1073/pnas.1307237110
124. Louie SM, Roberts LS, Mulvihill MM, Luo K, Nomura DK (2013) Cancer cells incorporate and remodel exogenous palmitate into structural and oncogenic signaling lipids. Biochim Biophys Acta 1831(10):1566–1572. doi:10.1016/j.bbalip.2013.07.008
125. Beyaz S, Mana MD, Roper J, Kedrin D, Saadatpour A, Hong SJ, Bauer-Rowe KE, Xifaras ME, Akkad A, Arias E, Pinello L, Katz Y, Shinagare S, Abu-Remaileh M, Mihaylova MM, Lamming DW, Dogum R, Guo G, Bell GW, Selig M, Nielsen GP, Gupta N, Ferrone CR, Deshpande V, Yuan GC, Orkin SH, Sabatini DM, Yilmaz OH (2016) High-fat diet enhances stemness and tumorigenicity of intestinal progenitors. Nature 531 (7592):53–58. doi:10.1038/nature17173
126. Nieman KM, Kenny HA, Penicka CV, Ladanyi A, Buell-Gutbrod R, Zillhardt MR, Romero IL, Carey MS, Mills GB, Hotamisligil GS, Yamada SD, Peter ME, Gwin K, Lengyel E (2011) Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. Nat Med 17(11):1498–1503. doi:10.1038/nm.2492
127. Hojman P, Dethlefsen C, Brandt C, Hansen J, Pedersen L, Pedersen BK (2011) Exercise-induced muscle-derived cytokines inhibit mammary cancer cell growth. Am J Physiol Endocrinol Metab 301(3):E504–E510. doi:10.1152/ajpendo.00520.2010

128. Aoi W, Naito Y, Takagi T, Tanimura Y, Takanami Y, Kawai Y, Sakuma K, Hang LP, Mizushima K, Hirai Y, Koyama R, Wada S, Higashi A, Kokura S, Ichikawa H, Yoshikawa T (2013) A novel myokine, secreted protein acidic and rich in cysteine (SPARC), suppresses colon tumorigenesis via regular exercise. Gut 62(6):882–889. doi:10.1136/gutjnl-2011-300776
129. Rubino F, Marescaux J (2004) Effect of duodenal-jejunal exclusion in a non-obese animal model of type 2 diabetes: a new perspective for an old disease. Ann Surg 239(1):1–11. doi:10.1097/01.sla.0000102989.54824.fc
130. Dixon JB, le Roux CW, Rubino F, Zimmet P (2012) Bariatric surgery for type 2 diabetes. Lancet 379(9833):2300–2311. doi:10.1016/S0140-6736(12)60401-2
131. Sams VG, Blackledge C, Wijayatunga N, Barlow P, Mancini M, Mancini G, Moustaid-Moussa N (2015) Effect of bariatric surgery on systemic and adipose tissue inflammation. Surg Endosc. doi:10.1007/s00464-015-4638-3
132. Kumar H, Salminen S, Verhagen H, Rowland I, Heimbach J, Banares S, Young T, Nomoto K, Lalonde M (2015) Novel probiotics and prebiotics: road to the market. Curr Opin Biotechnol 32:99–103. doi:10.1016/j.copbio.2014.11.021