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Obesity and cancer pathogenesis

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Abstract

Overweight and obesity have reached pandemic levels on a worldwide basis and are associated with increased risk and worse prognosis for many but not all malignancies. Pathophysiologic processes that affect this association are reviewed, with a focus on the relation of type 2 diabetes mellitus with cancer, lessons learned from the use of murine models to study the association, the impact of obesity on pancreatic cancer, the effect of dietary fats and cholesterol as cancer promoters, and the mechanisms by which the intestinal microbiome affects obesity and cancer.

Keywords

cancer and obesity; diabetes; murine models; pancreatic cancer; dietary fats; cholesterol; intestinal microbiome

Introduction

Overweight and obesity are expanding on a worldwide basis, reaching levels of 60–70% of the adult population in developed countries and increasing rapidly in developing countries as well.[1–3] Based on the National Health and Nutrition Examination Study (NHANES), 35.7% of U.S. adults and 17% of U.S. children and adolescents were obese in 2009–2010.[4,5] Obesity is more prevalent among the elderly[4] and shows an ethnic distribution such that the prevalence of obesity is greatest in non-Hispanic Blacks, followed by Hispanics, followed by Caucasians.[6,7] Estimates based on logistic regression suggest that by 2030, obesity among U.S. adults will increase by at least 33%, such that 42–51% of the adult population will be obese, with a severe obesity prevalence of 11%.[8] This increase in the prevalence of obesity has been accompanied by increases in its associated comorbidities, including type 2 diabetes mellitus (T2DM), cardiovascular disease, and cancer. The increase in obesity is associated with an increased risk for development of multiple malignancies, including colorectal cancer; esophageal adenocarcinoma; and cancer of the gastric cardia, gallbladder, pancreas, liver, kidney, postmenopausal breast, endometrium and thyroid, as well as non-Hodgkin lymphoma, multiple myeloma, and most likely ovarian cancer high-grade prostate cancer; the list continues to grow.[9–14] While obesity is associated with an increased risk for development of many malignancies, some, such as lung cancer, premenopausal breast

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cancer, and esophageal squamous cell carcinoma appear to have an inverse association with obesity.[12]

In addition to their associations with greater incidence of cancer, overweight and obesity increase the risk of death for patients with most of the malignancies listed above, as well as for patients with premenopausal breast cancer and squamous cell oral tongue cancer.[15,16] In the United States, the impact of overweight and obesity has been estimated to account for 14% of cancer deaths in men and 20% of cancer deaths in women.[17] In addition to its pathophysiologic effects on tumor growth, obesity complicates management of patients with cancer further by making it more difficult to determine correct doses for chemotherapy.[18–23] In contrast, maintaining normal weight at a BMI < 25 kg/m^2 is projected to prevent 90,000 cancer deaths per year in the United States.[17,24]

The association of obesity with cancer and the potential role of intentional weight loss in preventing cancer incidence and mortality have been demonstrated in two major bariatric surgery studies.[25–27] In the Swedish Obese Subjects (SOS) Study, over 4,000 obese patients (BMI ≥ 34 kg/m^2) were enrolled prospectively in a comparison of 2010 bariatric surgery patients to 2036 controls. During a median follow-up of 10.9 years (range 0–18.1 years) bariatric surgery was associated with a 40% reduction in cancer incidence.[25,26] In a retrospective study, 7925 patients (BMI ≥ 35 kg/m^2) who had undergone gastric bypass surgery in a single surgical practice in Utah were compared to 7925 matched controls.[27] During a mean follow-up period of 7.1 years (18 years total) there was a 60% decrease in cancer mortality associated with bariatric surgery.[27] Both groups were predominantly composed of women, 84% in the Utah study and 70% in the SOS study.[25–27] Interestingly, the SOS study reported that the decreased incidence of cancer in association with bariatric surgery occurred in obese women but not in obese men.[26]

These alarming statistics are of even greater concern for their impact on public health when one considers the following trends. First, the increased incidence of obesity in children and the likelihood that obese children will mature into obese adults means that more people will be exposed to the obesity-associated cancer-promoting conditions for longer periods in their lives, where increasing evidence indicates that longer exposure is associated with greater risk for cancer incidence[28,29] and cancer deaths.[30] Second, the aging or graying of the baby boomer population, those born between 1946 and 1964, is expected to significantly expand the population of older adults (i.e., those over 65 years of age) among whom cancer and obesity are more prevalent.[4,31] Third, as noted above, the incidence of obesity and severe obesity in this population is projected to increase over the next two decades.[4,32] Thus, we are facing a so-called “perfect storm” of public health trends with convergence of the obesity pandemic, expansion of the elderly population, and the graying of the baby boomers to an age where they are at greatest risk for cancer development.

The best way to interfere with the obesity-associated comorbidities, particularly cancer, is to maintain normal body weight throughout life and to modify lifestyle behaviors in order to control weight when obesity has already developed. Lifestyle guidelines to achieve these goals, targeting weight control and cancer prevention, have been established,[33] and mechanistic and research opportunities for interventions as well as overcoming obstacles to

these processes have been identified.[3435] Nonetheless, because of the refractory global and individual nature of the problem, obesity and its associated comorbidities constitute public health issue number one.

As a result of its dire public health implications and its intrinsic interest as a pathophysiologic phenomenon, the relation of obesity to cancer and its mechanisms, mediators, and potential interventions have become the subject of expanded research. These initiatives have been increasing since the association of obesity with cancer risk and prognosis was raised to high visibility in the biomedical community with publication of the results from the American Cancer Society Cancer Prevention Study II.[17,24,36] Nonetheless, the obesity–cancer relation still remains a surprise revelation to much of the public and some of the biomedical community as well, and greater awareness and understanding might contribute to more successful preventive and remedial interventions.

Current mechanisms by which obesity is postulated to promote cancer include (1) increased levels and bioavailability of growth factors such as insulin and insulin-like growth factor (IGF-1), (2) increased sex steroid hormones such as estrogen and factors affecting their metabolism, (3) altered adipocytokine levels such as leptin, adiponectin, and visfatin, all originally thought to primarily affect energy balance, but now known to have growth, immune, and tumor-regulatory functions, (4) low-grade inflammation and oxidative stress affecting growth-promoting cytokines and immune modulation, and more recently, (5) altered microbiomes, especially those composing the intestinal flora.[10,37,38] The goal of this review is to highlight recent developments that provide important insights in several, of these areas. In selected cases, the reader is referred to recent reviews that provide more comprehensive details on the specific subject.

In the following material, we review several different topics and approaches connected primarily by their relation to obesity-associated cancers and because of the recent insight they provide for understanding the process. The first section focuses on the impact of diabetes and cancer. Previously assumed to be two separate comorbidities associated with obesity, it has now become clear that diabetes and cancer have important mechanistic relations. Moreover, concerned patients with diabetes are beginning to ask questions about this relation, especially regarding the carcinogenic and/or potential therapeutic effects of agents used to treat diabetes. The second section, on animal models, provides recent insights into the obesity cancer issue gained from these experimental systems, especially as to the role of cancer stem cells. The third section provides a focus on recent studies combining the impact of epidemiology, molecular genetics, and murine models on the relation between obesity and pancreatic ductal adenocarcinoma. This focus was selected, because of exciting new developments and also because, of all the obesity-associated malignancies, pancreatic cancer is probably the most fulminant and refractory to therapy. Therefore it is a disease where novel, obesity-focused approaches to therapy could provide highly important contributions. Moreover, the major tumor types of obesity-associated cancers, postmenopausal breast[13,39–47] and colorectal cancer,[48–52] have been extensively reviewed. Recent reviews have likewise been published on the association of obesity with hepatocellular cancer (HCC), the fourth most common malignancy on a worldwide basis.[53–57] The fourth area reviewed provides a conceptual approach to understand the

contribution of dietary fats to cancer and their ability to affect the mediating processes in the presence or absence of obesity. In addition, this section reviews the exciting new research providing a pathway to explain how hypercholesterolemia may promote cancer through an estrogen mimetic process. A relatively new research area investigating the profound impact of the intestinal microbiome to obesity and cancer is reviewed in the final section. Overall, this review provides a highly transdisciplinary overview of some of the recent exciting developments in understanding the relationship between obesity and cancer and its pathogenesis.

Impact of diabetes on cancer

While T2DM and cancer are each comorbidities of obesity, T2DM, the metabolic syndrome, and their associated pathophysiologic effects, including insulin resistance, hyperinsulinemia, increased bioavailable IGF-1, and hyperglycemia function, also increase both the risk of multiple types of cancer and cancer mortality.[12,58–62] For example, the risk for development of post-menopausal breast cancer and related mortality are both increased in women with T2DM.[63–66] In addition, T2DM has been hypothesized to contribute to the disparity in survival among minority women with postmenopausal breast cancer, where Hispanic and African American women have higher rates of T2DM compared to Caucasian women,[67] and where Hispanic and African American women have lower rates of developing postmenopausal breast cancer, but higher mortality rates compared to Caucasians.[66,68] Other malignancies whose risk increases with T2DM include colorectal, endometrial, pancreatic, hepatocellular, and bladder cancer and non-Hodgkin lymphoma.[12] Interestingly, prostate cancer appears to be inversely associated with T2DM, possibly reflecting the lower testosterone levels that accompany T2DM.[69,70]

The insulin resistance and consequent hyperinsulinemia that accompany T2DM and metabolic syndrome serve to facilitate glucose uptake by muscle, fat, and liver mediated by type B insulin receptors. Elevated levels of insulin may also stimulate mitogenesis and growth in a number of tissues, especially embryonic and tumor tissues, containing type A Insulin receptors.[3,71–74] Elevated insulin levels may also increase IGF-1 and decrease IGF-binding proteins, thereby providing higher levels of biologically active IGF-1 proteins, which further interact with cell-surface receptors to stimulate tumor growth.[75,76] The growth- and tumor-promoting effects of insulin and IGF-1, starting with cell-surface receptors and progressing downstream through the phosphatidylinosotide 3-kinase (PI3K)–AKT–mTOR pathway regulating cell growth and differentiation, and the Ras–Raf–MEK–MAPK mitogenic pathway, have been extensively reviewed.[77–79]

An alternative mechanism by which hyperinsulinemia may contribute to cancer development and/or progression is through upregulation of cellular metabolic activity leading to DNA damage and potential mutagenesis. Applying elevated insulin concentrations at levels achievable *in vivo* during hyperinsulinemia to HT-29 and Caco-2 human colon cancer cell lines in culture resulted in increased mitochondrial production of reactive oxygen species and DNA strand breaks. Similar DNA damage was produced by application of high insulin levels in tissue culture to normal rat intestinal epithelium or normal human peripheral blood lymphocytes.[80] The contribution of elevated insulin levels

to increased cancer risk is supported also by epidemiologic studies indicating that therapeutic use of insulin or insulin secretagogues such as sulfonylureas are associated with increased risk of cancer in both animals and humans[59,60] In contrast, metformin, which is used to treat diabetes by interfering with hepatic gluconeogenesis, and consequently lowering insulin secretion, has been associated with a decreased risk for cancer development.[12,81,82] While metformin has an insulin-lowering effect, it also restricts growth in tissue culture and *in vivo* by insulin-independent mechanisms involving inhibition of activation of adenosine monophosphate kinase (AMPK) and consequently inhibiting the mTOR pathway, critical for cell proliferation.[81] Metformin was shown to increase the remission rate in diabetic women taking metformin who were receiving neoadjuvant therapy for breast cancer,[83] and metformin is currently undergoing early clinical trials for treating a variety of malignancies.[40,81,84–87]

Another class of antidiabetic therapies that may affect cancer are targeted at peroxisome proliferator-activated receptor γ (PPARγ), which is a lipid-activated transcription factor responsible for upregulating many of the components of adipocyte differentiation, fat storage apoptosis, and the anti-inflammatory response.[88] PPARγ agonists of the thiazolidinedione class, especially pioglitazone, have become important agents for the control of diabetes, hyperinsulinemia, hyperglycemia, and hyperlipidemia.[88] Pioglitazone has also been shown to prevent intestinal carcinogenesis in genetically predisposed and carcinogen-treated rodent models.[89,90]

From a mechanistic viewpoint, tumor cells, compared to normal cells, require increased uptake of glucose to support energy generation by aerobic glycolysis. Cancer cells also use increased glucose for synthesis of fatty acids, nucleotides, and other building blocks required for tumor growth.[91,92] From a diagnostic viewpoint, this requirement for increased glucose uptake by tumor cells relative to normal cells provides the basis for the increased uptake of [^{18}F]-fluorodeoxyglucose, which is used as a tracer molecule to identify tumors by positron emission tomography.[93] This process may be significantly influenced by obesity, diabetes, blood glucose, and insulin levels.[93] Since metabolizing glucose by the process of aerobic glycolysis yields less energy in the form of ATP than the metabolism of glucose by oxidative phosphorylation, and since tumor cells need even more glucose to synthesize the structural components required to expand tumor mass, this increase in glucose need is supported by diabetes-associated hyperglycemia. Further indication of the clinical impact of these observations can be found in a recent series of reports[94, 95] showing that a Western diet consisting of red meat, processed meat, refined grains, and sugary deserts was associated with increased risk of recurrence and inferior survival in patients with stage III colon cancer.[94] In a subsequent study to further examine the dietary components responsible for these adverse outcomes, it was shown that dietary glycemic load and carbohydrate content were both associated with poorer disease-free, recurrence-free and overall survival.[95] The adverse effects of the increased glycemic and carbohydrate loads occurred in patients with higher body mass index.[95] These studies suggest the high dietary glycemic load in patients with elevated body mass index, who are likely to have metabolic syndrome or T2DM, can lead to hyperglycemia, providing increased fuel for tumor growth and progression leading to more rapid mortality. These observations are further supported by a

recent report showing worse disease-free survival among 4,131 Korean colorectal cancer patients with T2DM compared to patients without T2DM.[96] These and other studies indicate the important need to incorporate pharmaceutical, behavioral, and potentially surgical approaches to weight control and reduction of fat mass in patients undergoing cancer therapy.[97–99]

Murine models, obesity, and cancer

Murine models of human malignancies provide important systems to study the impact of energy balance, including diet, obesity, and exercise on tumor initiation and progression. Overall, these studies have shown that high-fat diets (HFDs) and diet-induced obesity (DIO) serve as tumor promoters resulting in earlier appearance, greater frequency, accelerated growth, larger tumor size, and, in some cases, more frequent metastasis of genetically initiated tumors. These genetic alterations may develop spontaneously and/or be acquired hereditarily, they may be induced by DNA-damaging agents or they may be created by genetic manipulation.[100] For example, the *Min* (multiple intestinal neoplastic) mutation, resulting in a truncation mutation in the mouse adenomatous polyposis coli (*Pac*) gene, provides a model for both the human hereditary condition familial adenomatous polyposis and also for sporadic colon cancer in humans, where the gene is commonly mutated at an early time in tumor development.[101–103] Studies in C57BL/6J mice bearing the $Apc^{Min/+}$ genotype consistently demonstrate that HFDs accelerates development and increases size and number of intestinal tumors.[104] The tumor-promoting effects of HFDs are both concentration- and composition-dependent and can be stimulated even in HFD-fed obesity-resistant animals.[105] It is noteworthy, however, that in the *ob/ob* leptin-deficient, the *db/db* leptin receptor-deficient, and the A^y agouti mouse models, where obesity develops independent of diet composition, obesity still serves to promote neoplastic changes in intestine and other tissues.[90,106–110] Moreover, another recent study has shown that HFD-generated DIO continues to promote increased intestinal neoplasms, even when the carcinogen azoxymethane (AOM) is administered after the HFD has been replaced by regular chow.[111]

Using the $Apc^{1638/+}$ mouse model of intestinal neoplasia to investigate DIO-associated increases in tumors, it was observed that surgical removal of visceral fat from mice with DIO attenuates intestinal macroadenoma development in female but not male mice, compared with controls.[97,98] In contrast, caloric restriction in these mice reduced intestinal macroadenoma development in males but not females.[97] Attenuation of macroadenoma development was shown to occur at the micro- to macroadenoma transition, illustrating the role of obesity as a tumor promoter rather than initiator. Most interesting, however, is that these experiments now indicate that obesity and adipose tissue, independent of dietary fats, can each promote cancer, and the process is differentially influenced by gender.[97,105,111] It is noteworthy, however, that feeding a Western-style diet without mutagens to C57BL/6J mice for greater than 18 months resulted in benign or malignant intestinal tumors in approximately 40% of mice.[112] Thus, in addition to the numerous demonstrations that HFDs, obesity, and adipose tissue may all serve as promoters of cancer growth, it also appears that long-term exposure, greater than 1 year in mice, may actually exert a mutagenic/carcinogenic effect. Although the possibility remains, in these long term

experiments, that the HFD, obesity, and adipose tissue effects remain those of a promoter affecting acquired, sporadic mutations as opposed to serving as primary mutagen/carcinogen.

Comparing the effects of HFDs in different strains of mice, long-term feeding of a HFD, for more than one year, in C57BL/6J mice but not A/J mice has been shown to cause obesity and recapitulate all the steps of human non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), including steatosis, inflammation, ballooning degeneration, fibrosis, cirrhosis, and dysplasia leading to HCC.[113] Molecular analysis indicates the importance of the Myc pathway and NF-κB-associated inflammatory cytokines.[113] This observation is notable in that feeding C57BL6/J mice long-term HFDs leads to the development of malignancy, even without use of hepatocarcinogens or known predisposing genetic alterations. Nonetheless, these studies show interaction of genes with environment since a HFD leads to obesity and HCC in C57BL/6J but not A/J mice.[113] Similar results in terms of developing multiple, discrete hepatic dysplastic nodules characteristic of HCC, without use of hepatocarcinogens or genetic alterations, occurred in Tsumora, Suzuki, obese diabetes (TSOD) male mice with a polygenic disorder leading to diabetes and obesity while being maintained on a basal diet.[114] It is noteworthy that HCC in both the C57BL/6J and TSOD mice occurred after 12 months of age and long-term obesity.[113,114] As noted above, these cancers, resulting after long-term exposure to HFDs and long-term obesity, suggest the possibility of a fat-associated mutagenic/carcinogenic effect.

Following subcutaneous inoculation of tumor cells from a transplantable mouse forestomach carcinoma (MFC)-derived cell line, it was shown that mice with DIO compared to lean mice developed accelerated tumor growth, enhanced tumor size, and reduced apoptosis.[115,116] Tumors derived from obese mice were noted to have higher levels of intratumoral adipocyte content, suggesting the possibility of a paracrine process mediating the effects of adipocytes on tumor cell growth. Compared to lean mice, the DIO mice showed hyperglycemia, glucose intolerance, insulin resistance and elevated Visfatin levels, both in tumor cells and circulation, and elevated Sirt-1 and c-Myc proteins in tumor cells.[116,117] Visfatin, an adipocytokine secreted by adipocytes, was initially identified as pre-B cell colony-enhancing factor (PBEF), based on its activity as a growth factor for early stage B cells. Visfatin is now known to be identical TO nicotinamide phosphoribosyl transferase (Nampt).[118] It catalyzes the condensation of phosphoribosyl-1-pyrophosphate with nicotinamide, to form nicotinamide mononucleotide (NMN), a precursor in the salvage pathway generating NAD^+. Sirt1 is an NAD^+-dependent histone deacetylase, which deacetylates a variety of proteins including the p53 tumor suppressor, thereby promoting proliferation of cells with DNA damage. cMyc is a key transcription factor linked to the proliferation of tumor cells.[119] These proteins, cMyc, Sirt1, and Nampt have recently been shown to be upregulated in a variety of tumors and are proposed to be a tumor growth-promoting pathway.[120] Thus, the higher circulating and tumor levels of Nampt accompanied by elevated tumor levels of Sirt1 and cMyc in mice with DIO, compared to lean mice, provides another pathway by which obesity may promote gastric cancer and possibly tumors of other organs.

The adipokine leptin, important in regulating appetite, body weight, and energy balance[121] is elevated in proportion to body fat mass as a mechanism to control food intake. Deficiency of leptin action, which can result from mutation in the leptin gene (*ob*) or the leptin receptor gene (*db*), as well as from leptin resistance, results in dysregulated appetite control, obesity, and obesity-associated diabetes.[122–124] Tissue culture studies show that leptin stimulates crosstalk between breast cancer cells and the tumor microenvironment that promotes cell proliferation and migration, whereas leptin depletion reduces proliferation and migration.[125] Studies in mouse and human tumors and tumor-derived cell lines show that leptin stimulates both an increase and activation of growth-regulatory pathways including JAK/STAT, NF-κB, PI3KKinase/AKT/mTOR and MAP kinase in colorectal cancer and HCC[123,126] and inhibits apoptosis.[127]

Recent studies with the MMTV-Wnt-1 mammary tumor mouse demonstrate that obesity-mediated elevated levels of leptin promote survival and growth of breast cancer stem cells through promotion of stem cell self-renewal transcription factors NANOG and Sox2.[109,128] Leptin treatment has been shown to upregulate a number of growth-promoting pathways in breast cancer stem cells including the Stat3 transcription factor.[129,130] Knockdown of the leptin receptor in both mouse and human breast cancer cell lines reduces tumor growth.[128] More recently, a series of nanopeptides have been synthesized that block leptin effects *in vitro and in vivo* and interfere with growth of human HT29 colon and MCF-7 breast cancer cells. These leptin receptor antagonists interfere with several leptin-stimulated pathways including JAK/Stat3, MAPK, PI3K/AKT, cyclin D1, and E-cadherin.[131] Although still in early development, these studies hold promise for targeting leptin activity to control obesity-associated tumors.

While elevated leptin levels commonly seen in obesity may directly affect cancer cell growth *in vitro* and *in vivo*, recent studies show that, in diabetic MKR mice bearing orthotopic breast tumors, continuous infusion of leptin reduced tumor progression in mice while glucose tolerance improved. These paradoxical observations, suggesting that leptin may stimulate tumor growth, or show the opposite effect of controlling tumor growth, indicate that important differences are likely to be noted as adipocytokines and other biologic factors are manipulated to control both their tumor-promoting as opposed to their physiologic functions[132]

In another mouse model, HFDs have been shown to produce inflammation through upregulation of NF-κB signaling in the mouse prostate.[133] The transgenic TRAMP mouse, containing the prostate-specific rat probasin promoter linked to the SV40 large T antigen gene, has been shown to undergo more rapid development of prostate intra-epithelial neoplasia and cancer in obese mice and in mice fed a Western-type diet, enriched in fat and cholesterol, compared to those fed a regular chow diet.[134–137] TRAMP tumor cells injected into flanks of C57BL6 mice form tumors that are larger in HFD-fed animals compared to normal chow-fed animals. Tumors were enlarged in HFD-fed mice even when the mice were resistant to DIO.[138] TRAMP prostate tumor cell growth can be reduced by treatment with adiponectin, whose effect can be blocked by simultaneous treatment with leptin.[139] Leptin may also be involved in promoting prostate cancer cell growth in TRAMP mice in an androgen-independent manner.[140] Interestingly, feeding TRAMP mice a diet enriched with

fish oil reduced the overall incidence of tumors and more specifically of carcinoma, compared to high fat-fed mice.[141] Likewise, feeding mice a high-fat walnut-based diet reduced tumor size and IGF-1.[142] These latter studies show again that the tumor-promoting effects of fats are both concentration and composition dependent.

Sox2 is required for self-renewal of both stem cells and cancer stem cells.[143] Recent studies using a Sox2-green fluorescent protein fusion reporter to isolate Sox2-expressing stem cells from mouse foregut showed that these cells were capable of growing as esophageospheres in 3D culture.[143] Overexpression of Sox2 in the mouse esophagus and forestomach resulted in hyperplasia with increased proliferation and expansion of typical basal cell populations within both the esophagus and forestomach. In these mice, squamous cell carcinoma (SCC) developed in the forestomach but not in the esophagus. Subsequent studies showed increased IL-6 and Stat3 in forestomach tumors, and treatment with IL-6 in tissue culture resulted in abnormal morphology of both esophageal and forestomach-derived cells, supporting a role for the IL-6-Stat3 pathway in promoting transformation in Sox2-expressing esophageal cancer stem cells. This pathway and its role in tumor generation were further supported by treating mice with dexamethasone to suppress inflammation, resulting in reduced IL-6 accumulation and reduced tumor incidence. Transduction of Sox2-expressing esophageal stem cells with an active Stat3-expressing lentivirus, followed by their transplantation into immunodeficient NOD/SCID mice, confirmed the requirement for cooperation between Sox2 and Stat3 for tumor promotion *in vivo* and *in vitro*.[143] These investigators also reported that increased levels of phospho-Stat3 and phopho-Sox2 in 83 patients with human esophageal SCC correlated with poorer prognosis, as demonstrated by 5-year survival (14.3% vs. 42.9%, $P < 0.01$) in patients whose tumors express Sox2 only. Importantly, knockout of Sox2 and/or Stat3 in either mouse or human cell lines reduced their tumor-forming capacity in culture and in xenografts.

These studies in esophageal cancer clearly demonstrate a requirement for Sox2-expressing stem cells and stimulation by IL-6-type inflammation, both *in vitro* and *in vivo*.[143] IL-6 treatment increases Stat3 production, which together with Sox2 stimulates formation of mouse foregut SCC. It is interesting, however, that the incidence of esophageal SCC in humans is decreasing, while the incidence of esophageal adenocarcinoma is increasing along with the increased incidence of obesity.[144] As noted above, obesity is clearly associated with an increase in circulating IL-6 and other inflammatory cytokines. Also as noted above, the same factors, Sox2 and Stat3, along with NANOG and OCT4, have been shown to be upregulated and/or activated by the adipocytokine leptin, serving as a mediator of the obesity-associated increase in postmenopausal breast cancer.[109,128] In a study of 392 patients with Barrett's esophagus, risk of developing esophageal adenocarcinoma increased with increasing leptin concentration and decreasing adiponectin[145] Thus, it will be interesting to test the effect of obesity in the forestomach system outlined above to determine whether the addition of obesity and/or adipokines to this system will differentially stimulate tumor growth and/or histopathology. Other potential contributions to the development of esophageal adenocarcinoma have recently been reviewed.[144]

Obesity and pancreatic cancer

An association of obesity with pancreatic cancer has long been observed. Other risk factors for pancreatic cancer include tobacco use, pancreatitis, and T2DM.[146] More recent studies implicate GI tract microflora as well.[147] The combination of molecular biologic investigations, genetic-epidemiology studies, and murine-model approaches has provided important complementary insights into these relations. Obesity is associated with an increased risk in men and women of both pancreatic cancer occurrence and pancreatic cancer-associated mortality.[24,29,146,148] In 2004, the relative risk for pancreatic cancer associated with overweight and obesity was reported as ranging from 1.3 for BMI of 25–30 kg/m^2 to 1.7 for BMI of ≥ 30 kg/m^2. Based on percent overweight and obesity in 1999–2000, it was determined that 26.9% of cases of pancreatic cancer in the United States were attributable to overweight and obesity.[24] The American Cancer Society Cancer Prevention Study II, in which more than 900,000 U.S. adults were followed prospectively from 1982 to 1998, showed that the increased mortality of obesity associated with pancreatic cancer in men with BMI 35.0–39.9 kg/m^2 was RR = 1.49 (95% CI 0.99–2.22, $P < 0.001$) and for women with BMI 35–39.9 kg/m^2 was RR = 1.41 (95% CI 1.01–1.99) and for BMI ≥ 40, was RR = 2.76 (15% CI 1.74– .36, $P < 0.001$). For men and women who had never smoked, death from pancreatic cancer carried RR = 2.6 (95% CI 1.29 – 5.35, $P = .005$) for patients with BMI 35.0–39.9 kg/m^2. Among subjects from two large cohorts,[146] the Nurses' Health Study (NHS), with 117,041 women, and the Health Professionals Follow Up Study (HPFS), with 46,468 men, obesity significantly increased the relative risk of pancreatic cancer with RR = 1.72 (95% CI 1.92–2.48) for patients with BMI ≥ 30 kg/m^2 compared to those with BMI < 23 kg/m^2.

Based on initial BMIs obtained at time of study enrollment and after adjusting for age, sex, ethnicity, and tobacco use, survival from pancreatic cancer was found to be reduced by obesity with HR for death of 1.53 (95% CI 1.11–2.09) comparing BMI ≥ 35kg/m^2 to BMI < 25kg/m^2 (P trend = .001).[30,146] Patients with high BMI were more likely to present with more advanced disease. Fifty-seven point four percent of patients with BMI < 25 kg/m^2 had metastatic disease at time of diagnosis, whereas 72.5% of patients with BMI ≥ 30 kg/m^2 presented with metastatic disease. Moreover, the longer the duration of obesity preceding the diagnosis of pancreatic cancer, the stronger the association of increased HR for death. For patients with BMI ≥ 30 for 18–20 years, the HR was 2.31 (95% CI 1.48–3.6, $P < .001$), whereas for those with BMI ≥ 30 for 2–4 years the HR was 1.29 (95% CI 1.04–1.60 $P = .04$).[30] These observations indicate that long-standing obesity is more likely to be associated with shorter survival for pancreatic cancer and suggests obesity as a chronic promoter for pancreatic cancers with multiple opportunities over the time of exposure to serve as a potential target for preventive interventions.

Analyzing another series of 2249 cases and 3654 controls from the Pancreatic Cancer Consortium,[149] it was found that lifestyle factors, including smoking, diabetes for greater than 3 years, heavy alcohol use, and BMI greater than 30, moderately but significantly affected odds ratio risk for pancreatic cancer by 1.26–2.20. In comparison, non O-ABO genotype showed an OR 1.23–1.58 compared to the OO genotype, which had an OR of 1.0. Additional analysis suggested no further significant effect of genotype on pancreatic cancer

risk. Performing a gene–environment genome-wide association study (GWAS) in 2028 cases of pancreatic cancer versus 2109 matched controls from the Pancreatic Cancer Case Control Consortium (PanC4),[150] it was found that the inflammatory, NF-κB–mediated chemokine signaling pathway, associated with obesity, significantly modified the risk of pancreatic cancer ($P = 3.29 \times 10^{-6}$), while the calcium signaling pathway associated with insulin secretion and obesity showed a near significant interaction in modifying risk of pancreatic cancer ($P = 1.57 \times 10^{-4}$).[150] Epidemiologic studies have also shown *Helicobacter pylori* infection to be a risk factor for pancreatic cancer, potentially influenced by ABO blood type.[147] Although controversial, association of *H. pylori* colonization with obesity and T2DM have been reported.[151]

Pancreatic cancer has been extensively studied in murine models using engineered genetic alterations that resemble those observed in human tumors. These include activation of the KRas tumor promoter and inactivation of tumor suppressors such as pInk4/Arf or p53.[152, 153] These mouse models have been useful in studying tumor development and therapeutics[154, 155] and, recently, in evaluating the role of obesity in pancreatic cancer. These studies suggest that pancreatic ductal adenocarcinoma (PDA) is initiated by KRAS mutations in pancreatic acinar cells, followed by upregulation of KRAS expression in response to inflammatory stimuli or increased EGFR activity, resulting in acinar–ductal metaplasia.[154] Similar effects occur in hamster models, where inflammatory stimuli can be increased in response to HFD feeding.[154] Inflammation activates Stat3 and NF-κB in the pancreas, both of which are required for upregulation of NF-κB and transformation, but neither of which will produce pancreatic cancer in the absence of *KRAS* mutation[154,156] The inflammatory component can be interfered with by cyclooxygenase inhibitors[156] and metformin,[157] each of which can delay development of PDA in mouse models. Interestingly, metformin use has been associated with lower risk of PDA in humans with diabetes.[158] Potential mechanisms by which obesity promotes pancreatic cancer is by stimulating inflammation, including IL-6, Stat3 and NF-κB pathways; promoting epithelial mesenchymal transition; and interfering with autophagy, have recently been extensively reviewed.[159]

Using a mouse model with a conditional activating *KRas* G12D mutation,[160] it was shown that animals fed a high-fat, high-caloric diet, compared to those fed a low-fat diet, developed obesity associated with increased levels of circulating glucose, insulin, leptin, IGF-1, and increased premalignant pancreatic intraepithelial neoplasia (Pan IN), but not invasive pancreatic cancer. Although in these studies, Pan IN was clearly promoted by high-fat, high-caloric diet, the absence of frank development of pancreatic cancer may have been due to insufficient time for progression to invasive cancer and/or an absence of sufficient predisposing mutations.[160] Nonetheless, these experiments clearly demonstrate that an HFD serves as a promoter of the neoplastic premalignant process in pancreatic epithelial cells.

Pursuing the observation that pancreatic cancer in humans results from a series of sequential genetic changes in which tumor promoters are activated and tumor suppressors are inactivated, the effects of normal diet (ND), caloric restricted (CR) diet (70% of control calories) and HFDs were compared in mice with conditionally activated *KRas* mutations that were heterozygous for inactivation of the tumor suppressor Ink4a/Arf.[161] The HFD led to

DIO at 10 weeks associated with elevated serum insulin and IGF-1, while CR mice gained the least weight and had lower than normal levels of circulating insulin and IGF-1. Increased caloric content of diet resulted in progressive increase in pancreatic inflammation, fibrosis, and Pan IN. Pan IN occurred in all mice, independent of diet, but showed increased histopathological grade of neoplasia, with progression from mice fed CR diet, through ND and DIO mice. PDA did not occur in the CR mice, but did develop in ND-fed mice and showed further increase in incidence in DIO mice. Using immunohistochemistry, the authors showed increasing levels of phospho-AKT, phospho-mTOR, and phospho-S6 ribosomal protein with progression from CR diet to ND to DIO. In LID mice, with a deficiency in hepatic IGF-1 production, orthotopically injected KRas-activated Ink4a$^{+/-}$ tumor cells showed reduced levels of tumor cell proliferation. Growth of these cells was, however, stimulated by infusion of IGF-1.[161] These studies provide a clearly defined mouse model to study the mechanism(s) by which obesity promotes pancreatic cancer and demonstrate that mutations are clearly required in both tumor promoters such as Ras and tumor suppressors such as Ink4a/Arf for obesity stimulation of PDA. These studies also support an important role for IGF-1 as a tumor promoter, acting through the AKT, mTOR, and S6K pathway. Targeting this pathway could provide important therapeutic opportunities for prevention and/or treating obesity-promoted PDA.

Dietary fats and cancer

Studies of the impact of HFD and DIO on rodent models of intestinal cancer predominantly demonstrate that those lifestyle and physiologic modifiers act as tumor promoters and/or suppressors, which in most cases require a primary genetic alteration to either activate an oncogene and/or inactivate a tumor suppressor in order to develop into a malignancy.

Doerner and colleagues[100] reported that dietary fats promoted intestinal inflammation and malignancy independent of obesity, but dependent on type of dietary fat in *Apc*$^{Min/+}$ mice. Different fatty acid composition of HFDs could stimulate or suppress intestinal inflammation and tumor development. Further support for the concept that dietary fat, independent of obesity, promotes tumor growth comes from the demonstration that a high-fat, lard-based diet fed to obesity-resistant BALB/c mice promoted more rapid growth and metastasis and shortened survival in mice receiving an orthotopic inoculation of syngeneic 4T1, estrogen receptor–negative, mammary carcinoma cells. Supporting a role for inflammation as mediator of this process, the HFD was accompanied by increased macrophage infiltration into adipose tissue and increased circulating inflammatory cytokines including the adipocytokine leptin.[162]

Fatty acids affecting intestinal cancer can be divided into two groups, those that promote colon neoplasia, including medium-chain saturated fatty acids, lauric and myristic acids, long-chain saturated fatty acids, palmitic and stearic fatty acids, ω6 polyunsaturated fatty acids (PUFA), and linoleic and arachadonic acids, all of which have proinflammatory, tumor-promoting effects as their mechanism of increasing colon cancer risk, enhancing colon cancer development and increasing mortality. In contrast, unsaturated fatty acids such as oleic and conjugated linoleic acids and ω3 PUFAs including eicosapentaenoic, docosahexaenoic and linolenic acids all have anti-inflammatory properties, function as

tumor suppressors, and reduce tumor incidence and growth in mice predisposed to neoplasia owing to either genetic alteration or mutagen exposure.[100,163] These same principles apply to NAFLD, where hepatocyte lipotoxicity is associated with saturated fatty acids but not with monounsaturated fatty acids, with the effects of the former mediated through activation of -lysosomal permeabilization associated with mitochondrial damage, endoplasmic reticulum stress, and activation of apoptosis.[55]

Studies of ω3-, and ω6-PUFA content in adipocytes derived from visceral white adipose tissue from normal and obese patients, undergoing surgery for benign conditions or colorectal cancer, show a negligible variation in ω3-PUFAs across the different conditions. However ω6-PUFAs were increased in adipocytes from obese patients, with higher levels in adipocytes from obese patients with colon cancer compared to those in cells from obese patients who were cancer free.[164] These cells were analyzed for phosphorylated Stat (p-Stat), a transcription factor associated with inflammation and protumorigenic microenvironments,[165] and for PPARγ, important in normal adipocyte development and also for promoting anti-inflammatory processes.[88] Elevated p-Stat was found in adipocytes from both normal-weight and obese patients with colorectal cancer, but it was more significantly increased in cells from obese patients with colon cancer. In contrast, PPARγ was decreased in both non-obese patients with colon cancer and obese patients with and without colon cancer. Adiponectin, an adipocytokine with antiproliferative, anti-inflammatory, and proapoptotic effects was decreased in cells from patients with or without colon cancer.[164] Treatment of the adipocytes in tissue culture with the anti-inflammatory ω3-docosahexaenoic acid reduced inflammatory markers of cell-associated p-Stat3 and secretion of the proinflammatory cytokine IL-6 and upregulated PPARγ and adiponectin. These studies show association of an increased ω6-/ω3- ratio in visceral adipocytes from obese patients associated with a decrease in PPARγ and adiponectin in adipocytes from obese patients with and without colon cancer. These changes are further associated with an increase in activation of p-Stat3 in cells from obese patients with colorectal cancer. All of these changes can be corrected in tissue culture by treatment with DHA. These results, coupled with those outlined above, suggest a reciprocal proinflammatory, prooncogenic, tumor-promoting interaction between colon cancer and visceral adipocytes that can be modified by administration of selected lipids. As noted earlier, this relation may also be amenable to interference by thiazolidinediones.[88–90]

From a clinical epidemiology viewpoint, ω3-PUFAs have been noted to have multiple health benefits, and recent studies, although with mixed results, suggest that dietary ω3-PUFAs may decrease the risk of several malignancies, including breast, colon, lung, and prostate cancer.[43,166] Similarly, consumption of high quantities of olive oil was shown to be associated with decreased risk of upper aerodigestive and breast cancer and, possibly, colorectal cancer, whereas butter consumption was associated with increased risk.[163] Another series of natural product studies has recently been reported with dietary nut consumption where the beneficial effects are probably attributable to fatty acids. As noted above, feeding mice a high-fat walnut-based diet reduces prostate tumor size in TRAMP mice.[141] Recent studies in humans show that increasing nut intake is associated with decreased risk for obesity, metabolic syndrome, T2DM, pancreatic cancer, all-cause mortality, and, more specifically, cancer mortality.[167–169]

These studies are consistent with multiple epidemiologic investigations indicating that the type of fat leading to DIO and particularly its pro- or anti-inflammatory properties are important in the process of HFD- and DIO-promoted malignancy. These observations and those noted above, that dietary components, independent of obesity, and obesity, independent of HFDs, can each promote intestinal neoplasia, suggests that some common factors, potentially stored fats, inflammatory or immune cytokines, or intestinal microflora may be important contributors. These observations suggest also that weight loss to reduce obesity will not completely eliminate the cancer-promoting activity of DIO, at least not immediately. Clearly, research is needed to fully understand these pathways and their common mediators and to determine potential interventions to interfere with their consequences of promoting malignancy. Such agents would be highly useful, for example, in situations where obesity in adolescence may still be associated with delayed increased risk for cancer later in adult life, despite restoration of normal weight.[170,171]

Another abnormality, hypercholesterolemia, commonly associated with obesity, T2DM and metabolic syndrome.[172,173] is a risk factor for cardiovascular disease and cancer.[174] High cholesterol promotes increases in colon cancer risk in men and breast cancer risk in women. Cholesterol synthesis is inhibited by statins, which are competitive inhibitors of the cholesterol synthesis enzyme 3-hydroxyl-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase). Recent pharmacoepidemiology studies show significant decreases in colorectal cancer,[175] decreased overall cancer mortality,[176] and improved breast cancer survival[177] with statin use, especially with longer periods of statin use (≥ 4 years).[178]

Although the association of hypercholesterolemia with cancer has been established and pharmacoepidemiology studies have suggested that statin therapy could serve as a useful intervention, a potential mechanism by which cholesterol may promote cancer has just recently been identified.[179–181] The oxysteroid 27-hydroxycholesterol (27HC) is a primary metabolite of cholesterol, whose synthesis is catalyzed by the cytochrome P450 oxidase CYP27A1. Although obese mice do not normally develop hypercholesterolemia, mice engineered to develop hypercholesterolemia when fed a HFD also developed increased circulating 27HC. At concentrations achievable in patients, 27HC stimulates growth and metastasis in tissue culture and *in vivo* in ER^+ MCF-7 human breast cancer cells. Cholesterol and 27HC likewise stimulated spontaneous ER^+ mouse mammary tumors arising in transgenic mice and in mice transplanted with ER^+ mouse EO771 breast cancer cells. The tumor-promoting effects of cholesterol and/or 27HC were interfered with by cytochrome P450 monooxygenase CYP7B1, which catabolized and reduced cellular levels of 27HC. The effects of 27HC were likewise inhibited by treatment with the estrogen receptor antagonist fulvestrant. CYP27A1, responsible for synthesis of 27HC from cholesterol, was identified in both breast cancer cells and resident macrophages, suggesting that 27HC may be provided to breast cancer cells by both paracrine and autocrine mechanisms. Interestingly, elevated levels of CYP7B1 mRNA in human breast cancer cells was associated with improved survival.[179,180] These studies provide a plausible mechanism by which hypercholesterolemia, through conversion of cholesterol to 27HC, may act as an agonist to stimulate the estrogen receptor, thereby increasing cancer risk. It is noteworthy that these studies were carried out with established mouse or human mammary cancer cell lines or

with mice harboring the mouse mammary tumor virus (MMTV) transgene, indicating that 27HC is serving as a tumor promoter as opposed to a primary carcinogen.

Impact of intestinal microbiome on obesity and cancer

An important series of interactions occur between the intestinal microbiome, nutrient-derived metabolites, and body composition, with recent studies demonstrating mutual effects in which diet influences microbiome function and composition, and conversely, gut microflora composition and metabolism influence host physiology and pathology status.[182–184] The potential magnitude and complexity of these effects is indicated by the estimate that there are approximately 10^{14} organisms in the intestinal bacterial content,[185] including more than 800 species and 7000 strains of bacteria.[186] Intestinal bacteria outnumber host cells by 10-fold and there are 100-fold more genes in the intestinal microflora than in the human host genome.[187] Of the four major gut microbiologic phyla, including $Gram^-$ bacteroidetes and probacteria and $Gram^+$ acetenobacteria and firmicutes, 90% are bacteroidetes and firmicutes that exist in reciprocal relation to each other based on diet, body habitus, and other influences.[188]

The gut microflora contribute significantly in both a quantitative and a qualitative fashion to the metabolism of ingested nutrients, depending on which bacteria are resident and prevalent in the intestinal tract, which in turn is heavily influenced by dietary components. These bacteria affect the digestion and therefore the availability of food-derived energy metabolites, including sugars, triglycerides, and other products which can influence energy storage, body fat distribution, adipocyte-stimulated inflammatory factors, circulating endotoxins, and consequent disorders such as insulin resistance, diabetes, obesity, cancer, and cardiovascular disease.[189]

Obesity, whether genetic, as in *ob/ob* leptin-deficient mice, or DIO based on high-fat or Western-style diet, appears to be associated with an increase in firmicutes and a relative decrease in bacteroidetes.[183,190–193] The DIO phenotype in mice was shown to be associated with an increase in a specific class of firmicutes, mollicutes.[193] The expansion of this class of firmicutes was independent of the innate or adaptive immune status of mice. The increased abundance of mollicutes in the fecal contents of DIO mice was accompanied by a higher intestinal content of lactate, acetate, and butyrate, all of which can be metabolized into short-chain fatty acids, providing metabolites for increased adipose tissue development.[193] The obesity-prone phenotype, leading to increased fat deposition, was transmissible by transfer of fecal contents from Western diet–fed obese mice to normal-weight mice fed a relatively low-fat diet. Similar effects were implied in humans, based on the observation that a small number of obese patients, subject to low-fat or low-carbohydrate diets, showed a decrease in mollicutes accompanying weight loss. Interestingly, the use of bariatric surgery for treatment of obesity was also noted to alter gut microflora, decreasing gut firmicutes.[194]

The critical role of human gut microflora in fostering obesity was recently demonstrated by transmitting the lean or obese phenotype of the donor to germ-free C57BL/6J mice by gavage of fecal contents from human twin pairs discordant for obesity.[195] Comparing diets

of high versus low saturated fatty acids showed that the obesogenic protective effect of the lean twin–derived bacteria was less effective in the presence of an HFD. Overall, these observations confirm the importance of the intestinal microbiota in influencing adiposity, and also indicate a strong environmental–diet impact.[195]

In addition to the interaction of intestinal microbiota with diet and environment and their contribution to obesity, the gut microflora may also affect carcinogenesis by metabolizing ingested food products to generate mutagens such as N-nitroso compounds and heterocyclic amines.[187,196] Consequently, both obesity and obesity-associated alterations in gut flora may affect tumor initiation and promotion and the inflammatory aspects of metabolic diseases such as metabolic syndrome and diabetes.[182] The effect of gut flora on metabolic syndrome is indicated by the demonstration that treatment of obese mice with nonabsorbed antibiotics improves insulin resistance and metabolic syndrome.[197]

A strong demonstration of the impact of gut bacteria on malignancy is provided by infection with *H. pylori*, which is causally associated with gastric inflammation, epithelial–mesenchymal transition, and gastric malignancies.[198–200] Recent studies are suggestive of a link between *H. pylori* infections and obesity.[116]

Intestinal microflora may impact malignancy in multiple ways, which, in turn, may be further influenced by diet and obesity. Fermentation of carbohydrates and fat to generate a variety of short-chain fatty acids may contribute to increased availability of obesogenic metabolites, some of which stimulate inflammation and proinflammatory cytokines including IL-6, and TNF-α, which can drive inflammation and colorectal cancer.[54,201] Another potential effect of gut microflora on carcinogenesis acts through microbial metabolism of bile acids, mainly deoxycholic acid, which is implicated in promoting colorectal cancer.[202] These agents are derived by intestinal bacterial metabolism of bile acids formed in the liver and excreted into the gut in response to dietary fat and red meat.[185] Gut microflora may also affect cancer by promoting estrogen metabolism to increase generation of estradiol, thereby promoting estrogen-driven malignancies such as endometrial cancer and post-menopausal breast cancer,[185] each of which show increased risk of occurrence in obesity.[24]

An important example, implicating GI tract microflora as potential cancer promoters, is provided by fusobacteria, which are normal inhabitants of the oral mucosa and intestine and have been shown in increased abundance in saliva derived from obese women.[203] Studies using metagenomic analysis show an increased abundance of fusobacteria in patients with inflammatory bowel disease (IBD) and with various stages of colorectal neoplasia including adenomas and adenocarcinomas.[204,205] Biopsy samples of colorectal adenomas and adenocarcinomas show greater abundance of fusobacteria compared to normal mucosa, greater activation of NF-κB and greater abundance of NF-κB–associated inflammatory pathway components,[204,205] all of which have been shown to promote intestinal cancer. In studies to evaluate a potential causal relation with colorectal cancer, fusobacteria feeding was compared with streptococcal feeding to mice with the $Apc^{Min/+}$ genotype, who are predisposed to intestinal neoplasia due to inactivation of the *Apc* tumor suppressor gene. Compared to $Apc^{Min/+}$ mice fed streptococci, the mice fed the fusobacteria showed

accelerated development and higher numbers of intestinal tumors. Tumors in fusobacteria-fed *Apc*$^{Min/+}$ mice showed more abundant infiltrates of CD11B^{+} myeloid cells and granulocytes with unchanged CD3^{+} CD34^{+} and CD3^{+} CD8^{+} T lymphocytes. The latter alterations provide the basis for T cell suppression activity, which could modulate anti-tumor immunity resulting in tumor progression. In the *Apc*$^{Min/+}$ mice, the fusobacterial abundance was associated with increased expression of NF-κB proinflammatory pathway components including IL-1β, IL-6, IL-8, TNF-α, MMP3 and PTGS2 (COX2). These cytokines and inflammatory mediators are correlated with colorectal cancer in humans. Interestingly, the effect of fusobacteria in the NF-κB inflammatory pathway was not associated in the mouse with development of IBD. Further insight into the potential mechanisms by which fusobacteria may promote colorectal cancer derives from demonstrations that the fusobacteria adhesin FadA mediates adherence and endocytosis of the bacteria by binding to E-cadherin on intestinal epithelial cells. This results in downstream activation of β-catenin signaling and demonstrates that NF-κB signaling is associated with an increase in colorectal cancer cell growth.[206]

The intestinal microbiome may mediate a unique aging-related contribution to obesity-associated cancers. Recent studies show an important relationship between obesity and cancer mediated by associated alterations in intestinal flora that alter bile acid metabolism to generate cancer promoters, which together with inflammatory cytokines secreted from senescent cells may increase both the incidence and the rate of progression of HCC.[207] Although the experiments outlined below were conducted in mice, the described processes are all extant in humans and provide the basis for significant public health concerns, since, as noted earlier, we are at the beginning of a “public health perfect storm” with aging of the population in association with increasing obesity.

Senescent cells, in a state of cell cycle arrest, develop as a function of aging, replicative exhaustion, and/or genotoxic stress induced by radiation or chemical damage of DNA. These cells have been shown to develop a senescence-associated secretory phenotype (SASP) characterized by secretion of a common set of proteins including inflammatory and immune proteins, modulatory cytokines, and chemokines. Among the SASP proteins are IL-6, IL-7, IL-8, MCP-2, MIP3A, and growth factors such as GRO, HGF, IGFBPs, and CXCl3. These secretory products, derived from senescent fibroblasts, but not replicating fibroblasts, have been shown to promote the epithelial–mesenchymal transition and increase invasiveness of multiple breast cancer cell lines.[208] The major factors involved in promoting the neoplastic properties were shown, by replacement with specific factors and by use of blocking antibodies, to be IL-6 and IL-8.[208] The SASP phenotype is inducible *in vivo* in hepatic stellate cells by feeding neonatal mice a single dose of the chemical carcinogen 7,12-dimethylbenz(a)anthracene (DMBA) and is demonstrable by decreased cell proliferation, signs of DNA damage, and increased expression of IL-6, GROα, and CXCL9. Feeding a HFD to produce DIO in these DMBA-treated mice resulted in development of multiple HCCs in all treated mice, whereas only 5% of mice undergoing the same pre-treatment and then fed a normal diet developed HCC. The contribution of obesity, as opposed to HFD, to this process was demonstrated by production of similar results obtained by DMBA treatment of obese, leptin-deficient *ob/ob* mice. Conducting the same experiments in mice lacking the

IL1B gene, which encodes the IL-1β protein that functions as an upstream regulator of the SASP response,[207] confirmed the role of SASP factors in this process by showing that their decrease resulted in a decreased occurrence of HCC.

Previous metabolic epidemiology studies had shown an association of high dietary fat as a promoter of colon cancer, mediated, in part, by metabolism of bile acid–derived deoxycholate plus a primary mutagen, methylnitronitrosoguanidine (MNNG), and intestinal bacteria.[202,209] One mechanism by which deoxycholic acid (DCA) promotes colon cancer appears to involve suppression of p53 owing to stimulation of proteosome-mediated p53 degradation.[210] In the experiments outlined above, the HFD-fed mice with DIO showed an elevated level of serum DCA, now known to be generated by bacterial metabolism of primary bile acids in a 7α-dehydroxylation reaction carried out by strains of intestinal clostridia. To further define the process involved, the authors showed that the HFD-fed mice had a relative increase in $Gram^+$ clostridia in their feces, and that these bacteria were uniquely capable of metabolizing primary bile acids to DCA. Further proof of the role of DCA and the altered gut flora in this process was demonstrated by the use of a four antibiotic regimen or vancomycin alone, which suppressed the clostridia overgrowth, reduced the circulating concentration of DCA, and diminished both the size and number of HCCs. Similar metabolic processes have been identified in human cell lines and *in vivo* in humans as well, suggesting that similar processes and linkages between obesity, gut microflora, environmental toxins, and senescence in humans may contribute to hepatocellular carcinogenesis.[207]

The effect of HFD resulting in a change in intestinal microflora that alters primary bile acid metabolism and consequently affects intestinal pathology was recently shown in another mouse system.[211,212] Mice with an $IL10^{-/-}$ genotype, but not wild-type mice, showed a pro-inflammatory T helper cell–type response associated with an increased incidence of colitis when fed a Western-style diet high in saturated fat, 37% derived from milk (MF), but not with a diet high in PUFA derived from safflower oil. Both HFDs promoted a higher abundance of bacteroidetes and lower abundance of firmicutes compared to the low-fat diet, which promoted an increase in firmicutes. The saturated MF–based diet produced a selective overabundance of *Bilophila wadsworthia* capable of reducing sulfonic acid containing taurine-conjugated bile acids to generate H_2S and other byproducts promoting colitis. Further support for the contribution of this pathway to the development of colitis included the demonstration that overgrowth of *B. wadsworthia* was stimulated in $IL10^{-/-}$ mice by gavage with taurine-conjugated bile acids, but not by substitution with phosphate buffered saline (PBS) or glycocholic acid (GC). Likewise, the taurine conjugate–fed mice, but not PBS- or GC-fed mice, showed an increase in colitis. It is noteworthy that an increased abundance of *B. wadsworthia* has also been identified in mice with dextran sodium sulfate–induced colitis. Although development of cancer was not reported in these experiments, these colitis models of IBD are commonly used to predispose mice to carcinogen-mediated colonic cancer.[213]

These studies clearly indicate the extensive array of pathways potentially resulting from the interaction of gut flora, host genetics, complex immunologic systems, and environmental nutrients and toxins. The multitude of organisms and their different metabolic pathways

expand and contract in part according to the influence of different dietary components. As previously noted, not all HFDs are the same, as indicated by the differential colitis-stimulating effect of an HFD derived from saturated MF compared to an HFD derived from safflower oil. Moreover, these experiments show that while dietary components are critically important, they require appropriate host genotype and immune systems to manifest pathology. While the intestinal flora outnumbers the number of host cells, and the genome of the gut flora outnumbers the host genome, the contribution of all these components in association with dietary differences in nutrients and toxin exposures indicate the multitude of possibilities that will need to be investigated to identify both common and unique microbiological-mediated pathways by which energy balance, diet, and obesity affect malignancy and how they may be targeted for both prevention and control.

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