Diabetes, Obesity, and Breast Cancer

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The rates of obesity and diabetes are increasing worldwide, whereas the age of onset for both obesity and diabetes are decreasing steadily. Obesity and diabetes are associated with multiple factors that contribute to the increased risk of a number of different cancers, including breast cancer. These factors are hyperinsulinemia, elevated IGFs, hyperglycemia, dyslipidemia, adipokines, inflammatory cytokines, and the gut microbiome. In this review, we discuss the current understanding of the complex signaling pathways underlying these multiple factors involved in the obesity/diabetes–breast cancer link, with a focus particularly on the roles of the insulin/IGF system and dyslipidemia in preclinical breast cancer models. We review some of the therapeutic strategies to target these metabolic derangements in cancer. Future research directions and potential therapeutic strategies are also discussed. (***Endocrinology*** **159: 3801–3812, 2018)**

Breast cancer is the leading form of cancer in women and the second most common cause of cancer-induced death in the United States and worldwide (1, 2). The World Health Organization statistics show that the obese population, defined as those with a body mass index ≥30 kg/m^2, has been growing rapidly worldwide in recent decades (3). In the United States, more than two-thirds of adults are overweight (body mass index ≥25 kg/m^2) or obese (4). Obesity is an independent risk factor for a number of diverse cancers including breast cancer. Meta-analyses have reported an ~30% increased risk of recurrence or death in obese vs normal-weight women diagnosed with breast cancer (5). In the US Cancer and Steroid Hormone study, increasing body size was found to increase the risk of developing premenopausal triple-negative breast cancer (TNBC) by 67% and the risk of premenopausal luminal B breast cancer by 73% compared with women of normal weight (6, 7). Women with diabetes are also at greater risk of developing TNBC, compared with women without diabetes (8). TNBC is a subtype of breast cancer that does not express the estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor 2 (HER2). It is the subtype of breast cancer with the worst prognosis, due to the lack of targeted therapy and enhanced metastasis compared with other breast cancer subtypes (5, 9). Luminal B breast cancer is a molecular subtype of breast cancer that is usually ER positive, but has a high grade by histology and a high proliferative index and carries a worse prognosis than ER-positive luminal A breast cancer (10). Type 2 diabetes (T2D) and obesity are also associated with increased risk for postmenopausal breast cancer (11, 12). Obesity and diabetes frequently co-occur in the same individual. Obese individuals frequently have the metabolic syndrome and are therefore at higher risk of developing T2D. Insulin resistance in metabolic organs (skeletal muscle, liver, and adipose tissue) underlies the pathophysiology of the metabolic syndrome and T2D and is frequently observed in obese individuals (13). In this study, we will review the metabolic factors associated

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Abbreviations: 27HC, 27-hydroxycholesterol; ApoE$^{-/-}$, apolipoprotein E knockout; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; ER, estrogen receptor; FIAF, fasting-induced adipose factor; HER2, human epidermal growth factor receptor 2; HMGA1, high-mobility group A1; IGF-1R, IGF-1 receptor; IGFBP, IGF-binding protein; IR, insulin receptor; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LDLR$^{-/-}$, low-density lipoprotein receptor knockout; LPS, lipopolysaccharide; LXR, liver X receptor; PI3K, phosphatidylinositol 3-kinase; Stat, signal transducer and activator of transcription; T1D, type 1 diabetes; T2D, type 2 diabetes; TNBC, triple-negative breast cancer; VLDL, very-low-density lipoprotein; WT, wild-type.

with obesity, the metabolic syndrome, and T2D that are potentially involved in breast cancer growth and progression (Fig. 1) (14).

The Insulin and IGF Family of Ligands and Receptors

Hyperglycemia is the diagnostic hallmark of both type 1 diabetes (T1D) and T2D. Epidemiologic studies have shown a consistent positive correlation between T2D and the risk of developing and dying from certain cancers, including pancreatic cancer, hepatobiliary cancer, endometrial cancer, colorectal cancer, bladder cancer, non-Hodgkin lymphoma, prostate cancer, and breast cancer (11, 15–18). T1D is also associated with an increased risk of certain cancers (16, 19), although the cancers associated with T1D are different from those associated with T2D, suggesting a different mechanism may be involved. Many types of cancer cell take up more glucose than normal nontumor cells. In contrast to normal tissue, cancer cells predominantly rely on aerobic glycolysis rather than mitochondrial oxidative phosphorylation to generate energy, due to their altered metabolism (Warburg effect) (20). The Warburg effect leads to increased glucose uptake by the cancer cells. *In vitro* cancer cell studies, *in vivo* animal tumor models, and human studies all show that cancer cells frequently have high glucose uptake; however, *in vivo* studies suggest that despite the increased uptake of glucose by the tumor, hyperglycemia alone may not increase tumor growth without hyperinsulinemia (21–24). This suggests that although many cancer cells rely on glucose for metabolism, glucose is not the key driver of cancer growth and progression in the setting of obesity, the metabolic syndrome, and diabetes.

In contrast to patients with T1D, who are insulin deficient, individuals with early T2D have hyperinsulinemia secondary to insulin resistance. Elevated levels of circulating insulin or C-peptide (a biomarker of insulin secretion) are strongly associated with breast and colorectal cancer progression, recurrence, and mortality (25, 26). Therefore, hyperinsulinemia, rather than hyperglycemia, in diabetes is suggested to contribute to the increased risk of developing cancer and cancer progression (23). Insulin is a member of the insulin/IGF

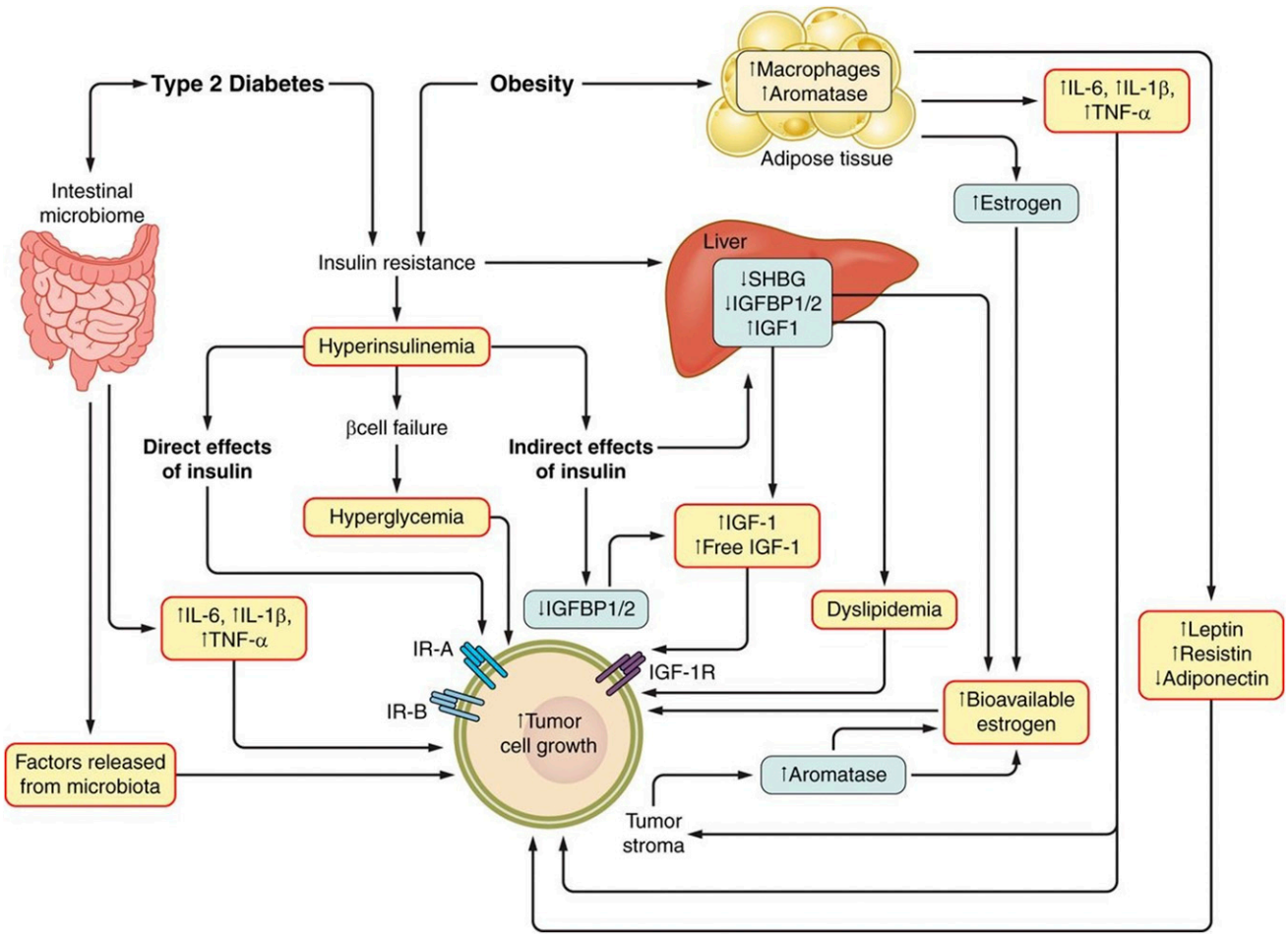

Figure 1. Potential mechanisms linking obesity/diabetes and cancer. IGFBP, IGF-binding protein; IR, insulin receptor; SHBG, sex hormone–binding globulin. Reproduced with permission from Gallagher EJ, LeRoith D. Obesity and diabetes: the increased risk of cancer and cancer-related mortality. Physiol Rev. 2015;95:727–748 (14).

family, which comprises insulin, IGF-1, IGF-2, IGF-binding proteins (IGFBPs), and their respective receptors (27, 28). Insulin signaling contributes to metabolic signaling pathways, cell survival, and proliferation signaling pathways. The traditional view of insulin and insulin receptor (IR) signaling was that in metabolic tissues, the IR regulates glucose, protein, and lipid metabolism through the phosphatidylinositol 3-kinase (PI3K)/AKT pathway, and in nonmetabolic tissues, it stimulates the RAS/RAF/MAPK kinase/ERK cascade to cause cell proliferation, survival, and migration (29–31). Insulin/IR signaling appears to have an important role in breast cancer. Previous studies have found that breast cancer tissues have significantly higher IR levels (average IR content: 6.15 ± 3.69 ng IR/0.1 mg protein) than normal breast tissues (0.95 ± 0.68 ng IR/0.1 mg protein) (32). Moreover, IR expression in breast cancers is not downregulated in the setting of hyperinsulinemia (33). Therefore, the hyperinsulinemia-IR signaling pathway may play a role in cancer progression, as proposed in breast cancer.

To study the role of hyperinsulinemia in tumor growth and migration in the absence of hyperglycemia, the LeRoith laboratory created a mouse model overexpressing a dominant-negative IGF-1 receptor (IGF-1R) specifically in skeletal muscle [named MKR for the muscle (M) lysine (K) to arginine (R) substitution in the tyrosine kinase motif of the IGF-1R] (34). The male MKR mice exhibit hyperglycemia, hyperinsulinemia, and dyslipidemia. However, the female MKR mice only develop hyperinsulinemia without hyperglycemia or dyslipidemia (34, 35). Therefore, the female MKR mice have served as an animal model for studying the specific effects of hyperinsulinemia on breast cancer development and progression. A number of transgenic and orthotopic breast tumor models were studied in the MKR mice. In each model, tumors grew faster and larger in MKR mice compared with control mice (35, 36). In addition, metastases to the lungs were increased in the MKR mice (36, 37). A β-3 adrenergic receptor agonist (CL-316,243) that reduced circulating insulin levels and a tyrosine kinase inhibitor that inhibited IR and IGF-1R activation reduced the tumor growth in MKR mice (35, 36, 38). Blockade of the PI3K/AKT/mammalian target of rapamycin pathway also attenuated primary tumor growth, which was reduced to the level of the wild-type (WT) mice (39, 40). These results suggested hyperinsulinemia could promote breast cancer growth and migration through the PI3K/AKT signaling pathway. To determine if insulin was acting through the IR or IGF-1R, human cell lines with IR silenced by short hairpin RNA were injected into the MKR mice. A decrease in cancer cell growth and metastasis was found in the MKR mice injected with cells that were transfected with IR short hairpin RNA (37). Furthermore, it was found that silencing the IR suppressed the epithelial-mesenchymal transition (EMT) in cancer cells (37).

Although insulin resistance is associated with impaired IR signaling in metabolic tissues, in tumor cells, there is no evidence that high levels of insulin lead to impaired activation of the IR signaling pathway that promotes cell proliferation (33, 41, 42). Why cancer cells do not demonstrate insulin resistance may in part be explained by the higher relative expression of the IR-A isoform compared with IR-B. The IR has two isoforms, IR-A and IR-B. IR-A lacks 12 amino acids due to the splicing out of exon 11 in the C-terminal of the α-subunit of IR; IR-B contains exon 11. Insulin has slightly higher affinity for IR-A than IR-B, but insulin metabolic signaling through IR-B is more efficient (43). Both IGF-1 and IGF-2 have higher affinity for IR-A than IR-B. Although IGF-1 binding to IR-A is weak, IGF-2 is considered an important ligand for IR-A (44). In normal tissues, IR-A is mainly expressed in fetal tissues, lymphocytes, brain, and spleen, whereas IR-B is predominantly expressed in liver and adipocytes (43). IR-A is frequently overexpressed in various malignant tumors including breast cancer. Higher IR-A/IR-B ratio has been associated with resistance to hormonal therapy in breast cancer (45). Increased high-mobility group A1 (HMGA1) protein, a chromatin-remodeling protein encoded by the HMGA1 oncogene, is a potential cause leading to total IR overexpression in cancer cells (46–49). One of the downstream effects of HMGA1 is to suppress p53, which is a tumor suppressor. p53 suppresses the promoter activity of both IR and IGF-1R (50). Recently, it was reported that discoidin domain receptor 1, which is an IR-A–interacting protein, specifically upregulates IR-A and IGF-1R expression in breast cancer cells (51). Additionally, a number of splicing factors control the IR-A/IR-B ratio. In the hepatocellular carcinoma, upregulation of certain splicing factors (CUGBP1, hnRNPH, hnRNPA1, hnRNPA2B1, and SF2/ASF) occurred in the setting of epidermal growth factor receptor (EGFR) signaling, leading to an increase in the IR-A/IR-B ratio (52). Loss of the splicing factor SRSF3 has also been found to lead to an increase of IR-A and predisposes to murine hepatocellular carcinoma (53). Precisely what splicing factors regulate IR splicing in other tissues and cancers remains to be determined, and whether cancers with higher IR-A/IR-B ratio are more susceptible to the effects of hyperinsulinemia is also unknown.

IGFs are polypeptide hormones that have similar tertiary structure to insulin. IGFs are synthesized in most tissues of the body, although most circulating IGF-1 is made in the liver. The circulating IGF levels are quite stable due to their interactions with IGFBPs, which

prevent the degradation of the IGFs (54, 55). GH/GH receptor signaling directly stimulates production of hepatic IGF-1, but has no effect on the expression of IGF-2 (56). Only the free IGFs (unbound to IGFBPs) are biologically available for binding to the IGF-1R (55). As hyperinsulinemia decreases IGFBP-1 and IGFBP-2 levels, insulin may indirectly enhance the IGF–IGF-1R signaling pathway by reducing the expression of certain IGFBPs and increasing bioavailable IGFs. The IR and IGF-1R are transmembrane tyrosine kinase receptors and have well known and common downstream cellular signal pathways, whereas the IGF-2R is the mannose-6-phosphate receptor and has no tyrosine kinase enzymatic activity. Traditionally, IGF-1/IGF-1R signaling has been studied in relation to cancer, though IGF-2 signaling through the IR-A has also been associated with cancer progression (44, 57–59). Some epidemiologic studies have shown that higher IGF-1 levels in the normal population correlate with an increased risk of breast, lung, prostate, and colorectal cancers (58). Furthermore, IGF-1R is overexpressed in several cancers, including liver, colorectal, breast, and prostate. The loss of tumor suppressor genes including BRCA1, p53, and PTEN lead to an increase in IGF-1R expression in tumor (60, 61). In animal studies, exposure to the high levels of IGF-1 was reported to increase tumor growth and metastasis (62, 63). Conversely, both chemically or genetically reducing circulating IGF-1 levels and administration of IGF-1R antibody in cancer cells can reduce tumor growth (61). The IGF-1R signal pathway has been proposed to be responsible for therapeutic resistance in several breast cancer subgroups, although the exact mechanism(s) is still not clear. Signaling through the IGF-1R pathway may play an important role in compensating for therapeutic inhibition of EGFR signaling pathway in breast cancer and may also contribute to breast cancer resistance to chemotherapy and radiotherapy (64). Inhibition of the IGF-1R was found to augment the activity of EGFR in cancer (65). The crosstalk between IGF-1 signaling and ER signaling is considered as a key mechanism of the hormone resistance in ER-positive breast cancer (66, 67). Approximately 20% of human HER2-positive breast cancers express IGF-1R (68). Direct interactions between the IGF-1R and HER2 have been reported and may contribute to the resistance to anti-HER2–targeted therapy (69). In the setting of obesity and diabetes, hyperinsulinemia may therefore directly contribute to tumor growth and progression or indirectly enhance tumorigenesis through IGF-1 signaling.

During the last two decades, many cancer clinical trials have targeted the IGF-1 signaling pathway using various methods in a number of cancers. Unfortunately, in almost all clinical studies, these approaches have had limited success (70, 71). The potential reasons for treatment failure are diverse; however, the possibility that the mitogenic IR pathway compensates for inhibition of the IGF-1 pathway is one of the most striking potential mechanisms. Preclinical studies have supported the hypothesis that silencing the IGF-1R may increase the sensitivity of tumors to signaling through the IR pathway (72, 73). Knockdown or blocking of the IR was reported to inhibit cell proliferation in response to insulin in ER-positive breast cancer cells resistant to endocrine therapies. However, this inhibition was attenuated in the hormone-sensitive ER-positive breast cancer cells, probably due to the IGF-1R/IR hybrid receptors. Although the primary ligand for IGF-1R/IR hybrid receptors is IGF-1, not insulin, insulin can still signal through the IGF-1R/IR hybrid receptors upon IR inhibition (74). Combined targeting of the IR mitogenic pathway and IGF-1R pathway might be valuable therapies for hormone-resistant and TNBC. The other possibilities include the use of monoclonal antibodies toward IGF-1 and IGF-2 ligands simultaneously. Trials using this approach are in fact currently under way (75, 76).

Overall, both IR and IGF-1R are extensively reported to be observed in all breast cancer subtypes (luminal A, luminal B, HER2, and TNBC). The activation of IR and IGF-1R (indicated by phosphorylated IR and IGF-1R) is present in all breast cancer subtypes and is related to poor survival (77). The IR isoforms ratio (IR-A/IR-B) is altered particularly in prognostically unfavorable luminal B cancers and hormone-resistant breast cancers (78). The IGF-1R expression is prognostically favorable in luminal A and B breast cancer but is unfavorable in HER2-positive and TNBC (79, 80). These differences in receptor expression may explain the differences in the sensitivity of certain breast cancers to the direct and indirect tumor-promoting effects of systemic hyperinsulinemia. Additionally, the differences in expression levels may explain why IGF-1R–targeted therapies have had limited success in certain patients. What causes these differences in receptor expression and whether regulation of the expression of the IGF-1R and IR isoforms can be targeted therapeutically remain to be determined.

Dyslipidemia

Dyslipidemia is a feature of the metabolic syndrome in patients with obesity and T2D. Obese patients and patients with diabetes frequently exhibit elevated circulating very-low-density lipoprotein (VLDL) cholesterol, triglycerides, small dense low-density lipoprotein (LDL) cholesterol, and reduced high-density lipoprotein (HDL) cholesterol (81). Elevated total cholesterol, elevated circulating triglycerides, and decreased HDL cholesterol

have been associated with an 18%, 15%, and 20% increased risk of cancer, respectively (82). In a recent meta-analysis, it was reported that the dietary cholesterol intake was closely associated with an increased risk of breast cancer occurrence (83). Cholesterol-lowering 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statin) have proven very effective in lowering circulating cholesterol and are widely used to prevent cardiovascular disease (84). Many studies indicated the link between statin administration and a lower risk of developing specific cancers (85–87). Some studies have suggested that statins reduced recurrence and mortality from prostate cancer and breast cancer (89). However, not all studies have consistently demonstrated these beneficial effects of statins, possibly due to heterogeneous populations or the use of different types of statins (86, 89, 90). Alternatively, the discrepant results on breast cancer outcomes may reflect different breast cancer subtypes having differing sensitivities to circulating cholesterol and/or statin therapy. It is important to consider differences in statins: the type of statin used, when it is used with respect to time of diagnosis of cancer (prediagnosis or postdiagnosis), and duration of treatment. Some statins are lipophilic (simvastatin, lovastatin, and atorvastatin), and others are hydrophilic (pravastatin, rosuvastatin, and fluvastatin) (91). In breast cancer mortality studies, if results were stratified according to statin type, hydrophilic statins had a benefit only when taken postdiagnostically, and lipophilic statins demonstrated survival benefits irrespective of when they were taken. These results suggested cholesterol may not be oncogenic but might promote tumor progression, and lowering circulating cholesterol may improve outcomes (91).

Transgenic animals with dyslipidemia have been used to model and investigate the effect of hyperlipidemia on cancer growth. Several laboratories reported that a high-cholesterol diet promoted tumor growth in mice with ER-positive breast cancer and prostate cancer (92, 93). As mice lack cholesteryl ester transfer protein, and therefore, high-cholesterol diets do not completely reflect human dyslipidemia, genetically modified models of dyslipidemia have also been used (94): the apolipoprotein E knockout ($ApoE^{-/-}$) mouse has elevated total, VLDL, and LDL cholesterol; the LDL receptor knockout ($LDLR^{-/-}$) mouse has elevated LDL cholesterol; the transgenic ApoE3 Leiden mouse has elevated VLDL and LDL cholesterol; and the adiponectin knockout mouse has decreased HDL and elevated LDL cholesterol (95–97). Each of these animal models of hypercholesterolemia has been used to study the effects of lipids on breast cancer growth and progression (95). The LeRoith laboratory found that $ApoE^{-/-}$ mice on a high-cholesterol diet had increased growth and metastasis of orthotopic murine ER-negative mammary tumors compared with WT mice (98). Increased Akt phosphorylation has been found in cancer cells in response to cholesterol, and treatment of these mice with a small-molecule inhibitor of PI3K (BKM120) reduced mammary tumor growth, suggesting the PI3K/Akt pathway is partly responsible for the protumorigenic effects of elevated cholesterol (98). LDL receptor (LDLR) is expressed at high levels on certain cancer cells. TNBC cells (MDA-MB-231) have higher levels of expression of the LDLR than ER-positive cells (MCF-7) (99). TNBC and Her2/Neu breast cancer cells with high LDLR expression were found to form larger tumors in $ApoE^{-/-}$ and $LDLR^{-/-}$ mice than in WT mice. Silencing the LDLR in such cancer cells led to decreased tumor growth in both $LDLR^{-/-}$ and $ApoE^{-/-}$ mice (100). Transgenic polyoma virus middle T antigen tumors in adiponectin knockout mice were found to have increased LDLR expression, increased cholesterol content. and accelerated tumor development (101). Similarly, ER-positive breast cancers grew faster in ApoE3-Leiden mice fed a high-fat diet compared with control mice (102).

Several mechanisms potentially contribute to the link between elevated cholesterol and breast cancer growth. As cholesterol is a major component of the plasma membrane, rapidly dividing cells such as cancer cells require large amounts of cholesterol for membrane synthesis; therefore, high levels of circulating cholesterol may provide the substrate for cell proliferation. However, cancer cells may be availing of elevated exogenous cholesterol in other ways. Cholesterol is the precursor of many sex hormones, including progesterone, estrogens, androgens, and their derivatives. The large cohort study in the Women's Health Initiative indicated the administration of the lipophilic statins independently contributed to a reduction in late-stage breast cancer, especially for the patients with ER-positive breast cancer and androgen receptor–positive breast cancer. The androgen receptor is expressed in some TNBC (103). These results suggest that cholesterol may be used by cancer cells to synthesize sex hormones and thus lead to resistance to systemic hormonal therapies. In addition to the steroid sex hormones, some oxysterol metabolites of cholesterol such as 27-hydroxycholesterol (27HC) and 25-hydroxycholesterol were recently found to play important roles in breast cancer growth (102, 104, 105). 27HC is an endogenous selective ER modulator. It has recently been shown to promote the growth of ER-positive human and murine breast cancers in mice. In functional studies, it was found that 27HC binds to ER to induce a conformational change. The effect of 27HC on the ER is different in various tissues. 27HC works as the ER antagonist in vascular endothelial cells and murine models of cardiovascular disease, whereas it acts as an ER agonist in

hepatoma, colorectal, and breast cancer cells. 27HC is also an agonist of liver X receptor (LXR), which induces EMT and subsequent metastasis when activated in breast cancer cells (106). Cholesterol levels are normally tightly controlled by both sterol regulatory element-binding protein-2 and LXR, which suppress cholesterol uptake via the LDLR and increase cholesterol efflux (107, 108). However, in human ER-negative breast cancer cells (MDA-MB-231), no downregulation of the LDLR occurs, and no increase in cholesterol efflux gene transcription is detected. Intracellular cholesterol concentrations are high in this breast cancer cell line (109, 110). The role of LXR in the proliferation of breast cancer is still controversial. Although some studies report that an agonist of LXR promoted both proliferation and lung metastasis of MCF-7 cell xenografts (102). Another group showed that LXR-activated macrophages reduced MCF-7 proliferation and increased apoptosis *in vitro* (111). Recently, the Nelson laboratory (112) reported that 27HC acts on immune myeloid cells residing at the distal metastatic sites, thus promoting an immune-suppressive environment to facilitate breast cancer metastasis.

In addition to statin treatment, other cholesterol-lowering therapies including the proprotein convertase subtilisin/kexin type 9 inhibitors and inhibitors of 27HC synthesis [sterol 27-hydroxylase (CYP27A1) inhibitors] may also potentially demonstrate benefit in patients with cancer, especially in the statin-resistant or statin-intolerant patients. Studies have not yet been performed with these agents to determine if they will improve responses to therapies, reduce recurrences, or prolong survival in the setting of cancer.

Adipose Tissue

Obese and many patients with T2D have significantly increased total adipose tissue mass compared with the normal-weight population. Large amounts of adipose tissue, including subcutaneous and visceral adipose tissue, surround many organs where cancers, such as the breast cancer, develop (113). Adipose tissue is an important endocrine organ that produces adipokines, inflammatory cytokines, and small amounts of estrogen by aromatization of androgens (114). These adipose tissue factors could affect other organs through both paracrine and endocrine effects. In addition, adipose tissue inflammation may be a favorable environment for the development of cancer. Recently, more studies suggest that adipose tissue factors (cytokines and adipokines) and adipose tissue inflammation also contribute to cancer progression.

Leptin is an important adipokine-regulating appetite and energy balance through its effects on the brain. Many obese individuals acquire leptin resistance and have high levels of circulating leptin (115). Leptin receptor expression has been detected in human breast cancer (116). Leptin binds to the leptin receptor, leading to the activation of several signaling pathways, including Janus kinase/signal transducer and activator of transcription (Stat) signaling, MAPK/ERK, PI3K/Akt, and suppressor of cytokine signaling pathways, promoting cancer cells survival, proliferation, and metastasis (116). A recent study found that enhanced leptin signaling promotes cancer stem cell enrichment and EMT, thus driving obesity-associated TNBC progression in transgenic MMTV-Wnt-1 mice, orthotopic murine E-Wnt and M-Wnt tumors, and human MDA-MB-231 xenografts (117).

Resistin, named for inducing resistance to insulin, is primarily produced by macrophages (118). It mediates insulin resistance by activating the Janus kinase–STAT signaling pathway to activate suppressor of cytokine signaling 3, which binds to endogenous IRS1 and IRS2 and promotes their ubiquitination and subsequent degradation (119). Resistin levels are elevated in patients with both obesity and T2D (120). Some studies suggested the increased resistin in tumor tissues and serum might be a biomarker for the diagnosis of breast cancer (121, 122). Recently, several groups have shown resistin promotes human breast cancer cell growth and metastasis through activation of Stat3 and the ERM family (ezrin, radixin, and moesin) of proteins (123–126).

Adiponectin is considered an anti-inflammatory adipokine. Epidemiological studies have demonstrated that in postmenopausal women with breast cancer, the circulating adiponectin levels are significantly lower than those in women without cancer (127). *In vitro* studies have reported that adiponectin suppresses the survival and proliferation of T47D, MCF-7, and MDA-MB-231 human breast cancer cells (128). Adiponectin can also inhibit the leptin-mediated migration and invasion of these human breast cancer cells (129, 130). Adiponectin is involved in several signal pathways that may contribute to the inhibition of carcinogenesis. Adiponectin could activate AMP-activated protein kinase, MAPK, and peroxisome proliferator–activated receptor α pathways and block leptin signaling (131–134). Interestingly, as discussed under "Dyslipidemia" in this review, adiponectin deficiency has been found to promote tumor growth, increasing cholesterol content and LDLR expression on breast cancer cells (101).

Gut Microbiome

The human microbiome is a dynamic and functional entity comprising microorganisms including bacteria, viruses, protozoa, and fungi (135). Most of the microbiome

is in the gastrointestinal tract and interdependent with the host. The microbiome influences the digestion, metabolism, epithelial homeostasis, local inflammation, cardiovascular, and immune functions of the host (136–139). A study from the Gordon laboratory (140) provided evidence that there are considerable differences in microbiome composition from obese people and lean people. Some studies consecutively exposed the connections between the gut microbiome and obesity. Fasting-induced adipose factor (FIAF), also called angiopoietin-like protein 4, is expressed in the intestine, liver, muscle, and adipose tissue. It is selectively suppressed in the intestinal epithelium. FIAF is an inhibitor of the circulating lipoprotein lipase, which is an enzyme to hydrolyze triglycerides to promote their release from the lipoprotein such as chylomicrons and VLDLs (141, 142). Knocking out FIAF in the obese germ-free mice indicated FIAF is a key regulator on adipose storage for the gut microbiome (143). Another molecular mechanism involved in the microbiome-induced obesogenic progression is lipopolysaccharide (LPS). LPS is a proinflammatory factor existing in the cell wall of gram-negative bacteria. It can be absorbed by the intestine epithelium after the bacteria die. In the intestine, LPS promotes intestinal permeability and induces the production of inflammatory cytokines such as TNF-α and IL-6 (144, 145).

Microbiome perturbations were found to increase the risk of some cancers. The most well-known case is the infection of *Helicobacter pylori*, which can cause gastric cancer (146). Many studies reported that *Fusobacterium nucleatum*, which is on the surface of >50% of colorectal adenomas, promotes chronic inflammation in the intestinal tumor microenvironment (147). Studies have also examined links between microbiome alterations and breast cancer. Plottel and Blaser (148) defined a group of human gut organisms as the "estrobolome": "the aggregate of enteric bacterial genes whose products are capable of metabolizing estrogens." A high level of the estrobolome could promote the intestinal reabsorption of deconjugated estrogens into the circulation. Epidemiologic studies suggested that some gut microbiome might also affect breast cancer risk through estrogen-independent pathways (149). Another recent study indicated that a bacterial metabolite, lithocholic acid, can limit the proliferation of breast cancer cells both *in vitro* and *in vivo* (150). Overall, these studies demonstrate that obesity and diabetes are associated with differences in the intestinal floral composition. Some of these changes may increase cancer risk and development by contributing to inflammation and altering metabolism. Other bacteria may secrete tumor-suppressing factors. Improving our understanding of the composition and characteristics of the microbiome and learning how to manipulate it for our benefit may provide a nontoxic way of improving systemic metabolism and preventing and treating cancer.

Conclusions

As obesity and diabetes affect more and more people, it is critical to understand the mechanisms through which they contribute to the development and progression of specific cancers. It is becoming clear that targeting the cancer with specific therapies but ignoring systemic metabolic dysfunction may contribute to resistance to cancer therapy and treatment failure. As our understanding of the mechanisms tying systemic metabolism to cancer grows, it will help to tailor therapies to specific cancer targets altered by metabolic dysfunction or to identify the patients who will benefit from therapies to treat specific metabolic abnormalities.

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