

Obesity and Cancer: Local and Systemic Mechanisms

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Annu. Rev. Med. 2015. 66:297–309

The *Annual Review of Medicine* is online at
med.annualreviews.org

This article's doi:
10.1146/annurev-med-050913-022228

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Keywords

cancer risk, body mass index, inflammation, insulin resistance, adipose tissue, metabolic syndrome, macrophages, adipocytes

Abstract

Obesity is a leading modifiable risk factor for the development of several epithelial malignancies. In addition to increasing risk, obesity also confers worse prognosis for many cancers. Obesity represents an overall state of energy imbalance frequently associated with systemic effects including insulin resistance, altered hormone signaling, and high circulating levels of proinflammatory mediators. In addition to its systemic effects, obesity causes subclinical white adipose inflammation including increased tissue levels of proinflammatory mediators. Both local and systemic effects are likely to contribute to the development and progression of cancer. An understanding of the interplay between local and systemic alterations involved in the obesity–cancer link provides the basis for developing interventions aimed at mitigating the protumorigenic effects.

WAT: white adipose tissue

INTRODUCTION

Obesity rates are rising worldwide, and population data link obesity to the increased incidence of several common cancers. We can expect an epidemiologic shift from previously known modifiable risk factors, such as smoking and alcohol consumption, toward obesity as a risk factor for malignancy. Obesity is defined conventionally as a body mass index (BMI) ≥ 30 kg/m² [(weight in kg)/(height in m)²]. Rates of obesity are predicted to exceed 60% in some parts of the United States unless current trends abate (1). Already, more than two-thirds of the adult population in the United States is overweight or obese (2).

Among its many health consequences, obesity is increasingly recognized as a risk factor for numerous malignancies (3, 4). Obesity also portends worse cancer-specific outcomes after diagnosis in several tumor types including those of the breast, esophagus, colon, prostate, kidney, ovary, uterus, liver, tongue, and others (5–8). Additionally, obesity is a poor prognostic factor for both adenocarcinoma and squamous cell carcinoma histologies (9, 10). The precise mechanisms underlying this obesity–cancer link are not yet well understood. However, emerging data suggest that both systemic and local tissue-specific effects are important. The identification of high-risk individuals based on pathophysiology rather than anthropometric measures should facilitate the development of clinical trials that ultimately yield mechanism-based strategies to reduce the cancer burden.

The primary function of white adipose tissue (WAT) is to store energy as lipid and to maintain energy homeostasis. Unchecked hyperadiposity as a result of excess caloric intake or reduced caloric expenditure leads to expansion of adipose compartments via hyperplasia and/or adipocyte hypertrophy. Under these conditions, WAT is altered, resulting in changes in production of steroid hormones and adipokines, metabolic disorders, and chronic subclinical inflammation (11, 12). These alterations have been implicated in carcinogenesis, tumor progression, and metastasis (12).

Dysfunctional adipose biology does not occur only in the obese, nor does it develop in all obese individuals. Metabolically healthy obese individuals (a minority with the phenotype) have been reported to have smaller adipocytes and fewer metabolic complications than the majority of obese individuals (13–15). Moreover, insulin resistance and WAT inflammation have been reported to occur in subsets of lean individuals (16, 17). These observations are partly explained by the limitations of BMI as a reflection of overall health or specifically the quality of adipose tissue. For example, the different adipose depots (i.e., subcutaneous versus visceral or truncal versus appendicular) in a single individual may be subjected to different physiologic conditions (18). Adipose tissue heterogeneity among patients may account for some of the conflicting epidemiologic data regarding obesity, defined by BMI, and cancer progression (19). If the phenotype (obesity) does not always accurately predict the physiology, then understanding the mechanistic relationship between obesity and cancer in the context of adipose dysfunction may provide a more informative approach toward developing effective prevention and treatment strategies for a well-defined, high-risk population. Below, we review both the local and systemic consequences of adipose tissue dysfunction in the context of carcinogenesis and tumor progression.

SYSTEMIC EFFECTS OF DYSFUNCTIONAL ADIPOSE TISSUE

Adipose tissue dysfunction, which commonly occurs in association with the obese state, leads to a number of systemic changes that increase one's risk of developing cancer. These alterations include changes in circulating levels of several hormones, adipokines, and inflammatory mediators, which are discussed below (**Figure 1**).

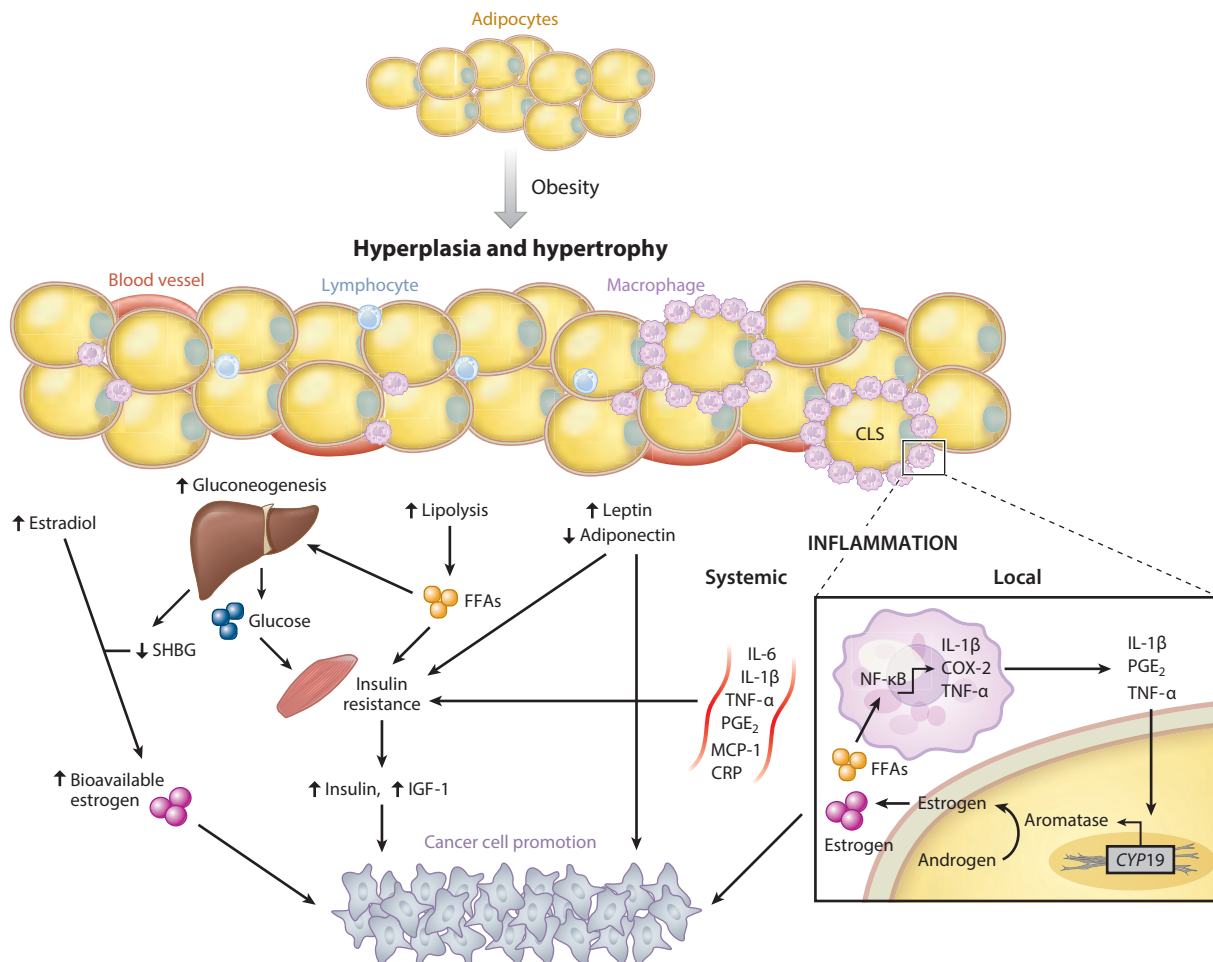


Figure 1

Local and systemic consequences of white adipose tissue dysfunction. CLS, crown-like structure; COX-2, cyclooxygenase-2; CRP, C-reactive protein; FFAs, free fatty acids; IGF-1, insulin-like growth factor-1; IL-1β, interleukin-1β; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; PGE₂, prostaglandin E₂; SHBG, steroid hormone-binding globulin; TNF-α, tumor necrosis factor-α.

Effects of Adipose Tissue on Insulin Signaling and Lipid Metabolism

Insulin resistance, characterized by hyperinsulinemia, occurs in most obese people. Diabetes has been associated with an increased incidence of several malignancies, including breast, endometrial, colorectal, pancreatic, and hepatocellular cancers (20, 21). After diagnosis, insulin resistance is associated with worse prognosis in several cancers, including malignancies of the breast and others (22–24). There are many potential mechanisms that can explain these associations. Insulin can stimulate the synthesis of insulin-like growth factor-1 (IGF-1), which has multiple effects that have been linked to tumor progression. For example, both insulin and IGF-1 have potent mitogenic effects on tumor cells. Specifically, insulin and IGF-1 bind to their respective cell surface receptors and activate the PI3K/Akt/mTOR and Ras/Raf/MAPK pathways (21, 25, 26).

ER: estrogen receptor

AR: androgen receptor

FFA: free fatty acid

Both IGF-1 and insulin interact with estrogen signaling pathways to promote hormone-dependent breast cancers. Aromatase activity is stimulated by IGF-1 in adipose stromal cells (27). Along with IGF-1-mediated upregulation of aromatase, insulin inhibits hepatic synthesis of steroid-hormone-binding globulin (SHBG) (4). SHBG binds steroid hormones (e.g., estradiol, testosterone, dihydrotestosterone) in a biologically inactive state. Increased free estradiol and androgens, as a result of lowered SHBG levels, are then available to stimulate the growth of estrogen receptor (ER)– and androgen receptor (AR)–expressing breast and prostate cancers.

In addition to its central role in signaling cascades that are employed by the cancer cell to promote proliferation and invasion, insulin suppresses lipolysis under normal physiologic conditions. However, this latter function is impaired in the obese state (28). Increased lipolysis also occurs in the setting of inflamed WAT (6). Both mechanisms result in increased release of free fatty acids (FFAs) into the circulation, providing additional building blocks for tumor cell proliferation. Additionally, increased circulating FFAs lead to ectopic lipid accumulation in other organs such as the liver, pancreas, and kidneys, which further promotes insulin resistance, hyperglycemia/diabetes, dyslipidemia, and hypertension (29). This group of conditions, collectively known as the metabolic syndrome, has been associated with central obesity and the development of cardiovascular disease (30). It is not surprising, then, that the metabolic syndrome, which incorporates multiple mechanisms that promote tumor progression as discussed above, has recently been implicated in the etiology and progression of several cancers, including breast, colon, and others (31–34).

Effect of Adipose Tissue on Circulating Steroid Hormones

Estrogen. The differential effects of menopause on cancer incidence observed in epidemiologic studies point to the potential role of estrogen in the development and progression of these malignancies. Obesity is a well-known risk factor for the development of breast cancers that express the estrogen and progesterone receptors in postmenopausal women (35). Similarly, elevated BMI increases the risk of developing endometrial cancer in postmenopausal women (36). Obesity appears to have different effects in younger patients. For example, obesity appears to increase the risks of colorectal cancer and possibly malignant melanoma in premenopausal women (36). Prior to menopause, estrogen is predominantly produced in the ovary. After cessation of ovarian function with menopause, estrogen production continues to a much lesser degree via peripheral conversion, primarily in the adipose tissue, of androgens by the cytochrome P450 enzyme aromatase. Paradoxically, the incidence of ER-positive breast cancers increases with age despite the drop in circulating estradiol levels after menopause (37). Increasing adiposity with age has been suggested to contribute to this phenomenon, as total and free circulating estrogen levels are known to be increased in obese compared with normal-weight postmenopausal women (38). However, it is becoming increasingly apparent that crosstalk between estrogen, insulin and IGF-1, and adipokine signaling pathways plays an important role. Furthermore, locally produced estrogens and ligand-independent activation of ER- α have been associated with tumorigenesis (39). A key feature of obesity, local adipose tissue inflammation, has been implicated in activation of estrogen signaling (discussed in a later section). This may tie some of these observations together in a rational fashion.

Estrogen may promote tumor development and progression through a number of complex mechanisms. Direct effects of estrogens include stimulation of cellular proliferation and inhibition of apoptosis via ER- α agonism as well as induction of vascular endothelial growth factor and angiogenesis (40, 41). Furthermore, mutagenic effects of estrogen via genotoxic metabolites have also been suggested to play a role in estrogen-mediated carcinogenesis (40). Therapeutic targeting of ER with selective estrogen receptor modulators (SERMs) such as tamoxifen and raloxifene and disruption of tumor supply of estrogen with aromatase inhibitors have demonstrated the clinically

important role of estrogen in the development and progression of hormone receptor-positive breast cancer.

Androgens. The relationships between obesity, androgens, and cancer are less clear. Although obesity has not been consistently shown to correlate with overall prostate cancer risk, elevated BMI has been associated with worse prognosis and more aggressive prostate tumors (42–44). The mechanisms underlying these epidemiologic observations are not well elucidated. Interestingly, inflammatory cytokines, e.g., interleukin-6 (IL-6), and IGF-1 have been shown to activate the AR, thereby promoting prostate cancer cell survival and proliferation (45). Given that obesity is associated with decreased circulating levels of androgens in men (46), androgen-independent activation of the AR may underlie the connection between obesity and aggressive prostate cancers. Accordingly, obesity-related inflammation, which is associated with upregulation of proinflammatory mediators both locally and systemically, may contribute to activation of the AR, thereby promoting prostate cancer progression.

Effect of Adipose Tissue on Circulating Adipokines

Adipokines, including leptin and adiponectin, are adipocyte-derived hormones with pleiotropic effects including regulation of caloric intake and metabolism, crosstalk with insulin signaling and inflammatory pathways, and promotion of angiogenesis and cellular proliferation (12, 47). Increased BMI is associated with elevated leptin levels, whereas adiponectin levels generally decrease with greater adiposity. Importantly, the overall metabolic health of the fat pad, in addition to absolute adipose mass, is a key determinant of its secretory profile (47). The increased leptin-to-adiponectin ratio associated with obesity has been implicated in neoplastic transformation and tumor progression (48).

Adiponectin. Epidemiologic and preclinical studies point to a protective role of adiponectin against tumorigenesis. In preclinical models, adiponectin inhibited the proliferation of colon, prostate, endometrial, and breast cancer cells (49–52). Adiponectin has also been shown to induce apoptosis in endometrial and hepatocellular cancer cells (51, 53). Adiponectin activates adenosine monophosphate-activated protein kinase (AMPK), leading to upregulation of p21 and G1 cell cycle arrest (54). In animal models, impaired adiponectin production has been shown to promote mammary tumor development by upregulation of PI3K/AKT/mTOR signaling and downregulation of phosphatase and tensin homolog (PTEN) (55). Consistently, epidemiologic data support an antitumor effect associated with adiponectin. Higher circulating adiponectin levels have been associated with decreased risk of postmenopausal breast cancer as well as better prognosis (56, 57). Conversely, decreased adiponectin levels are associated with increased breast cancer risk (58). Higher adiponectin levels have been associated with decreased risk of other cancers including those of the uterus and colon, although data are conflicting regarding prostate cancer (59–62).

Leptin. The major physiologic role of leptin involves regulation of appetite and energy balance via a negative feedback loop between the central nervous system and peripheral adipose tissue (63). Hyperadiposity disrupts this balance and is associated with elevated leptin levels. As with adiponectin, preclinical and epidemiologic studies suggest an important role of leptin in cancer risk and progression. Both leptin and its functional receptor, OB-Rb, have been implicated in a number of malignancies. Preclinical studies have demonstrated leptin-mediated increases in cell proliferation and survival via OB-Rb in breast, endometrial, ovarian, colon, and androgen-insensitive prostate cancer cells (64–67). However, epidemiologic data are conflicting regarding

leptin levels and increased cancer risk. Elevated circulating leptin levels and increased expression of OB-Rb have been associated with increased colon adenoma risk in men, but not in women (68). Additionally, some studies have reported associations between elevated leptin levels and risk of breast and endometrial cancers whereas others have not (12). These conflicting data suggest that the leptin-adiponectin balance may be more directly related to cancer risk. For example, leptin was shown to block the antiproliferative effects of adiponectin on prostate cancer cells (69), and adiponectin has been shown to inhibit the proliferative effects of leptin on hepatocellular carcinoma cells (53). All of this suggests that the leptin-to-adiponectin ratio may provide a more accurate assessment of cancer risk related to adipose tissue health.

Adipose Tissue Dysfunction and Systemic Inflammation

It is well recognized that obesity is associated with chronic, subclinical inflammation characterized by elevated levels of circulating proinflammatory mediators known to promote neoplasia and tumor progression (4, 70, 71). Levels of C-reactive protein (CRP), a biomarker of inflammation, are commonly increased in the blood of obese individuals (72). Elevated circulating levels of TNF- α and IL-6 occur in obese women and have been associated with the development and progression of breast tumors (12). Additionally, systemic inflammation characterized by elevated levels of prostaglandin E₂ (PGE₂) metabolite in the urine is associated with increased risk of developing postmenopausal breast cancer (73, 74). Thus, obesity-related systemic inflammation has critical potential implications for tumor development, growth, and spread.

Circulating chemokines, including monocyte chemoattractant protein-1 (MCP-1), promote the recruitment of monocytes to adipose tissue, where the cells differentiate and become macrophages. In addition to playing a role in recruitment, MCP-1 was recently found to stimulate macrophage proliferation *in situ* in adipose tissue (75). Inflamed adipose tissue may play a critical role in the pathogenesis of several cancers, including organs with epithelium surrounded by or adjacent to fat, such as breast, colon, pancreas, and kidney (76). However, other organ sites are not shielded from the effects of adipose tissue inflammation, given its systemic consequences such as insulin resistance. This systemic inflammation establishes a feed-forward loop through which local WAT inflammation is perpetuated (i.e., via effects of MCP-1), thus creating an enhanced inflammatory milieu within the obese fat pad.

DYSFUNCTIONAL ADIPOSE TISSUE: LOCAL EFFECTS AND THE TUMOR MICROENVIRONMENT

As noted above, obesity is associated with both systemic and local WAT inflammation. The microenvironment of tumors has been described to closely resemble that of wounds, including an influx of activated immune cells with local production of proinflammatory mediators (77). Similarly, WAT from obese patients is infiltrated by leukocytes, including macrophages and T lymphocytes (28), which may create a microenvironment that favors tumor growth and metastasis (78).

Adipocyte Interactions

Inflammation of WAT is now recognized as an important component of obesity-related disorders that comprise the metabolic syndrome, such as diabetes mellitus and cardiovascular diseases (28). However, an emerging understanding of the complex interactions between adipocytes and immune cells within the WAT stromal vascular fraction points to a key role of adipose inflammation in

CLS: crown-like structures

tumor growth and development. Specifically, infiltrating macrophages can account for up to 40% of the cellular content of the obese fat pad and are an important source of inflammatory mediators that significantly impair insulin sensitivity—both locally and systemically (79). The adipocyte–macrophage interaction is emerging as a central theme linking adipose tissue inflammation and the protumorigenic microenvironment. Adipocyte hypertrophy and death are associated with increased production of TNF- α , IL-6, MCP-1, and myeloid cell recruitment (80). Macrophages infiltrate adipose tissue and surround the dead or dying adipocyte in a histologically characteristic pattern known as crown-like structures (CLS) (81). These inflammatory foci were first observed in visceral and subcutaneous fat in association with the metabolic syndrome and have more recently been found to occur in the mammary gland of obese mice and the WAT of the human breast (termed CLS-B) (82, 83). The presence of CLS-B was associated with activation of NF- κ B and increased levels of TNF- α , IL-1 β , IL-6, and cyclooxygenase-2 (COX-2)–derived PGE₂. Consistent with these findings, gene expression analyses have identified selective enrichment of macrophage markers in breast tissue from obese women (84). As described above, several of these proinflammatory mediators were found to circulate at increased levels in obese women with breast cancer and are also associated with inferior outcomes. For example, higher serum levels of IL-6 have been associated with diminished survival in patients with metastatic hormone-refractory breast cancer (85).

A critical consequence of CLS-B and the associated increase in tissue levels of proinflammatory mediators is increased transcription of the *CYP19* gene encoding aromatase, the rate-limiting enzyme in estrogen biosynthesis (86). Several of the proinflammatory mediators associated with CLS-B, including TNF- α , IL-1 β , IL-6, and PGE₂, are known to induce aromatase expression (86–88). Estrogen biosynthesis and upregulation of the progesterone receptor, an ER- α -regulated gene, are stimulated by increased aromatase activity. This enhanced estrogen signaling, a direct consequence of WAT inflammation, has critical clinical implications as a potentially targetable mediator of obesity-associated breast cancer. Indeed, targeting of estrogen and ER signaling by ovarian ablation and by use of SERMs and aromatase inhibitors has proven to be an effective approach in the prevention and treatment of hormone-dependent breast carcinomas, the most common subtype of breast cancer (40). Thus, WAT inflammation directly promotes local ER signaling and provides a key link between obesity and the development of postmenopausal breast cancer. It may be that locally produced estrogens, as a result of obesity-related WAT inflammation, are the key drivers of hormone-dependent breast cancer development in postmenopausal women. Notably, ligand-independent activation of ER signaling may also be increased in inflamed tissue. These effects could help explain the clinical paradox that the incidence of estrogen-driven breast cancers peaks more than a decade after ovarian production diminishes to near zero.

It is important to note that the density of CLS in breast and other inflamed adipose depots generally correlates with BMI (80, 81, 83). However, a minority of lean women have been found to harbor CLS-B and ~10% of obese women do not (83). In addition, aromatase activity correlates more strongly with the severity of WAT inflammation than with BMI (83). Thus, inflammation specifically, rather than obesity alone, is an important determinant of aromatase activity in the breast and may represent the more meaningful target for intervention. The presence and severity of CLS-B are not merely surrogates of BMI, although they are closely associated with it. Consistently, some obese individuals, as defined by BMI, are in fact metabolically healthy (13–15). This point is of high clinical relevance regarding the accurate selection of at-risk populations for prevention and therapeutic clinical trials. In other words, selection of patients via assessment of adipose tissue biology rather than anthropometric methods will likely be critical in developing successful interventions.

Local Inflammation and Metabolic Dysfunction

Increased BMI is associated with larger adipocyte size and adipocyte death (83). Macrophages within the CLS phagocytose the dead adipocyte and become foam cells (89). Macrophage-mediated clearance of the dead adipocyte may be associated with an inflammatory response (90). Toll-like receptors (TLR) are a family of highly conserved transmembrane proteins that are centrally involved in the recognition of microbial pathogens as well as endogenous threats typically related to tissue damage. Stimulation of TLR4 prototypically occurs via binding of lipopolysaccharide, a component of the cell wall of gram-negative bacteria, leading to activation of the innate immune response. Changes in bowel wall permeability and perturbations of intestinal microbiota related to high-fat diet consumption have also been suggested to promote a TLR4-mediated inflammatory response (91). Similarly, FFAs have been suggested to engage TLR4 on the macrophage cell membrane leading to increased NF- κ B-dependent expression of proinflammatory genes that encode TNF- α , IL-1 β , and COX-2 (92). Cytokines such as TNF- α stimulate lipolysis, leading to further release of FFAs and thus establishing an inflammatory feed-forward loop.

Taken together, the data reviewed thus far establish an obesity \rightarrow inflammation \rightarrow aromatase signaling axis that is active in the human breast and likely in other adipose depots (**Figure 1**). This places inflammation at the center of estrogen-dependent breast cancer pathogenesis for many patients. In addition, inflammation is a key contributor to carcinogenesis via estrogen-independent mechanisms. The other negative effects of inflammation arise in part because increased production of proinflammatory mediators in dysfunctional adipose tissue can directly stimulate tumor development and progression. This has critical potential implications for sites anatomically neighboring adipose tissue depots. Furthermore, tumorigenesis and metastasis may also be promoted at distant sites as a result of endocrine and systemic consequences of adipose tissue dysfunction. Finally, proinflammatory feed-forward loops are simultaneously established both locally and systemically, and they sustain and amplify a state of chronic inflammation with proneoplastic propensity. Interrupting this harmful state of chronic inflammation will require efficient and accurate identification of at-risk populations and interventions that target the pleiotropic consequences of dysfunctional adipose tissue.

INTERVENTIONAL APPROACHES AND FUTURE DIRECTIONS

Elucidating the systemic and local mechanisms involved in the obesity–cancer link and the ways in which these processes interface provides a framework for the development of rational strategies to prevent cancers or improve postdiagnosis outcomes. A detailed discussion of strategies that have shown promise in the preclinical and clinical trial settings is beyond the scope of this review, but potential approaches may be generally categorized as (*a*) preventing or reversing the obese state, (*b*) targeting metabolic derangements associated with adipose tissue dysfunction, and (*c*) targeting WAT inflammation. Weight reduction, exercise, and bariatric surgery have shown promise in interrupting both systemic and local mechanisms underlying the obesity–cancer link (93–96). However, it can be difficult to maintain an improved state of energy balance. Several widely used medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), metformin, and statins, may be helpful in attenuating metabolic dysfunction or WAT inflammation. As with other targeted therapies, it is important to identify the at-risk population to maximize the potential benefit of these medications (97–100). Inclusion of unselected populations may explain, in part, the conflicting epidemiologic support for these agents in cancer prevention. Therefore, the development of clinically feasible tools, such as blood-based biomarkers of risk, is a critical research goal. As in

other diseases, development of a reliable surrogate that provides lead time before the manifestation of disease may be critical to changing public health.

The need for noninvasive, blood-based biomarkers that predict the presence of dysfunctional and/or inflamed WAT is underscored by the observation that not all obese individuals harbor unhealthy adipose tissue and that some lean individuals do (28). Therefore, reliance on BMI alone in developing intervention strategies is likely to prove suboptimal. This makes the identification of biomarker signatures of adipose dysfunction that predict favorable response to interventions a high priority because they would be more clinically valuable than conventional risk assessment alone. Given the multiple molecular derangements associated with altered adipose biology (**Figure 1**), a number of candidate biomarkers have been identified. Studies involving paired serum/plasma and WAT samples are currently under way to develop an algorithm that incorporates several molecules to accurately predict the presence of WAT inflammation. Such a biomarker signature could be used to identify eligible patients for clinical trials and to assess treatment response once enrolled.

As we continue to identify molecular alterations that mediate the relationships between obesity, adipose dysfunction, and cancer, it will be important to understand the complex crosstalk between these local and systemic mechanisms in order to develop comprehensive, effective interventions. In the near term, noninvasive biomarker signatures of WAT dysfunction are needed to accurately select high-risk patients who are most likely to benefit from interventions aimed at adipose tissue biology. A number of interventions have proven effective for managing obesity-related comorbidities such as cardiovascular disease and diabetes. Prospective clinical trials aimed at improving energy balance and tempering the protumorigenic microenvironment engendered by dysfunctional and inflamed adipose tissue are urgently needed as we continue to see acceleration in obesity rates worldwide.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

This work was supported by grants NIH/NCI R01CA154481, UL1TR000457 of the Clinical and Translational Science Center at Weill Cornell Medical College, the Conquer Cancer Foundation of the American Society of Clinical Oncology, the Botwinick-Wolfensohn Foundation (in memory of Mr. and Mrs. Benjamin Botwinick), and the Breast Cancer Research Foundation.

LITERATURE CITED

1. Levi J, Segal LM, St. Laurent R, et al. 2012. *F as in Fat: how obesity threatens America's future 2012*. Trust for America's Health Rep. <http://healthyamericans.org/report/100/>
2. Flegal KM, Carroll MD, Ogden CL, Curtin LR. 2010. Prevalence and trends in obesity among US adults, 1999–2008. *JAMA* 303:235–41
3. Calle EE, Kaaks R. 2004. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat. Rev. Cancer* 4:579–91
4. van Kruijsdijk RC, van der Wall E, Visseren FL. 2009. Obesity and cancer: the role of dysfunctional adipose tissue. *Cancer Epidemiol. Biomark. Prev.* 18:2569–78
5. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. 2003. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N. Engl. J. Med.* 348:1625–38

6. Iyengar NM, Morris PG, Hudis CA, Dannenberg AJ. 2013. Obesity, inflammation, and breast cancer. In *Obesity, Inflammation, and Cancer*, ed. AJ Dannenberg, NA Berger, pp. 181–217. New York: Springer
7. Yoon HH, Lewis MA, Shi Q, et al. 2011. Prognostic impact of body mass index stratified by smoking status in patients with esophageal adenocarcinoma. *J. Clin. Oncol.* 29:4561–67
8. Iyengar NM, Hudis CA, Dannenberg AJ. 2013. Obesity and inflammation: new insights into breast cancer development and progression. In *American Society of Clinical Oncology 2013 Educational Book*, pp. 46–51. Alexandria, VA: Am. Soc. Clin. Oncol.
9. Iyengar NM, Kochhar A, Morris PG, et al. 2014. Impact of obesity on the survival of patients with early-stage squamous cell carcinoma of the oral tongue. *Cancer* 120:983–91
10. Berger NA. 2014. Obesity-associated gastrointestinal tract cancer: from beginning to end. *Cancer* 120:935–39
11. Guilherme A, Virbasius JV, Puri V, Czech MP. 2008. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. *Nat. Rev. Mol. Cell Biol.* 9:367–77
12. Hursting SD, Digiovanni J, Dannenberg AJ, et al. 2012. Obesity, energy balance, and cancer: new opportunities for prevention. *Cancer Prev. Res.* 5:1260–72
13. Xu XJ, Gauthier MS, Hess DT, et al. 2012. Insulin sensitive and resistant obesity in humans: AMPK activity, oxidative stress, and depot-specific changes in gene expression in adipose tissue. *J. Lipid Res.* 53:792–801
14. Kloting N, Fasshauer M, Dietrich A, et al. 2010. Insulin-sensitive obesity. *Am. J. Physiol. Endocrinol. Metab.* 299:E506–15
15. Denis GV, Obin MS. 2013. “Metabolically healthy obesity”: origins and implications. *Mol. Aspects Med.* 34:59–70
16. Chen S, Chen Y, Liu X, et al. 2014. Insulin resistance and metabolic syndrome in normal-weight individuals. *Endocrine* 46:496–504
17. Deepa M, Papita M, Nazir A, et al. 2014. Lean people with dysglycemia have a worse metabolic profile than centrally obese people without dysglycemia. *Diabetes Technol. Ther.* 16:91–96
18. Lee MJ, Wu Y, Fried SK. 2013. Adipose tissue heterogeneity: implication of depot differences in adipose tissue for obesity complications. *Mol. Aspects Med.* 34:1–11
19. Park J, Euhus DM, Scherer PE. 2011. Paracrine and endocrine effects of adipose tissue on cancer development and progression. *Endocr. Rev.* 32:550–70
20. Khandekar MJ, Cohen P, Spiegelman BM. 2011. Molecular mechanisms of cancer development in obesity. *Nat. Rev. Cancer* 11:886–95
21. Pollak MN, Schernhammer ES, Hankinson SE. 2004. Insulin-like growth factors and neoplasia. *Nat. Rev. Cancer* 4:505–18
22. Goodwin PJ, Ennis M, Pritchard KI, et al. 2002. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. *J. Clin. Oncol.* 20:42–51
23. Ma J, Li H, Giovannucci E, et al. 2008. Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. *Lancet Oncol.* 9:1039–47
24. Barone BB, Yeh HC, Snyder CF, et al. 2008. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. *JAMA* 300:2754–64
25. Wong KK, Engelman JA, Cantley LC. 2010. Targeting the PI3K signaling pathway in cancer. *Curr. Opin. Genet. Dev.* 20:87–90
26. Zoncu R, Efeyan A, Sabatini DM. 2011. mTOR: from growth signal integration to cancer, diabetes and ageing. *Nat. Rev. Mol. Cell Biol.* 12:21–35
27. Lueprasitsakul P, Latour D, Longcope C. 1990. Aromatase activity in human adipose tissue stromal cells: effect of growth factors. *Steroids* 55:540–44
28. Rosen ED, Spiegelman BM. 2014. What we talk about when we talk about fat. *Cell* 156:20–44
29. Hofbauer KG. 2002. Molecular pathways to obesity. *Int. J. Obes. Relat. Metab. Disord.* 26(Suppl. 2):S18–27
30. Alberti KG, Eckel RH, Grundy SM, et al. 2009. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 120:1640–45

31. Pothiwala P, Jain SK, Yaturu S. 2009. Metabolic syndrome and cancer. *Metab. Syndr. Relat. Disord.* 7:279–88
32. Capasso I, Esposito E, Pentimalli F, et al. 2010. Metabolic syndrome affects breast cancer risk in postmenopausal women: National Cancer Institute of Naples experience. *Cancer Biol. Ther.* 10:1240–43
33. Porto LA, Lora KJ, Soares JC, Costa LO. 2011. Metabolic syndrome is an independent risk factor for breast cancer. *Arch. Gynecol. Obstet.* 284:1271–76
34. Rosato V, Bosetti C, Talamini R, et al. 2011. Metabolic syndrome and the risk of breast cancer in postmenopausal women. *Ann. Oncol.* 22:2687–92
35. Cleary MP, Grossmann ME. 2009. Minireview: obesity and breast cancer: the estrogen connection. *Endocrinology* 150:2537–42
36. Reeves GK, Pirie K, Beral V, et al. 2007. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ* 335:1134–45
37. Li CI, Daling JR, Malone KE. 2003. Incidence of invasive breast cancer by hormone receptor status from 1992 to 1998. *J. Clin. Oncol.* 21:28–34
38. Key TJ, Appleby PN, Reeves GK, et al. 2003. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J. Natl. Cancer Inst.* 95:1218–26
39. Lorincz AM, Sukumar S. 2006. Molecular links between obesity and breast cancer. *Endocr. Relat. Cancer* 13:279–92
40. Yager JD, Davidson NE. 2006. Estrogen carcinogenesis in breast cancer. *N. Engl. J. Med.* 354:270–82
41. Pequeux C, Raymond-Letron I, Blacher S, et al. 2012. Stromal estrogen receptor- α promotes tumor growth by normalizing an increased angiogenesis. *Cancer Res.* 72:3010–19
42. Giovannucci E, Rimm EB, Liu Y, et al. 2003. Body mass index and risk of prostate cancer in U.S. health professionals. *J. Natl. Cancer Inst.* 95:1240–44
43. Jayachandran J, Banez LL, Aronson WJ, et al. 2009. Obesity as a predictor of adverse outcome across black and white race: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) Database. *Cancer* 115:5263–71
44. Parker AS, Thiel DD, Bergstralh E, et al. 2013. Obese men have more advanced and more aggressive prostate cancer at time of surgery than non-obese men after adjusting for screening PSA level and age: results from two independent nested case-control studies. *Prostate Cancer Prostatic Dis.* 16:352–56
45. Loneragan PE, Tindall DJ. 2011. Androgen receptor signaling in prostate cancer development and progression. *J. Carcinog.* 10(20). doi: 10.4103/1477-3163.83937
46. Dhindsa S, Miller MG, McWhirter CL, et al. 2010. Testosterone concentrations in diabetic and nondiabetic obese men. *Diabetes Care* 33:1186–92
47. Tilg H, Moschen AR. 2006. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat. Rev. Immunol.* 6:772–83
48. Housa D, Housova J, Vernerova Z, Haluzik M. 2006. Adipocytokines and cancer. *Physiol. Res.* 55:233–44
49. Bub JD, Miyazaki T, Iwamoto Y. 2006. Adiponectin as a growth inhibitor in prostate cancer cells. *Biochem. Biophys. Res. Commun.* 340:1158–66
50. Kim AY, Lee YS, Kim KH, et al. 2010. Adiponectin represses colon cancer cell proliferation via AdipoR1- and -R2-mediated AMPK activation. *Mol. Endocrinol.* 24:1441–52
51. Cong L, Gasser J, Zhao J, et al. 2007. Human adiponectin inhibits cell growth and induces apoptosis in human endometrial carcinoma cells, HEC-1-A and RL95 2. *Endocr. Relat. Cancer* 14:713–20
52. Grossmann ME, Nkhata KJ, Mizuno NK, et al. 2008. Effects of adiponectin on breast cancer cell growth and signaling. *Br. J. Cancer* 98:370–79
53. Sharma D, Wang J, Fu PP, et al. 2010. Adiponectin antagonizes the oncogenic actions of leptin in hepatocellular carcinogenesis. *Hepatology* 52:1713–22
54. Fogarty S, Hardie DG. 2010. Development of protein kinase activators: AMPK as a target in metabolic disorders and cancer. *Biochim. Biophys. Acta* 1804:581–91
55. Lam JBB, Chow KHM, Xu A, et al. 2009. Adiponectin haploinsufficiency promotes mammary tumor development in MMTV-PyVT mice by modulation of phosphatase and tensin homolog activities. *PLOS ONE* 4(3):e4968
56. Miyoshi Y, Funahashi T, Kihara S, et al. 2003. Association of serum adiponectin levels with breast cancer risk. *Clin. Cancer Res.* 9:5699–704

57. Duggan C, Irwin ML, Xiao L, et al. 2011. Associations of insulin resistance and adiponectin with mortality in women with breast cancer. *J. Clin. Oncol.* 29:32–39
58. Mantzoros C, Petridou E, Dessypris N, et al. 2004. Adiponectin and breast cancer risk. *J. Clin. Endocrinol. Metab.* 89:1102–7
59. Soliman PT, Wu D, Tortolero-Luna G, et al. 2006. Association between adiponectin, insulin resistance, and endometrial cancer. *Cancer* 106:2376–81
60. Xu XT, Xu Q, Tong JL, et al. 2011. Meta-analysis: circulating adiponectin levels and risk of colorectal cancer and adenoma. *J. Dig. Dis.* 12:234–44
61. Michalakis K, Williams CJ, Mitsiades N, et al. 2007. Serum adiponectin concentrations and tissue expression of adiponectin receptors are reduced in patients with prostate cancer: a case control study. *Cancer Epidemiol. Biomark. Prev.* 16:308–13
62. Li H, Stampfer MJ, Mucci L, et al. 2010. A 25-year prospective study of plasma adiponectin and leptin concentrations and prostate cancer risk and survival. *Clin. Chem.* 56:34–43
63. Friedman JM, Halaas JL. 1998. Leptin and the regulation of body weight in mammals. *Nature* 395:763–70
64. Sharma D, Saxena NK, Vertino PM, Anania FA. 2006. Leptin promotes the proliferative response and invasiveness in human endometrial cancer cells by activating multiple signal-transduction pathways. *Endocr. Relat. Cancer* 13:629–40
65. Choi JH, Park SH, Leung PC, Choi KC. 2005. Expression of leptin receptors and potential effects of leptin on the cell growth and activation of mitogen-activated protein kinases in ovarian cancer cells. *J. Clin. Endocrinol. Metab.* 90:207–10
66. Hoda MR, Keely SJ, Bertelsen LS, et al. 2007. Leptin acts as a mitogenic and antiapoptotic factor for colonic cancer cells. *Br. J. Surg.* 94:346–54
67. Onuma M, Bub JD, Rummel TL, Iwamoto Y. 2003. Prostate cancer cell–adipocyte interaction: leptin mediates androgen-independent prostate cancer cell proliferation through c-Jun NH2-terminal kinase. *J. Biol. Chem.* 278:42660–67
68. Chia VM, Newcomb PA, Lampe JW, et al. 2007. Leptin concentrations, leptin receptor polymorphisms, and colorectal adenoma risk. *Cancer Epidemiol. Biomark. Prev.* 16:2697–703
69. Grossmann ME, Mizuno NK, Bonorden MJ, et al. 2009. Role of the adiponectin leptin ratio in prostate cancer. *Oncol. Res.* 18:269–77
70. Olefsky JM, Glass CK. 2010. Macrophages, inflammation, and insulin resistance. *Annu. Rev. Physiol.* 72:219–46
71. Pierce BL, Ballard-Barbash R, Bernstein L, et al. 2009. Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients. *J. Clin. Oncol.* 27:3437–44
72. Visser M, Bouter LM, McQuillan GM, et al. 1999. Elevated C-reactive protein levels in overweight and obese adults. *JAMA* 282:2131–35
73. Morris PG, Zhou XK, Milne GL, et al. 2013. Increased levels of urinary PGE-M, a biomarker of inflammation, occur in association with obesity, aging, and lung metastases in patients with breast cancer. *Cancer Prev. Res.* 6:428–36
74. Kim S, Taylor JA, Milne GL, Sandler DP. 2013. Association between urinary prostaglandin E2 metabolite and breast cancer risk: a prospective, case-cohort study of postmenopausal women. *Cancer Prev. Res.* 6:511–18
75. Amano SU, Cohen JL, Vangala P, et al. 2014. Local proliferation of macrophages contributes to obesity-associated adipose tissue inflammation. *Cell Metab.* 19:162–71
76. Howe LR, Subbaramaiah K, Hudis CA, Dannenberg AJ. 2013. Molecular pathways: adipose inflammation as a mediator of obesity-associated cancer. *Clin. Cancer Res.* 19:6074–83
77. Mantovani A, Allavena P, Sica A, Balkwill F. 2008. Cancer-related inflammation. *Nature* 454:436–44
78. Coussens LM, Werb Z. 2002. Inflammation and cancer. *Nature* 420:860–67
79. Osborn O, Olefsky JM. 2012. The cellular and signaling networks linking the immune system and metabolism in disease. *Nat. Med.* 18:363–74
80. Monteiro R, Azevedo I. 2010. Chronic inflammation in obesity and the metabolic syndrome. *Mediators Inflamm.* 2010:1–10
81. Cinti S, Mitchell G, Barbatelli G, et al. 2005. Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. *J. Lipid Res.* 46:2347–55

82. Subbaramaiah K, Howe LR, Bhardwaj P, et al. 2011. Obesity is associated with inflammation and elevated aromatase expression in the mouse mammary gland. *Cancer Prev. Res.* 4:329–46
83. Morris PG, Hudis CA, Giri D, et al. 2011. Inflammation and increased aromatase expression occur in the breast tissue of obese women with breast cancer. *Cancer Prev. Res.* 4:1021–29
84. Sun X, Casbas-Hernandez P, Bigelow C, et al. 2012. Normal breast tissue of obese women is enriched for macrophage markers and macrophage-associated gene expression. *Breast Cancer Res. Treat.* 131:1003–12
85. Bachelot T, Ray-Coquard I, Menetrier-Caux C, et al. 2003. Prognostic value of serum levels of interleukin 6 and of serum and plasma levels of vascular endothelial growth factor in hormone-refractory metastatic breast cancer patients. *Br. J. Cancer* 88:1721–26
86. Subbaramaiah K, Morris PG, Zhou XK, et al. 2012. Increased levels of COX-2 and prostaglandin E2 contribute to elevated aromatase expression in inflamed breast tissue of obese women. *Cancer Discov.* 2:356–65
87. Zhao Y, Agarwal VR, Mendelson CR, Simpson ER. 1996. Estrogen biosynthesis proximal to a breast tumor is stimulated by PGE2 via cyclic AMP, leading to activation of promoter II of the CYP19 (aromatase) gene. *Endocrinology* 137:5739–42
88. Irahara N, Miyoshi Y, Taguchi T, et al. 2006. Quantitative analysis of aromatase mRNA expression derived from various promoters (I.4, I.3, PII and I.7) and its association with expression of TNF-alpha, IL-6 and COX-2 mRNAs in human breast cancer. *Int. J. Cancer* 118:1915–21
89. Shapiro H, Pecht T, Shaco-Levy R, et al. 2013. Adipose tissue foam cells are present in human obesity. *J. Clin. Endocrinol. Metab.* 98:1173–81
90. Underhill DM, Goodridge HS. 2012. Information processing during phagocytosis. *Nat. Rev. Immunol.* 12:492–502
91. Pendyala S, Walker JM, Holt PR. 2012. A high-fat diet is associated with endotoxemia that originates from the gut. *Gastroenterology* 142:1100–01
92. Lee JY, Sohn KH, Rhee SH, Hwang D. 2001. Saturated fatty acids, but not unsaturated fatty acids, induce the expression of cyclooxygenase-2 mediated through toll-like receptor 4. *J. Biol. Chem.* 276:16683–89
93. Chlebowski RT, Blackburn GL, Thomson CA, et al. 2006. Dietary fat reduction and breast cancer outcome: interim efficacy results from the Women's Intervention Nutrition Study. *J. Natl. Cancer Inst.* 98:1767–76
94. Campbell KL, Foster-Schubert KE, Alfano CM, et al. 2012. Reduced-calorie dietary weight loss, exercise, and sex hormones in postmenopausal women: randomized controlled trial. *J. Clin. Oncol.* 30:2314–26
95. Imayama I, Ulrich CM, Alfano CM, et al. 2012. Effects of a caloric restriction weight loss diet and exercise on inflammatory biomarkers in overweight/obese postmenopausal women: a randomized controlled trial. *Cancer Res.* 72:2314–26
96. Ligibel JA, Goodwin PJ. 2012. NEW and RENEW: building the case for weight loss in breast cancer. *J. Clin. Oncol.* 30:2294–96
97. Goodwin PJ, Pritchard KI, Ennis M, et al. 2008. Insulin-lowering effects of metformin in women with early breast cancer. *Clin. Breast Cancer* 8:501–5
98. Dannenberg AJ, Altorki NK, Boyle JO, et al. 2001. Cyclo-oxygenase 2: a pharmacological target for the prevention of cancer. *Lancet Oncol.* 2:544–51
99. Higgins MJ, Prowell TM, Blackford AL, et al. 2012. A short-term biomarker modulation study of simvastatin in women at increased risk of a new breast cancer. *Breast Cancer Res. Treat.* 131:915–24
100. Hudis CA, Subbaramaiah K, Morris PG, Dannenberg AJ. 2012. Breast cancer risk reduction: no pain, no gain? *J. Clin. Oncol.* 30:3436–38



Contents

A Tale of Two Tumors: Treating Pancreatic and Extrapancreatic Neuroendocrine Tumors <i>Daniel M. Halperin, Matthew H. Kulke, and James C. Yao</i>	1
Metformin in Cancer Treatment and Prevention <i>Daniel R. Morales and Andrew D. Morri</i>	17
Neoadjuvant Therapy for Breast Cancer <i>Dimitrios Zardavas and Martine Piccart</i>	31
Neuroblastoma: Molecular Pathogenesis and Therapy <i>Chrystal U. Louis and Jason M. Shobet</i>	49
Pharmacogenetics of Cancer Drugs <i>Daniel L. Hertz and James Rae</i>	65
Recent Therapeutic Advances in the Treatment of Colorectal Cancer <i>Kristen K. Ciombar, Christina Wu, and Richard M. Goldberg</i>	83
Regulation of Tumor Metastasis by Myeloid-Derived Suppressor Cells <i>Thomas Condamine, Indu Ramachandran, Je-In Youn, and Dmitry I. Gabrilovich</i>	97
Targeting HER2 for the Treatment of Breast Cancer <i>Mothaffar F. Rimawi, Rachel Schiff, and C. Kent Osborne</i>	111
The DNA Damage Response: Implications for Tumor Responses to Radiation and Chemotherapy <i>Michael Goldstein and Michael B. Kastan</i>	129
Pathogenesis of Macrophage Activation Syndrome and Potential for Cytokine-Directed Therapies <i>Grant S. Schulert and Alexei A. Grom</i>	145
Cardiovascular Disease in Adult Survivors of Childhood Cancer <i>Steven E. Lipshultz, Vivian I. Franco, Tracie L. Miller, Steven D. Colan, and Stephen E. Sallan</i>	161
Advances in Nanoparticle Imaging Technology for Vascular Pathologies <i>Ananth Annapragada</i>	177

Vasopressin Receptor Antagonists, Heart Failure, and Polycystic Kidney Disease <i>Vicente E. Torres</i>	195
ADAMTS13 and von Willebrand Factor in Thrombotic Thrombocytopenic Purpura <i>X. Long Zheng</i>	211
Current Therapies for ANCA-Associated Vasculitis <i>Lindsay Lally and Robert Spiera</i>	227
Changing Practice of Anticoagulation: Will Target-Specific Anticoagulants Replace Warfarin? <i>Gowthami M. Arepally and Thomas L. Ortel</i>	241
The Mechanisms and Therapeutic Potential of SGLT2 Inhibitors in Diabetes Mellitus <i>Volker Vallon</i>	255
Extranuclear Steroid Receptors Are Essential for Steroid Hormone Actions <i>Ellis R. Levin</i>	271
Impact of the Obesity Epidemic on Cancer <i>Pamela J. Goodwin and Vuk Stambolic</i>	281
Obesity and Cancer: Local and Systemic Mechanisms <i>Neil M. Iyengar, Clifford A. Hudis, and Andrew J. Dannenberg</i>	297
The JAK-STAT Pathway: Impact on Human Disease and Therapeutic Intervention <i>John J. O'Shea, Daniella M. Schwartz, Alejandro V. Villarino, Massimo Gadina, Iain B. McInnes, and Arian Laurence</i>	311
Management of Postmenopausal Osteoporosis <i>Panagiota Andreopoulou and Richard S. Bockman</i>	329
The Gut Microbial Endocrine Organ: Bacterially Derived Signals Driving Cardiometabolic Diseases <i>J. Mark Brown and Stanley L. Hazen</i>	343
H7N9: Preparing for the Unexpected in Influenza <i>Daniel B. Jernigan and Nancy J. Cox</i>	361
Treatment of Recurrent and Severe <i>Clostridium Difficile</i> Infection <i>J.J. Keller and E.J. Kuijper</i>	373
Emerging Technologies for Point-of-Care Management of HIV Infection <i>Hadi Shafiee, ShuQi Wang, Fatih Inci, Mehlika Toy, Timothy J. Henrich, Daniel R. Kuritzkes, and Utkan Demirci</i>	387

Understanding HIV Latency: The Road to an HIV Cure <i>Matthew S. Dababieh, Emilie Battivelli, and Eric Verdin</i>	407
Lessons from the RV144 Thai Phase III HIV-1 Vaccine Trial and the Search for Correlates of Protection <i>Jerome H. Kim, Jean-Louis Excler, and Nelson L. Michael</i>	423
T Cell–Mediated Hypersensitivity Reactions to Drugs <i>Rebecca Pavlos, Simon Mallal, David Ostrov, Soren Buus, Imir Metushi, Bjoern Peters, and Elizabeth Phillips</i>	439
Synthetic Lethality and Cancer Therapy: Lessons Learned from the Development of PARP Inhibitors <i>Christopher J. Lord, Andrew N.J. Tutt, and Alan Ashworth</i>	455
Lysosomal Storage Diseases: From Pathophysiology to Therapy <i>Giancarlo Parenti, Generoso Andria, and Andrea Ballabio</i>	471
From De Novo Mutations to Personalized Therapeutic Interventions in Autism <i>William M. Brandler and Jonathan Sebat</i>	487
Ketamine and Rapid-Acting Antidepressants: A Window into a New Neurobiology for Mood Disorder Therapeutics <i>Chadi G. Abdallah, Gerard Sanacora, Ronald S. Duman, and John H. Krystal</i>	509

Indexes

Cumulative Index of Contributing Authors, Volumes 62–66	525
Cumulative Index of Article Titles, Volumes 62–66	529

Errata

An online log of corrections to *Annual Review of Medicine* articles may be found at
<http://www.annualreviews.org/errata/med>