

Energy Balance and Cancer

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Editors

Obesity, Inflammation and Cancer

 Springer

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Preface: What's Old Is New Again and Now It's Red Hot

As the worldwide obesity pandemic expands, obesity has been associated with an increased risk of more and more cancer types. The original malignancies shown to be associated with obesity included esophageal adenocarcinoma, colon cancer, renal cell cancer, postmenopausal breast cancer, endometrial cancer, and advanced prostate cancer. More recently, obesity has been identified as a risk factor for cancers of the pancreas, gall bladder, and ovary and several hematologic malignancies including leukemia, lymphomas, and myeloma, and the list continues to grow.

From a historical viewpoint, while early studies considered the possibility that inflammation initiated the process of carcinogenesis, this was generally considered to be a local effect associated with tissue injury or chronic infection. With elucidation of DNA structure and function and development of the concept of chemical carcinogens as mutagens, attention turned to identification of activated oncogenes and deactivated tumor suppressor genes in the carcinogenic process. Separate studies demonstrated that inflammation extended beyond the local site, mediated by cellular and humoral components. As noted above, independent epidemiologic studies confirmed an association of obesity with cancer incidence, morbidity, and mortality. Studies to identify the mediators of these processes focused on the effects of obesity on growth factors and hormones and the mechanisms of carcinogenesis they commonly affect. More recently, it has become apparent that adipose tissue, in addition to serving as a fat storage depot, is an intensely active metabolic organ. In obesity, low-grade chronic adipose tissue inflammation occurs, resulting in multiple cellular and humoral inflammatory factors. Seminal studies showing that systemic metabolic disorders, such as insulin resistance, could be mediated, in part, by inflammatory cytokines, synthesized and secreted by adipose tissue, resulted in a whole new approach to understanding and attempting to control obesity-associated comorbidities. Moreover, elucidation of the prostaglandin pathway and its role in inflammation, as well as the observations that anti-inflammatory agents, especially the nonsteroidal anti-inflammatory drugs (NSAIDs), could prevent the development and progression of several forms of neoplasia, provided a major stimulus to the field. A major goal of ongoing research is to inhibit inflammation as an approach to cancer prevention and control.

The above brief description traces the complex transdisciplinary evolution of this area of research endeavor. Not only does it illustrate the impact of sometimes divergent disciplines on the evolution of a concept, but it also indicates the potential value of moving forward in this field with a transdisciplinary approach. Accordingly, the goal of this volume of *Energy Balance and Cancer*, volume 7 in the series, is to highlight the cutting-edge transdisciplinary science linking obesity, inflammation, and cancer. We are grateful to all the authors listed below for their contributions to this volume and look forward to their collective impact in further advancing this rapidly developing field.

This volume first provides information on inflammation as an important link between obesity and insulin resistance, which is in itself linked to promotion of cancer through hyperinsulinemia. The volume then covers some of the most important mechanisms by which obesity leads to inflammation, including the novel inflammasome concept, alterations in chromatin structure, circulating inflammatory factors, unique cellular interactions between adipocytes and macrophages, and the direct link of dietary fat to inflammation and cancer. Subsequently addressed in this volume are a number of target organs and interventional strategies for disrupting inflammation and their effects on cancer prevention and control.

In Chap. 1, Lesley G. Ellies, Andrew Johnson, and Jerrold M. Olefsky (University of California, San Diego) describe the mechanisms by which obesity stimulates low-grade inflammation leading to insulin resistance. Chapter 2, written by Tuo Deng, Christopher J. Lyon, Nan Zhang, Helen Y. Wang, Rong-fu Wang, and Willa A. Hsueh (Weill Cornell Medical College) and Jun Cui (Sun Yat-sen University), reviews the basis for understanding the emerging concept of the inflammasome and its mechanisms of activation and role in obesity. Gerald V. Denis and Deborah J. Bowen (Boston University School of Public Health) describe in Chap. 3 chromatin-based, transcription co-regulatory mechanisms that may link obesity, inflammation, and cancer. Carey Nien-Kai Lumeng (University of Michigan Medical School), in Chap. 4, describes the important role that adipose tissue macrophages play in breast and ovarian cancer. In Chap. 5, Stephanie K. Doerner and Nathan A. Berger (Case Western Reserve University School of Medicine) discuss the impact of different dietary fatty acids on promoting or suppressing colorectal cancer. In Chap. 6, Anamay Sharma, Ahmed Elebiary, Sonia Chowdhury, and Navtej Buttar (Mayo Clinic) describe the contribution of gastric reflux to inflammation in Barrett's esophagus and esophageal adenocarcinoma and potential interventions. In Chap. 7, Stephanie K. Doerner (Case Western Reserve University School of Medicine) and Jason D. Heaney (Baylor College of Medicine) describe the role of obesity-induced intestinal inflammation on colorectal cancer incidence. In Chap. 8, Neil M. Iyengar, Patrick G. Morris and Clifford A. Hudis (Memorial Sloan-Kettering Cancer Center) and Andrew J. Dannenberg (Weill Cornell Medical College) review the emerging evidence supporting the contribution of adipose tissue and chronic breast inflammation to the development of breast cancer. In Chap. 9, the relation of obesity, inflammation, and hepatocellular cancer is discussed by Naim Alkhouri and Arthur McCullough (Cleveland Clinic Lerner College of Medicine at Case Western Reserve University), and in Chap. 10, Jorge Blando, Achinto Saha, Kaoru Kiguchi, and John

DiGiovanni (University of Texas at Austin) describes the role of obesity and inflammation in prostate cancer. Louise R. Howe (Weill Cornell Medical College), in Chap. 11, describes the central role of cyclooxygenase-derived prostaglandins as potential mediators of obesity-related cancer and outlines how targeting this pathway may be protective against obesity-associated carcinogenesis. In Chap. 12, Harmony F. Turk, Jennifer M. Monk, Tim Y. Hou, and Robert S. Chapkin (Texas A&M University) discuss mechanisms through which n-3 polyunsaturated fatty acids interfere with the inflammatory process to suppress carcinogenesis, and in Chap. 13, Gary Stoner and Li-Shu Wang (Medical College of Wisconsin) describe key mechanisms by which naturally occurring dietary compounds reduce the harmful effects of inflammation and the risk for cancer development. In Chap. 14, Stephen D. Hursting, Nikki A. Ford, Sarah M. Dunlap, and Laura M. Lashinger (University of Texas at Austin) and Marcie J. Hursting (Clinical Science Consulting) describe the modification of inflammatory pathways and their impact on cancer by diet and caloric restriction. Ahmad Salameh and Mikhail G. Kolonin, in Chap. 15, describe an innovative approach to adipose tissue control by vascular targeting. In Chap. 16, Michael Gleeson (Loughborough University) describes the anti-inflammatory effects of exercise.

Overall, this volume on Obesity, Inflammation, and Cancer provides an up-to-date status report on the latest developments and state-of-the-art understanding of the role of inflammation in mediating the effects of obesity on cancer and describes possible strategies for targeting inflammation as an approach to cancer prevention and control. The book should be useful for students, researchers, and clinicians, especially those interested in the role of inflammation and its impact on cancer. It is our expectation that this volume will both stimulate research on the role of inflammation in cancer etiology and progression and lead to new approaches and clinical trials for cancer prevention and control by targeting obesity-related inflammation.

New York, NY, USA
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Chapter 3

Uncoupling Obesity from Cancer: Bromodomain Co-regulators That Control Inflammatory Networks

Gerald V. Denis and Deborah J. Bowen

Abstract As the epidemic of overweight and obesity spreads, the number of individuals at risk for metabolic complications of obesity, including cardiovascular disease, type 2 diabetes, and cancer, is expected to increase. Importantly, the risks of complications are not evenly distributed, because not all obesity is biochemically identical. Here we describe “metabolically healthy obese” humans and animal models that show remarkable protection from insulin resistance and glucose intolerance, despite severe obesity. A hallmark of these patients and animals is their reduced inflammatory profile, which we hypothesize confers protection not only from cardiometabolic risk in obesity but also from obesity-associated cancers. Research is urgently required to investigate the basis for this protection, to identify treatment options and prevention strategies for at-risk populations. We explore novel insights into chromatin-based, transcriptional co-regulator mechanisms that link apparently unrelated diseases, with the idea that certain molecularly targeted strategies could moderate multiple risks in obesity. We voice concern that low socioeconomic status citizens are particularly at risk for cardiometabolic disease and obesity-associated cancer, in part because many such individuals live in inflammatory and obesogenic environments. An integrated and hypothesis-driven approach is needed to study and protect these vulnerable and underserved populations from the rising tide of obesity-associated cancer.

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3.1 The Problem of Obesity-Associated Cancer

Diet-induced overnutrition that causes unhealthy weight gain, defined in humans as *overweight* (Body Mass Index [BMI] 25.0–29.9 kg/m²), *obesity* (BMI ≥30.0–39.9 kg/m²), and *morbid obesity* (BMI ≥40.0 kg/m²), has many medical complications. The realization that obesity had become a serious public health concern was initially driven by projected increases in the prevalence of metabolic complications, such as elevated risk for stroke, cardiovascular disease, and type 2 diabetes. The complications of obesity also include dyslipidemia, hypertension, sleep apnea, hepatosteatosis, and glucose intolerance [1]. However, attention has been recently focused on a particularly worrisome complication: obesity-associated malignancy [2, 3]. Recent epidemiological reports have caused serious disquiet that, despite overall declines in cancer rates, particularly the rates for tobacco-associated cancers, the rates of obesity-associated cancers are climbing. Obesity is now thought to be one of the most important preventable causes of several cancers [4]; these include esophageal adenocarcinoma, colorectal cancer, breast cancer in postmenopausal women (but not premenopausal women), and cancers of the endometrium, kidney, pancreas, liver, and gallbladder [3, 5, 6]. The National Cancer Institute, American Cancer Society, and American Association for Cancer Research have been using their influence and expert opinion in recent years to increase the public profile and research portfolio devoted to this problem and its allied risk factors. Obesity-associated malignancies have been estimated to account for 14 % of male and 20 % of female US cancer mortality, notably colorectal cancer and postmenopausal breast cancer [2]. This chapter will present some of the molecular, cellular, and immunological features that link obesity and its complications to cancer.

In view of recent data from the US Centers for Disease Control and Prevention [7], showing that all US states now report at least 20 % prevalence of obesity among adults, as well as the classification of 1.7 billion people worldwide as overweight [8], obesity-associated cancer is positioned to become one of the defining preventable diseases of our time. Diabetes is also a serious complication among the chronic disease burdens of obesity. In fact, overweight and obesity are now well established to be the direct cause of most cases of type 2 diabetes [9]. Three hundred and sixty-six million cases worldwide was a frequently cited early estimate of the incidence of type 2 diabetes by 2030 [10]. Alarming, more recent estimates have adjusted upward the anticipated number of diabetic individuals to 439 million by 2030 [11]. Almost all of the incidence will be driven by overweight and obesity. The anticipated further increases in BMI worldwide [12] predict that the seriousness of the problem of obesity-associated cancer will also deepen in coming decades.

3.2 Molecular Features of Insulin-Resistant Obesity

The molecular mechanisms that explain how obesity contributes to cancer risk are still largely unknown in detail. Early epidemiological investigation of obesity and its comorbidities identified an association between the incidence of

type 2 diabetes and obesity [13]. Some of the key features of insulin-resistant obesity include elevated concentrations of blood glucose in fasted subjects and impaired glucose tolerance, as well as elevated blood concentrations of insulin in fasted subjects and reduced insulin sensitivity. Leptin, which is a critical regulator of appetite, is produced by adipocytes and is elevated in obesity in proportion to adipose tissue mass [14]. This hyperleptinemia in obesity has been frequently described as “leptin resistance,” a term now thought to lack clinical utility [15]. In addition, insulin-resistant obesity frequently features reduced serum concentrations of adiponectin [16, 17], an insulin-sensitizing adipokine [18] that exhibits beneficial, antiatherogenic effects. These characteristics are commonly observed together in obese subjects [19–21] and animal models [22] and reflect the growing inability of peripheral tissues of the obese subject, such as skeletal muscle and fat stores, to transport glucose from blood into cells at normal levels of insulin present in the circulation. This state has been described as peripheral insulin resistance. Commonly, the pancreatic β -cells of such a subject are required to secrete ever higher levels of insulin to compensate for the peripheral insulin resistance. In humans and certain rodent models, this chronic hyperinsulinemia and accompanying β -cell dysfunction are two of the defining characteristics of insulin-resistant obesity and are often associated with increased serum levels and bioavailability of the related mitogenic factor, insulin-like growth factor (IGF)-1 [23].

These clinical presentations provoked questions about which biochemical features of insulin resistance and type 2 diabetes were important for carcinogenesis in obesity. Signal transduction through the insulin receptor and IGF-1 receptor [24] is thought to increase cancer risk in obesity [25, 26]. Fasting insulin concentrations have been used convincingly as a prognostic factor for overall survival among breast cancer patients, with the highest hazard ratio associated with the highest insulin concentrations [27]. Leptin also promotes mitogenic [28–31] and invasive [32] effects in a variety of human cancer cell lines [33–35] and tumor models in animals [36]. For example, leptin-deficient mice appear to be protected from mammary carcinogenesis [37–39]. Adiponectin not only protects insulin-sensitive glucose transport but also appears to be inversely correlated with susceptibility to certain obesity-associated cancers [40–42]. Furthermore, the leptin-adiponectin ratio has been proposed to be a critical predictor of cancer risk [38]. These features have been well summarized elsewhere [43–45]. However, the co-occurrence of these multiple factors in obesity has made it difficult to define the relative importance of each. Overall, rodent models have tended to show that alteration of any single factor in isolation affects mitogenesis, tumor progression, or other relevant parameter of the malignancy. Experimental designs that use rodent models in which multiple variables are manipulated simultaneously to influence cancer risk do not permit straightforward interpretation; thus, the field remains divided about which cellular and molecular factors are of paramount importance for specific obesity-associated cancers.

3.3 Insulin-Resistant Obesity Is Also an Inflammatory Disease

One of the earliest described immunological features of insulin-resistant obesity was subclinical, unresolved, chronic inflammation, which occurs both systemically [47, 67] and in white adipose tissue [48], which is infiltrated with pro-inflammatory macrophages [49–52]. Specifically, such patients demonstrate elevated serum concentrations of acute phase proteins and pro-inflammatory cytokines [53], such as interleukin (IL)-1 β , IL-6, and C-reactive protein, that improve over time after intentional weight loss [54, 55, 67] or bariatric surgery [56]. Exposure of glucose-transporting cells to the pro-inflammatory cytokine tumor necrosis factor (TNF)- α was demonstrated as long ago as 1993 to promote insulin resistance directly [57]. Adipose tissue depots, composed of white adipocytes, are typically inflamed, that is, infiltrated with Th1- and Th17-polarized T cells [58] and pro-inflammatory macrophages, both in obese humans [59–63] and animal models [50, 51, 59, 64–66] of diet-induced obesity. In insulin-resistant obesity, the pro-inflammatory macrophages that infiltrate these depots secrete significant amounts of pro-inflammatory cytokines, which, in addition to TNF- α [57], include IL-6, IL-8, and monocyte chemoattractant protein (MCP)-1/chemokine (C–C motif) ligand (CCL)2 [46, 67]. Systemic inflammation is also a feature of insulin-resistant obesity, as indicated by elevated serum levels of C-reactive protein [68] and several of the aforementioned and other cytokines [61]. Furthermore, chemokines such as MCP-1/CCL2 also serve to recruit additional leukocytes, such as peripheral blood monocytes that express the C–C motif chemokine receptor (CCR) 2 [50, 51, 60], to infiltrate the insulin-resistant adipose depot in a deepening cycle of unresolved, chronic inflammation. Thus, a feed-forward loop is established that is difficult for homeostatic forces in the immune system to oppose [58]. Failure of the anti-inflammatory balance may also be an independent, critical factor in the emergence of the many comorbidities of obesity.

Moreover, certain specific, histological features define insulin-resistant adipose tissue. The adipocytes frequently become stressed as their storage limits are exceeded, leading to a large number of apoptotic adipocytes, a process that is thought to recruit additional leukocytes [59]. The dead and dying adipocytes of stressed white adipose tissue appear surrounded with a ring of pro-inflammatory macrophages (CD68⁺ in humans [69]) that are histologically termed “crown-like structures” [59] and are associated with fibrosis [70] and increased metabolic risk [71–74]. How these structures arise and are resolved by weight loss or drug treatments is not well understood. In mouse models, the macrophages that infiltrate metabolically unhealthy white adipose tissue tend to express a surface phenotype, that is, CD11b⁺ CD11c⁺ F4/80⁺ by flow cytometry, that identifies them as pro-inflammatory. These pro-inflammatory macrophages have been directly implicated in the decline of metabolic health of adipocytes in white adipose tissue in different adipose depots in animal models [75, 76] and humans [101]. Early in the kinetics of diet-induced obesity in rodent models, adipocyte death and the development of whole-body insulin resistance [65] also correlate with a switch in macrophage

polarization toward the classically activated, pro-inflammatory (so-called M1) phenotype and away from the alternatively activated, anti-inflammatory (“M2”) phenotype [78]. The CD11c⁺ adipose tissue macrophage populations also transiently remodel the white adipose tissue, which then exhibits activities connected with M2-associated genes, such as increased expression of arginase, IL-10, IL-4, and transforming growth factor (TGF)- β [79]. The net balance of these M1 and M2 inputs defines the profile and magnitude of white adipose tissue inflammation. Relatively high expression of M1 cytokines is associated with metabolic complications of obesity, including insulin resistance. However, in human adipose depots, the molecular details of putative M1 phenotypes and function, and the M1/M2 switch, are less well understood than in animal models.

T cells are also recruited to white adipose tissue in diet-induced obesity through “regulated on normal T cell expressed and secreted” (RANTES/CCL5) and its receptor CCR5 in white adipose tissue [80, 81], where the Th1/Th2 polarization and proliferation of T cells are influenced by macrophage-produced cytokines [82]. T cells play a major role in insulin resistance [62] through macrophage recruitment [83]. T cell polarization between the pro-inflammatory (interleukin-17 producing) subtype (Th17 [84]) and the anti-inflammatory (IL-10 producing) T regulatory subtype (Foxp3⁺ Treg [85]) also influences metabolism in white adipose tissue. A pro-inflammatory imbalance in CD4⁺ T cell subsets has been demonstrated both systemically and in adipose depots of type 2 diabetic subjects [58]. The balance of pro-inflammatory and anti-inflammatory cytokines and T cell subsets remains perturbed in insulin-resistant obesity; some investigators hypothesize the adipocyte/T cell cross talk is the critical factor that promotes disease pathogenesis, whereas others hypothesize that macrophages have primary importance. The interpretations have remained controversial. Recent data from human studies also supports a central role for B cells in the pathogenesis of type 2 diabetes in obese subjects [58, 86, 87]. The independent and interdependent roles of T cell subsets, B cell subsets, and monocyte/macrophage polarization, and their specific cross talk with adipocytes that influences risks for obesity-associated cancer and type 2 diabetes, define a central focus of the exciting new field of immunometabolism [58].

Outside the adipose depots, the immune system of the obese and insulin-resistant subject demonstrates systemic, pro-inflammatory changes in T cell, B cell, and myeloid subset differentiation and function that exacerbate the deepening cytokine/chemokine imbalance as metabolism deteriorates in diet-induced obesity. Animal models demonstrate that stoppage of immune cell-mediated inflammatory cascades by any one of several diverse techniques (e.g., genetic, small molecule, or antibody-based) frequently delays or prevents insulin resistance [88, 89]. If metabolic parameters improve through dietary intervention, adipose tissue inflammation also typically improves [90]. The long-established links between chronic, unresolved inflammation and cancer therefore provide a basis to hypothesize that the presence of crown-like structures, for example, or elevation of other local and systemic inflammatory markers, is positively associated with cancer risk for obesity-associated cancers that have an inflammatory component.

3.4 Insight from Unexpected Results

Obesity-associated malignancies are not linked to every type of cancer. Apart from lung cancer, which is associated with cigarette smoking [91, 92] or asbestos inhalation and not with obesity [3], certain other cancers are also clearly not associated with obesity, including but not limited to astrocytoma; glioma; Kaposi's sarcoma; neuroblastoma; head, neck, and oral cancer; pituitary cancer; retinoblastoma; salivary cancer; and testicular cancer. A possibly relevant, shared feature of these cancers is that they do not originate in or near visceral adipose tissue. Compared to subcutaneous depots, the visceral or "central" adipose depot [63, 93, 94] is the most inflamed in obese insulin-resistant patients [95–97] and is independently associated with cardiometabolic risk. In animal models, the epididymal adipose depot of male mice is regarded as a good model for visceral adipose tissue inflammation in diet-induced obesity [59, 65, 66]. Likewise, many (but not all) of the obesity-associated cancers are resident in or likely influenced by inflamed visceral adipose tissue. All female breast carcinomas, for example, are surrounded by significant adipose depots in humans and the mammary fat pad in mice. It is likely that the metabolic and inflammatory properties of this adipose depot are highly relevant to specific aspects of breast cancer progression, invasiveness, metastasis, or recurrence, although this area has not received sufficient attention from investigators.

The observation that insulin-resistant obesity features *systemic* elevations of pro-inflammatory cytokines, as well as systemically elevated glucose, insulin, IGF-1, leptin, and depleted adiponectin, raises a problem. Why are not all cancers obesity-associated? If the argument is made that insulin and IGF-1 signaling cross talk, as well as leptin-promoted, broad-spectrum mitogenesis or diminished protection from adiponectin, are critical factors that explain obesity-associated cancers, why should so many cancers be unrelated to obesity? Presumably these systemic factors affect diverse tissues roughly equally, although different cells of origin of the tumor likely respond differently to the complex endocrine and metabolic microenvironment in each tissue. A recent repeated measures study from the Women's Health Initiative suggests that, at least in the case of colorectal cancer risk in postmenopausal women, the most important association is with elevated glucose, not elevated insulin [98]. It seems likely that additional features of the obese subject influence carcinogenesis and perhaps stratify risk for obesity-associated cancer.

Although insulin-resistant obesity is a chronic inflammatory disease, 20–30 % of adult obese individuals preserve a *reduced* inflammatory profile. The white adipose tissue of these un-inflamed, adult subjects shows lower numbers of infiltrating leukocytes [72], while systemically, serum concentrations of pro-inflammatory cytokine are lower [99, 100] than in insulin-resistant obese adult subjects. These un-inflamed subjects exhibit normal or near-normal glucose tolerance [72] (Fig. 3.1), reduced cardiovascular disease risk [77], and lack metabolic syndrome [72, 102, 169]. They remain relatively "metabolically healthy" with low-inflammatory profiles despite obesity [103, 104, 169] and represent an important off-diagonal population for which cardiovascular risk appears to be uncoupled from obesity [105, 106].

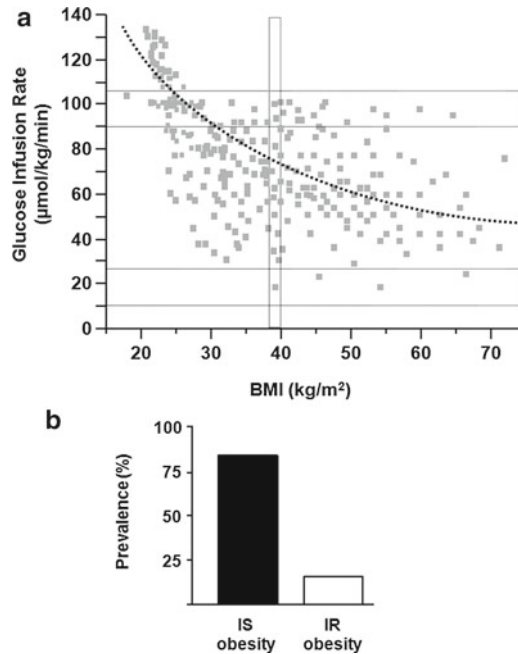


Fig. 3.1 “Metabolically healthy obesity.” (a) Glucose infusion rates (GIR) in 237 subjects for a broad range of BMI and metabolic health. Insulin sensitivity was determined by GIR during the steady state of a euglycemic-hyperinsulinemic clamp. The highest and lowest quintiles of GIR are marked (*horizontal boxes*) to show that the frequency of insulin resistance is very low in healthy obesity. A regression curve (*dotted line*) of GIR over BMI is based on all available patients. The BMI stratum 39–40 identifies a continuous distribution (*vertical box*) of rates to show that there is no clear separation between insulin-sensitive and insulin-resistant obesity. Note that certain, rare individuals with unusually high BMI (>60) nevertheless display normal, healthy GIR during the clamp. (Subject exclusion criteria were diabetes, hypertension, acute or chronic inflammatory disease with leukocyte count >8,000 Gpt/L, CRP >5.0 mg/dL or clinical signs of infection, and other relevant criteria as detailed in ref. [77].) (b) Prevalence of insulin-sensitive (GIR >80 μmol glucose/kg/min) and insulin-resistant (GIR <40 μmol glucose/kg/min) healthy obesity (data from Blüher M (2010)). The distinction of metabolically ‘healthy’ from ‘unhealthy’ obese individuals. *Curr Opin Lipidol*, 21(1):38–43 are reproduced with permission from M. Blüher and Wolters Kluwer, publishers)

The well-established association between unresolved, chronic inflammation and cancer [107, 108] (e.g., between Crohn’s disease and colorectal cancer [109]) suggests that inflamed adipose tissue in insulin-resistant obese adults plays a critical role in obesity-associated carcinogenesis. We have previously hypothesized that the low-inflammatory features and preserved glucose tolerance of these subjects *also protects against risks for obesity-associated cancers* [110].

How do these metabolically healthy obese individuals remain un-inflamed? We have focused on a recently described transcriptional mechanism that may link chronic inflammation, obesity, and cancer [140]. Bromodomain-containing transcriptional co-regulators [112] bind to acetylated histones [113–115] in the

nucleosomal chromatin of mammals and target specific genes for transcriptional activation or repression. In this way, they functionally resemble SWItch/Sucrose NonFermentable (SWI/SNF) nucleosome remodeling complexes, which also contain bromodomain subunits and function to activate or silence coordinated networks of genes [116]. Bromodomains are protein motifs of about 110 amino acids in length [117, 118], comprised of four antiparallel α -helices that are linked by connecting loops, which form a binding pocket that is specific for acetylated lysine [119]. These motifs are found in transcription factors, histone acetylases, and related chromatin-directed proteins that are important for gene regulation [117, 120, 121]. Previous work has shown that the double bromodomain-containing proteins Brd2 [122, 123] and Brd4 [124] couple histone acetylation to transcription [125, 126] and are critical for transcriptional control of cell cycle genes [127–131]. Increased or deregulated expression of either protein is oncogenic. In humans, reciprocal chromosomal translocation of *BRD4* [132] creates a dangerous oncoprotein that promotes an aggressive, poorly differentiated, and incurable carcinoma of the midline, called NUT midline carcinoma, that afflicts relatively young people [133, 134]. Remarkable recent studies with small molecule inhibitors of the binding interface between the acetylated lysines and bromodomain have revealed that the chromatin-bromodomain interaction is “druggable” [135], which came as a surprise to the field. Conventional wisdom had held that interactions with such protein motifs in chromatin were unappealing targets for the development of small molecule inhibitors. In the case of midline carcinoma [136] and other human malignancies [137–139], such drugs appear to have significant anticancer benefit [140]. These developments linked Brd2 and Brd4 with cancer and chromatin-controlled networks of gene expression that are coordinated through shared complexes, analogous to the SWI/SNF-regulated array of genes. But the chromatin-based connections between cancer, obesity, and inflammation remained obscure until unexpected results from a bromodomain-manipulated mouse model appeared.

We initially developed a mouse model for Brd2 transgenic expression [141] and showed that upon B cell-restricted expression of Brd2, mice upregulate B cell mitogenic responses through cyclin A transactivation [131] and eventually develop a B cell malignancy [141]. This cancer exhibits a transcriptional fingerprint most similar to the “activated B cell” (ABC) form of diffuse large B cell lymphoma in humans [142], with an inflammatory signature. Surprisingly, whole-body reduction of Brd2 in “Brd2 hypomorph” mice, by *lacZ* gene disruption, caused the development of a glucose-tolerant type of obesity that features elevated serum adiponectin and a remarkably attenuated inflammatory profile [143]. These results suggested that the Brd2 hypomorphic mouse might represent a useful model for human subjects who are metabolically healthy obese (Fig. 3.1) [144]. These humans share with the Brd2 hypomorphic mice a low-inflammatory profile [77, 103, 105] and less reduction in serum adiponectin concentrations despite obesity [72]. The elevated concentrations of adiponectin measured in adiponectin transgenic mice are also metabolically protective [170], although neither adiponectin expression nor any other loci apart from *Brd2* were directly manipulated in Brd2 hypomorphic mice. More significantly, the chromatin-directed networks that these bromodomain-containing co-regulators

control likely connect cancer, obesity, and inflammation directly, through coordinated co-activation or co-repression of interacting networks of genes; certain diseases likely share the same or overlapping sets of gene expression co-regulators. This topic has been reviewed [140].

In forthcoming work, we show that small molecule inhibitors of these bromodomain proteins or shRNA ablation are effective as anti-inflammatory strategies, acting as global “uncouplers” of signal transduction that normally activate transcription of diverse cytokine genes [111]. Because many cancers have an inflammatory component, it is reasonable to hypothesize that the inflammatory microenvironment of certain tumors will exacerbate carcinogenesis, tumor progression, invasion, metastasis, or recurrence. Targeted uncoupling of signal transduction from transcription through bromodomain protein-specific small molecule inhibitors [140] may prove to be a novel and efficacious therapeutic or preventive approach to reduce the inflammatory cascades that contribute to obesity-associated cancer. The combined anti-inflammatory [145] and anticancer [136–138] effects of bromodomain protein inhibition are already established. Our previous work has shown that reduced expression of Brd2 protein, equivalent to a haploinsufficient phenotype, de-represses specific genes that are important for metabolism. These reduced levels are sufficient *simultaneously* to stimulate insulin gene transcription in β -cells [143, 146], to increase adipogenesis in pre-adipocytes through stimulation of peroxisome proliferator-activated receptor (PPAR) γ -directed transcriptional programs [143, 147]. The hyperadiponectinemia of obese Brd2 hypomorphic mice [143] suggests that Brd2 is also normally required to corepress transcription of the murine adiponectin gene (*Adipoq*), although this hypothesis has not yet been tested. Conversely, Brd2 reduction also ablates the production of pro-inflammatory cytokines in macrophages such as TNF α , IL-1 β , IL-6, and MCP-1 [111, 140, 144]. Taken together with the anticancer properties of Brd2 reduction through attenuated cell cycle progression, as discussed above, these coherent transcriptional and metabolic features (stimulated insulin production, increased adipogenesis, and increased adiponectin production; and reduced production of multiple pro-inflammatory cytokines) lead us to propose a Brd2 mechanism for broad protection against obesity-associated malignancy. Small molecule inhibitors that target this family of transcription co-regulators, or naturally occurring single nucleotide polymorphisms in the human *BRD2* locus that reduce Brd2 expression, may therefore confer multiple forms of metabolic and cancer protection to obese patients.

Several phenotypes of unintended weight loss, such as chronic heart failure [148], share a systemic inflammatory profile [149], with marked elevations in serum levels of IL-1 β , IL-6, and TNF α . These observations suggest a mechanistic relationship between the immune system, metabolism, and energy balance, reinforcing the aforementioned argument. Furthermore, it has been noted that “unhealthy aging” [150] is often associated with a pro-inflammatory, pro-senescent phenotype in somatic cells, the local production in skeletal muscle and adipose depots of inflammatory cytokines that are associated with muscle wasting syndromes, and frailty in geriatric patients [151–153]. Investigators have been considering the cause and effect relationships among unresolved, chronic inflammation, energy imbalances associated with weight

loss or weight gain, and cancer risk. Many of these relationships may work in both directions. It is reasonable therefore to hypothesize that a chromatin-based therapeutic strategy to treat these connected phenotypes may have broad benefit for more than one type of risk and may be useful for geriatric patients.

3.5 Other Links Between Obesity, Inflammation, and Social Determinants

One social determinant that plays a role in inflammatory disease processes is socioeconomic status (SES). Asthma rates in children are two to three times higher in poor families than in wealthy families; SES shows a dose response relationship with asthma diagnosis and severity [154]. Public housing residents and inner city dwellers, who are among the poorest of urban dwellers in the United States, report higher rates of asthma than do private home and apartment dwellers [155]. This disease arises from allergic reactions to irritants and allergens that are commonly found in public housing, including dust mites, pets, rodents, mold, and cockroaches [156]. Massachusetts public housing has been linked to some of the highest national rates of asthma [157]. The prevalence of asthma is highest among African American families, with overall prevalence of 40 % of adults and 56 % of children [158]. These same populations, that is, poor and low SES individual and public housing residents, report two to three times the obesity rates of other residents who are higher along the SES continuum [159]. According to the American Lung Association, there is no evidence that asthma can cause lung cancer. However, there is evidence that asthma is associated with obesity [155, 160–162]. The risk of asthma has been reported in one study [163] to be up to three times greater for obese subjects compared to lean subjects (odds ratio for obese vs. normal BMI=2.28, 95 % CI: 1.76, 2.96). These observations suggest that socioeconomic factors also influence risk for obesity-associated morbidity, including type 2 diabetes and cancer. Specifically, there may be a rationale to investigate the relationship between asthma, obesity, and obesity-associated cancer. For example, does poverty produce obesity and inflammation, enhancing opportunities for the development of asthma? Are these issues causally related or simply comorbidities of living in high poverty settings? If we are able to reduce one set of comorbid conditions, as is under investigation now in Boston and elsewhere [164–166], will that outcome reduce or alter others?

Several sociological, economic, and behavioral factors have been established to link obesity and type 2 diabetes incidence to cancer incidence. As discussed above, there is strong epidemiological evidence that SES is correlated with both the prevalence of obesity and diabetes and with lung cancer mortality, a malignancy that is associated with smoking (Fig. 3.2a). There is no known molecular association between lung cancer and obesity [3]. However, the use of tobacco in cigarette, cigar, and pipe smoke is strongly associated with lung, tracheal, and oral *cancers* [167]. Furthermore, low SES individuals suffer disproportionately higher health risks due to increased prevalence of smoking [168]. These correlations among chronic diseases that have no downstream molecular connection suggest that the problem of obesity-associated cancer is more complicated in its structural and upstream origins

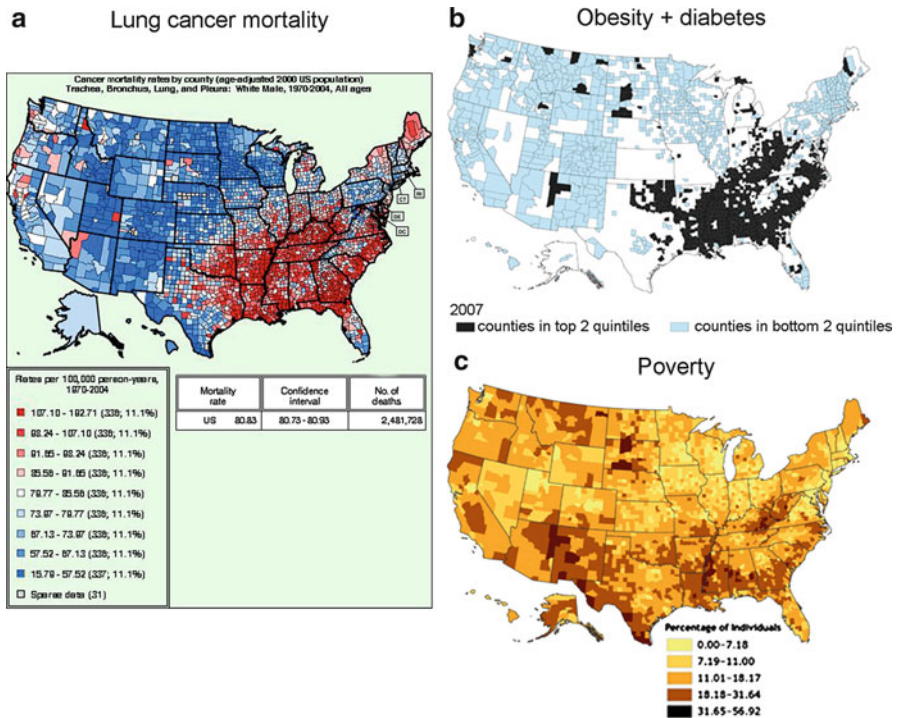


Fig. 3.2 Overlapping morbidities. (a) Lung cancer mortality. Mortality among 3,056 United States counties for cancer of the lung, trachea, bronchus, and pleura in white males of all ages, 1970–2004 (age-adjusted 2000 US population). Calculated from *National Cancer Institute data drawn from Atlas of Cancer Mortality in the U.S., 1950–1994*; rates per 100,000 person-years presented here in nine equal intervals with a diverging red/blue color scheme. The national rate was 80.83 (CI 80.73–80.93) per 100,000, with the total number of deaths 2,481,728. <http://ratecalc.cancer.gov/ratecalc/>. (b) Diabetes and obesity diagnoses. Estimates among 3,141 United States counties for age-adjusted rates of both diagnosed diabetes and obesity presented together. Estimates were calculated from Census and Behavioral Risk Factor Surveillance System (self-reported) data for 2006–2008. The national proportion of US adults who were obese in 2008 was 26.1%. In 2007, 8% of the US population, or 24 million individuals, were diabetic, of which 5.7 million were estimated to be undiagnosed. <http://www.cdc.gov/diabetes/pubs/factsheets/countyvlvestimates.htm>. (c) Socioenvironmental map of poverty. County-level data from United States Census Bureau statistics for 2004. Estimated percentage of population living below the poverty threshold as defined by US Census methods is defined by size of family and ages of members and includes information about earnings, unemployment compensation, workers’ compensation, Social Security, Supplemental Security Income, public assistance, veterans’ payments, survivor benefits, pension or retirement income, interest, dividends, rents, royalties, income from estates, trusts, educational assistance, alimony, child support, assistance from outside the household, and other miscellaneous sources (http://www.cdc.gov/dhdsp/maps/sd_poverty_2004.htm, <http://www.census.gov/hhes/www/poverty/about/overview/measure.html>)

than a one-to-one correspondence between an obesity exposure and a cancer rate. In other words, the same causal factors that produce increased levels of obesity might also be at work to promote increased rates of lung cancer and lung cancer mortality, as well as type 2 diabetes (Fig. 3.2b). Obesity and cancer are likely to be linked

through their upstream causes: downturns in the economy, the nature of work and labor markets, social stratification and economic inequality (Fig. 3.2c), and lack of opportunity and local infrastructure that set the stage for and contribute to the human biochemical mechanisms at work in carcinogenesis. As research identifies the central role of social determinants in chronic disease development, investigators need to pay closer attention to the common origins, even if not directly biologically linked. The social and structural origins of this problem demand structural solutions beyond the power of the prescribing physician's pen: it is clear that *certain specific environments are both obesogenic/diabetogenic and carcinogenic*. Solutions will require focused political will, participation of corporations and community groups, entrepreneurs, school districts, and local employers, not just obese Americans and their physicians.

3.6 Interactions Among Biological and Social Factors

Ultimately, we need to understand both the biology and the social forces that govern obesity to reduce this burden in modern, industrialized societies. The movement toward tailored or “personalized” medicine may be one way in which both perspectives can be not only accommodated but relied upon as translated intervention tools to reduce obesity. For example, identification of an individual's likelihood of being a metabolically unhealthy obese person may provide additional motivation to engage in healthy behaviors. Alteration of the shape of environments for individuals and groups, such that there are clear and accessible food and activity choices, will help families facing both obesity- and asthma-related health issues. Increasing the opportunity for non-obesogenic activities might be a necessary investment for individuals who become inflamed if they become obese or maintain obesity. It may be helpful for the current conditions to consider obesity as a health problem that, for some, causes clear measurable changes related to a variety of chronic diseases, but that is ultimately preventable. Translating the basic research on vulnerability to inflammation with obesity into usable interventions will require new ways of thinking about environment, motivation, and human behavior. From the discussion in this chapter, it is clear that we have begun to consider the broad, powerful mechanistic connections among inflammation, obesity, and cancer and the need to link the cellular, serological, and dietary environments of obese, at-risk individuals to exposures in the built environment, urban infrastructure, and economic policy. Without transdisciplinary, innovative, “out-of-the-box” thinking, the problem of obesity-associated cancer will prove too difficult to address effectively. We therefore call for additional funding and research to investigate these unexpected connections among important variables, with focused conversation among molecular biologists, immunologists, geneticists, cancer and endocrine clinicians, epidemiologists, sociologists, public housing officials, and public health officials. In view of the increasing seriousness of the obesity epidemic, time is running out for this conversation to plan for research and policy priorities.

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The authors report no conflicts of interest.

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