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'Metabolically healthy obesity': Origins and implications

Gerald V. Denis^{a,*} and Martin S. Obin^b

Gerald V. Denis: gdenis@bu.edu; Martin S. Obin: Martin.obin@tufts.edu

^aImmunology Training Program, Cancer Research Center and Boston Nutrition Obesity Research Center, Boston University School of Medicine, 72 East Concord St. Room K520, Boston, MA, USA

^bObesity and Metabolism Laboratory, JMUSDA-Human Nutrition Research Center on Aging at Tufts University, 711 Washington St., Boston, MA, USA

Abstract

When humans eat more and exercise less, they tend to become obese and unhealthy. The molecular pathways that link obesity to serious diseases like Type 2 diabetes and cardiovascular disease have become a subject of intensive scientific investigation because the exploding prevalence of obesity worldwide represents a grave new threat to the health of hundreds of millions of people. However, obesity is not always destiny. Two important clinical populations have been valuable to understand the mechanisms behind this conundrum: individuals who exhibit metabolic dysfunction, diabetes and elevated cardiovascular disease risk despite a lean body type, and individuals who are relatively protected from these dangers despite significant obesity. Study of this second group of 'metabolically healthy obese' people in particular has been revealing because such individuals exhibit specific, identifiable, anatomic, cellular and molecular features that set them apart from the rest of us who suffer declining health with increasing weight. Here, we examine some of these features, including some mouse models that are informative of mechanism, and suggest hypotheses for further study, including the possibility that genes and pathways of the immune system might offer new diagnostic or therapeutic targets.

1. Introduction

1.1. The problem of obesity

Human metabolism promotes a central tendency in response to high calorie diets and inactivity: obesity. Many serious diseases, such as metabolic syndrome (MS) and Type 2 diabetes (T2D) are directly attributable to elevated body mass index (BMI), so that the increased prevalence of overweight (BMI 25–29.9), obesity (BMI 30) and morbid obesity (BMI 40) has generated widespread alarm in the United States and internationally. Obesity also promotes cardiovascular disease (CVD), hypertension, stroke and cancer (Van Gaal et al., 2006; Guh et al., 2009). Worldwide, 1.7 billion people are currently classified as overweight (Haslam and James, 2009). Some years ago, the World Health Organization estimated that by 2030, 370 million people worldwide would be expected to be suffering from T2D, driven primarily by obesity, compared to 177 million in 2000 (Wild et al., 2004). However, this estimate appears to have been unduly conservative; midway through 2011 the number of diabetic adults worldwide reached 347 million. The same report indicates that the

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*Corresponding author. Tel.: +1 617 414 1371; fax: +1 617 638 5673 (G.V. Denis), tel.: +1 617 556 3079; fax: +1 617 556 3224 (M.S. Obin).

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US now has the highest BMI of the high-income countries (Finucane et al., 2011). All US states report that the prevalence of adult obesity is at least 20%; one in three American adults are now obese. The health care costs associated with these diseases will be ruinous; the annual costs for care now account for nine percent of all medical spending: about \$147 billion. No American political party, governmental or nongovernmental organization has adequately planned for the expected impact on the nation's resources. Furthermore, demand for medical intervention is expected to grow: bariatric surgeries in America increased from 13,000 in 1990 to 100,000 in 2003 (Santry et al., 2005) and 200,000 in 2006 (Pear, 2006). In the face of this catastrophe, community-, school-, and Federally-based intervention programs to encourage better eating patterns and increased physical activity are attempting to blunt the expected collision of disease prevalence with budget and taxation realities, but concern remains grave.

2. Obesity and metabolic dysfunction

In pre-T2D obesity, specific anatomical, cellular, immunological and molecular changes are associated with progressive deterioration in metabolic function, including elevated blood glucose and reduced glucose clearance, measured in peripheral blood after oral bolus; hyperinsulinemia, insulin resistance (IR) and dyslipidemia, which contribute to MS; and increasing dysfunction of pancreatic islet β -cells that culminates in β -cell failure and insulin dependence. MS has been defined as any three or more of: fasting plasma glucose of 5.6–6.9 mmol/liter; waist circumference >102 cm (in men) or >88 cm (in women); fasting triglycerides \geq 1.7 mmol/liter; high-density lipoprotein-cholesterol <1.0 mmol/liter (in men) or <1.3 mmol/liter (in women); and blood pressure \geq 130/85 mmHg or current treatment for hypertension (Grundy et al., 2005; Janiszewski and Ross, 2010). Insulin sensitivity has been defined by the homeostasis model [(fasting glucose \times fasting insulin)/22.5]. IR has been defined in the revised Adults Treatment Panel III (2001) as a homeostasis model assessment (HOMA) IR level in the top quartile of the distribution among subjects without diabetes (Matthews et al., 1985). Some investigators adopt a stringent measure of IR, with a value of HOMA >2 as a criterion. Nevertheless, there is no universally accepted definition of MS.

3. Features of unhealthy adipose tissue

3.1. Central obesity

It has been appreciated since 1947 that subcutaneous, or lower body obesity, typified by a 'pear-shaped' body distribution of adipose tissue common in women, is associated with metabolic protection (Vague, 1947), whereas central obesity, an 'apple-shaped' distribution common in men, is associated with MS and CVD (Lapidus et al., 1984; Donahue et al., 1987). The size of the intra-abdominal fat depot is strongly correlated with MS (Fujioka et al., 1987; Després et al., 1989) and reduced levels of an insulin-sensitizing adipokine, adiponectin (Côté et al., 2005). Visceral white adipose tissue (WAT) is correlated with hepatosteatosis and hepatic IR (Bergman et al., 2006) and is a risk factor for glucose intolerance, independent of BMI and subcutaneous depot size (Després et al., 1989; Pouliot et al., 1992). Visceral storage capacity is relatively low compared to subcutaneous. Without available storage, lipid is distributed to hepatic, cardiac, skeletal muscle and other highly undesirable locations, called ectopic fat deposition (Dubois et al., 2006), contributing to metabolic damage. Ectopic fat arises upon insufficient adipogenesis in the obese, pre-diabetic individual (Trayhurn et al., 2008). However, pro-adipogenic drugs of the thiazolidinedione (TZD) family, rosiglitazone (AvandiaTM), pioglitazone (ActosTM) and troglitazone (RezulinTM), nicknamed 'glitazones', can induce WAT to expand (Tan and Vidal-Puig, 2008; Tontonoz and Spiegelman, 2008). TZDs have clinical efficacy; they stimulate peroxisome proliferator-activated receptor (PPAR) γ (Rosen et al., 1999, 2000) transcriptional programs that promote adipogenesis. However, unfavorable side effect

profiles prompted the US Food and Drug Administration in 2011 to issue new restrictions on glitazones, leaving the future of this drug class uncertain.

3.2. Adipocyte stress and fibrosis

Lean and obese humans are born with a limited number of adipocytes, thus obese individuals have been thought to expand WAT through hypertrophy, not hyperplasia (Spalding et al., 2008). Adipocytes are individually 'wrapped' in a supporting sheath of extracellular matrix (ECM), in particular collagens. Remodeling of the ECM, and cycles of collagen breakdown/ re-deposition in particular, are essential for adipocyte and adipose tissue expansion (Chun et al., 2006). However, in the obese state, excessive, dysregulated deposition of collagens and other ECM components (i.e., fibrosis) eventually constrains adipocyte expansion, thereby promoting adipocyte stress, inflammatory/stress kinase activation and resulting AT and systemic metabolic dysfunction (Henegar et al., 2008; Halberg et al., 2009; Khan et al., 2009; Divoux et al., 2010). Collagen VI is specifically implicated in the pathogenesis of obesity-associated AT fibrosis and metabolic dysfunction, as collagen VI deposition is increased in WAT of obese, insulin resistant humans (Spencer et al., 2010), and the absence of this ECM component in obese (knockout) mice permits greater adipocyte hypertrophy while normalizing key metabolic parameters (Khan et al., 2009; see Section 5). Collagen VI deposition and AT fibrosis in human WAT is coincident with the presence of 'alternatively activated' (CD150⁺) adipose tissue macrophages (ATMs) that are known to promote ECM remodeling and wound healing (Spencer et al., 2010; see also Shaul et al., 2010).

3.3. Chronic inflammation

In diet-induced obesity, adipose tissue is often in a chronic, subclinical state of inflammation (Shoelson et al., 2006) caused by cytokines like tumor necrosis factor (TNF)- α that directly promote IR (Hotamisligil et al., 1993; Bastard et al., 2006). In both humans and rodent models of obesity, these cytokines are produced by infiltrating ATMs (Weisberg et al., 2003; Xu et al., 2003), which communicate with T cells (Kintscher et al., 2008) and B cells (discussed in this volume in detail by Nikolajczyk et al.). Obese IR humans also exhibit an elevated inflammatory profile (Kahn et al., 2006; Kim et al., 2006) that correlates well with cardiometabolic risk (Blüher, 2009, 2012) and central obesity (Lemieux et al., 2001). Immunohistochemistry of insulin-resistant adipocytes in diet-induced obesity has revealed that ATMs surround dead or dying adipocytes in "crown-like structures" (CLS) (Cinti et al., 2005; discussed in this volume in detail by Carey et al.) and promote fibrosis (Keophiphath et al., 2009) that is virtually diagnostic of metabolically unhealthy WAT. Consistent with this pattern, the larger adipocytes of IR obese individuals also express an elevated pro-inflammatory adipokine signature (Skurk et al., 2007). Interestingly, women with a common reproductive disorder, called Polycystic Ovary Syndrome (PCOS) that features anovulatory infertility, exhibit chronic, systemic low-grade inflammation that is more commonly associated with IR obesity (Tarkun et al., 2004). Aspirin was one of the first anti-inflammatory drugs recognized to have efficacy for T2D (Colwell, 1997). Indeed, sodium salicylate was used as long ago as the late 19th century to reduce blood glucose in these patients (Ebstein and Muller, 1876). Although it is well established that reduction of pro-inflammatory factors in human obesity potentially mitigates insulin resistance, there is clearly an urgent need for new immunological agents to treat insulin-resistant obesity in the clinic (Nikolajczyk et al., 2012). Despite its efficacy in many cases, aspirin is far from innovative.

4. Informative exceptions to the pattern

A lay observer might be tempted to paraphrase Tolstoy and suggest that lean individuals seem to be mostly alike, whereas obese individuals are different, each in their own way.

Some are apple shaped, some pear shaped, some morbidly obese, some mildly so, whereas some, like sumo wrestlers, are impressively obese but remain robustly athletic. However, not all individuals with metabolic dysfunction are obese. For example, PCOS women show impaired glucose tolerance and insulin hypersecretion, although about half of such women are lean and some are underweight (Vrbíková et al., 2004).

4.1. MONW

The phenotype of the ‘metabolically obese but normal weight’ (MONW) individual (Fig. 1), first identified by Ruderman and colleagues (Ruderman et al., 1981; Ruderman et al., 1998) and characterized by hyperinsulinemia, hyperglycemia, IR, impaired glucose tolerance, hypercholesterolemia and hypertriglyceridemia, but normal adipocyte volume and BMI, suggests that there must be genes and signal transduction pathways that ordinarily couple obesity to IR, and that these are deficient in certain individuals. These characteristics in a lean individual mark a departure from common human patterns, in which metabolic disease is a consequence of weight gain. Yet, these phenotypes are very prevalent. For example, PCOS has been diagnosed in up to 10% of one study of women of reproductive age (Goodarzi et al., 2011) and MONW in 12.7% of normal-weight subjects in a Korean study (Lee, 2009). Elevated risk for CVD is seen among both MONW (Ruderman et al., 1982) and PCOS individuals (Goodarzi et al., 2011), as well as elevated risk for hypertension, T2D and other metabolic complications. Thus, metabolic dysfunction and CVD risk come in many sizes and shapes (Fig. 1).

4.2. Mouse models of the MONW individual

Recent study of Goto-Kakizaki rats (Xue et al., 2011) has shown that the Major Histocompatibility Complex (MHC) genes *RT1-Ba*, *Bb* and *Db1*, which are homologous to human *HLA-DQA1*, *HLA-DQ beta 1 chain-like* and *HLA-DRB1*, respectively, are differentially expressed in a phenotype associated with IR and increased inflammation, but a defect in pre-adipocyte differentiation and lack of obesity, which taken together resembles MONW individuals. The field would benefit from additional models of this phenotype.

4.3. MHO

Another important ‘off-diagonal’ population is characterized by certain obese individuals that exhibit a normal CVD risk profile, without increased risk for atherosclerosis, hypertension or T2D. This group, which also displays an absence of dyslipidemia, hyperuricemia and hypertension (Bonora et al., 1991; Wildman et al., 2008) has been thought of as ‘metabolically healthy obese’ (MHO, Fig. 1) (Sims, 2001). MHO adults have been defined as abdominally obese (BMI ≥ 30 kg/m²) and lacking MS (Meigs et al., 2006). In hyperinsulinemic/euglycemic clamp studies, they demonstrate higher rates of glucose infusion than IR obese subjects, indicative of preserved whole-body glucose disposal (Klötting et al., 2010). However, there is no universally accepted definition of the MHO phenotype.

MHO individuals are also prevalent; by general agreement they comprise up to 25%, but not more than 30%, of the adult obese population. There is variance in the reported prevalence of MHO individuals: they comprised 15.2% of total subjects and 47.9% of obese subjects in a Korean study (Lee, 2009), and 11% of obese subjects in an Italian study (Calori et al., 2011). Others have concluded that the MHO phenotype does not define a discrete subpopulation of obese individuals, but is more precisely thought of as continuous distribution of preserved insulin sensitivity as a function of increasing BMI (Blüher, 2010, 2012; Klötting et al., 2010). Furthermore, it is not fully understood whether MHO individuals are genetically or epigenetically predisposed to maintain their insulin sensitivity as they age, or whether the phenotype is inherently unstable and can evolve rapidly to an IR state (Kim

and Reaven, 2008). Sumo wrestlers, for example, often convert from a metabolically healthy to an unhealthy state upon retirement from the ring (Matsuzawa, 1997). At this stage, it seems wise to think of MHO as a syndrome or a cluster of traits that have some interpretive value, rather than as a clear category with specific prognostic implications.

Some commentators dislike the term ‘metabolically healthy obese’ because of the implication that these individuals are somehow normal. In fact, ultrasound studies reveal worrisome subclinical changes in certain subjects in this population, such as thickening of the intima-media of the common carotid artery and decreased flow-mediated dilation of the brachial artery, which suggests deterioration in endothelial function and nascent atherosclerosis (Oflaz et al., 2003). MHO biology is still associated with gall bladder disease, osteoarthritis and other co-morbidities (Guh et al., 2009) including cardiomyopathy. A more precise term might be ‘metabolically protected obese’ because not only are a number of deleterious factors reduced in these individuals, but other protective factors are relatively undiminished, such as serum adiponectin (Berg and Scherer, 2005; Matsuzawa, 2006). In some MHO subjects, adiponectin concentrations even exceed the values seen in normal BMI individuals (Aguilar-Salinas et al., 2008). Interestingly, a meta-analysis of PCOS women showed that both lean and obese subjects have significantly lower adiponectin than normal controls (Toulis et al., 2009), consistent with the contention that increased metabolic risk need not be a result of elevated BMI.

5. Features of the MHO individual

5.1. Reduced central obesity

The MHO phenotype is strongly associated with a smaller visceral depot, although not necessarily with expanded subcutaneous; the clamped glucose infusion rate strongly correlates with visceral WAT area (Klötting et al., 2010). Population studies suggest that propensity to accumulate fat in central or peripheral depots has a strong genetic component (Bouchard et al., 1990; Wajchenberg, 2000), thus certain features of the MHO phenotype are likely to be heritable (Després et al., 1992), including body fat distribution.

5.2. Reduced adipocyte stress

In humans, WAT fibrosis as measured by collagen VI expression is positively correlated with IR and inflammatory markers, such as the number of ATMs (Spencer et al., 2010). The relationship between stress/fibrosis and unhealthy WAT (Pasarica et al., 2009) supports a hypothesis that alleles of genes that encode different forms of collagen or enzymes that modify collagen, such as lysyl oxidase (Huang et al., 2010), correlate with the ability of WAT to expand and remodel in obesity while avoiding stress and remaining metabolically healthy. Adipocyte size *per se* in both omental and subcutaneous depots is also strongly negatively correlated with metabolic health (Klötting et al., 2010; Spencer et al., 2010), with smaller adipocytes and preserved insulin-sensitive glucose transport characteristic of MHO individuals. A hypothesis follows that some MHO humans will show increased adipogenesis, based on functional allelic variants of PPAR γ , PGC-1 α , PRDM16 or other components of the adipogenic transcriptional program that expand subcutaneous WAT. Not much clinical evidence has yet been marshaled to support this idea, although Patti et al. (2003) noted in a study of Mexican–American subjects that expression of PGC-1 α and PPAR γ -directed transcriptional networks are decreased in pre-diabetic and T2D obese subjects. Their metabolic dysfunction, including reduced oxidative metabolism and attenuated mitochondrial electron transport, is consistent with defective PGC-1 α and PPAR γ function, although primary adipogenesis was not studied in this cohort. Well matched MHO and IR obese human subjects should be evaluated for these hypothesized variants.

5.3. Reduced inflammation

MHO individuals display a reduced inflammatory profile (Karelis et al., 2005), with reduced hepatosteatosis (O'Connell et al., 2011), lower numbers of infiltrating ATMs and CLS in WAT (Klötting et al., 2010) and reduced serum levels of TNF- α , monocyte chemoattractant protein-1 (O'Connell et al., 2011), interleukin (IL)-6 and C-reactive protein (Klötting et al., 2010). Elevated serum adiponectin and reduced ATM infiltration are the strongest predictors of preserved ability to clear glucose (Combs et al., 2004; Klötting et al., 2010); in men, preserved adiponectin levels are associated with a reduced rate of myocardial infarction (Pischon et al., 2004). Adiponectin also promotes protective (M2) macrophage differentiation (Ohashi et al., 2010). The mechanistic details of the ways in which macrophages, T cells, B cells and adipocytes respond to dietary interventions, bariatric surgery or drug treatment for IR, or can be mobilized for therapeutic benefit, are very poorly understood which has provoked active inquiry (Nikolajczyk et al., 2012). Study of MHO individuals is likely to reveal critical new principles for how their specific anatomical, cellular, immunological and molecular features (Succurro et al., 2008) protect them from T2D and CVD.

6. Murine models of the MHO individual: fatter but fitter mice

Mouse models of obesity have provided robust insights into human obesity and its metabolic complications, including metabolically protected obesity. In this section we highlight genetic models in which murine obesity is associated with a salutary profile of glucose–insulin homeostasis and adipocyte/AT function. The models selected are representative of five (overlapping) categories of proximate physiological effect: (1) altered expression of adipokines or inflammatory mediators, (2) disrupted inflammatory signal transduction, (3) reduction or enhancement of AT immune cell populations, (4) attenuated adipocyte stress, and (5) enhanced adipogenesis and/or adipocyte lipogenesis. Intriguingly, in several of these models, the MHO phenotype is associated with *greater* obesity, including greater hypertrophic obesity. Because weight loss *per se* is metabolically beneficial, we do not discuss the myriad examples in which metabolic protection is associated with reduced adiposity or body weight, including those in which metabolic improvements in obese mice are obtained following ablation or supplementation of specific innate or adaptive immune cell populations (see articles by Lumeng and by Snyder–Cappione and Nikolajczyk, this volume).

6.1. Adiponectin transgenic mouse

Adiponectin is an anti-inflammatory, insulin-sensitizing adipokine expressed exclusively by adipocytes that exerts beneficial effects on lipid and glucose homeostasis via multiple mechanisms, most notably via ceramidase activity and AMPK/ SIRT1-dependent activation of PGC-1 α (Iwabu et al., 2010; Holland et al., 2011). Elevated (~2-fold) circulating adiponectin is a hallmark and predictor of the MHO phenotype in humans (Klötting et al., 2010). Adiponectin transgenic mice on an *ob/ob* background (AdTg) have 2- to 3-fold higher levels of circulating adiponectin than *ob/ob* controls (Kim et al., 2007). These AdTg mice become extraordinarily obese on a normal 'chow' diet, weighing on average 40 g more than *ob/ob* mice. This extreme obesity largely reflects preferential hyperplastic expansion of subcutaneous AT depots, although visceral depots and adipocytes are also reduced in size to wild-type (*ob/+*) levels. Remarkably, despite morbid obesity, AdTg mice remain insulin sensitive and glucose tolerant, have fewer AT macrophages and inflammatory markers, less liver steatosis and improved circulating insulin, glucose and triacylglycerol. Thus, adiponectin overexpression results in a hyper-obese mouse with predominantly subcutaneous fat, smaller adipocytes, attenuated inflammation and metabolic protection – i.e., all hallmark features of human MHO.

Significant effort is currently directed toward the development of novel therapeutics that elevate production and secretion of the metabolically effective, high molecular weight (HMW) form of adiponectin. Some success has been reported with natriuretic peptides (Tsukamoto et al., 2009) and biflavonoids (Liu et al., 2007). More recently overexpression of the disulfide bond A oxidoreductase-like protein in fat (fDsbA-L) was reported to increase levels of total and HMW adiponectin and to confer resistance to obesity-associated IR through these effects on adiponectin expression (Liu et al., 2012).

6.2. Brd2 hypomorph

The *Brd2* gene is located near the TNF- α locus in the class II MHC region of human chromosome 6. Recent work has shown that a leaky knockout of this gene in mice produces a hypomorphic phenotype characterized by extreme obesity coincident with elevated adiponectin (nearing levels of male AdTg mice) and protection from IR (Wang et al., 2009). These mice show hepatosteatosis and hyperinsulinemia, but *hypoglycemia* and *better* clamped glucose infusion rates than wild type (Wang et al., 2012; Jornayvaz et al., forthcoming). Brd2 ordinarily co-represses PPAR γ -dependent transcription, thus reduced Brd2 in the animals resembles TZD treatment and adipogenesis is potentiated (Denis et al., 2010). Reduced expression of Brd2 also creates a low-inflammatory environment (Belkina and Denis, 2010, 2012; Belkina et al., 2010; Belkina et al., forthcoming) that protects against cytokines that would ordinarily cause IR in adipocytes. Endotoxin-stimulated production of pro-inflammatory cytokines such as TNF- α , IL-1 β and IL-6 from bone marrow-derived macrophages is reduced by about half, compared to wild type controls, establishing a 'protective deficiency'. In MHO humans, it is not yet clear if certain alleles in inflammatory loci create such mild hypo-responsiveness to inflammation signal transduction to confer protection. Consideration of the association among MHC alleles and complex human diseases with an inflammatory component provokes the hypothesis that certain MHO individuals are protected from adipose tissue inflammation and metabolic complications because of specific alleles in their MHC. Several genes in the MHC are likely candidates, including *LTA*, which encodes lymphotoxin- α and is important for the inflammatory component of coronary artery disease (Ozaki et al., 2002); *TNF*, *BRD2* and *HLA-DRB1*. These alleles should be evaluated for correlation with the MHO phenotype.

6.3. COL6 KO mice

As discussed above, recent studies suggest that excessive deposition of collagen(s) or other ECM components (fibrosis) promotes inflammatory and metabolic pathology in individuals with hypertrophic obesity. In a seminal study, collagen VI (COL6) KO mice crossed onto the genetically obese *ob/ob* background developed dramatically-hypertrophic adipocytes and greater AT mass in both the gonadal and mesenteric depots, but had lower fasting glucose, enhanced glucose tolerance and reduced circulating triacylglycerol following lipid challenge as compared with control *ob/ob* mice (Khan et al., 2009). This metabolic protection was associated with reductions in ER stress markers, stress kinase (JNK, ERK) activation and adipocyte death, as well as with lower systemic IL-6 and TNF- α following LPS challenge. Thus, reducing AT collagen promotes the development of metabolically 'protective' adipocyte hypertrophy and an MHO phenotype. A plausible interpretation is that the (hyper)obese COL6 KO mouse uncouples hypertrophy *per se* from obesity complications and suggests that therapeutic approaches that reduce adipocyte stress can maintain metabolically healthy fat storage in enlarged adipocytes.

6.4. TBP-2/Txnip/VDUP1 KO mice

Thioredoxin binding protein (TBP)-2 is a member of the α -arrestin protein family with demonstrated roles in the regulation of cell fate, immune responses and energy metabolism. TBP-2 is a negative regulator of adipogenesis, in part through its inhibitory actions on

PPAR γ expression and activity (Chutkow et al., 2010; Yoshihara et al., 2010; Chutkow and Lee, 2011; see also Chen et al., 2008). Consistent with these observations, TBP-2 KO mice fed either a normal or HFD diet or TBP-2 KO mice on an *ob/ob* background consumed more energy and gained significantly more weight (up to 100%) and adiposity (up to 50%) than similarly-fed WT or *ob/ob* mice (Chutkow et al., 2010; Yoshihara et al., 2010). Notably, greater adipose mass reflected adipocyte hyperplasia in multiple AT depots (Chutkow et al., 2010). Despite greater adiposity, both models of obesity in TBP-2 KO mice were more glucose tolerant and insulin sensitive than obese controls, reflecting augmented glucose transport in AT and skeletal muscle and improved glucose-stimulated insulin secretion (GSIS). Thus, as in AdTg mice (see above) adipose accretion by adipocyte hyperplasia is associated with an MHO phenotype in obese TBP-2 KO mice. HBC-19 mice that express a naturally-occurring TBP-2 truncation mutation also become more obese than WT mice but retain glucose tolerance and insulin responsiveness (Chen et al., 2008). Moreover, HcB-19 mice crossed with the *ob/ob* mice become even more obese than *ob/ob* mice, but are protected against peripheral insulin resistance, β -cell apoptosis and subsequent T2DM. The protection from β -cell apoptosis despite morbid obesity in mice lacking functional TBP-2 was demonstrated in β cell-specific TBP-2 KO mice to reflect enhanced Akt/Bcl-xL signaling and associated mitochondrial protection (Chen et al., 2008).

6.5. Tumor-progression locus 2 (TPL2) KO mice

TPL2 (MAP3K8) is a serine/threonine kinase that is activated by TNF α , TLR4-signaling and inflammatory mediators that activate the NF κ B and MAPK pathways (Vougioukalaki et al., 2011). Thus, TPL2 is uniquely situated to integrate inflammatory signaling pathways that promote obesity-associated inflammation and IR. Perfield et al. (2011) placed TPL2 KO mice on a HFD for 16 weeks and reported increases in body weight, adipose depot weights and gonadal adipocyte size comparable to those observed in HFD-fed WT mice. However, HFD-fed KO mice had decreased fasting glucose and insulin, and improved glucose dynamics in euglycemic/hyperinsulinemic clamp studies. This protected metabolic phenotype was associated with reduced MAPK (ERK, JNK) activation in peripheral tissues, as well as with reduced frequency of CLS and attenuated inflammatory gene expression in the epididymal fat depot. Thus, the absence of TPL2-dependent inflammatory signaling confers an MHO phenotype of reduced AT inflammation and enhanced insulin sensitivity despite hypertrophic obesity.

6.6. Apoptosis inhibitor of macrophage (AIM) KO mice

AIM (also known as Spa, Api6, and CD5L) is a macrophage-secreted member of the scavenger receptor cysteine-rich superfamily (SRCR-SF). AIM expression and serum levels are upregulated in murine obesity (reviewed in Miyazaki et al., 2011). Macrophage-derived AIM is taken up by adipocytes via CD36-mediated endocytosis. AIM inhibits fatty acid synthase, thereby stimulating lipolysis and the release of fatty acids (Kurokawa et al., 2010). This release of fatty acids activates adipocyte chemokine production via TLR4 (Kurokawa et al., 2011). The pathophysiologic impact of AIM on inflammation and obesity complications was assessed in AIM-deficient (AIM KO) mice (Kurokawa et al., 2011). AIM KO mice fed a HFD for 12 weeks became more obese than WT mice. However, greater adiposity was associated with fewer M1 macrophages, reflecting reductions in AT chemokine expression. Systemic protection was also evident, including reduced circulating TNF α , IL-6 and IL-1 β , enhanced insulin-dependent phosphorylation of Akt and GSK3 β in peripheral tissues and improved GTT and ITT performance (Kurokawa et al., 2011). Thus, despite greater adiposity, impaired recruitment of M1 macrophages into AT protects AIM KO mice from the inflammatory and metabolic complications of obesity.

7. Future directions

7.1. MHC genes and metabolic risk

It is well known that alleles in the class I and II MHC, which is located in humans on the short arm of Chromosome 6 at p21.3, are linked to Type 1 diabetes, specifically through the mobilization of autoimmune processes during childhood (Grant and Hakonarson, 2009). Here, the β -cells of pancreatic islets are destroyed by autoreactive T cells, leading directly to irreversible, insulin-dependent diabetes, but the details of this process are beyond the scope of the present discussion of obesity and T2D. Many autoimmune and inflammatory diseases are associated with the class II MHC (de Bakker et al., 2006), particularly inflammatory bowel disease (IBD), rheumatoid arthritis (RA), lupus and ankylosing spondylitis (Handunnetthi et al., 2010). Reports continue to emerge that emphasize new significant associations, such as most recently, between multiple sclerosis and *HLA-DRB1* alleles (Sawcer et al., 2011). Study of this region for correlation of diseases with specific genes has been particularly difficult because it is the most polymorphic region of the human genome; numerous inflammation-relevant alleles exhibit non-random association (linkage disequilibrium). Certain class II MHC genes that are implicated in IBD and RA, such as *TNF* (also at 6p21.3), are also clearly important for IR and T2D.

Genome-wide association studies of Pima Indians (Malhotra et al., 2011), an aboriginal American people who have the highest prevalence of T2D in the world, have shown a significant association between the *BRD2* SNP rs12216336, with a risk allele frequency of 0.87 and BMI. Individuals homozygous for the risk allele have a mean BMI that is 4 kg/m² higher than individuals homozygous for the non-risk allele, supporting the hypothesis that *BRD2* is an obesity susceptibility gene in this population (Muller et al., 2011). Recent results link *Brd2* levels directly to regulation of transcriptional activity of the *Ins1* promoter in mouse embryonic stem cells (Wang et al., 2012), suggesting that *Brd2* regulates insulin production, insulin sensitivity and chronic inflammation in insulin-resistant obesity. Reinforcing this concept, meta-analyses of the literature have concluded that there is likely an association among inflammatory markers, obesity/IR and certain inflammatory diseases, such as RA. Patients with RA exhibit elevated risk for IR, T2D and CVD (Wasko et al., 2011), likely mediated through elevated TNF- α . Interestingly, *BRD2* polymorphism has also been independently linked to RA (Mahdi et al., 2009). Elevated serum inflammatory profiles, reduced adiponectin (Ozgen et al., 2010) and IR likely co-vary and contribute to common comorbidities, such as CVD and atherosclerosis that is prevalent among obese IR patients (Mangge et al., 2010; Westlake et al., 2011).

Certain individuals with this 'pro-inflammatory phenotype', who are prone to a cluster of diseases of chronic inflammation (*e.g.* CVD, IBD, RA), would be predicted upon the development of overweight or obesity to exhibit higher relative risk for T2D and obesity-associated cancers, for example, than the mean risk of the obese population (Denis, 2010; Belkina and Denis, 2012; Denis and Bowen, 2013). If the population distribution of inflammatory responses is symmetrical and two-tailed, as many as 18 million Americans could be included in this 'at-risk' cohort, but the relevant biomarkers are unknown. Three hypothetical relationships are summarized in Fig. 2. To address such a question, it would be crucial therefore to stratify obese populations by inflammatory markers and IR, and compare their co-morbidity incidence. Thus, there is clear need for deeper analysis of the MHC, with the translational goal of developing an intervention component to address patients at the greatest risk for multiple serious conditions that build on their underlying inflammatory status.

7.2. Shared chromatin complexes integrate apparently unrelated diseases

Biochemical crosstalk likely links certain diseases discussed above through a limited, shared subset of chromatin-directed co-regulators, such as the double bromodomain protein family (Denis, 2010; Belkina and Denis, 2012). An overall hypothesis that integrates many of the phenomena discussed is presented in Fig. 3. Manipulation of this single chromatin-directed co-regulator Brd2 reveals that transcriptional networks are related through shared molecular complexes, much the same way that SWI/SNF chromatin remodeling complexes both activate and repress related sets of genes. Reduced action of Brd2 alleviates of Brd2 co-repression of PPAR γ and insulin gene transcription, which is pro-adipogenic and shifts energy balance towards storage (Fig. 3B), while *simultaneously* ablating both inflammation and cancer through reduced transcription of inflammatory cytokine genes and cell cycle genes (Belkina and Denis, 2012; Denis and Bowen, 2013). Thus, this hypothesis predicts that the MHO phenotype will be associated with reduced occurrence or progression of cancer for the obesity-associated malignancies (Chadid et al., forthcoming).

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Abbreviations

AIM	apoptosis inhibitor of macrophage
ATM	adipose tissue macrophage
BMI	body mass index
CLS	crown-like structure
CVD	cardiovascular disease
ECM	extracellular matrix
HOMA	homeostasis model assessment
IBD	inflammatory bowel disease
IL	interleukin
IR	insulin resistance
MHC	major histocompatibility complex
MHO	metabolically healthy obese
MONW	metabolically obese normal weight
MS	metabolic syndrome
PCOS	polycystic ovary syndrome
PPAR	peroxisome proliferator-activated receptor
RA	rheumatoid arthritis
TBP	thioredoxin binding protein
TPL2	tumor-progression locus 2
T2D	Type 2 diabetes

TNF	tumor necrosis factor
TZD	thiazolidinedione
WAT	white adipose tissue

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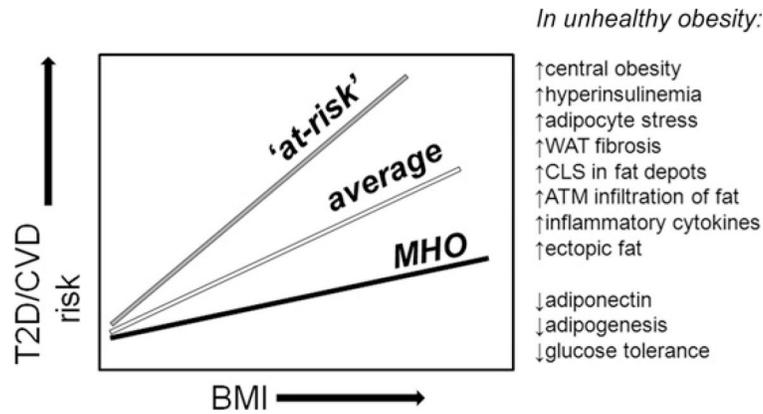
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	<i>Lean body type</i>	<i>Obese body type</i>
<i>Healthy metabolism</i>	Lean, healthy	MHO
<i>Unhealthy metabolism</i>	MONW	Obese, unhealthy

Fig 1.

A classification model for obese and metabolic phenotypes. A 'two-by-two' map of the effects of obesity on health, with two off-diagonal entries.

**Fig 2.**

Three populations of humans or mouse models define risk profiles for obesity-driven metabolic dysfunction. As BMI increases, the risks of T2D and CVD increase, but less steeply for MHO individuals than for the general population. MHO individuals are characterized by less serious increases in central obesity, adipocyte stress and other factors. On the other hand, this model predicts that some individuals will experience greater risk than the general population; these individuals (*'at-risk'*) may have predisposition to chronic inflammatory disease, hyper-reactive T cell function, or unresolved co-morbidity such as rheumatoid arthritis, lupus or other autoimmune disorders. ATM; adipose tissue macrophage; BMI, body mass index; CLS, 'crown-like' structures; CVD, cardiovascular disease; MHO, metabolically healthy obese; T2D, Type 2 diabetes; WAT, white adipose tissue.

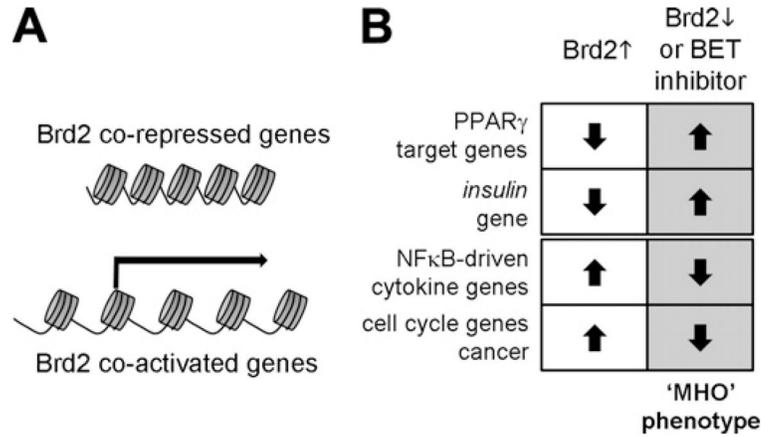


Fig 3. Hypothesis for crosstalk among Brd2-regulated genes. (A) Certain genes are transcriptionally co-repressed by Brd2, such as PPAR γ target genes (Wang et al., 2009) and the *insulin-1* gene (Wang et al., 2012), whereas other genes are transcriptionally co-activated by Brd2, such as cyclin A (Sinha et al., 2005), which causes cell cycle acceleration and cancer (Greenwald et al., 2004) and pro-inflammatory cytokine genes (Belkina et al., 2010; Belkina et al., forthcoming). (B) Brd2 action permits the MHO phenotype to be interpreted as a coherent transcriptional phenotype of increased adipogenesis (Wang et al., 2009; Belkina and Denis, 2010), reduced inflammation and reduced obesity-associated cancer (Belkina and Denis, 2012; Chadid et al., forthcoming; Denis and Bowen, 2013).