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MINI REVIEW

Oxidative stress and inflammation interactions in human obesity

Isabel Bondia-Pons · Lisa Ryan · J. Alfredo Martinez

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Abstract Obesity is often characterized by increased oxidative stress and exacerbated inflammatory outcomes accompanying infiltration of immune cells in adipocytes. The oxidative stress machinery and inflammatory signaling are not only interrelated, but their impairment can lead to an inhibition of insulin responses as well as a higher risk of cardiovascular diseases and associated features. Mitochondria, in addition to energy transformation, play a role in apoptosis, cellular proliferation, as well as in the cellular redox state control. Under certain circumstances, protons are able to re-enter the mitochondrial matrix via different uncoupling proteins, disturbing free radical production by mitochondria. Disorders of the mitochondrial electron transport chain, over-generation of reactive oxygen species, and lipoperoxides or alterations in antioxidant defenses have been reported in situations of obesity and type-2 diabetes. On the other hand, obesity has been linked to a low grade pro-inflammatory state, in which impairments in the oxidative stress and antioxidant mechanism could be involved. The current scientific evidence highlights the need of investigating the interplay between oxidative stress and inflammation with obesity/diabetes onset as well as the interactions of such factors either as a cause or consequence of obesity. The signaling mediated by the activation of inflammatory markers or nuclear factor kappa β and other transcription factors as central regulators of inflammation are key issues to understanding oxidative stress responses in obesity. This review aims at summarizing the main mechanisms and interplay factors between oxidative stress and inflammation in human obesity according to the last 10 years of research in the field.

Keywords Obesity · Inflammation · Oxidative stress · Cytokines · Hypoxia

I. Bondia-Pons · J. A. Martinez (✉)
Department of Nutrition, Food Science, Physiology and Toxicology Research Building, University of Navarra,
C/ Irunlarrea 1,
31008 Pamplona, Spain
e-mail: jalfmtz@unav.es

L. Ryan
Functional Food Centre, Department of Sport and Health Sciences, Oxford Brookes University,
Gipsy Lane, Headington,
Oxford OX3 0BP, UK

Introduction

An increase in oxidative stress-derived inflammation has been hypothesized to be a major mechanism in the pathogenesis and progression of obesity-related disorders [21]. Additionally, a rise in inflammatory cytokine levels might drive a further increase in oxidative stress, setting up a vicious cycle [72]. The complex and intimate association between both increased oxidative stress and increased inflammation, not only in obesity but also in related disorders such as type-2 diabetes and cardiovascular disease (CVD), makes it

difficult to establish the temporal sequence of the relationship. Deciphering the causes of obesity and related metabolic disorders is a challenge, in part because so many body systems are affected. Disturbances in one organ or tissue can compromise the function of several others, therefore separating cause and effect is often difficult [111]. When energy intake exceeds energy expenditure, the resulting state of nutrient excess can trigger responses in many cell types such hepatocytes, myocytes, adipocytes, endothelial, and immune cells, giving rise to metabolic dysfunction [40, 56]. Each of these responses share the ability to activate signaling pathways (such as the c-Jun N-terminal kinase and the inhibitor of kappa B kinase beta pathways) promoting inflammation [111]. Thus, inflammation appears to be a common endpoint in human obesity.

This review aims at summarizing the main mechanisms and interplay factors between oxidative stress and inflammation in human obesity according to the last 10 years of research in the field.

Inflammation and obesity

Inflammation is a physiological response of the organism to harmful stimuli, be they physical, chemical, or biological. The response provided usually results in the reestablishment of systemic metabolic homeostasis. Obesity is characterized by the activation of an inflammatory process in metabolically active sites such as adipose tissue, liver, and immune cells [47]. However, obesity impairs it and, as such, it elicits a stress response [109]. This response is characterized by increasing levels of glucocorticoid, a steroid hormone facilitated and needed for the development and differentiation of preadipocytes. In addition, there is a sharp increase in circulating levels of proinflammatory cytokines, adipokines, and other inflammatory markers [47]. In fact, the secretion of proinflammatory factors by the adipose tissue, and, most importantly, the regulation of their secretion by increasing adiposity, substantiates the hypothesis for an ongoing low-grade inflammatory process during obesity. In this context, one of the major contributions in the understanding of the inflammatory nature of obesity was the identification of the cytokine tumor necrosis factor-α (TNF-α) [42]. Later on, elevated circulating levels of other molecules such as interleukin (IL)-6 [25], fibrinogen, C-reactive protein (CRP) [113], monocyte chemotactic protein-1 [91], serum amyloid A [116], as well as plasminogen activator inhibitor-1 (PAI-1) [13] or resistin [52] in obese states supported the relation between inflammation and obesity in humans. For instance, IL-6 seems to impair insulin signaling in part by down-regulation of insulin receptor substrate 1 (IRS1) and up-regulation of the suppressor of cytokine signaling (SOCS)-3 [86]. Actually, SOCS-3 belongs to a family of inflammatory mediators, the SOCSs contributing to obesity-induced insulin resistance, which constitute a negative feedback pathway in cytokine signaling [57].

Resistin, which is expressed primarily by macrophages in humans, seems to be involved in the recruitment of other immune cells and the secretion of proinflammatory factors, including TNF-α [4]. Human resistin may interfere with insulin signaling by stimulating the expression of phosphatase and tensin homolog deleted on chromosome ten (PTEN), which dephosphorylates 3-phosphorylated phosphoinositide (PIP(3)); and many of their inflammatory related functions appear to be regulated by activation of the NFκB transcription factor [4].

Dysregulated production or secretion of adipokines owing to adipose tissue dysfunction can then contribute to the pathogenesis of obesity-linked complications such as inflammatory phenomena. The identification of the secreted frizzled-related protein 5 (SFRP5), a new adipokine with anti-inflammatory properties that has beneficial effects on metabolic dysfunction [76], has opened a new way to understand the interplay between nutrition and inflammation. SFRP5 was expressed at high levels in mouse white adipose tissue but was downregulated in the adipose tissue of various obese rodents, as well as in the visceral adipose tissue of obese individuals with adipose tissue inflammation and insulin resistance [76].

Various dietary compounds including long chain omega-3 fatty acids [7], antioxidants [18], prebiotics, and probiotics [54, 73] have also the potential to modulate predisposition to inflammatory conditions and may have a role in their management [8]. These components act through a variety of mechanisms that include decreasing inflammatory mediator production through effects on cell signaling and gene expression. Lipid mediators, including lipoxins, resolvins, and protectins, are also major players in dismantling the inflammatory response, a process called inflammatory

resolution. A new class of molecules, maresins, has also been identified in this process, which are produced by macrophages from the omega-3 fatty acid DHA, and can diminish neutrophil accumulation at inflammation sites as well as enhance phagocytosis in macrophages [93].

However, as pointed out by Calder et al. [8], the putative effect of nutritional compounds in strengthening the regulatory networks controlling inflammatory responses should be studied in more detail using conditions and models in which a stress is applied to the homeostatic control of inflammation [22].

In this context, not only epidemiological but also well-controlled clinical studies have indeed shown that the Mediterranean Diet or its main components are associated with a lower inflammatory status and/or improved endothelial function [6, 22, 23, 38].

Immunity and activation of inflammatory signaling pathways in obesity

Activation of the immune response in obesity is mediated by specific signaling pathways, with Jun N-terminal kinase (JNK) and IκB kinase β/nuclear factor κ-light-chain-enhancer of activated B cells being the most well studied [47, 60].

The transcription factor NF-κB promotes immunity by controlling the expression of genes involved in inflammation. NF-κB regulates expression of the inflammatory mediators that recruit monocytes, drive differentiation to macrophages, and direct macrophage cell fate determination. NF-κB regulated genes direct the differentiation of distinct immune cell types [3].

Recent studies have shown that macrophages are key mediators of obesity-induced insulin resistance (IR), with a progressive infiltration of macrophages into obese adipose tissue [36]. Adipose tissue macrophages along with the adipocytes produce a wide range of mediators to the pro-inflammatory response [101]. Differentiated macrophages can be categorized as M1 and M2 activated macrophages. M1 macrophages produce cytokines such as IL-1β, IL-6, TNF-α, creating a proinflammatory environment that blocks adipocyte insulin action, contributing to the development of IR and type-2 diabetes mellitus [36]. In contrast, immunoregulatory M2 macrophages secrete IL-10, an anti-inflammatory cytokine, which may protect against inflammation. Therefore, NF-κB-dependent differentiation of monocytes into either M1 or M2 macrophages, in response to cytokines produced by lymphocytes and other immune cells, seems to be a critical factor in the development of inflammatory metabolic diseases, including obesity [59, 75]. Thus, a predominant change in secretion of macrophage-cytokines takes place from anti-inflammatory to proinflammatory nature. The latter, together with non-esterified fatty acids (NEFA), activate key regulators of inflammation such as c-JNK, inhibitor of KB kinase β (IKKβ) within insulin target cells [36]. The activity of both JNK and IKKβ is increased in obesity, resulting in the further activation of pro-inflammatory transcription factors including activator protein 1 (c-Jun/Fos) and NF- κB [81]. This leads to the serine phosphorylation of the insulin receptor substrate that interferes with insulin action. Adipocytes from different body depots may have major differences in their inflammatory phenotype, with visceral fat expressing the more detrimental phenotype and subcutaneous fat the most benign phenotype [50].

Inflammatory signaling pathways are also modulated by lipids [71]. Free fatty acids bind innate immune receptors such as Toll-like receptor (TLR) 4 and TLR2. These receptors are expressed in adipose tissue and their expression is induced in obese subjects [106]. The TLR family plays a role in pathogen recognition and initiation of the innate immune response [96]. TLR4 stimulation results in the activation of both JNK and IKKβ [96].

Interestingly, macrophages may not be the only immune cell to infiltrate the adipose tissue during obesity [35, 83]. In this sense, the functional role of T cell accumulation has recently been characterized in adipose tissue. Among these leucocytes, the helper T cells can be divided either in Th1 or Th2. Th1 cells are typically pro-inflammatory and are induced by interferon (IFN) γ. These white cells produce obese adipose-expressed pro-inflammatory cytokines such as IFNγ, IL-12, and TNF-α. On the contrary, Th2 cells are anti-inflammatory cells induced by IL-4 and produce lean adipose tissue-expressed cytokines such as IL-4, 5, 10, and 13 [35]. T cell accumulation may be indeed a primary event in adipose tissue inflammation [48].

Other factors shown to link inflammation to obesity include kinases such as extracellular signal-regulated kinases (ERK) and mammalian target of rapamycin (mTOR), genes such as glycogen synthase kinase 3 (GSK3β) and S-phase kinase-associated protein 1 (S6K), whereas nuclear receptors such as PPARs and

liver X receptors have been shown to inhibit the activation of inflammatory pathways [41].

The role of the inflammasome in obesity

The NOD-like receptors (NLRs) are a family of molecules that recognize both pathogen- and danger-associated molecular patterns and are thus important sensors of cellular stress that result from infection and cellular instability [46, 94, 114]. Activation of the NLR proteins NLRP3, NLRP1, and NLRC4 results in the recruitment of the inflammasome-adaptor protein and pro-caspase-1 into a highly regulated protein complex known as the inflammasome [58]. The inflammasome activation initiates downstream inflammatory cytokine production, mainly IL-1β and IL-18 [17]. Recent studies have identified a unique role for inflammasome regulation in the induction and pathogenesis of multiple autoimmune and inflammatory disorders [67]. In this sense, obesity-related factors and endogenous markers of cellular stress can lead to unchecked activation of the inflammasome and provoke inflammation and subsequent destruction of vital organs [58].

A new study by Wang et al. [107] demonstrated that monocyte-produced microparticles (MP) contain inflammasome components, and that those from lipopolysaccharide-treated cells also carry IL-1β. Binding of these latter MP to endothelial cells leads to activation of NF-κB and ERK1/2 signaling pathways and upregulation of adhesion molecules [107]. Further research will be needed to determine if this also occurs in vivo, and which receptors mediate the MP-endothelial cell binding event, but so far points out the emerging role for microparticles in endothelial activation.

Further studies have reported that the NLRP3 inflammasome senses obesity-associated molecular patterns; an important mechanism that participates in the development of insulin resistance [99, 104, 110]. The influx of macrophages, T cells, and B cells in adipose tissue in obesity and release of pro-inflammatory mediators by these cells cause insulin resistance. The mechanisms that regulate the activation of these immune cells in adipose tissue are still largely unclear; however, NLRP3 inflammasome activation in adipose tissue macrophages may be one of regulators of immune activation in obesity [17]. In this sense, inflammasome-mediated caspase-1 activation in adipose tissue and liver has been shown to impair insulin-signaling and glucose homeostasis [99]. Studies using knock-in reporter mice suggest that NLRP3 is largely expressed in myeloid cells [34]. It appears that the hematopoietic compartment may play a predominant role in sensing of obesity-related danger associated molecular patterns and subsequent production of IL-1β and IL-18 [104, 110]. As it is known, obesity is associated with an increase in ceramides, saturated fatty acids, reactive oxygen species (ROS), mitochondrial dysfunction, and ATP release from necrotic adipocytes. Interestingly, all these factors have been shown to activate the NLRP3 inflammasome in macrophages [53, 99, 104, 110] and its inhibition has been shown to lower obesity-associated inflammation and improve insulin sensitivity in animal studies [99, 104]. In addition, a detailed metabolic and molecular phenotyping of mice deficient in NLRP3 recently demonstrated that the inflammasome controls energy expenditure and adipogenic gene expression during chronic overfeeding [99]. These findings reveal a critical role of the inflammasome in obesity and insulin resistance and suggest inhibition of the inflammasome as a potential therapeutic strategy.

Inflammation and adipose tissue hypoxia

Adipose tissue hypoxia is a potential cause of adipose tissue inflammation in obesity, resulting from adipocyte hypertrophy. A disproportionate increase in cell dimensions lengthens the distance oxygen must diffuse, which may lead to a hypoxic state in enlarged adipocytes [80]. Hypoxia unleashes two responses. The first is through hypoxia-inducible factor (HIF-1a) and the second is the unfolded protein response, which occurs in the endoplasmic reticulum [31, 100]. HIF-1a is a key regulator in the response to alterations in oxygen tension and modulates the expression of inflammation-related adipokine genes in human adipocytes, such as leptin, vascular endothelial growth factor (VEGF), and angiopoietin-like protein 4 [31]. In addition, the HIF-1a mRNA has been reported to be overexpressed in morbid obesity [9] and proposed as a protein marker of hypoxia in human obesity [102]. A study based on hypoxia-signaling pathway PCR arrays aiming at obtaining a more global view of hypoxia-sensitive gene expression in human adipocytes identified one particular gene, metallothionein-3 (MT-3) as a highly hypoxia-inducible gene in human adipocytes [108]. The primary function of this molecule in adipocytes may be protection against hypoxic stress

The expression of facilitative glucose transporters, mainly GLUT-1 and GLUT-4, is also induced by low O2 tension in human adipocytes, and this is accompanied by a parallel increase in glucose uptake [112].

Furthermore, increased uncoupling protein-1 in the adipose stromal vascular fraction of obese subjects [74] suggests that hypoxia may in fact regulate thermogenic and oxidative functions in obesity.

Impairment of the endoplasmatic reticulum function

Inflammation may be also a response to endoplasmic reticulum (ER) stress [33, 47]. The ER is a cytosolic organelle that participates in the regulation of lipid, glucose, cholesterol, and protein metabolism, apart from being the site of TG droplet formation. In some cells, nutrient excess impairs ER functioning, activating the "unfolded protein response" (UPR). Like ROS, this response can induce inflammation [90]. ER stress and the unfolded protein response are linked to major inflammatory and stress-signaling networks through the three stress-sensing proteins found in the ER membrane. They are inositol requiring enzyme 1 (IRE-1), pancreatic ER kinase (PERK), and activating transcriptor factor-6 (ATF-6) [90]. The activation of those mediators attenuates the cellular workload, decreasing protein translation, clearance, and degradation of excess proteins from the ER lumen; and induces repair, by inducing an antioxidant response and chaperone transcription to assist with unfolded proteins; and ER biogenesis, towards recovery and survival of the cell [60]. However, if the ER stress is not relieved, the UPR may also induce cell death via apoptosis and subsequent activation of inflammation by the UPR [115].

Viral infections and obesity

An understanding of any possible contribution of causal factors is essential for the proper management of obesity. In this sense, viral infections have been considered as a possible cause of obesity [1] alongside other traditionally recognized causes. Despite the four viruses: canine distemper virus [61], Rous-associated virus-7 [11], Borna disease virus, and Scrapie agent [10] have been reported to induce the so called "infectobesity" in animal models, the interest for the viral etiology of human obesity appeared with the adenovirus family [19]. Fifty human adenovirus serotypes have been so far described. The virus can be transmitted very easily via respiratory, droplet, venereal, and fecal-oral routes. Interestingly, adenovirus-36 (Ad-36) infection has been linked with obesity in animal models [19, 77] and in humans [2]. Both in vitro and ex vivo studies in rats demonstrated that Ad-36 modulates adipocyte differentiation, leptin production, and glucose metabolism [105]. Symptoms in the human studies on Ad-36 included an increase in adipose tissue combined with low levels of serum cholesterol and triglycerides [2, 19]. The underlying mechanism causing these symptoms remains unknown, but it has been hypothesized that obesity in Ad-36 infected individuals may be caused by changes in brain chemistry, in liver, and may stimulate the differentiation of preadipocytes as a reaction to viral infection [1].

However, further epidemiologic studies are needed to establish a causal link between the viral infections and human obesity, to determine whether these results can be used in future management and prevention of obesity [70].

Oxidative stress and obesity

The production of ROS is considered one of several adverse cellular responses to nutrient excess in obesity. These molecules are ubiquitous, highly reactive, short-lived derivatives of oxygen metabolism produced in all biological systems that react with surrounding molecules at the site of formation [87]. ROS are generated during glucose or free fatty acids oxidation by mitochondria and from metabolic processes elsewhere in the cell. These species include mainly superoxide radical, hydroxyl radical, and hydrogen peroxide. In physiological conditions, cells exhibit a self-protective antioxidant activity against oxidative damage made up of enzymatic (ex. superoxide dismutase, catalase, glutathione peroxidase) and non-enzymatic (ex. vitamins E and C) components [103]. When ROS production is increased the disturbed balance between oxidant and antioxidant factors results in a pro-oxidative condition [39]. This oxidative stress can then damage cellular structures and triggers an inflammatory response [40, 87]. Oxidative stress has been associated with adiposity, insulin resistance, and metabolic syndrome [29, 68], suggesting that oxidative stress could be an early event in the pathology of these chronic diseases [12]. Advanced oxidized plasma proteins (AOPPs), which are indicators of nitrosative stress, have

been reported to be higher in obese than in lean adolescents, with the highest levels in subjects with co-ocurring metabolic syndrome [51]. AOPPs are positively correlated with visceral adiposity, TG, lipid peroxidation, and insulin levels and inversely with the degree of body mass reduction [39]. Moreover, diverse studies have reported a positive association of total body fat and waist circumference with oxidative stress-mediated endothelial dysfunction [78], and more recently with vascular endothelial cell NADPH oxidase activity [26, 95].

Altered mitochondrial function

Mithochondria are double-membraned cell organelles specialized in converting energy-yielding macronutrients into ATP via oxidative phosphorylation [37]. This process is very efficient, but a small percentage of electrons may prematurely reduce oxygen forming toxic free radicals potentially impairing the mithochondria function [65]. Growing body of research demonstrates that altered mitochondrial energy production, particularly in skeletal muscles, is a major anomaly capable of setting off a chain of metabolic events leading to obesity [89]. The failure of the skeletal muscle mitochondria to oxidize fat properly leads to increased triglyceride synthesis and ectopic lipid deposits [87,89]. The accumulation of long-chain fatty acyl coenzyme A molecules, which are fatty acid derivatives ordinarily oxidized by mitochondria to generate adenosine 5′-triphosphate, which is essential for many cellular processes, is one of the cellular responses to nutrient excess [111]. Together with a decreased mitochondrial activity, a vicious cycle is created by further raising the concentration of these fatty acid derivatives [111]. Cellular infiltration by excess triglycerides can impair cellular function and can also lead to oxidative stress through increased ceramide formation, increased byproducts of lipid peroxidation, increased nitric oxide synthase, and inflammatory cytokine production and excess ROS formation [43,89]. Disruption of mitochondrial function as seen in obesity can increase the production of these unstable molecules, resulting in additional cellular injury by damaging lipid membranes, nuclear and mitochondrial nucleic acids, and proteins, especially essential respiratory chain enzymes, creating a vicious cycle of impaired beta-oxidation [89].

Under certain conditions, protons can also reenter the mitochondrial matrix through different uncoupling proteins (UCPs), which leads to heat dissipation without contributing to ATP formation, but affects the control of free radicals production by mitochondria [85]. Later studies have shown that UCPs have an important role in the pathogenesis of various metabolic disorders, including obesity and diabetes [15, 98]. These mitochondrial membrane transporters might play a major role in the energetic metabolism and thermogenesis. Overall, UCP2 could be of interest because of its ubiquitous expression and its important expression in adipose and skeletal tissues [98]. Polymorphisms of the UCP2 gene have been described in various case–control studies in different populations [44, 88]. In this context, two polymorphisms of the UCP2 gene (rs660339 and rs659366) were recently associated with body fat distribution and risk of abdominal obesity in a cross-sectional study with Spanish population [66].

An examination of mitochondrial factors revealed that loss of uncoupling protein 5 (UCP5) modifies the energy balance and increases free radicals through upregulation of uncoupling protein 3 (UCP3). The increased superoxide content induces c-Jun N-terminal kinase 1 (JNK1) kinase activity, which in turn affects Forkhead transcription factors (FOXO) localization through a compensatory dephosphorylation of Akt [92]. The resulting nuclear FOXO increases expression of target genes, including mitochondrial superoxide dismutase.

Studies of gene variants related to inflammation, oxidative stress, and obesity

The expression of genes is highly dependent on, and regulated by, nutrients and dietary bioactive compounds found in food [14]. A variety of dietary components can alter gene expression, as well as the genetic makeup of an individual may coordinate its response to diet [64]. Research in gene–environment interactions have identified genetic polymorphisms associated with individual susceptibility to obesity, inflammation, and oxidative stress. The relation between diet and single-nucleotide polymorphisms (SNPs) that impact on inflammation and oxidative status has been recently reviewed by Curti et al. [14].

As it is well-known, PPARγ is a nuclear hormone receptor, regulator of adipocytes-specific genes contributing to adipocytes differentiation, susceptibility to obesity, and insulin sensitivity [45]. The most prevalent

SNP variant related to PPARγ gene is the Pro12Ala, which is associated with type 2 diabetes, obesity, and other clinical disorders [16, 28]. However, there are studies where no association of this SNP variant has been found with obesity [30, 63]. The associations between common variations in the IL-6 gene and obesity have also been examined in a number of studies [5, 49]. Among the SNPs in the promoter region, −174 G/C (rs1800795) is the most prevalent and of greatest biological importance [32]. The presence of C allele has been related with a higher risk of obesity, high BMI, and high waist circumference [5, 79]. Carriers of the CC genotype had lower energy expenditure and insulin sensitivity, hence implying a causative role in IR and obesity. In a Spanish study, after a 3-year intervention with a Mediterranean-style diet conducted in a high CVD risk population, CC individuals with the −174 G/C polymorphism were predicted to have the greatest reduction in body weight. At baseline, these individuals had the highest BW and BMI [84].

Monocyte chemoattractant protein-2 (CCL2) is a multifunctional chemokine implicated as a potential target in many disease states. CCL2 was first identified by its ability to regulate monocytes, macrophages, and other inflammatory cells at sites of inflammation, but it has recently been shown to be a major component of insulin resistance in obese mice [62]. Furthermore, CCL2 is an insulin responsive gene that decreases insulin-stimulated glucose uptake and increases the expression of adipogenic genes [62, 91].

However, it has to be pointed out that relevance and magnitude of nutrient–gene interaction needs to be further elucidated by emphasizing the study of the combined effect of SNPs in different genes, as well as haplotypes.

Given the estimated heritability of BMI, genetic approaches can be a useful tool with which to dissect the mechanisms involved in weight regulation and understand the susceptibility to obesity. To date, the main experimental approaches used to identify human obesity-associated genes include linkage studies, association studies, and candidate gene studies [82].

By genotyping on average 350,000–500,000 SNPs covering more than 75% of the genome, genome-wide association studies (GWASs) conducted in population-based cohorts assessed for BMI or in case–control designs for obesity have led to the identification of several interesting genetic loci. The first loci detected were variants in the fat mass and obesity associated (FTO) gene [20, 27] and variants approximately 200 kb downstream of melanocortin 4 receptor (MC4R) [55]. Altogether, more than 20 genetic loci relevant for body weight regulation have been identified by GWAS approaches [97]. Nevertheless, the common variants uncovered in GWASs are characterized by modest effect sizes (per-allele odds ratios between 1.2 and 1.5), and the proportion of variability explained by GWAS-identified loci to date remains relatively modest (<10%). Therefore, there is the possibility that the heritability of obesity-related phenotypes may have been overestimated. In fact, it is difficult to distinguish between purely environmental effects and interactions between the environment and epigenetic factors. However, recent genome-wide measurement of epigenetic variation using techniques such as DNA methylation-specific microarrays [24, 69] might help to find the missing heritability in human obesity in the following decade.

Conclusions

Inflammation status and oxidative stress phenomena appear to be narrowly interacting in the obese condition. Thus, the activation of inflammatory cytokines such as TNF-α, IL-6, and inflammatory-related molecules such as NFκβ and other transcription factors is commonly found in obesity either as a trigger or as a consequence of obesity. Glucocorticoids overproduction in obese subjects has been also associated with the interplay of obesity and inflammation.

The role of immunity in the activation of inflammatory responses mediated by macrophages and monocytes is another field of interactions with an excessive body fat deposition, where fatty acids and immune cells might be important actors. The involvement of the inflammasome in obesity is another contributor to explain some of the adverse metabolic features associated to the accumulation of adipose tissue and the interactions between proinflammatory resources and metabolic stress. Furthermore, the hypoxia situation in the adipose tissue of obese subjects and the impairment of endoplasmatic reticulum functions have been claimed to mediate in the inflammation and oxidative stress interactions, probably accompanying mitochondrial alterations and ROS overproduction.

Finally, some implications of “infecto-obesity” on inflammatory processes have been reported, while

elegant investigations concerning the importance of carrying SNP on genes influencing both obesity and inflammation such as PPAR and IL6 are the way to confirm the mutual impact between inflammation and oxidative status on obesity.

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