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REVIEW

Redox-inflammatory synergy in the metabolic syndrome[1]

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Abstract: Metabolic syndrome (MetS) comprises interrelated disease states including obesity, insulin resistance and type 2 diabetes (T2DM), dyslipidemia, and hypertension. Essential to normal physiological function, and yet massively damaging in excess, oxidative stress and inflammation are pivotal common threads among the pathologies of MetS. Increasing evidence indicates that redox and inflammatory dysregulation parallels the syndrome's physiological, biochemical, and anthropometric features, leading many to consider the pro-oxidative, pro-inflammatory milieu an unofficial criterion in itself. Left unchecked, cross-promotion of oxidative stress and inflammation creates a feed-forward cycle that can initiate and advance disease progression. Such redox-inflammatory integration is evident in the pathogenesis of obesity, insulin resistance and T2DM, atherogenic dyslipidemia, and hypertension, and is thus hypothesized to be the "common soil" from which they develop. The present review highlights the synergistic contributions of redox-inflammatory processes to each of the components of the MetS.

Key words: metabolic syndrome, oxidative stress, inflammation, obesity, diabetes, dyslipidemia, atherosclerosis, hypertension.

Résumé : Le syndrome métabolique comprend des états pathologiques interreliés dont l'obésité, la résistance à l'insuline et le diabète de type II, la dyslipidémie athérogène et l'hypertension. Essentiels à la fonction physiologique normale et pourtant massivement dommageables en excès, le stress oxydant et l'inflammation sont des traits communs centraux des pathologies du syndrome métabolique. De plus en plus de preuves indiquent que la dérégulation redox et inflammatoire coïncide avec les caractéristiques physiologiques, biochimiques et anthropométriques du syndrome, poussant plusieurs à considérer le milieu pro-oxydant et pro-inflammatoire comme un critère en soi non officiel. La promotion croisée non contrôlée du stress oxydant et de l'inflammation crée cercle vicieux qui peut initier et accélérer la progression de la maladie. Une telle intégration redox-inflammation est évidente dans la pathogenèse de l'obésité, la résistance à l'insuline et le diabète de type II, la dyslipidémie athérogène et l'hypertension, et l'hypothèse qu'elle serait le 'terrain de prédilection' à partir duquel elle se développe a été proposée. Cet article de revue souligne les contributions synergiques des processus redox et inflammatoires dans chacune des composantes du syndrome métabolique. [Traduit par la Rédaction]

Mots-clés : syndrome métabolique, stress oxydant, inflammation, obésité, diabète, dyslipidémie, athérosclérose, hypertension.

A syndrome by any other name

A thesaurus comes readily to hand when trying to find new ways to describe metabolic syndrome (MetS), a state comprising physiological, biochemical, and anthropometric anomalies induced by genetic, environmental, and psychosocial factors that predispose an individual to type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). Indeed, a comprehensive but convoluted and sometimes venomous literature chronicles the attempt to ascribe clinical utility to the clustering of associated cardiometabolic risk factors, including insulin resistance, central obesity, hypertension, and dyslipidemia. Variously called "syndrome X," "the deadly quartet," "insulin-resistance syndrome," and presently, "metabolic syndrome," its history reflects the conceptual evolution that has occurred and the vacillating emphases that have been applied within a complex and multifactorial disease process.

Clinical definitions for the MetS outnumber the risk factors themselves, with at least 9 organizations and expert groups having proposed no fewer than 7 different sets of diagnostic criteria, each with their own particular flavor. A discussion of the merits and drawbacks of each of these is beyond the scope of this review; therefore, readers are directed to the excellent articles by Kassi et al. (2011) and Reaven (2011). A generally accepted definition for MetS was created in 2009 by a joint committee including the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) and the International Diabetes Federation (IDF). This consensus or harmonized definition requires a clinical diagnosis of MetS to satisfy any 3 of the following criteria: fasting glucose ≥100 mg/dL, elevated waist circumference (according to population and country-specific definitions), triglycerides ≥150 mg/dL, high density lipoprotein (HDL) cholesterol 40 mg/dL in men and 50 mg/dL in women, and blood pressure ≥130/85 mm Hg (1 mm Hg = 133.322 Pa) (Alberti et al. 2009). Notably, there is no obligatory component, contrasting with the glucocentric and obesity-centric definitions by the World Health Organization and the IDF, respectively (Kassi et al. 2011). This was a deliberate goal of

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Abbreviations: 8-OHdG, 8-oxo-7,8-dihydro-2′-deoxyguanosine; AGE, advanced glycation end product; AGER1, advanced glycation end product receptor 1; Ang II, angiotensin II; apoA-I, apolipoprotein A-I; BMI, body mass index; CRP, C-reactive protein; GSH, glutathione; GSHPx, glutathione peroxidase; HDL, high density lipoprotein; H_2O_2, hydrogen peroxide; IFN-γ, interferon-γ; IL, interleukin; JNK, Jun N-terminal kinase; LOX, lectin-like oxidized LDL receptor; MAPK, mitogen-activated protein kinase; MCP, monocyte chemoattractant peptide; MetS, metabolic syndrome; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; NO, nitric oxide; NOS, nitric oxide synthase; NOX, NADP/NADPH oxidase; $O_2^{\bullet-}$, superoxide anion radical; $ONOO^-$, peroxynitrite; oxLDL, oxidized LDL; PON, paraoxonase/arylesterase; RAAS, renin–angiotensin–aldosterone system; RAGE, receptor for advanced glycation end product; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; T_H, helper T cell; TNF-α, tumor necrosis factor-α; T2DM, type 2 diabetes mellitus; XO, xanthine oxidase.

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the new harmonized definition, owing to problematic generalizability of the previous systems owing to compositional population factors including race, ethnicity, sex, and age (Alberti et al. 2009). Moreover, depending on the criteria used, differing thresholds and cutoffs confounded estimates of prevalence. Regardless of definition, however, MetS is highly prevalent in Western countries and is on the rise. According to the National Health and Examination Survey 2003–2006, roughly 34% of participants met the criteria for MetS, and cohort data suggested a 5% increased prevalence over a 15-year period (Kassi et al. 2011). Furthermore, although the World Health Organization projects that 300 million people will suffer from MetS and its sequelae by 2025, Symonds et al. (2009) argue that this figure likely underestimates the real burden, given the rapidly increasing and earlier onset of childhood obesity and insulin resistance, 2 early markers of MetS.

Academic and clinical communities alike are divided as to the value of adopting MetS as a diagnostic tool, and these positions are likely to remain entrenched pending a better understanding of the associated disease processes. Potential mechanisms underlying MetS include fetal programming (Symonds et al. 2009; Power and Schulkin 2012; Rinaudo and Wang 2012), adipocyte dysfunction (Weisberg et al. 2003; Ouchi et al. 2011; Osborn and Olefsky 2012), dietary and (or) environmental pollutants (Lim et al. 2010; Vlassara and Striker 2011; Bremer et al. 2012; Stanhope 2012), sleep and stress (Maury et al. 2010; Tamashiro et al. 2011), genetic predisposition (Symonds et al. 2009; Ordovas et al. 2011), and prothrombotic (Rizzo et al. 2009; Drummond et al. 2011; Navab et al. 2011), pro-oxidative (Rizzo et al. 2009; Khaper et al. 2010; Drummond et al. 2011; Styskal et al. 2012), and pro-inflammatory states (Khaper et al. 2010; Navab et al. 2011; Osborn and Olefsky 2012). Indeed, given their ubiquitous presence as key contributors to the various disease processes of MetS, a major deficiency of MetS definitions is the lack of specific criteria for oxidative stress and inflammation. As will be discussed in this review, redox-inflammatory stress is a universal feature of MetS that may well prove to be the "common soil" from which obesity, insulin resistance and T2DM, atherogenic dyslipidemia, and hypertension develop. We will examine each of these components of MetS, emphasizing the roles of oxidative stress and inflammation in their pathogenesis, while paying particular attention to the conservation of redox-inflammatory mechanisms. We begin by describing oxidative stress and inflammation in terms of their normal and pathological functions.

Oxidative stress and inflammation

Oxidative stress refers to the overall cellular or systemic load of potentially harmful reactive oxygen species (ROS) generated during cellular metabolism or via interaction with exogenous stimuli. Endogenous sources of free radicals include the mitochondrial electron transport chain, NADH/NADPH oxidase (NOX), the xanthine–xanthine oxidase (XO) system, and many other redox reactions. Examples of ROS include superoxide anion radical ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), hydroxyl radical, and hypochlorous acid. Reactive nitrogen species (RNS) include free radicals such as nitric oxide (NO) as well as nonradicals such as peroxynitrite ($ONOO^-$), which is generated via the ready reaction of NO and $O_2^{\bullet -}$ (Kaul et al. 1993). ROS and RNS initiate cascades of harmful events including DNA damage, protein nitration, lipid peroxidation, and activation of matrix metalloproteinases (MMPs) contributing to cardiovascular remodeling and ultimately, dysfunction (Paravicini and Touyz 2006; Vasdev et al. 2006; Khaper et al. 2010; Shen 2010).

To detoxify free radicals, cells have evolved various enzymatic (i.e., superoxide dismutase (SOD), catalase, and glutathione peroxidase (GSHPx)) and nonenzymatic antioxidants (i.e., glutathione (GSH), antioxidant vitamins). Oxidative stress results when an abundance of ROS, exceeds the capacity of the antioxidant defenses to detoxify them (Singal et al. 1998; Khaper et al. 2010). However, despite its potential for damage, it is essential to note that ROS generated under physiological conditions play important beneficial roles, including acting as signaling molecules in a variety of cell signaling pathways, often as second messengers. Indeed, ROS act to modulate the activity of specific transcription factors including nuclear factor (NF)-κB and activator protein-1, and are also integral to defense mechanisms, such as oxidative burst in phagocytosis, neutrophil function, and shear-stress-induced vasorelaxation (Singal et al. 1998; Paravicini and Touyz 2006; Khaper et al. 2010). It activates mitogen-activated protein kinases (MAPK), including extracellular signal-related kinase, the c-Jun N-terminal kinases (JNK), and the p38 kinase via apoptosis signal-regulated kinase 1, protein kinases A and C, and via direct inhibition of MAPK phosphatases, effecting myriad cellular responses to a vast array of signaling mediators including oxidative and inflammatory stressors. Moreover, ROS promote proliferation, survival, and elaboration of antioxidant defenses via phosphoinositide 3-kinase, nuclear factor erythroid 2-related factor 2/antioxidant response element (ARE) (Paravicini and Touyz 2006; Vasdev et al. 2006; Khaper et al. 2010; Shen 2010).

Inflammation is another integral aspect of homeostatic regulation that can both exert beneficial effects and contribute to disease pathogenesis. Inflammation is a tightly regulated, complex tissue response to deleterious stimuli that serves to attenuate stressors and facilitates the healing process (Khaper et al. 2010; Donath and Shoelson 2011; Osborn and Olefsky 2012). Myriad signaling molecules are involved in the inflammatory response including prostaglandins and C-reactive protein (CRP), soluble CD40 ligand, adiponectin, and inflammatory cytokines, including tumor necrosis factor (TNF)-α and interleukin (IL)-6. Many of these are increasingly used as biomarkers for the systemic inflammation associated with MetS (Rabkin 2009; Donath and Shoelson 2011). Cytokine signaling is essential for the function of the innate and adaptive immune system, playing numerous roles in the host's inflammatory response including recruitment of neutrophils, monocytes, and dendritic cells by chemokines (Nian et al. 2004; Khaper et al. 2010). In short, inflammatory cytokines are ubiquitous critical mediators of the inflammatory response to a wide variety of harmful or potentially harmful stimuli throughout the body. However, in pathophysiological conditions the dysregulation of various processes can lead to chronic inflammation, where the elaborated activity of inflammatory mediators and processes can be massively damaging (Nian et al. 2004; Kaur et al. 2009; Khaper et al. 2010; Donath and Shoelson 2011; Osborn and Olefsky 2012).

Redox and inflammatory mechanisms are highly integrated in disease pathogenesis, cross-promoting one another in a feed-forward cycle that may play an important role in the development and progression of MetS. In this review, we discuss the interplay of redox-inflammatory signaling in 4 key components of MetS: obesity, insulin resistance and T2DM, atherogenic dyslipidemia, and hypertension. In the following section, we explore the roles of oxidative stress and inflammation in the pathogenesis of obesity.

Obesity is a state of heightened redox-inflammatory stress

The past 2 decades saw obesity surpass malnutrition and infectious disease as the greatest contributor to morbidity and mortality in developed and developing nations alike. Staggeringly, more than 2/3 of North American adults are either overweight (BMI ≥25 kg/m^2) or obese (BMI ≥30 kg/m^2) (Lau et al. 2007), the rates of obesity having doubled in both the United States and Canada since the early 1990s (Shields et al. 2011). More troubling still, childhood obesity increased 5-fold in Canada during that span and has been accompanied by earlier onset of obesity-related diseases, a trend that shows no signs of diminishing (Lau et al. 2007). Indeed, over-

weight adolescents are 16 times more likely than the normal-weight adolescents to manifest MetS (Symonds et al. 2009). Today there remains no question that obesity can properly be called an epidemic, nor that it is driving the parallel epidemic of T2DM (Osborn and Olefsky 2012). Oxidative stress and inflammation feature prominently among these pivotal interrelated components of MetS. In this section, we summarize the known redox-inflammatory contributions to obesity to the focused nature of this review, interested readers are directed to the more comprehensive articles on obesity by Ouchi et al. (2011) and Osborn and Olefsky (2012).

The 2 most widely used definitions of MetS — those from the NCEP-ATP III and IDF — focus specifically on waist circumference, which is a surrogate measure of central obesity (Kassi et al. 2011). The primary cause of insulin resistance, obesity is inextricably linked to T2DM and the other metabolic and cardiovascular derangements of MetS (Xu et al. 2003). Fundamental to these effects is its promotion of a chronic low-grade inflammatory state, evidenced clinically by a correlation between visceral adipose mass and serum CRP (Brooks et al. 2010) that is largely mediated by the newly emerging endocrine functions of adipokines. Variously known as pro- or anti-inflammatory in effect, the relative adipokine balance is thought to be crucial in determining global inflammatory state and contributing to, or even causing, syndromic metabolic perturbations. In what has been described as a shift from "healthy" to "toxic" fat in MetS, pathological adipokine expression is associated with the expansion of visceral adiposity in central obesity and leads to dysregulated modulation of insulin sensitivity, lipid profile, endothelial function, and redox-inflammatory state (Brietzke 2010).

Key pro-inflammatory adipokines include IL-6, leptin, and TNF-α, but novel members of this group have recently been recognized: angiopoietin-like protein 2, CC-chemokine ligand 2, CXC-chemokine ligand 5, IL-18, lipocalin 2, nicotinamide phosphoribosyltransferase, resistin, and retinol-binding protein 4 (Ouchi et al. 2011). Adiponectin is the most significant anti-inflammatory adipokine described to date as well as the most intensively studied, and was recently joined by secreted frizzled-related protein 5 (Ouchi et al. 2011). Notably, ROS activate while adiponectin opposes nuclear factor κB (NF-κB)-mediated signaling cascades, which can stimulate TNF-α and IL-6 production. Moreover, ROS, TNF-α, and IL-6 are known to inhibit adiponectin (Hosogai et al. 2007), making plausible a potentiating role for oxidative stress in pro-inflammatory adipokine elaboration. Such systems of intra-adipose communication and counter-regulation appear to break down with increasing obesity and adipocyte dysfunction, suggesting that therapies aimed at correcting adipokine imbalance may prove valuable for treating obesity-related metabolic and CVDs (Ouchi et al. 2011; Osborn and Olefsky 2012).

Both obesity and pregnancy are states of low-grade inflammation and oxidative stress, and these milieus can worsen when pregnancy is complicated by hypertension, hyperglycemia, or nutrient restriction (Symonds et al. 2009; Power and Schulkin 2012; Rinaudo and Wang 2012). A recently articulated hypothesis holds that maternal obesity may increase the risk of chronic metabolic disease in both fetus and mother, owing to aberrant endocrine signaling between adipose and placental tissues. Here, overwhelmed regulatory systems are postulated to cause maternal pancreatic tissue breakdown, altered fetal development, and persistent metabolic derangement (Power and Schulkin 2012). This concept is supported by evidence that amplified levels of IL-10 play a crucial protective role in buffering against pro-inflammatory insults during pregnancy (Tinsley et al. 2010; Kalkunte et al. 2011). Interestingly, these data also suggest a potential epigenetic mechanism for the transgenerational inheritability of obesity (Power and Schulkin 2012). That said, while the heritability of BMI is thought to range from 40% to 70%, gene analyses and association studies have revealed that only about 10% of the variance of MetS is linked to genetic predisposition, indicating that environment and epigenetic imprinting constitute the majority influence (Bremer et al. 2012).

Pro-inflammatory milieus can induce, and in turn be exacerbated by a pro-oxidant environment, which is strongly associated with obesity in both humans and laboratory animals (Styskal et al. 2012). Serum markers of oxidative stress, including 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-OHdG), thiobarbituric acid reactive substances, and 8-epi-prostaglandin F2α, are elevated in obese humans, and both plasma and adipose lipid peroxidation and H_2O_2 are elevated in obese mice (Furukawa et al. 2004). One mechanism of obesity-related oxidative stress is thought to be accelerated substrate processing in mitochondrial respiration, owing to excessive glucose and fatty acid levels in high-calorie diets. This concept is supported by evidence for increased mitochondrial $O_2^{\bullet-}$ production in various tissues of high-fat diet and (or) obese mice, including adipose tissue (Curtis et al. 2010). Increased $O_2^{\bullet-}$ generation via NOX, expression of which has been demonstrated under both high-fat and high-glucose conditions, has also been reported as a potential source of oxidative stress (Shen 2010). Moreover, obesity-related down-regulation and decreased activity of adipose antioxidant enzymes including SOD, catalase, and GSHPx have been reported (Furukawa et al. 2004), indicating the presence of a significant redox imbalance. These and other data point to an important role for oxidative stress in the pathogenesis of obesity-related diseases that has been postulated as the "missing link" between inflammation and obesity (Page et al. 2011).

Adipose tissue is mainly composed of adipocytes, but also includes pre-adipocytes, fibroblasts, lymphocytes, and macrophages. Their relative distribution changes according to increasing adipose mass and adipocyte dysfunction, correlating with adipose tissue fibrosis (Khan et al. 2009) and increased macrophage infiltration (Weisberg et al. 2003). Evidence for macrophage accumulation in inflamed adipose of individuals having highly dysfunctional metabolic control suggests insufficient phagocytosis of dead adipocytes that likely worsens inflammation (Apovian et al. 2008). Importantly, ROS have been shown to promote inflammatory macrophage infiltration via multiple mechanisms, including stimulation of the pro-inflammatory mediators IL-6 and monocyte chemoattractant peptide-1 (MCP-1) (Sung et al. 2002), and induction of adipocyte senescence (Minamino et al. 2009). Similarly, elevated pro-inflammatory fatty acids resulting from overnutrition act as ligands for cell surface toll-like receptors (Furukawa et al. 2004; Shi et al. 2006), which activate signaling cascades culminating in NF-κB activation, promoting infiltration of neutrophils, lymphocytes, and macrophages, and stimulating inflammatory cytokine production (Nikolajczyk et al. 2011). Besides increased accumulation, macrophage phenotype also contributes to redox-inflammatory status in obesity. Whereas obese mice express M1 macrophages in adipose that produce pro-inflammatory cytokines including TNF-α and IL-6 as well as ROS and RNS, lean mice express the M2 phenotype macrophages, which stimulate production of the anti-inflammatory IL-10 and suppress pro-inflammatory cytokine expression (Ouchi et al. 2011). T cell subsets are thought to regulate macrophage phenotype polarization, with $CD8^+$ and $CD4^+$ effector T cells stimulating pro- and anti-inflammatory cascades, respectively. Taken together, obesity-related alterations in type 1 and 2 helper T cell (T_H1 and T_H2) signaling may dictate macrophage phenotype, promoting either a pathological state characterized by a pro-inflammatory/pro-oxidant environment, or a protective one replete with anti-inflammatory and antioxidant factors (Ouchi et al. 2011).

Other evidence from both human and animal models suggests that systemic and adipose tissue renin–angiotensin–aldosterone system (RAAS) overactivation occurs in obese states, blockade of which improves insulin sensitivity (Lastra et al. 2009). Here, an-

giotensin II (Ang II) has been shown to inhibit lipolysis and promote lipogenesis, as well as inducing ROS-mediated adipose tissue expression of pro-inflammatory cytokines IL-6, IL-8, and MCP-1 in an NF-κB-dependent manner (Kalupahana and Moustaid-Moussa 2012). ROS were also recently linked to inflammasome-dependent activation of caspase-1 and IL-1β, which inhibit adipocyte differentiation, impair insulin signaling, and contribute to high-fat-diet-induced obesity (Stienstra et al. 2010; Barker et al. 2011). Moreover, inflammasome inhibition decreased IL-18 and interferon (IFN)-γ expression in obese mice (Vandanmagsar et al. 2011). These data support the hypothesis that IL-1β and TNF-α act cooperatively to propel chronic inflammation, underscoring the need for a pan-cytokine approach to immunomodulation of metabolic diseases (Wen et al. 2012).

In summary, many potential mechanisms modulate inflammatory and redox states to influence obesity-related derangements of MetS. Although as yet poorly elucidated, the evidence supports cross-promotion of inflammatory and oxidative processes in obesity, leading to greater adipose dysfunction in a classic "vicious cycle". Hypotheses for common soil regulation of inflammation and oxidative stress in obesity include micro-RNAs (Hulsmans et al. 2011) and the postulation that elevated melanogenesis in adipose of obese subjects may indicate an anti-inflammatory and/or antioxidant role for melanin therein (Page et al. 2011). In the following section, the interdependent contributions of inflammation and oxidative stress to insulin resistance and the development of T2DM are discussed.

Redox-inflammatory stress drives insulin resistance and type 2 diabetes

T2DM, the most common metabolic disorder and the leading cause of cardiovascular, renal, and myriad other comorbidities, affects roughly 285 million people worldwide and is predicted to increase to 438 million by 2030 (Shaw et al. 2010). Associated with risk factors such as obesity, aging, and sedentary lifestyle, its pathogenesis is complex and remains incompletely understood, but the central pathological mechanism is decreased insulin-stimulated glucose uptake, or insulin resistance. The disease process advances as the compensatory abilities of pancreatic islet β-cell expansion and secretory function is exceeded by the degree of peripheral insulin resistance, leading to insulin deficiency and ultimately T2DM (Donath and Shoelson 2011). Rapidly emerging as a primary factor in its pathogenesis, elevated oxidative stress driven by adipogenic diets and impaired glucose and fatty acid metabolism appears to precede and persist throughout the development of insulin resistance and T2DM (Vlassara and Striker 2011; Styskal et al. 2012). Similarly, immune system alterations and inflammation are increasingly recognized as contributors to these processes, with oxidative stress a likely driver in their induction and perpetuation (Donath and Shoelson 2011; Vlassara and Striker 2011; Styskal et al. 2012). In this section, we discuss redox-inflammatory stresses as they pertain to T2DM. Owing to the focused nature of this review, interested readers are directed to the more comprehensive articles on insulin resistance and T2DM by Styskal et al. (2012) and Donath and Shoelson (2011).

Oxidative damage is evident even prior to the onset of clinical T2DM, with multiple studies demonstrating elevated urinary 8-OHdG in individuals categorized as prediabetic, as well as increased levels in diabetic versus nondiabetic patients (Al-Aubaidy and Jelinek 2011; Styskal et al. 2012). Hyperglycemia has been shown to increase oxidative stress and directly inhibit antioxidant defenses including GSH, vitamins E and C, SOD, GSHPx, and glutathione reductase activity (Shen 2010; Yuan et al. 2010). Excess ROS results from glucose- and lipid-induced impairment of mitochondrial function and increased NOX activity in T2DM (Shen 2010). It is thought that this mitochondrial dysfunction and elevated ROS may both contribute to, and be a consequence of, impaired autophagy (Gonzalez et al. 2011), possibly relating to diminished activity of the transcription factor Nrf-2/ARE (Cheng et al. 2011). Interestingly, these oxidative mechanisms in T2DM pathogenesis represent a reversal of the normal ROS-mediated regulation of glucose handling, because H_2O_2 is known to modulate glucose-stimulated insulin release from β-cells as well as systemic insulin signaling (Goldstein et al. 2005; Styskal et al. 2012). Moreover, this demonstrates the tenuous redox balance in β-cells, which have very low basal antioxidant capacity and are particularly susceptible to oxidative damage (Vlassara and Striker 2011).

Mounting evidence suggests that inflammation is also an important factor in the pathogenesis of T2DM. Elevated circulating levels of cytokines and chemokines including IL-1β and IL-6, and acute-phase proteins including CRP are not only demonstrated in patients with T2DM, but have predictive value (Pradhan et al. 2001; Donath and Shoelson 2011). A model for the loss of immunological homeostasis in T2DM has been proposed whereby B cell-derived IL-10 and cytokine–cytokine balance regulate immune and adipose cell inflammatory cytokines in the nondiabetic individual. It is postulated that upon pathological insults in T2DM, such as overnutrition-driven activation of monocytes and B-cells, adipocyte necrosis, macrophage infiltration and differentiation, and obesity-related aberrant adipokine signaling, decreased IL-10 and other anti-inflammatory mediators are overwhelmed by elaboration of pro-inflammatory cytokines and adipokines (Nikolajczyk et al. 2011). Thus, both pro-oxidant and pro-inflammatory states characterize the impaired insulin production and sensitivity that leads to T2DM. Although their relationship remains unclear, it has been hypothesized that persistent redox imbalance compromises host defenses, increasing basal oxidative stress and promoting chronic inflammation (Vlassara and Striker 2011). In the following paragraphs, we discuss several examples of potential pathological redox-inflammatory mechanisms contributing to insulin resistance and T2DM.

As has been documented in a variety of disease states, redox–cytokine interaction is known to exacerbate pro-oxidant and pro-inflammatory milieus (Khaper et al. 2010). Similarly, oxidative stress may lead to insulin resistance via stimulation of pro-inflammatory cytokine expression. Indeed, ROS has been shown to activate NF-κB and trigger pro-inflammatory MCP-1 expression, inducing production of cytokines including TNF-α and IL-6, and increasing macrophage infiltration and adipocyte death (Weisberg et al. 2003; Furukawa et al. 2004; Minamino et al. 2009; Ouchi et al. 2011; Styskal et al. 2012). In turn, TNF-α and IL-6 can cause decreased insulin sensitivity by promoting inhibition of the critical insulin receptor substrate 1 protein; a process that is also induced by ROS (Hotamisligil 1999; Styskal et al. 2012). Each of these inflammatory and oxidative mechanisms inhibit IRS-1 via the common avenue of stress-signaling MAPKs including JNK and the possibly inhibitory κB kinase-β (IKKβ) (Henriksen et al. 2011; Styskal et al. 2012), inhibition of which is associated with improved insulin sensitivity (Yuan et al. 2010; Henriksen et al. 2011). Indeed, ROS and ER stress can induce IKKβ to activate NF-κB, stimulating expression of its many downstream pro-inflammatory cytokine gene targets (Arkan et al. 2005; Donath and Shoelson 2011). Moreover, p38 MAPK is implicated in the H_2O_2-induced impairment of insulin signaling, markedly reducing insulin-mediated Akt and glycogen synthase kinase-3β phosphorylation and glucose transport activity at lower concentrations, and causing proteolysis and inactivation of IRS proteins at higher concentrations (Henriksen et al. 2011).

Interestingly, intersecting regulation of redox-inflammatory elements occurs in the host defense against advanced glycation end products (AGEs), a class of dietary pro-oxidants that are abundant in thermally processed foods that have received increased attention of late. It has been suggested that the increased consumption AGE-rich foods in contemporary society gradually

leads to suppression of innate host defenses and excess ROS, leading to inflammation, obesity, insulin resistance, and diabetic complications (Vasdev et al. 2006; Vlassara and Striker 2011). Such a phenomenon has been demonstrated in mice, wherein AGE restriction was also shown to decrease oxidative stress and improve T2DM and its complications despite the presence of hyperglycemia, a high-fat and high-caloric diet, obesity, and advanced age (Vlassara and Striker 2011). In humans with T2DM, elevated serum AGEs predict morbidity and mortality (Kilhovd et al. 2007), and AGE restriction decreased systemic levels of AGEs, oxidative stress, and inflammation, as well as hyperinsulinemia (Uribarri et al. 2011). Here, AGEs appear to act via multiple mechanisms, including the promotion of monocyte and macrophage stimulation (Goldin et al. 2006), and inducible NOS-dependent mitochondrial ROS-mediated suppression of cytochrome *c* oxidase and ATP generation in β-cells (Zhao et al. 2009). Besides antioxidants and AGE degradation, the host defense against AGE toxicity involves 2 key receptors — advanced glycated end product receptor 1 (AGER1) and receptor for advanced glycation end product (RAGE) — which suppress and promote ROS and inflammation, respectively. AGER1, which normally acts to oppose RAGE, is suppressed in T2DM, leading to RAGE-induced oxidative stress and inflammation that is mediated by factors including p38 MAPK and JNK (Vlassara and Striker 2011). This commonality in signaling pathways among RAGE, redox, and inflammatory processes represents the so-called "RAGE axis" wherein increased pro-oxidant, pro-inflammatory, and prothrombotic molecules cross-promote one another via perpetuating cycles of RAGE-induced oxidative stress, leading to worsening of T2DM and its complications (Yan et al. 2010).

Insulin resistance and T2DM appear to be driven by various pro-oxidant and pro-inflammatory processes. Importantly, multiple lines of evidence support significant redox-inflammatory integration, suggesting that potential therapies should be directed at multimodal targets. In addition, other recent findings are consistent with this concept, including the observation of dual redox-inflammatory regulation via the lipid-mediating endocannabinoid system (Horváth et al. 2012) and peroxisome proliferator-activated receptor α (Hiukka et al. 2010). In the following section, relationships between oxidative stress and inflammation are explored in the context of another key aspect of MetS, dyslipidemia.

Atherogenic dyslipidemia centres on redox-inflammatory integration

The 2009 consensus definition for MetS cites 2 dyslipidemic states among their 5 criteria (any 3 of which are required): triglycerides 150 mg/dL or greater, and HDL cholesterol <40 mg/dL in men and <50 mg/dL in women (Alberti et al. 2009). Atherogenic dyslipidemia, or the atherogenic lipoprotein phenotype, which is associated with visceral adiposity and insulin resistance, comprises, together with the prevalence of small, dense LDL particles, hypertriglyceridemia and low HDL cholesterol (Rizzo et al. 2009). Despite its exclusion as a strict criterion, recent evidence suggests that small, dense LDL may be a significant biomarker for MetS (Gazi et al. 2006), and some argue that consideration of the "lipid triad" of hypertriglyceridemia, low HDL cholesterol, and small, dense LDL represents the best approach to treating MetS (Rizzo et al. 2009). Oxidative and inflammatory stresses are central to abnormal lipid metabolism and function, as well as atherogenesis (Rizzo et al. 2009; Navab et al. 2011; Lahoute et al. 2011). In this section, we describe how the interaction of lipids with redox-inflammatory elements contributes to atherogenic dyslipidemia, a major player in MetS. Owing to the focused nature of this review, interested readers are directed to the more comprehensive articles on dyslipidemia and atherosclerosis by Navab et al. (2011) and Rizzo et al. (2009).

LDL incorporation into the subendothelial space and its subsequent oxidation to oxidized LDL (oxLDL) is crucial to the atherogenic process, whereupon it stimulates an inflammatory cascade — including pro-inflammatory cytokine and chemotactic factor production, lymphocyte and monocyte recruitment, and aberrant cholesterol accumulation by macrophages — culminating in plaque formation (Lahoute et al. 2011). It is well established that the rate of atherogenesis correlates directly with LDL cholesterol and inversely with HDL cholesterol (Briel et al. 2009). Indeed, atherosclerosis does not occur in the absence of LDL or other cholesterol-rich, apolipoprotein B-containing lipoproteins (Navab et al. 2011), and removal of circulating oxLDL virtually arrested atherosclerosis in a mouse model (Ishigaki et al. 2008). Underscoring the base importance of oxidative stress in this process, oxLDL level has even been proposed as a potentially superior biomarker to LDL cholesterol for CVD risk (Rizzo et al. 2009). Moreover, recent findings in multiple systems have linked up-regulation of lectin-like oxLDL receptor-1 (LOX-1) to pathological conditions including obesity, T2DM, dyslipidemia, and hypertension (Lu et al. 2011; Luo et al. 2011; Yan et al. 2011). Importantly, both oxLDL and LOX-1 are known to promote inflammation via NF-κB activation, and stimulate endothelial dysfunction and apoptosis (Lu et al. 2011; Luo et al. 2011).

Dyslipidemia is a heightened redox-inflammatory state, with atherogenic lipoproteins strongly associated with markers of oxidative stress including $O_2^{\bullet-}$ and malonaldehyde, and markers of inflammation including CRP, TNF-α, IL-6, NF-κB, serum amyloid-α, lipoprotein-associated phospholipase A2, and fibrinogen (Kotur-Stevuljevic et al. 2007; Siasos et al. 2011). Such markers are evident prior to clinically apparent atherosclerosis, indicating that integrated redox-inflammatory factors occur throughout the atherogenic process (Kutuk and Basaga 2003; Rizzo et al. 2009). The primary site of ROS production in atherogenic dyslipidemia is the endothelium, with NOX, XO, uncoupled endothelial nitric oxide synthase (eNOS), and mitochondria the principal sources (Rizzo et al. 2009). The most prevalent species of ROS are $O_2^{\bullet-}$ and H_2O_2, which along with NOX can in turn induce further NOX and XO activity, creating a powerful oxidative cycle (Paravicini and Touyz 2006; Rizzo et al. 2009; Shen 2010). The inflammatory component of atherogenic dyslipidemia involves activation of both innate and adaptive immunity — primarily in response to oxLDL, LOX-1, and heat shock proteins — and persists from initiation through disease progression (Lahoute et al. 2011; Lu et al. 2011). Here, different and sometimes paradoxical roles for T and B cell subsets have been described, with T_H1, T_H2, and B-2 cells exerting a pro-atherogenic effect via IFN-γ, IL-4, IL-12, and IL-18, while regulatory T, T_H2, and possibly B-1 cells serve a protective, anti-atherogenic function (Lahoute et al. 2011). Additionally, natural killer T cells, have also recently been implicated in dyslipidemia and atherogenesis (Braun et al. 2010).

Another crossroads for redox-inflammatory stress is HDL regulation and function. HDL's main functions are cholesterol efflux and reverse cholesterol transport, but it also has significant antioxidant and anti-inflammatory properties. Much of this derives from the many and varied proteins with which HDL can associate, and especially its major protein, apolipoprotein A-I (apoA-I), as well as paraoxonase/arylesterase 1 (PON1). Indeed, by attenuating inflammatory lipid oxidation products, apoA-I, PON1, and HDL lipids can each suppress production of pro-inflammatory mediators including IL-8 and MCP-1 (Navab et al. 2000). Other anti-inflammatory functions include inhibition of NOX activity (Peshavariya et al. 2009) and vascular adhesion molecule expression (Rye et al. 2009), and regulation of macrophage-mediated TNF-α production (Navab et al. 2011). Much of HDL's beneficial effect derives from apoA-I, which while employed clinically is problematic and expensive, prompting the creation of apoA-I mimetic peptides (Sherman et al. 2010). Of these, a molecule called 4 F has been shown to have potent antioxidant and anti-

inflammatory effects in animal models of T2DM, atherosclerosis, renal disease, and diet-induced cognitive decline, and is currently under study in clinical trials as a treatment for obesity and MetS (Sherman et al. 2010; Navab et al. 2011).

As mentioned, HDL cholesterol level is inversely correlated with atherosclerosis-related events (Briel et al. 2009). However, many individuals who experience cardiovascular events have high levels of HDL; this is due to the limitation that HDL measurement describes HDL pool size, but not HDL functional capacity (Navab et al. 2011). Indeed, because HDL and its associated proteins are oxidatively modified during inflammation, their anti-inflammatory and antioxidant functions are impaired, rendering them less able to suppress LDL oxidation and inflammation (Navab et al. 2000). In fact, inflammatory stimulation of myeloperoxidase and its binding to HDL actually convert HDL to a pro-inflammatory effector (Undurti et al. 2009). Perhaps unsurprisingly, high levels of these dysfunctional HDLs are associated with increased risk of CVD (Corsetti et al. 2010).

Taken together, it is clear that redox-inflammatory processes drive dyslipidemia and atherogenesis, their coordinated effects critical to each step of disease progression. Although much remains unclear, it is heartening to note the rapid pace with which genetic and proteomic studies of metabolic disorders are advancing our knowledge of how genes and environment interact to produce altered lipid profile, inflammation, and other metabolic derangements (Davidsson et al. 2010; Ordovas et al. 2011). Indeed, given the powerful redox-inflammatory influence on epigenetic and epiproteomic regulation, it is likely that oxidative stress and inflammation will continue to be central to our evolving understanding of dyslipidemia, atherosclerosis, and MetS. In the next section, we explore the redox-inflammatory contributions to hypertension.

Redox-inflammatory stress links hypertension to CVD

Increased blood pressure is a criterion of MetS, and hypertension is an important risk factor for cardiovascular, renal, and other diseases that are increasingly common owing to factors including inactivity, obesity, and a high-fat and high-calorie diet (Alberti et al. 2009; Schulz et al. 2011). Although extensively studied, the etiology of hypertension remains incompletely understood, but is clearly multifactorial and strongly influenced by redox-inflammatory processes. In this section, we identify areas where integration of oxidative stress and inflammation promote vascular dysfunction, remodeling, and hypertension. Owing to the focused nature of this review, interested readers are directed to the more comprehensive articles on hypertension by Leibowitz and Schiffrin (2011) and Paravicini and Touyz (2006).

Whereas redox signaling is essential for normal maintenance of vascular integrity and function, redox imbalance is a major contributor to pathological vascular remodeling processes in hypertension. As previously discussed, these include causal roles in atherogenic processes such as inflammation, apoptosis, fibrosis, and endothelial dysfunction (Touyz and Briones 2011). Hypertensive states are associated with increased ROS including $O_2^{\bullet-}$ and H_2O_2, and decreased antioxidant activity, indicating that arterial redox balance is of critical importance (Rodrigo et al. 2011; Touyz and Briones 2011). For example, endothelium-dependent vasodilation, arterial stiffness, and markers of oxidative stress were improved by antioxidant administration in an animal model of hypertension (Plantinga et al. 2007) and in patients with MetS (Cangemi et al. 2007). Moreover, increased ROS in the rostral ventrolateral medulla activated central sympathetic outflow in hypertensive rats, indicating the exceedingly broad functions of oxidative stress in vascular dysfunction (Hirooka 2011). These and other factors have led to the hypothesis that oxidative stress may represent the common soil linking vascular dysfunction and hypertension with cardiovascular risk factors and disease.

As with each aspect of MetS, the presence of a chronic low-grade inflammatory state is a critical factor in the pathogenesis of hypertension. Like oxidative stress, inflammation is intimately involved in vascular dysfunction and remodeling, inducing processes including immune cell activation and infiltration, cytokine elaboration, adhesion molecule up-regulation, and promotion of oxidative stress (Leibowitz and Schiffrin 2011). Important roles for both innate and adaptive immunity have been described, with increasing emphasis on mechanisms involving macrophages (Moore and Tabas 2011) and T cell subsets (Hoch et al. 2009). Moreover, immunomodulatory interventions have been shown to be effective in experimental models of hypertension, resolving not only the elevated blood pressure but also the associated inflammatory and oxidative stresses (Barhoumi et al. 2011; De Miguel et al. 2011). These and other data demonstrate a central role for immunity in CVD, ushering in a new paradigm that promises new avenues for prevention and treatment of diseases including hypertension (Leibowitz and Schiffrin 2011).

Redox-inflammatory cross-promotion occurs throughout hypertension pathogenesis, but it is especially prominent in the RAAS-induced generation of oxidative and inflammatory processes leading to vascular dysfunction and remodeling. Dysregulated metabolic states including hyperglycemia, insulin resistance, and dyslipidemia have been shown to activate various components of the RAAS in pancreas, adipose, and immune cells and tissues, suggesting that RAAS plays an important role in promoting oxidative stress and inflammation in MetS (Putnam et al. 2012). It is increasingly recognized that adipose tissue is a significant supplier of both local and systemic RAAS components, inhibition of which occurs via redox-inflammatory stress and is thought to underlie the obesity-related treatment-resistant hypertensive phenotype characteristic of MetS (Chaudhary et al. 2011; Dorresteijn et al. 2012). Notably, RAAS blockade may be efficacious in treating hypertension (Sharma 2004), as well as T2DM (Tocci et al. 2011) and atherogenic dyslipidemia (Kintscher et al. 2007).

Redox-inflammatory signaling intersects with Ang II-induced hypertension via the up-regulation of NOX, causing increased vascular oxidant stress (Paravicini and Touyz 2006). Activation of NOX, and particularly the NOX1 and NOX2 isoforms, results in increased $O_2^{\bullet-}$ production, which damages vascular tissues, impairs relaxation owing to NO inactivation, and promotes $ONOO^-$ formation (Rabkin 2009; Khaper et al. 2010; Drummond et al. 2011). $ONOO^-$ oxidizes and inactivates antioxidants including GSH, glutathione reductase, SOD, and cysteine, as well as the co-factor tetrahydrobiopterin, facilitating the uncoupling of endothelial NOS and its conversion from a vasculoprotective enzyme to a $O_2^{\bullet-}$-producing one (Drummond et al. 2011). Moreover, the pro-inflammatory cytokine and adipokine IL-18 enhances NOX-mediated ROS production (Elbim et al. 2005), and can be induced in Ang II-hypertension. Studies have consistently demonstrated increased circulating levels of IL-18 in hypertensive patients that appears to be independent of other risk factors including obesity (Rabkin 2009). Taken together, these factors indicate the presence of a robust RAAS-mediated redox-inflammatory signaling cycle in hypertension.

Several other examples of redox-inflammatory stress in hypertension are noteworthy. For example, the pathological oxidation of a wide array of signaling proteins contributes greatly to vascular tissue dysfunction and remodeling. Activation of the pro-inflammatory transcription factor NF-κB (Anrather et al. 2006) induces proliferation and migration of vascular smooth muscle cells (Lassègue and Griendling 2010), as well as expression of endothelial adhesion molecules including intercellular adhesion molecule-1 and vascular cell adhesion protein-1 (Dworakowski et al. 2008). Importantly, ROS also oxidize and activate proteinases including MMP-2 and MMP-9 (Hopps and Caimi 2012), which serve as key mediators of vascular remodeling. This has engendered the

hypothesis that MMP activation — which is associated with T2DM, hypertension, and MetS — represents a significant linkage among metabolic and cardiovascular derangements and explains the broad therapeutic efficacy of certain proteinase inhibitors (Hopps and Caimi 2012; Schmid-Schönbein 2012). Finally, it is interesting to note that the mechanisms linking obstructive sleep apnea syndrome with obesity and hypertension are thought to result from hypoxia-induced oxidative stress and inflammation (Kohler and Stradling 2010).

Concluding remarks

Ubiquitous, capricious, and essential, oxidative stress and inflammation are major features of the metabolic and cardiovascular. As such, they are fundamentally inseparable from the pathological processes that shape MetS, and as we have maintained throughout this review, from one another. Through common regulatory controls and synergistic cellular mechanisms, cross-promotion of oxidative stress and inflammation occurs in a classic vicious cycle spanning disease initiation and progression, and may represent the common soil linking MetS with CVD. This integration presents both challenge and opportunity, for as our understanding grows, so too will our capacity to design therapies aimed at multimodal targets within redox-inflammatory stress-signaling pathways.

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