Redox homeostasis and nitro-oxidative stress in obesity-linked inflammation.

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Abstract

It is now well accepted that most chronic diseases have a common feature which is “low-grade” inflammation. Whether inflammation is causal or rather consequent to these diseases is still a matter of debate. A key factor of inflammation is considered to be “oxidative stress”, which is the result of an alteration of redox homeostasis which is critical for the regulation of physiological cell and organ metabolism and proliferation. The term “oxidative stress” is however often used in an inappropriate manner as the primary target of the initial oxidative radical, superoxide ion, is nitric oxide which, being in large excess, acts as a “buffer”, yielding reactive nitrogen species. It is only once the superoxide fluxes exceed the nitric oxide fluxes that true “oxidative stress” occurs. Nitro-oxidative stress is a more appropriate term which takes into account the evolving generation of reactive nitrogen and oxygen species and their effects on cell and organ pathophysiology. The molecular bases of redox homeostasis and nitro-oxidative stress will be presented and discussed using obesity-linked inflammation as a pathophysiological example.
I. Redox homeostasis and nitro-oxidative stress

Introduction and major molecular players

Severe oxidative stress is fortunately a rather extreme situation observed mainly under pathological situations and the reductive mechanisms present in the cell are most often able to prevent or revert the oxidized molecules to their native reduced state [1], with the notable exception of carbonylated proteins [2], certain lipid peroxidation products such as malondialdehyde and 4-hydroxynonenal [3] and DNA [4]. These mechanisms are referred to as “redox homeostasis or regulation” and determine the activity of a series of key enzymes involved in cell metabolism, differentiation and proliferation. A major actor of redox regulation which is often neglected is NO[5,6]. This low reactivity free radical is the preferential target of the primary oxidative species superoxide ion, $\text{O}_2^-$, which oxidizes it ten times more rapidly than any cellular macromolecule [7,8] (Fig. 1). It therefore acts as a buffer for $\text{O}_2^-$, especially as under “basal” physiological conditions its concentration exceeds that of superoxide ($10^{-12} – 10^{-11}\text{M}$) by at least two orders of magnitude [9]. This ratio is subject to change, depending on the activation of superoxide generating enzymes including NADPH oxidases (NOX 1-5 and DUOX 1 and 2), xanthine oxidase (XO), mitochondrial respiratory chain complexes and uncoupled endothelial NO$^+$ synthase (NOS 3) and reducing systems including thioredoxins, glutaredoxins, peroxiredoxins, catalase, glutathione peroxidase (GR) and the Trx system [5,10] (Fig. 1).

Fig. 1: Schematic representation of the major mechanisms and reactions involved in redox signaling with emphasis on the generation and degradation of reactive oxygen species (ROS)
At low NO\(^\text{−}\) (i.e. 10\(^{-9}\) M), and O\(_2\text{−}\) (i.e. 10\(^{-11} - 10^{-10}\) M) concentrations where [NO\(^\text{−}\)] >> [O\(_2\text{−}\)], the latter will essentially regulate NO\(^\text{−}\) bioavailability for activating soluble guanylate cyclase (sGC) which produces cyclic GMP (cGMP), responsible for vasodilation. Activation of sGC occurs through reversible binding of NO\(^\text{−}\) with sub-nanomolar affinity, and is called nitrosylation. O\(_2\text{−}\) can also regulate the generation of NO\(^\text{−}\) by endothelial NOS (eNOS) by uncoupling it from tetrahydrobiopterin (BH\(_4\)). The major oxidation product of NO\(^\text{−}\) when O\(_2\text{−}\) production increases to yield an \([\text{NO}^-]/[\text{O}_2^-] = 2 – 3\) [11], is the nitrosonium ion NO\(^+\). This unstable ion can S-nitrosate specific Cys residues (R-Cys-SH) of glutathione (GSH) and several proteins to R-Cys-SNO [12,13] (Fig. 2).

The exact mechanism of S-nitrosation is unknown, but may involve the formation of N\(_2\)O\(_3\) as the concentration of NO\(^+\) under “cellular” conditions is elusive due to its extremely short half-life. Another hypothesis is that S-nitroso-glutathione (GSNO) may serve as a source for protein S-nitrosation [14] (Fig. 2). This is directly involved in the cell’s redox equilibrium, regulating thioredoxin activity through modification of its Cys\(^{69}\) residue [7]. Indeed, thioredoxin together with thioredoxin reductase and glutaredoxin together with glutathione are major reductive systems of the cell, depending on NADPH. Conversely, thioredoxin is inactivated by oxidation of its Cys\(^{32}\) and Cys\(^{35}\) residues, leading to apoptosis [7]. This emphasizes the importance of the NO\(^\text{−}\)/O\(_2\text{−}\) ratio at low fluxes of these species for maintaining cell metabolism and life. The half-life of superoxide in aqueous solution at pH 7 is around 5" [15], but much shorter in the cell due to the presence of SOD, and that of NO\(^+\) ranges between 0.01" and 2" in cells and around 2 x 10\(^{-3}\)" in blood [5]. Considering the slow diffusion rate in cytoplasm, it is clear that in order to react, both radicals need to be produced at the same subcellular location.

Thus, S-nitrosation is a very unstable posttranslational modification which is readily reduced under physiological conditions. However, it may regulate the activity of a variety of enzymes, e.g. caspases, glyceraldehyde 3-phosphate dehydrogenase (GAPDH), aldose reductase and transcription factors (e.g. NF-κB), among others [13,16]. Due to its instability, it is very difficult to assess S-nitrosation as the cell’s redox status is almost impossible to maintain during sample extraction procedures [17].
When \( \text{O}_2^- \) fluxes increase further and its levels become equimolar with or higher than those of \( \text{NO}_2^- \), the two radicals react to form peroxynitrite (ONOO\(^-\)) \([5]\) (Fig. 2). This ion has a half-life of less than 1\(^{\text{st}}\) in the cell and in the extracellular milieu, and its biological effects are thought to occur at concentrations between 10 nM and 5 \( \mu \text{M} \) \([13]\). However, whereas ONOO\(^-\) concentrations may reach micromolar concentrations during inflammatory events, the levels at which it exerts its physiological effects is probably rather in the low nanomolar range \([18]\). The local subcellular or extracellular concentrations of peroxynitrite entirely depend on the expression level and localization of the superoxide- and \( \text{NO}_2^- \)-generating enzymes. Its biological effects are concentration dependent. At concentrations < 500 nM, peroxynitrite specifically nitrates defined tyrosine (Tyr) residues of selected proteins (Fig. 2). Although peroxynitrite has also been reported to nitrate tryptophane (Trp) residues, this seems to be a rare event and its physiological relevance, especially in eukaryotes, is questionable \([19]\).
The list of Tyr-nitrated proteins has been steadily growing over the past 10 years reaching close to 100 [20], which remains however far below that of phosphorylated proteins. Nitroproteins have been reported in virtually all cellular compartments and in the extracellular milieu [21]. Of note, whereas nitration was initially thought to be an irreversible posttranslational modification, it has now been reported to be reversible, with kinetics corresponding to those of enzymatic reversion of other protein modifications such as e.g. phosphorylation [22-24].

At higher concentrations (low micromolar), ONOO- will also oxidize methionine (Met) residues, resulting in their sulfoxidation [25] and sulfenylate certain cysteine thiols (Cys-SH) [8,26]. These can react with GSH to cause protein glutathiolation as e.g. for eNOS [27]. In zinc fingers, which allow binding of transcription factors to DNA, oxidation of adjacent Cys residues causes the formation of disulfide bridges, releasing Zn-atoms and disrupting their structure, blocking transcription. Peroxynitrite can also oxidize and inactivate protease inhibitors as well as Ca** pumps, causing major cell dysfunction. It will also peroxidize lipids, break DNA strands and nitrate mitochondrial respiratory chain complexes, which are unaffected at lower concentrations [5,8,13] (Fig. 2). Even under these conditions, nitration of mitochondrial proteins appears to be reversible [28]. However, such effects can be very deleterious to the cell, leading to apoptosis.

**nNOS, eNOS, iNOS and cellular location**

In addition to the proximity and simultaneous activation of NO• and O2•-/ generating systems, substrate availability also is an important factor. Whereas O2, being the substrate for O2•- production is generally available at sufficient concentrations (except in mitochondria during metabolic or respiratory stress), this is not always the case for arginine, the only substrate of NOS to generate NO•. An example of this is what occurs during macrophage activation. When iNOS (NOS2) is expressed at very high levels and turned on, the arginine pool is rapidly depleted. Under such circumstances, iNOS will change its catalytic activity to oxidation, generating O2•- instead of NO•. In addition to arginine, NOS also requires NADPH, FAD, Zn** and molecular oxygen.
The third parameter is the presence and activity of the reductive systems: mainly the Trx system which includes thioredoxin, thioredoxin reductase and NADPH, the Grx system which comprises glutaredoxin, glutathione reductase, reduced glutathione (GSH) and NADPH, as well as the superoxide dismutases SOD-and 2 together with catalase and glutathione peroxidase (GPX). As indicated, these reductive systems also need common cofactors, essentially NADPH and GSH resulting in a cross-talk between them. Finally, the subcellular location of the generation systems also plays a crucial role. The NOXs are transmembrane proteins located essentially in caveolae, XO is cytosolic and respiratory chain complexes are mitochondrial. Even more complex, NOSs show translocation depending on (patho)physiological situations and their S-nitrosation or oxidation state. It is thus impossible to draw general conclusions regarding the effects of ONOO' on cell functions and biological responses without taking these factors into account.

The three NOS isoforms nNOS (neuronal NOS, NOS1), iNOS (NOS2) and eNOS (NOS3) are active under a homodimeric form and use L-arginine as a substrate and O₂ and NADPH as co-substrates. They all use FAD, FMN and BH₄ as cofactors. When activated, they produce NO⁺, citrulline and limited amounts of O₂⁻. All three are activated by calmodulin, but whereas binding of this molecule to nNOS and eNOS requires increased cytosolic Ca²⁺ concentrations (via intracellular mobilization), it is tightly bound to iNOS even at low Ca²⁺ concentrations [29]. Thus, as opposed to eNOS/nNOS, which are activated by various extracellular mediators, iNOS is constitutively active and its effects seem to be regulated primarily through its expression levels [29].

nNOS essentially generates NO⁺ in the CNS, acting as a “long-term” mediating neurotransmitter. It is also secreted by nitrergic nerves, which innervate smooth muscle, eliciting the generation of cGMP. This mechanism seems essential for regulating vascular tone and thus blood pressure. It is also expressed in the myocardium, where it is mainly localized in the sarcoplasmic reticulum (SR), regulating ryanodine receptor 2 Ca²⁺ release channel and phospholamban phosphorylation, important for Ca-influx into the SR. In skeletal muscle, nNOS plays a major role in muscle mass regulation. A splice-variant, nNOSα has been reported to translocate to
the nucleus, inducing mitochondriogenesis through NO·-mediated activation of the PGC1α pathway [30]. Another variant, nNOSβ colocalizes with soluble guanylate cyclase (sGC) in the cis-golgi to produce cGMP [31]. A third variant, nNOSμ is localized in the dystrophin glycoprotein complex (DGC), involved in vasodilation and activation of the Akt/PKB pathway through ONOO- [32]. In addition, nNOS can be regulated by mitochondrial ROS [33] and by S-nitrosation in skeletal muscle [34]. These are examples of how the subcellular localization of NOS can determine firstly the generation of NO, secondly the targets and effects of NO· and thirdly, its potential oxidation to nitrosonium and peroxynitrite.

The regulation of eNOS is comparable to that of nNOS in that its activation requires Ca²⁺ concentrations of at least 100 nM for calmodulin binding. There are other mechanisms which can modulate its activity, among which the phosphorylation by PKB/Akt and its subcellular translocation [9]. This translocation depends on redox regulation [35]. Superoxide ions can cause glutathiolation of eNOS, inhibiting it through “uncoupling” of the BH₄ cofactor [36]. In this configuration, eNOS generates O₂·⁻ instead of NO⁻. In addition, eNOS has been reported to be subject to S-nitrosation, which inhibits its dimerization required for its enzymatic activity [37]. Regarding its subcellular localization, under basal conditions eNOS appears to be mainly located in caveolae bound to caveolin-1, functioning as an inhibitor [38]. By contrast, caveolin-1 stimulates eNOS expression and eNOS-produced NO· stimulates endocytosis [31]. Interestingly, eNOS induces S-nitrosation of caveolin-1 which depolymerizes its oligomers [39]. These regulatory mechanisms are remarkable and extremely interesting, as they have been observed in diabetic patients’ skeletal muscle vessels [28]. Finally, eNOS appears to also be regulated by Tyr-nitration. When nitrated, calmodulin binds to eNOS in a Ca²⁺-independent fashion. Subsequent activation of eNOS then depends on the nitration site of calmodulin. Whereas nitration of Tyr⁹⁹ inhibits it, Tyr¹³⁸ nitration results in increased NO production [40].

Whereas n- and eNOS activities are essential for maintaining physiological metabolism at the cellular and at the systemic levels, iNOS is the major actor in inflammation, especially during acute inflammation [41]. This does not mean that the first two isoforms are not involved in inflammation as their activity and location are directly modulated by ROS up to the point that
eNOS can switch to an $O_2^-$ generating enzyme when uncoupled. This uncoupling is a typical consequence of low-grade chronic inflammation, observed in hypertension, dyslipidemia, metabolic syndrome (MetS), prediabetes (PD) and type 2 diabetes (T2D), resulting in endothelial damage and vascular remodeling [42,43]. Similar examples exist for nNOS [44,45].

iNOS, being constitutively active, differs in that its biological effects are primarily regulated by its degree of expression, which is modulated by among others by inflammatory mediators and cytokines. Once its expression is induced it can generate NO for several days at micromolar fluxes [46]. Besides its regulation at the transcriptional and translational levels, its activity is also tightly controlled both by proteolytic degradation and, as stated earlier, by arginine bioavailability [47]. iNOS is found in a variety of cell types, but its major expression site is leukocytes. In these cells, cytokines and bacterial lipopolysaccharides (LPS) mimicking infection, can induce a strong expression. Other factors such as protein-protein interactions, e.g. with p53 and thrombospondin, also regulate iNOS activity [48]. An interesting role of iNOS is the dominant NO concentration gradient it induces in tissues. Whereas local NO levels adjacent to cytokine-activated macrophages are micromolar and thus cytotoxic, a few cell layers further its concentration is much lower, exerting anti-apoptotic and proliferative effects, protecting tissue and stimulate healing following damage by invading pathogens [48].

In summary, generation of micromolar fluxes of NO and formation of RNS/ROS cannot be considered as deleterious or detrimental per se. Since most posttranslational modifications caused by RNS are less toxic than those due to ROS and are reversible, NO$^-$ can be considered as a buffer for $O_2^-$ and thus as a complement to the reductive systems, allowing restoration of the redox equilibrium and normal cellular homeostasis. Cytotoxic effects will only occur when RNS concentrations exceed the cells’ reducing capacity, causing lipid peroxidation and DNA strand breaks, leading to apoptosis. This happens when the $O_2^-$ concentration exceeds that of NO$^-$, producing highly reactive oxidants (OH$^-$ and NO$_2^-$ radicals) which can cause irreversible protein carbonylation and DNA strand breaks [5,8,13] (Fig. 2).
II. Obesity and inflammation

Oxidative stress is a major risk factor for non-communicable diseases, including cardiometabolic, neurodegenerative, osteoarticular, kidney and oncologic pathologies, which are leading causes of disability and early death [49-53]. High oxidative stress levels have been associated with low-grade chronic inflammation. More precisely, both oxidative stress and inflammation have been shown to exacerbate one another [54]. Low-grade chronic inflammation is a common pathologic state in obesity, in particular associated with metabolically unhealthy overweight and obesity [55,56]. Metabolically unhealthy overweight (MUOV) and metabolically unhealthy obesity (MUO) have been defined as the two sub-phenotypes of overweight and obesity associated with at least one cardiometabolic abnormality amongst inflammation, oxidative stress, hyperglycaemia, insulin resistance, dyslipidaemia and/or hypertension, as well as an increased risk of developing cardiometabolic comorbidities [56-59]. Conversely, metabolically healthy obesity (MHO) and metabolically healthy overweight (MHOV), emerged as the new concept of the healthy overweight and obesity sub-phenotypes, characterised by high values of body mass index (BMI ≥ 25 kg/m²), yet an absence of the aforementioned cardiometabolic issues [58,60,61]. MHOV accounts for about 50% of the overweight phenotypes and MHO accounts for about 30% of the obesity phenotypes [58].

MHO might convert into MUO in some individuals, in particular in the absence of high levels of cardiorespiratory fitness [58,62]. The transition from a MHO to a MUO profile also occurs in the presence of a chronic state of subclinical inflammation including high levels of C-reactive protein (CRP) serum concentrations in addition to different other mediators of inflammation, in particular tumor necrosis factor (TNF-α) and interleukins (IL)-6 and IL-8, as well as adipokines such as adiponectin, leptin and resistin. Low-grade chronic inflammation leads to insulin resistance [63-68] resulting in prediabetes with a potential evolution to T2D.

Furthermore, MUO is characterised by adipose tissue dysfunction due to its infiltration by immune cells including macrophages and lymphocytes, which lead to low-grade inflammation, insulin-resistance, metabolic syndrome, type 2 diabetes, hypertension and dyslipidemia [69-74]. These comorbidities have in particular been associated with visceral adiposity [75]. In the
presence of a positive energy balance, the hyperplasia and hypertrophy of the adipocytes in subcutaneous fat have been shown to be protective against cardiometabolic complications in obesity, preserving the MHO phenotypes. However, in the presence of a dysfunctioning subcutaneous adipose tissue characteristic of the MUO phenotypes, the subcutaneous fat displays a very limited storage capacity which leads to an ectopic accumulation of the fat, in particular in the visceral area, a chronic low-grade inflammation and the development of insulin-resistance and related cardiometabolic comorbidities [76,77].

Visceral obesity characterised by visceral adipose tissue (VAT) accumulation is a major risk factor for developing MUOV and MUO [55]. Repeatedly, VAT liberates pro-inflammatory cytokines into the portal vein, in particular TNF-α, inducing low-grade chronic inflammation leading to the development of cardiovascular diseases associated with MUOV and MUO [78]. The adipocytes are hypertrophied in the individuals having overweight and obesity, which might partly deprive them from oxygen, inducing a lack of vascularisation and a hypoxia leading to the expression of the inflammatory genes in the expanded adipocytes [79]. The hypoxic state is particularly marked in the visceral adipocytes, compared to the subcutaneous adipocytes [79,80]. When prolonged, the hypoxic state has been shown to increase inflammation and insulin resistance [81,82]. In addition, the macrophage infiltration into visceral adipose tissue has been shown to be higher than in subcutaneous fat, which might be responsible for the inflammatory processes linking the ectopic accumulation of fat and the health-related issues [79,83-85].

Furthermore, pro-inflammatory adipokines disorders have been highlighted in MUO as inducing the inflammatory reactions related to increased adiposity [86]. In particular, the pro-inflammatory processes observed at the visceral adipose tissue level are mainly induced by the adipokines. For example, leptin resistance resulting from the visceral adiposity increase dysregulates the leptin signalling and fuels inflammation through the increase of cytokine production in the blood [63,87,88]. The expression of leptin in the visceral adipose tissue has been associated with the angiotensin-converting enzyme 2 (ACE2) expression, highly concentrated in
the visceral adipocytes and significantly associated with the comorbidities observed in the individuals having MUO, in particular hypertension [89]. Furthermore, the expression of the adiponectin gene is very low in the visceral adipose tissue, in comparison to its expression in the subcutaneous fat compartment, blunting its anti-inflammatory properties in MUO [79,90]. Currently, more than 20 adipokines which have been associated with increased adiposity, are released by the adipocytes and induce the release of a series of inflammatory cytokines, such as resistin, interleukin 1, interleukin 6 and TNF-α [67,91,92] (Fig. 3). Actually, the adipose tissue contains a high number of immune cells (macrophages, mast cells, B cells, Th1 CD4 T and CD8 T cells) which increase in both number and activity, in obesity thereby leading to a pro-inflammatory status [69].

Furthermore, the white adipose tissue (WAT) located in the visceral adipose tissue (VAT) has been associated with a higher pro-inflammatory action than in subcutaneous WAT (SWAT), due to a higher macrophages availability than in the latter [93-95]. In addition, the inflammation of the VAT is associated with a low lipogenic markers expression in visceral obesity that has been associated with cardiometabolic diseases. Adipocyte hypertrophy has also been shown to be more pronounced in VAT than in subcutaneous adipose tissue (SAT), triggering the development of insulin-resistance and type 2 diabetes [93,96,97]. There are two major differences which are intimately interrelated between lean and hypertrophic VAT found in obesity, regarding its immune phenotype. First, the adipokines secreted by adipocytes in people with a lean phenotype are predominantly adiponectin, adipsin and omentin, whereas in hypertrophic VAT these adipokines decrease and conversely leptin, visfatin, resistin and chemerin are increased [98] (Fig. 3). These latter adipokines have proinflammatory properties and favour the attraction of inflammatory immune cells. Thus, whereas in low VAT depots one finds essentially eosinophils, iNKT, Tregs, Th2 cells and M2 macrophages, hypertrophic VAT is infiltrated by monocytes which differentiate into M1 macrophages, neutrophils, Th1, Th17 and B lymphocytes [98] (Fig. 3). The interleukin profile is modified accordingly. In low VAT depots, these are essentially IL-4, IL-10 and IL-13 which induce the differentiation of the macrophages to the “anti-inflammatory” M2 phenotype. In visceral obesity, the “anti-inflammatory” interleukins are
decreased and the “pro-inflammatory” cytokines, TNF-α, IL-1β, IL-6, IL-18 and MCP-1 are secreted, in particular by the M1 macrophages [98,99] [100,101] (Fig. 3). In addition, the now larger adipocytes have increased lipolysis and release free fatty acids which also trigger the differentiation of the resident M2 and newly attracted monocytes to the inflammatory M1 phenotype [98,99]. This inflammatory response also induces adipocyte necrosis thereby releasing other pro-inflammatory substances (Fig. 3).

Fig. 3: Impact of obesity on the metabolism and immune status of visceral adipose tissue and its effects on reactive species generation. Consequences on skeletal muscle and mitochondrial dysfunction are highlighted.

III. Obesity and nitro-oxidative stress

As described above, in obesity VAT becomes a site of chronic inflammation [98,99]. In addition to the immune cells, especially the M1 macrophages which generate large amounts of ROS and hence also of RNS, the hypertrophic adipocytes also display increased ROS production due to altered mitochondrial function [102]. Not only is the biogenesis and thus the density of mitochondria decreased in these adipocytes, but so are also their metabolic functions such as fatty acid and branched-chain aminoacid (BCAA) oxidation, oxidative phosphorylation, beta
oxidation and Krebs or tricarboxylic acid (TCA) cycle are all impaired. Slowdown of the TCA cycle which is further aggravated by reduced glucose uptake and oxidation, results in additional reduction of mitochondrial ATP synthesis and respiration. This decreased respiration due to substrate deficit is the major cause for increased ROS and RNS generation by the hypertrophic adipocytes' mitochondria (Fig. 3).

Recently a new paradigm called mitochondrial transfer has emerged. This mechanism, reported in several cells, consists in the extrusion of mitochondria which are subsequently taken up by “acceptor” cells [103]. In obesity, the hypertrophic adipocytes extrude dysfunctional mitochondria which are taken up either locally by macrophages [104], fibroblasts and progenitors or by more distant targets where they may contribute to affect cell differentiation and metabolism [105,106].

Interestingly, similar observations have been made in the skeletal muscle [107-109] in obesity as well. Indeed, skeletal muscle becomes infiltrated by the adipose tissue which exhibits the same inflammatory phenotype as found in visceral obesity [110]. The same causes having the same effects, muscle also displays an inflammatory profile in this situation (Fig. 3).

Skeletal muscle accounts for the main tissue and mitochondrial mass of the body. Mitochondrial dysfunction therefore not only has major metabolic effects including insulin-resistance, but also contributes in a very significant manner to increased ROS and RNS generation. In the case of obesity, skeletal muscle together with VAT therefore becomes the major sites of nitro-oxidative stress.

The question whether nitro-oxidative stress precedes or follows inflammation is still a matter of speculation and debate, but their close entanglement is a clear fact leading to a vicious circle [111] but understanding its mechanisms paves the way for novel therapeutic strategies.
References


Figure Legends

Fig. 1: Schematic representation of the major mechanisms and reactions involved in redox signaling with emphasis on the generation and degradation of reactive oxygen species (ROS)

Fig. 2: Schematic representation of the major mechanisms and reactions involved in redox signaling with emphasis on the generation and effects of reactive nitrogen species (RNS)

Fig. 3: Impact of obesity on the metabolism and immune status of visceral adipose tissue and its effects on reactive species generation. Consequences on skeletal muscle and mitochondrial dysfunction are highlighted.