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# Redox regulation of the immune response: nitro-oxidative stress and antioxidants regulate macrophage, neutrophil, and T and B lymphocyte, and dendritic and natural killer cell functions.

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**Abstract**

An immune-inflammatory response is accompanied by increased nitro-oxidative stress. The aims of this mechanistic review are to review: a) the role of redox sensitive transcription factors and enzymes, ROS/RNS production and the activity of cellular antioxidants on the activation and performance of macrophages, dendritic cells, neutrophils, T cells, B cells and natural killer cells; b) the involvement of high-density lipoprotein (HDL), apolipoprotein (Apo)A1, paraoxonase (PON)-1, and oxidized phospholipids in the regulation of the immune response; and c) the detrimental effects of hypernitrosylation and chronic nitro-oxidative stress on the immune response. The redox changes during immune-inflammatory responses are orchestrated by the actions of nuclear factor (NF)-κB, HIF1α, the mechanistic target of rapamycin (mTor), the phosphatidylinositol 3-kinase (PI3K) / protein kinase B (AKT) signalling pathway, mitogen-activated protein (MAP) kinases, 5' AMP-activated protein kinase (AMPK), and peroxisome proliferator-activated receptor (PPAR). The performance and survival of individual immune cells is under redox control and sensitive to intracellular and extracellular levels of ROS/RNS and is heavily influenced by cellular anti-oxidants including the glutathione and thioredoxin systems, nuclear factor erythroid 2-related factor 2 (Nrf-2), and the HDL complex. Chronic nitro-oxidative stress and hypernitrosylation inhibit the activity of those antioxidant systems, the tricarboxylic acid cycle, mitochondrial functions, and the metabolism of immune cells. In conclusion, those redox-associated mechanisms modulate metabolic reprogramming of immune cells, macrophage and T helper cell polarization, phagocytosis, production of pro- versus anti-inflammatory cytokines, immune training and tolerance, chemotaxis, pathogen sensing, antiviral and antibacterial effects, Toll-like receptor activity, and endotoxin tolerance.

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Key words: oxidative stress, nitrosative stress, immune response, inflammation, antioxidants, LPS

**Introduction.**

The instigation of the innate immune response commences as a result of recognition of an invading pathogen by organ specific resident macrophages, dendritic cells, fibroblasts, pericytes, and in many cases endothelial cells (1-4). This recognition is effected by engagement with cytosolic or membrane bound toll-like, nod-like, or NOD-like pattern recognition receptors which leads to the activation of these sentinel cells and the release of high levels of cytokines and chemokines (3-5). Once released these molecules activate endothelial cells which then express chemokines and adhesion factors (6, 7) resulting in the recruitment, binding and activation of neutrophils, monocytes, macrophages, and platelets allowing the migration of the myeloid cells into tissues to reach the sites of infection (8-10).

The multiple phenotypical and functional roles of myeloid cells are enabled by metabolic reprogramming involving changes in levels of glycolysis, fatty acid oxidation, the tricarboxylic acid (TCA) cycle activity, involvement of the pentose phosphate pathway, and mitochondrial respiration (11-13). This is also true for neutrophils, T cell activation and differentiation into helper, effector, and cytotoxic subsets (14), B cell activation differentiation and antibody production (15) and the activation and cytotoxic properties of natural killer cells (16).

These metabolic and redox changes are orchestrated and regulated by the cooperative and or antagonistic actions of nuclear factor (NF)-κB, HIF1alpha, the mechanistic target of rapamycin (mTor), the phosphatidylinositol 3-kinase (PI3K) / protein kinase B (AKT) signalling pathway, mitogen-activated protein (MAP) kinases, 5' AMP-activated protein kinase (AMPK), and peroxisome proliferator-activated receptor (PPAR) and involve increases in

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reactive oxygen species (ROS) production by mitochondrial respiration and or the upregulation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. These transcription factors, enzymes, and effector molecules are all redox sensitive as is the performance of mitochondria (17-23). Hence, it comes as no surprise to learn that the performance of individual immune cells is under redox control and sensitive to intracellular and extracellular levels of nitric oxide (NO) (24, 25) and ROS (26-28) and is also heavily influenced by the activity of nuclear factor erythroid 2-related factor 2 (Nrf-2) and cellular anti-oxidants (29-31). The performance of individual immune cells is also regulated by oxidized phospholipids (32-35), high density lipoprotein (HDL), apolipoprotein A1 (ApoA1), paraoxonase-1 (PON-1) activity (36-38), and indoleamine 2, 3-dioxygenase (IDO) (39, 40). The levels and immune functions of these molecular players are also under redox control (41).

This paper has three aims. Firstly, to detail the role of redox sensitive transcription factors and enzymes, ROS and reactive nitrogen species (RNS) production and the activity of cellular antioxidants on the activation and performance of macrophages, dendritic cells, neutrophils, T cells, B cells and natural killer cells. Secondly, to explain the involvement of HDL, ApoA1, PON-1, and oxidized phospholipids in the regulation of the immune response. Thirdly, to explain the detrimental effects of chronic oxidative and nitrosative stress on the performance of individual immune cells and the immune response as a whole. We will begin with a discussion of the effects of these factors on macrophage activation and performance which offers a vehicle to illustrate many of principles involved in metabolic reprogramming and the effects of individual signalling molecules thus avoiding unnecessary repetition in later sections of the paper.

## 1 Metabolic reprograming and redox factors involved in macrophage activation.

### 1.1 Metabolic reprogramming in macrophages

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Macrophages may be activated by cytokines, ROS and pattern recognition receptors (PRR) engagement by pathogen-associated molecular patterns (PAMPS), damage-associated molecular patterns (DAMPS) and commensal LPS leading to the activation of NF-κB (42-44) and the PI3K/AKT signalling pathway (45, 46). Upregulated NF-κB activity results in increased transcription of proinflammatory cytokines and chemokines, inducible NO synthase (iNOS) and HIF1 alpha (42-44). Increased PI3K signalling also leads to the upregulation of mTOR (47-49) which in turn reinforces the upregulation of HIF1α (45, 46). These signalling pathways, enzymes and transcription factors play an essential role in maintaining macrophage activation and M1 polarisation by driving metabolic reprogramming involving downregulation of ATP production by mitochondrial oxidative phosphorylation and fatty acid oxidation (50, 51) to ATP production via aerobic glycolysis (52).

The shift to aerobic glycolysis is an indispensable metabolic event for M1 macrophages in terms of maintaining and increasing phagocytosis, production of ROS and proinflammatory cytokines and unsurprisingly its inhibition may impair phagocytosis, ROS production, and secretion of proinflammatory cytokines (53-55). Maintenance of this state is dependent on the activity of a range of transcription factors most notably mTOR and HIF1α with the latter playing the dominant role in enabling the continuance of glycolysis also under normoxic conditions (49, 56).

HIF1α acts as a modulator of transcription by changing the methylation status of hypoxia responsive elements (HRE) in the promoter regions of target genes involved in the termination of oxidative phosphorylation (OXPHOS) and the instigation of aerobic glycolysis (57). For example, HIF1α upregulation suppresses the activity of electron chain (ETC) enzymes (58, 59), decreases mitochondrial activity and induces mitochondrial autophagy (60, 61). Increased activity of this transcription factor also supresses genes involved in fatty acid oxidation (FAO) (62, 63). HIF1 also actively suppresses metabolism through the TCA cycle

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by directly *trans*-activating the gene encoding pyruvate dehydrogenase kinase 1 (PDK1) (64) and inactivating pyruvate dehydrogenase (65). In addition, HIF1-regulated gene expression reduces the production of acetyl-CoA and succinyl-CoA (66).

HIF1 increases glycolytic flux increasing the expression of glucose transporters (GLUT1 and GLUT3) (67), HIF1α also stimulates glycolysis by increasing levels of the hexokinases HK1 and HK2 (68), aldolase A (ALDA), and enolase 1 (ENO1) (69), and phosphoglycerate kinase 1 (PGK1) (70). Finally, HIF1 also increases the transcription of lactate dehydrogenase A (LDHA), which plays an indispensable role in maintaining a continuous supply of $NAD^+$ thereby enabling the continuation of glycolysis (71). HIF1-regulated gene expression diverts glucose and fatty acid-derived carbons from being catabolised to acetyl-CoA, while glutamine-derived carbons are diverted from being catabolised to succinyl-CoA (66). While the role of HIF1α in instigating and regulating the transition between OXPHOS and aerobic glycolysis is of paramount importance, it should be emphasised that the activation of mTOR also plays a significant role in this endeavour on two counts. Firstly, mTor stabilises and enhances the activity of HIF1α and secondly, increases the rate of glycolysis, AKT, forkhead box transcription factors (FoxO), hexokinase II, and Myc proto-oncogene (72-74). Upregulated mTOR also plays a significant role in further reducing OXPHOS by upregulation of NO and interferon (IFN)-γ production, thereby compromising the activity of the mitochondrial ETC (75). In total, the actions of mTOR inhibit M2 polarisation (76) and stimulate M1 polarisation (77, 78).

The pentose phosphate pathway (PPP) main role is to utilise the energy released from the metabolism glucose-6-phosphate into ribulose-5-phosphate to form NADPH which is used in the production of NADPH oxidase and as the reducing equivalent enabling the function of the glutathione (GSH) and thioredoxin anti-oxidant systems (13, 79). The activation of M1 polarised macrophages also results in several other aspects of metabolic reprogramming in

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order to maintain the inflammatory status and prolong survival. Most notably are the upregulation of the cytosolic PPP (50, 80), increased lipid synthesis, and decreased lipid catabolism (62, 81), altered glutamine and arginine metabolism (81, 82), and a “broken” TCA cycle (83) (84). These parameters are discussed below commencing with the Toll-Like Receptor (TLR) and pro-inflammatory cytokine-mediated reprogramming of the lipidome (85).

Lipid biosynthesis is essential for membrane remodelling and in M1 macrophages the process depends on the production of acetyl-CoA from citrate ATP-citrate lyase (ACLY) (86). The activity of his enzyme rapidly increases in activated macrophages. In addition, intracellular fatty acids may be used for the synthesis of triglycerides for energy storage, glycerophospholipids, cardiolipins and sphingolipids for membrane synthesis, and eicosanoids for signalling processes (81). The increase in lipid synthesis is largely enabled and regulated by upregulation of sterol regulatory element binding protein-1 (SREBP-1) by TLR-4 and PI3K-activated mTOR (87) (73), and by increased activity of NF-κB and the presence of pro-inflammatory cytokines (88, 89).

Increased activity of SREBP-1 and ACLY also play an important and, arguably, an indispensable role in maintaining the inflammatory function of M1 macrophages. For example, SREBP-1 activation enhances the production of inflammatory cytokines, ROS, and inflammasome activation (88, 89) and ACLY silencing or inhibition is sufficient to reduce the expression of inflammatory mediators such as NO and ROS (12).

Changes in the metabolism of several amino acids occurs in M1 polarisation. For example, glutamine is metabolised to alpha-ketoglutarate via increased glutaminolysis leading to succinate accumulation and increased HIF1α stimulation which plays an essential role in inflammasome activation and interleukin (IL)-1 production (80). The activation of M1 macrophages also results in elevated levels of iNOS, which catalyses the conversion of arginine to NO and citrulline with the former acting as a source of other reactive nitrogen species, and

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the latter acting as a source of increased NO production via the citrulline–NO cycle (82). Readers interested in the mechanisms underpinning this process are invited to consult the work of (90). The NO produced by this process also plays a significant role in the "metabolic rewiring" of M1 macrophages by influencing a range of adaptive processes as reviewed in (91).

M1 polarised macrophages are also characterized by accumulation of cytosolic citrate stemming from decreased activity of isocitrate dehydrogenase (IDH) (50) and upregulated activity of the mitochondrial citrate carrier (CIC) in exchange with malate (92, 93). The increased activity of IDH is mediated by ADP levels (94) and CIC is upregulated by several inflammatory mediators such as tumor necrosis factor (TNF)-α, IFN-γ, or commensal LPS via the upregulation of NF-κB and or STAT-1 (92, 95). In this scenario, citrate exerts a multiplicity of indispensable roles enabling macrophage function and inflammatory status such as increasing NO, ROS, and prostaglandin E2 (PGE2) production (92, 96).

Cytosolic citrate can also act as a source of NADPH either as a result of malate import into mitochondria via CIC, and the subsequent formation of pyruvate via malic enzyme, or the conversion of citrate into alpha-ketoglutarate via the action of cytosolic IDH (97, 98) Cytosolic citrate is also a substrate of ACLY, producing acetyl-CoA and oxaloacetate and upregulates acetyl coA carboxylase (ACC) stimulating lipid synthesis (99).

Activated M1 polarised macrophages are characterised by high levels of cytosolic itaconate from cis-aconitate drawn from the Krebs cycle via a significant inflammation-mediated upregulation of macrophages aconitate decarboxylase 1 (ACOD1) (100, 101). Itaconate may play a role in immunomodulation, suppression of inflammation and tolerance (102, 103). Itaconate also inhibits mitochondrial respiration, increases stabilisation of HIF1α, activation of Nrf-2 via alkylation of KEAP-1 (84, 104). Finally, itaconate accumulation leads to the inhibition of succinate dehydrogenase leading to the accumulation of succinate leading to numerous proinflammatory and prooxidative consequences (103, 105, 106). For example,

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elevated levels of succinate oxidation in a cellular environment of little or no ATP generation induces a phenomenon described as reverse electron transport (RET) whereby electrons flow "backwards" along the ETC to complex I which is accompanied by large increases in the genesis and release of ROS (107, 108). High levels of cytosolic succinate may induce an increase in lysine group succylation in the cellular proteome which many influence protein activity via changes in charge and conformation (109). The mechanisms involved are beyond the scope of this review but it is important to note that this post-translational modification offers another route relaying subtle redox mediated metabolic changes to protein function (110). Finally, once externalised, succinate can bind to the G protein coupled succinate receptor 1 (SUCNR1) which is expressed on the surface of activated M1 polarised macrophages (111, 112) which is one mechanism involved in sustaining and amplifying their inflammatory effects (12, 113).

**1.2 M2 polarised macrophages**

In an environment of elevated IL-4 and or IL-13 activated M1 polarised macrophages may ultimately be polarised towards a range of anti-inflammatory and tissue healing phenotypes classified as M2a, M2b, M2c, and M2d which for the purposes of this paper may be usefully described as "M2" (114-116). Macrophage M2 polarization involves tyrosine phosphorylation and activation of a signal transducer and activator of transcription 6 (Stat6), (117, 118). The latter then activates a wide range of M2 macrophage-specific genes such as arginase 1 (*Arg1*), GATA binding protein 3 (GATA3), CD36, matrix metalloproteases (MMPs), FIZZ1, and PPARγ (119, 120). IL-4 and IL-13 also upregulate the activity of transforming growth factor (TGF)-β, suppressor of cytokine signalling 1 (SOCS-1), and insulin-like growth factor 1 (IGF-1) which act to suppress the production of pro-inflammatory cytokines and promote tissue repair (114, 115, 121) Unlike M1 polarisation, M2 polarisation

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is associated with a return to OXPHOS and increased FAO (114, 115). In addition M2 polarised macrophages possess an intact TCA cycle (114, 115).

M2 macrophages are also characterized by activation of the nuclear liver X receptor LXR activation, which regulates cholesterol homeostasis and lipid synthesis (122) Overexpression or activation of LXRα dampens M1 responses and inflammation by inhibiting the activity of NF-κB and activator-protein 1 (AP-1) (123, 124). One major element reinforcing the transition from M1 to M2 polarisation is the change in the metabolism of arginine. In M1 polarised macrophages, elevated activity of iNOS leads to the metabolism of arginine to produce citrulline and NO which is a major element in maintaining the switch towards aerobic glycolysis as explained above (84). However, in M2 polarised macrophages, the increased transcription of arginase-1 metabolises arginine to ornithine and urea which play a vital role in M2 macrophage survival, proliferation, and tissue repair (120) (125). Glutamine metabolism is also of particular importance in M2 macrophages for two main reasons. Firstly, oxidation of this amino acid is an essential source of acetyl CoA in an inflammatory environment leading to depleted environmental glucose levels thereby maintaining TCA activity (126, 127) (128). Secondly, glutaminolysis mediated increases in α-ketoglutarate and activation of the glutamine–UDP-*N*-acetylglucosamine (GlcNAc) pathway reinforces M2 polarisation (126). Readers interested in a mechanistic consideration of this area are invited to consult the work of (121).

There are major differences in the molecular entities involved in the regulation of the metabolic bioenergetic pathways involved in the transition to M2 polarisation compared to those governing these parameters in macrophages undergoing M1 polarisation In the case of M2 polarisation the main players are AMPK and PPAR-γ whose activities are briefly described below.

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AMPK stimulates OXPHOS and FAO while inhibiting NF-κB and mTOR thereby decreasing inflammation and reducing levels of HIF1α and terminating aerobic glycolysis (129-132). AMPK inhibits acetyl-CoA carboxylase (ACC), increases glycolytic flux, mitogenesis, lipases, autophagy, and lysosomal degradation (133, 134). PPAR-γ upregulates FAO, maintains mitochondrial membrane potential, mitochondrial citrate synthase, and numerous genes involved in regulating mitochondrial function such as peroxisome proliferator-activated receptor-gamma (PGC)-1α and transcription factor A (TFAM) (135-138), and downregulates NF-κB but upregulation of Nrf-2 (135-137). PPAR also upregulates the activity of level liver X receptor (LXR).(139) which regulates cholesterol and lipid homeostasis while also playing an additional role in reducing inflammation and inhibiting glycolysis via the inhibition of NF-κB (123, 124). Finally, PPAR-γ promotes the oxidation of glutamine (126) whose importance in M2 polarisation has been discussed above (140).

**1.3 Redox regulation of macrophage activation functions and survival.**

Macrophage ROS levels affect the activity of STAT-1, MAPKs, and NF-κB leading to overall increases in inflammatory signalling (141). ROS levels also affect the assembly of NADPH oxidase subunits at the plasma membrane and regulate the formation of corrosive RNS species such as peroxynitrite, thereby influencing H202-mediated intracellular signalling and macromolecule damage (142). Chronically increased ROS or NO is associated with the development of macrophage dysfunction and senescence (143-145). The mechanisms driving this phenomenon appear to involve the persistent upregulation of NF-κB, STAT-3, IL-10, and TGF-β, and potentially the upregulation of PD-1 (144, 146, 147).

There is also ample evidence that macrophage functions and polarisation patterns are influenced by GSH levels and overall activity of the GSH system (148, 149). For example, increased GSH oxidation compromises phagocytosis and macrophage survival (150, 151). The

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GSH system also plays a major in regulating the inflammatory status of activated M1 by regulating production of PGE2, NO, and pro-inflammatory cytokines, while protecting macromolecules from oxidative damage via activity as a ROS scavenger (152) (153). The antiviral responses initiated following M1 macrophage activation such as the upregulation of the transcription factors STAT-1, Irf7, and Irf9 are also dependent on an optimally functioning GSH system and are compromised by GSH depletion (154).

Thioredoxin (TRX)-1 affects the inflammatory status of macrophages by modulating the activity of macrophage receptors, and macrophage migration inhibiting factor (MIF) (155). The regulatory role of TRX on MIF signalling reduces the pro-inflammatory status of M1 macrophages by decreasing production of TNF-α and monocyte-chemoattractant protein (MCP)-1 and encourages M2 polarisation (156, 157) (158). The precise mechanisms underpinning this phenomenon are relatively complex and readers interested in this area are referred to the work of (159).

Nrf2 upregulation also exerts an anti-inflammatory effect in activated macrophages by decreasing the activity of inflammatory cytokines such as IL-6 and IL-1β (160, 161). The mechanism involves Nrf2 binding at the relevant gene promoter sites resulting in the inhibition of the recruitment of RNA Polymerase II complex (162). Nrf-2 upregulation also results in increased expression of CD163 and Arg1 (161, 163) and affects the transcription of a multitude of genes involved in the switch between M1 to M2 polarisation (160, 161).

## 2. Metabolic reprograming and redox factors involved in DC activation.

### 2.1 Metabolic reprogramming in dendritic cells.

Dendritic cells (DC) are considered to be the archetypal antigen presentation cells (APC) and play the dominant role in linking innate and humoral immunity (164). In physiological conditions, tissue resident DCs drain to the lymph nodes and, thereafter, present

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self-antigens to T cells, thereby maintaining immune tolerance as reviewed in (165). However, following pathogen invasion, TLR- mediated activation of DCs is followed by numerous changes in function and phenotype resulting in their active migration to lymph nodes, the production of pro-inflammatory cytokines and the activation of T lymphocytes (166).

Resting state DCs rely on OXPHOS-driven TCA cycle activity fuelled by glutaminolysis and FAO to meet their energy needs (167) (168). Their overall metabolism is regulated by AMPK (168). However, following pathogen recognition, TLR activation results in activation of NF-κB, PI3K/AKT signalling, mTOR, and PPAR-γ and a rapid shift to aerobic glycolysis and lactate production in a similar manner to M1 polarised macrophages discussed above (169, 170). In addition, glycolytic intermediates are shunted into the PPP while increased NO production inhibits the ETC. Moreover, citrate is withdrawn from the TCA acting as an indispensable player in the fatty acid synthesis that maintains and increases inflammatory cytokine, NO, and ROS production (171, 172) and the acute switch to glycolytic metabolism is facilitated by PI3K /AKT signalling (173). However, chronic aerobic glycolysis is enabled and regulated by mTOR and HIF1α activation (174, 175). In addition, upregulation of mTOR and the subsequent increase in HIF1α activity induces the transcription of iNOS (176, 177) leading to NO-mediated suppression of mitochondrial OXPHOS via reversible inhibition of ETC complex I, III, and IV in much the same manner as the case in activated M1 polarised macrophages (17, 178, 179). mTOR activation also initiates and regulates lipid synthesis and mitochondrial biogenesis via the downstream upregulation of SREBPs and PPAR and stimulates IL-6, IL-1, and TNF-α production, via the upregulation of AKT, FOXO3, and Myc (180). mTOR activation also acts as the enabler and master regulator of DC migration, maturation and endocytosis (180).

**2.2 Redox regulation of DC activation and function**

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Phagosomal ROS levels, secondary to increased NOX-2 activity, play an essential role in the MH1-mediated cross presentation of digested antigens to CD8 T cells (181) (182). In this context, it is noteworthy that CD8 T cell activation also requires the upregulation of mtROS production (183). DC production of ROS following TLR activation also plays a major role in the maturation and the priming of CD4 T cells (184, 185). Many aspects of DC function are influenced by GSH system activity. For example, GSH levels regulate DC differentiation and function as antigen presentation cells (186). DC GSH levels also determine T cell polarisation patterns by affecting the production of "polarising 2 cytokines such as IL-27 and IL-12 (187, 188). GSH depletion is associated with the differentiation of naive T cells along the T helper (Th)-2 pathway (188) and GSH depletion inhibits DC maturation and inflammatory cytokine production leading to profound cellular dysfunction (189). There is also some evidence to suggest that DCs directly influence the redox state of activated T cells via the transfer of thioredoxin (190).

Redox homeostasis within activated DCs is regulated by Nrf-2 which also acts to restrain T cell proliferation by repressing production of IL-12 and upregulating IL-10 (191, 192). Conversely, Nrf2-deficient DCs generate increased numbers of activated T helper cells but reduced numbers of T regulatory cells and stimulate T cell proliferation (193). Moreover, Nrf-2 depletion, and the resultant pro-oxidative state in DCS encourages a Th-2 pattern of differentiation in naive T cells (194, 195). Finally, Nrf-2 also plays an important role in the transition between glycolysis to OXPHOS in tolerogenic DCs which enables their long term survival (196).

There is considerable evidence of DC dysfunction in illnesses underpinned by chronic inflammation and oxidative stress (197, 198). Such dysfunction may be directly or indirectly driven by increased levels of ROS, RNS, and inflammatory cytokines, directly or indirectly. Direct effects include damage to functional macromolecules and increased activation of

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apoptotic pathways (199, 200). Indirect effects include increased Wnt signalling (90), epigenetic dysregulation and compromised TLR activity (201-203). These mechanisms are discussed in detail in the work of (166).

## 3. Metabolic reprogramming and redox regulation of neutrophil activation.

### 3.1 Metabolic reprogramming in neutrophils.

Neutrophils have been long recognised as the first responders of the innate immune response playing an indispensable role in the destruction of invading pathogens. However, there is increasing evidence that these leucocytes also play a major regulatory role in humoral immunity via a pattern of sophisticated cross talk with other immune cells (204-206). Importantly, these regulatory activities extend beyond regulation the activity of myeloid cells and also involve modifying the activity of T cells, marginal zone B cells, and natural killer cell homeostasis (204-206). There is also considerable evidence of functionally distinct subsets and extensive cellular plasticity enabling a range of functions depending on cellular location and inflammatory status (207, 208). These immune cells may be activated and or primed by a multiplicity of stimuli such as inflammatory cytokines, chemokines, growth factors, PRRs (mainly c-type lectin receptors), opsonins (C3a and IgG) and G protein coupled receptors (GPCRs) (209) (210).

In physiological conditions, activated neutrophils rely on glycolysis to meet their energetic needs (211). This is also true in inflammatory environments (212). However, neutrophils adjust their metabolism to carry out their various effector functions such as phagocytosis, degranulation, oxidative burst, NET formation, and chemotaxis (213). The weight of evidence suggests that NET formation is reliant on glycolysis with extensive involvement of lactate production, the PPP, and glutamine metabolism as sources of NADPH for NOX generation (214, 215). This metabolic reprogramming also supplies NOX activity and

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superoxide production ultimately underpinning the production of hydrogen peroxide ($H_2O_2$), hydroxyl radicals (OH.), and hypochlorous acid (HClO) used in the performance of the neutrophil oxidative burst following their phagocytosis of invading pathogens (211, 216-218). The metabolic changes underpinning chemotaxis are somewhat more complicated, however, and involve mitochondrial activity in addition to upregulated glycolysis (219, 220). This activity supplies ATP which activates membrane bound P2Y2 receptors following the receipt of chemotactic stimuli (219, 220). Readers interested in details of the mechanisms involved are invited to consult the work of (221). Mitochondrial activity supplies the ATP required for neutrophil activity in regions of profound glucose deprivation which may occur in an environment of extreme inflammation and also plays a dominant role in neutrophil autophagy and survival via FAO (211) (222).

These metabolic changes underpinning neutrophil activity in inflammatory environments are primarily regulated by the cooperative activity of NF-κB (43, 223), HIF1α (224, 225) and mTOR (211, 226). The multiple and arguably pivotal roles of the latter include the regulation of NET production, autophagy, oxidative burst, phosphorylation and stabilisation of NOX and HIF1α (226, 227). mTOR also increases the surface expression of GLUT1 and increases mitochondrial biogenesis and FAO via the upregulation of PPARγ and SREBPs (72). Increased levels of mTOR activity increase production of leukotrienes, prostaglandins, and resolvins, and secretion of pro-inflammatory cytokines via the phosphorylation of AKT (228). mTORC1 also exerts an inhibitory effect on oxidative phosphorylation by upregulation of IFN-γ and NO which inhibits the activity of enzymes in the ETC (229).

While mTOR upregulation plays an indispensable role in the optimal function of activated neutrophils it should be stressed that other enzymes and transcription factors are also important regulatory factors enabling pathogen destruction while restraining excessive

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inflammation and preventing excessive survival. For example, PI3K plays disparate roles in enabling chemotaxis and endothelial crawling chemotaxis via an intricate pattern of "cross talk" with Rho family GTPases (230) (231). On the other hand, AMPK plays a major role in regulating and restraining NF-κB and pro-inflammatory cytokine production limiting tissue inflammation and destruction while optimising chemotaxis and phagocytosis (232, 233). Finally, PPAR-γ also regulates migration and restrains inflammation by inhibiting NF-κB while stimulating the production of anti-inflammatory mediators such as IL-10 (211, 234).

### 3.2 Redox regulation of neutrophil activation and function.

The function of individual neutrophils is heavily influenced by cellular redox status in terms of cellular antioxidant system activity and or ROS/RNS production. For example, excessive ROS production may compromise the initiation and outcome of phagocytosis (235), result in a dysregulated or decreased oxidative burst (236) and production of NETs (237). In addition, there is accumulating evidence to suggest that intracellular and extracellular levels of ROS are involved in neutrophil "sensing " of pathogens and consequent activation of the NLRP3 inflammasome and cytokine production (238, 239). Chronically upregulated ROS and cytokine production may also result in the internalisation of membrane chemokine receptors most notably CXCR2 (240) thereby decreasing neutrophil migration.

Upregulated NO also inhibits neutrophil migration, crawling and adhesion (241-243). Mechanistically, this is achieved via downregulation of adhesion factors such as ICAM-1,VCAM-1, E-Selectin and P-selectin compromising neutrophil binding to the endothelium, subsequent crawling, and transmigration to inflammatory centres (244). Neutrophil migration may also be compromised by increased levels of peroxynitrite formed by combination of NO and superoxide cations (245-248). There is evidence to suggest that the tyrosine nitration

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mediated inhibition of P-selectins (245-247) and upregulation of haem oxygenase (HO-1)-1(249) are involved.

A multitude of neutrophil functions are also heavily influenced by the activity of the cellular antioxidant system. For example, Nrf-2 activity influences the efficiency of neutrophil phagocytosis (250), recruitment to sites of inflammation (251), and prolonged survival (252). The glutathione system also plays an important role in the regulation of the various functions displayed by activated neutrophils most notably the activity of glutathione reductase which plays an indispensable role in sustaining neutrophil respiratory burst and NET production (253, 254) while also influencing optimal phagocytotic activity (255, 256). It is noteworthy that the basal activity of the GSH system in neutrophils appears to be lower than that found in myeloid cells (257), rendering these immune cells vulnerable to depleted GSH levels (257). This may result in compromised cytoskeletal reorganisation needed to effect chemotaxis and transmigration leading to reduced recruitment to sites of inflammation, impaired degranulation, and early apoptosis (258, 259). In this context, it should be noted that prolonged neutrophil activity depletes levels of GSH, likely due to excessive production of myeloperoxidase (MPO) which may occur in an environment of chronic inflammation and nitro-oxidative stress (260-262).

TRX also appears to play a major role in the regulation of neutrophil chemotaxis as a result of its release from infected cells and or inflamed tissues (263, 264). This effect appears to be a result of desensitisation of neutrophils towards monocyte chemoattractant protein-1 (MCP-1) (264, 265), thereby restraining neutrophil recruitment into inflammatory tissues (266). The mechanisms involved are not fully understood but they appear to rely at least in part on the oxidation state of functional cysteine residues within the TRX protein most notably the redox state of cys80 (264).

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## 4 Metabolic reprogramming and redox regulation in T cell activation.

### 4.1 Metabolic reprogramming in T cells.

T cell activation follows the ligation of the T cell receptor (TCR) and the major histocompatibility complex molecules by antigen presentation cells. The resultant signalling cascade results in the activation of nuclear factor of activated T cell (NFAT1), activation protein (AP)-1 and NF-κB (267). TCR ligation also increases the production of ROS by mitochondria and NOXs (268) which subsequently regulates the signalling pathways required for enabling and regulating T cell activation, proliferation, and differentiation (268).

Unsurprisingly, T cell activation and differentiation requires extensive metabolic reprogramming (269-273). In general, such reprogramming is regulated by the collaborative activity of PI3K/AKT, mTOR, HIF1α, and c-Myc (274, 275) (276). However, it should be stressed that the metabolic pathways involved in the reprogramming of distinct T cell subsets display important differences (277-279). The metabolic needs of naïve T and memory T cells, and T regulatory cells are relatively modest and are met by a reliance on OXPHOS and FAO (274, 279, 280). However, the differentiation, proliferation, and various effector functions of effector CD4 and CD8 cells require the rapid supply of ATP from aerobic glycolysis and NADPH supplied by increased activity of the PPP and glutaminolysis, which is largely mediated by increased activity of HIF1α and mTOR (278, 281-284) (285).

The role of fatty acid metabolism in T cell activation and differentiation also displays significant subset related differences. For example, effector T cell activity relies on fatty acid uptake and FAS while utilization of stored fatty acids is a feature of T memory cells (286, 287). Uniquely, the relative reliance on FA uptake versus FA synthesis exerts a major influence on the differentiation of naive T cells into Tregs or Th-17 cells (287, 288). In particular, uptake of environmental FA is a characteristic feature of Treg development while Th-17 differentiation relies on ACC mediated FA synthesis (288). Readers interested in a

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consideration of the mechanisms underpinning these observations are invited to consult the work of (276).

TCR signalling also results in the upregulation of several amino acid transporters facilitating the uptake of branch chain amino acids such as alanine, cysteine, leucine, glycine, and glutamine (289-291). These amino acids in combination with increased PPP activity play an indispensable role in promoting the rapid increase in GSH needed for T cell survival and function (285). Increased glutamine catabolism following T cell activation, mediated by mitochondria dependent oxidation, is of particular importance as the resultant increase in α-ketoglutarate production stimulates TCA activity and fuels increased OXPHOS (268, 292). TCR-dependent uptake of glutamine, valine, and leucine also plays an indispensable role in the differentiation of Th-1 and Th-17 cells, inflammatory T cell responses, the development of effector and memory CD8 cells which is effected at least in part by the activation of mTOR (293-295) (296).

**4.2 Redox regulation of T cell activation and function.**

ROS levels increase rapidly following T cell activation by TCR engagement (297, 298) and play an indispensable role in driving T cell activation, proliferation and differentiation (268, 292). Unsurprisingly, given the information discussed above, ROS play an indispensable role in the differentiation patterns and the disparate effector functions of various T lymphocytes. For example, a Th-2 polarised phenotype is encouraged by excessive microenvironmental ROS (299). Conversely, Th-1 and Th-17 polarisation occur when microenvironmental levels of ROS are low (300). Excessive ROS levels either resulting from high levels of production or compromised cellular anti-oxidant defences may result in mitochondrial membrane polarisation with fatal consequences for T cell activation and survival

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following TCR engagement (301). Similarly, prolonged or chronic ROS upregulation may result in T cell hyperresponsiveness, exhaustion, and anergy (302-306).

Several mechanisms appears to underpin this phenomenon including compromised mitochondrial ETC activity and dynamics (303, 307), upregulation of PD-1 (308, 309), dysregulated NF-κB signalling, chronic IKKβ signalling (310-312), and oxidation of functional cysteine groups in proteins (313, 314) (315). Finally, excessive ROS production may lead to dysregulated T cell homeostasis by differentially modulating T cell homeostasis as effector T cells are more susceptible to ROS mediated cell death than Tregs (201, 316, 317).

Nrf-2 transcription is upregulated following TCR engagement on naive T cells and plays a major role in restraining the inflammatory activity of T cells and encourages a Th-2 pattern activated following TCR activation (318, 319). The results obtained from animal studies also suggest that the upregulation of Nrf-2 increases the proliferation of Tregs (320) and amplifies their immunosuppressant and cytotoxic functions (321).

As previously discussed, GSH synthesis is rapidly upregulated following TCR activation and plays an indispensable role in T cell survival and function (285). Increased de novo GSH synthesis also suppresses Th-17 differentiation while encouraging the production of Tregs. Conversely, GSH depletion or loss of de novo GSH synthesis in a state of chronic nitro-oxidative stress (322) compromise mTOR, NFAT, and N-Myc function, thereby abrogating the metabolic reprograming enabling the maintenance of aerobic glycolysis and leading to the termination of T cell activation (323-325). Tregs also appear to exert at least some of their cytotoxic and immunosuppressant functions on effector T cells by decreasing their GSH synthesis (326).

The TRX system activity also exerts a range of influences on T cell activation and proliferation with increased TRX-1 production playing an important role in restraining their activation and encouraging the development of Tregs from naive T cells while decreasing their

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differentiation down the Th-1 and Th-17 pathways (327). TRX-1 upregulation is also important in enabling effector and regulatory T cell survival and function in an environment of chronic nitro-oxidative stress by protecting membrane protein thiols from oxidation (328, 329). There is also some evidence to suggest that increased TRX-1 activity is needed to maintain production of IL-2 (330) and T helper mediated activation of B cells (331).

## 5. Metabolic reprogramming and redox regulation in B cell activation.

### 5.1 Metabolic reprograming in B cells.

B-cell receptor (BCR) or cytokine mediated activation of naive B cells results in activation of PI3K phospholipase C gamma 1 (PLCG1) resulting in calcium mobilization and NF-κB activation and upregulation of c-Myc, HIF1α, AKT, mTOR and STAT-6 (332). Once activated these lymphocytes migrate to germinal centres and display increased rates or glycolysis and OXPHOS (333-335). In the case of activated B cells, short term metabolic reprogramming and increased glycolysis is regulated by PI3K, HIF1α, AKT and STAT-6 signalling (333-335) and the role of mTOR appears to be confined to the upregulation of GLUT-1 (336). It is noteworthy that GSK3 appears to have a major role in the regulation of glycolysis in activated B cells and may also regulate ROS production and changes in mitochondrial dynamics (336, 337). However, while mTOR may not be the primary player in the regulation of glycolysis, sustained germinal centre B cell BCR signalling requires activation of mTOR (338, 339). mTOR also plays an essential role in somatic hypermutation and the formation of memory B cells via the rapid activation of the unfolded protein response (UPR) (340-342).

There is evidence to suggest that the relative levels of OXPHOS and glycolysis differ in plasmablasts and memory B cells with glycolysis being dominant in the former and OXPHOS being dominant in the latter to enable their long term survival (343). B1 and B2

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subsets also appear to display differing metabolic profiles with aerobic glycolysis, PPP, and FAO more active in B1 compared to B2 (343). The production of high affinity antibodies by plasmablasts is an energetically demanding process and requires rapid increases in glucose consumption and mitochondrial mass accompanied by significant changes in mitochondrial dynamics (337, 344, 345) reviewed (343). Unsurprisingly, the weight of evidence suggests that functional mitochondria are an indispensable element in B cell differentiation and effector functions (346). The process of antibody formation is also regulated by AMPK which plays an essential role in enabling memory B cell formation and survival in part by regulating mitochondrial dynamics and suppressing the activation of mTOR (347, 348). Readers interested in a detailed consideration of the role of AMPK in the regulation of mitochondrial dynamics are invited to consult an excellent review by (133).

**5.2 Redox regulation of B cell activation and function.**

Elevated levels of hydrogen peroxide are required to initiate and maintain BCR signalling (349, 350). This is initially provided by the activity of NOX-2 (351), but in the longer term the source of hydrogen peroxide is mtROS (349, 350). In addition, the cellular redox state and mtROS production also plays and essential role in B cell survival, differentiation and IgM production (352, 353). However excessive mitochondrial mtROS production may inhibit the activation of B cells and their differentiation into antibody-producing plasmablasts (354). Gross overproduction of mtROS may also inhibit the production of antibodies by downregulating CD19 expression (355). Finally, chronically upregulated ROS can upregulate the consumption of IgM antibodies (356, 357).

In this context, it is noteworthy that B cell activation is also accompanied by the concomitant upregulation of the TRX and GSH system with the latter involving increased activation of the cystine transporter xCT and increased uptake of cysteine (353). The

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upregulation of the TRX and GSH systems by activated B cells enables their medium term survival (358) and increased activity of both systems correlates with increased production of IgM (353). Finally, there is evidence associating increased Nrf-2 expression in activated B cells with increased survival and increased resistance of ROS mediated apoptosis (359-361).

## 6 Metabolic reprogramming and redox regulation of NK cell activation.

### 6.1 Metabolic reprograming in natural killer cells.

Ligand engagement with inhibitory receptors such as members of the Killer-cell Immunoglobulin-like Receptor (KIR) family result in the phosphorylation of Immunoreceptor Tyrosine based Inhibitory Motif (ITIM) resulting in the recruitment of several phosphatases which dephosphorylate Immunoreceptor Tyrosine based Activation Motif (ITAM) reinforcing inhibitory signalling and preventing natural killer activation (362, 363). On the other hand, engagement of multiple activation receptors such as natural cytotoxicity receptors (NCR), NKp30, NKp46, and NKp44 leads to the phosphorylation of ITAM by numerous Src tyrosine kinases leading to the recruitment and subsequent activation of the tyrosine kinase ZAP-70 and SYK which initiate a downstream phosphorylation cascade resulting in the activation of PI3K JNK1/2 and p38 and the recruitment of PLC-γ (364-366). The latter activates IP3 and DAG signalling leading to the activation of AP-1, NFAT and NF-κB (362, 367). The net effect of this signalling cascade is cytoskeletal reorganisation and the release of chemokines, inflammatory cytokines, and lytic granules containing granzyme A, B and perforin (368). This is a simplified description of the signalling mechanisms involved in natural killer cell activation and only features the elements germane to the central theme of this paper. Readers interested in a more detailed and comprehensive treatment of this subject as invited to consult elegant reviews by (369) and (370).

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Unsurprisingly, the various effector and regulatory functions of activated natural killer cells are enabled by metabolic programming which in this instance is underpinned by the upregulation of glucose driven glycolysis, OXPHOS, increased fatty acid synthesis, and increased glutamine metabolism (371-374). Metabolic reprogramming, glycolysis, and increased mitochondrial activity are regulated by mTOR which is highly up-regulated in natural killer cells in response to multiple routes of stimulation including IL-15 and IL-3 stimulation (373, 375, 376). The upregulation of this kinase is also responsible for increased fatty acid synthesis and glutamine metabolism by activated natural killer cells via the upregulation of SREBPs and nMyc (371, 377).

Upregulated PI3K/mTOR signalling in alliance with NF-κB and STAT-3 transcriptional activity is responsible for the upregulation of HIF1α protein synthesis in inflammatory conditions (378, 379). The importance of mTOR and HIF1α in natural killer proliferation and function is difficult to overemphasise as reduced HIF1α and mTOR activity are associated with loss of cytotoxic activity, as evidenced by decreased production of perforin and granzyme B, and premature apoptosis (373, 380) (381).

**6.2 Redox regulation of natural killer cell activation and function.**

Increased ROS production in the form of hydroxyl radicals plays an important role in enabling natural killer cell mediated cytolysis by promoting the release of granzyme B and perforin (382). In addition, increased production of ROS enables natural killer cell division and proliferation following pathogen invasion (383). There is evidence to suggest that Nrf-2 activation acts as an immunological checkpoint following natural killer cell activation restraining activation and regulating effector functions (384, 385).

The upregulation of GSH synthesis plays an essential role in enabling the proliferation and cytotoxic functions of natural killer cells and conversely GSH downregulation results in

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compromised functions and recruitment to sites of inflammation (386, 387) (388). The upregulation of TRX1 also plays a pivotal role in natural killer cell survival by maintaining cytoprotective sulfhydryl residues present in the cell membrane in a reduced state in an inflammatory environment (389, 390). This phenomenon would appear to play a vital role in the protection of those cells from hydrogen peroxide mediated natural killer cell dysfunctions (389, 390). However, this level of protection is clearly limited as there is copious evidence that chronic nitro-oxidative stress results in natural killer cell hypofunction and loss of cytotoxic activity (391-393) (394). There is evidence to suggest that this is due to compromised hydrogen peroxide signalling following NOX-2 hyperactivity (391, 395). However, there is also evidence that natural killer function may be impaired by excessive production of NO (393).

Thus far, we have considered the role of redox regulated intracellular elements in modulating the response of individual immune cells and the immune response as a whole. We now turn to a brief consideration of redox factors which are underdiscussed, namely oxidized phospholipids and the high-density lipoprotein (HDL) complex, comprising HDL, paraoxonase (PON)1, and apolipoprotein (Apo)A.

## 7 Role of the HDL complex and oxidized phospholipids in the immune response.

### 7.1 Role of HDL, ApoA1 and PON-1 in the regulation of the immune response

HDL attenuates the activation of TLR-4 by stimulating cholesterol efflux from membrane lipid rafts (MLR) thereby attenuating downstream signalling pathways and inhibiting and NF-κB activation (Catapano et al., 2014; Kaji, 2013; Mineo and Shaul, 2012; Suzuki et al., 2010; Zhu et al., 2010) (Ruysschaert and Lonez, 2015). HDL also inhibits TLR-4 signalling by activating the CREB family member activating transcription factor 3 (ATF-3), which offers another route to inhibition of NF-κB (De Nardo et al., 2014). Readers interested in a detailed discussion of the mechanisms involved are referred to (Zhao et al., 2016). HDL

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also exerts broadly inhibitory effects on the activation of other immune cells which is also effected by the disruption of MLRs (Kaji, 2013). For example, HDL inhibits DC activation, maturation, and the ability of these APCs to present antigens to T lymphocytes thereby inhibiting Th-1 and Th-17 differentiation (Perrin-Cocon et al., 2012; Tiniakou et al., 2015). HDL-mediated MLR disruption also underpins direct anti-inflammatory and immunosuppressive effects on T and B lymphocytes (Robinson et al., 2017). The inhibitory effects on B cells include suppression of BCR activation, and APC functions (Carpintero et al., 2010; Gupta and DeFranco, 2007; Wang et al., 2012). Inhibitory influences on T cells include downregulated TCR activity and inhibition of Th-1 and Th-17 differentiation (Robinson et al., 2017). Readers, interested in a detailed consideration of mechanisms underpinning these differing effects are invited to consult an elegant review of the subject by (Gupta and DeFranco, 2007). There is also data to suggest that HDL inhibits the activity of the complement system (Gordon and Remaley, 2017; Vaisar et al., 2007) and restricts monocyte and macrophage chemotaxis (Kontush, 2014; Murphy et al., 2012). Finally, HDL also appears to exert a unique immunoregulatory role by activating the immunosensory molecule long pentraxin 3 (PTX-3) (Norata et al., 2010; Ortega-Hernandez et al., 2009).

While the data above has been discussed in the context of the entire HDL complex it should be noted that the effects are largely reliant on the performance of its constituent apolipoproteins and enzymes most notably apolipoprotein A1(ApoA1) and the enzyme PON-1 (Brites et al., 2017; Carnuta et al., 2017) (Yamada et al., 2017). ApoA1 plays the dominant role in T cell homeostasis by regulating the balance between Th-17 and Tregs (Gaddis et al., 2019). In particular, reduced levels of ApoA1 are associated with a decrease in Treg numbers and an increase in phenotypic switching to a Th-17 phenotype (Gaddis et al., 2019; Tiniakou et al., 2015; Wilhelm et al., 2010). ApoA1 may also improve mitochondrial functions by modulating levels and structure of cardiolipin thereby increasing the activity of the ETC

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(Dadabayev et al., 2014). ApoA1 also plays an indispensable role in stabilising PON-1 within the HDL particle thereby maintaining the activity of the latter enzyme (Hine et al., 2012; Viktorinova et al., 2018). This is an important effect as PON-1 activity exerts many positive effects on many parameters regulating the activity of immune cells.

For example, PON-1 ameliorates ROS-induced damage to mitochondria, thereby maintaining and potentially improving the function of these organelles in an environment of chronic nitro-oxidative stress (García-Heredia et al., 2013; White et al., 2017; White et al., 2016). In addition, PON1 may exert positive effects on glucose metabolism and aerobic glycolysis via upregulation of GLUT-1 (Koren-Gluzer et al., 2013). PON1 also increases the activity of the PPP (Garcia-Heredia et al., 2013) and stimulates FAO (Garcia-Heredia et al., 2013). The latter appears to be effected at least in part by modulating the activity of PPAR-γ (Nagy et al., 2013) as reviewed in: (Meneses et al., 2019).

PON-1 also plays an indispensable role in limiting levels of oxidized phospholipids due to its ability to hydrolyse lipid hydroperoxides (Aslan et al., 2011; Mehdi and Rizvi, 2012; Novak et al., 2010; Perla-Kajan and Jakubowski, 2010) (Marek et al., 2018). Unsurprisingly, decreased activities of PON1 leads to increased immune cell membrane lipid peroxidation and elevated levels of circulating oxidized lipoproteins (Ferretti and Bacchetti, 2012; Mastorikou et al., 2008). From the perspective of this paper this are important data as oxidized phospholipids are generated as part of the inflammatory immune response and play significant immunoregulatory roles (32-35).

**7.2 Role of oxidized phospholipids in the regulation of the immune response.**

Evidence suggests that the bulk of oxidized phospholipids present in the circulation exists as immune complexes with natural IgM and IgG due to its status as an oxidation specific epitope (OSE) and role as an autoantigen (396) (397). The weight of evidence also suggests

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that oxidized phospholipid complexes are proinflammatory (398) (399) and elicit inflammatory responses via several routes which include recruitment of the complement cascade (400) and producing inflammatory responses in human macrophages largely by engagement with Fc gamma receptor 1 (401, 402). There is also accumulating evidence to suggest that these complexes activate mature DCs leading to a primed inflammasome thereby exaggerating IFN-γ and IL-1 production (403-405). Moreover DCs activated and primed via this mechanism appear to have the capacity to activate naive T cells and induce Th-17 polarisation (406, 407) (405).

Oxidized phospholipids make a major contribution to the development of inflammation and oxidative stress by engaging neutrophil pattern recognition receptors leading to the formation of NETs (408, 409). In addition, oxidized phospholipid engagement with monocytes, macrophages, DCs and natural killer cells may induce epigenetic and metabolic reprogramming leading to a state described as immune training. This is important as this process effectively endows these leucocytes with a de facto memory resulting in an exaggerated inflammatory, or anergic, response to future antigenic challenge (410, 411). The mechanisms driving the metabolic and epigenetic changes described above appear to depend, at least in part, on mTOR induced assembly of NADPH oxidase and subsequent increases in ROS mediated signalling (411, 412).

The final section of this paper deals with the detrimental effects of chronic nitro-oxidative stress on immune cell function and the performance of the immune response as a whole. In physiological conditions, cytosolic hydrogen peroxide derived from the activity of NOX or mitochondria plays an indispensable role in the regulation of redox sensitive cellular signalling pathways (413) (414). These roles are mainly effected by the reversible two electron oxidation of cysteine thiolate anions (415) (416, 417). However, in conditions of excessive ROS production, hyperoxidation of thiolate anions to sulfonic acid essentially incapacitates reversible cysteine oxidation as an effective signalling mechanism locking functional cysteines in the oxidized mode (90, 418).

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The other signalling system involved in regulating the activity of redox sensitive proteins and enzymes in physiological conditions is reversible S-nitrosylation. The mechanisms involved are reviewed in (419) and (17). However, pathological levels of ROS disables the mechanisms responsible for maintaining the reversibility of S-nitrosylation inducing a cellular state described as protein hypernitrosylation (202). Hyperoxidation and S-nitrosylation can result in impaired function of the redox sensitive transcription factors and enzymes regulating metabolic reprogramming in immune cells whilst compromising mitochondrial functions, and seriously compromising immune cell activation and function. Chronic nitro-oxidative stress also compromises the activity of HDL, apoA1, and PON-1 whilst increasing the density of oxidized phospholipids further dysregulates the immune response (41). Finally, chronic nitro-oxidative stress also leads to the activation of indoleamine, 2-3 dioxygenase (IDO) which may result in a state of profound immune suppression (420). The section below deals with these factors beginning with the effects of hypernitrosylation and hyperoxidation on transcription factors and enzymes.

## 8 The detrimental effects of chronic nitro-oxidative stress on the immune response.

### 8.1 Chronic nitro-oxidative stress on transcription factors and enzymes.

S-nitrosylation exerts a significant inhibitory effect on NF-κB function by reducing the binding of subunits to DNA thereby decreasing the activity of the complex as a transcription factor (421-423) thereby decreasing the expression of target effector genes (421, 424). The effect is largely due to S-nitrosylation mediated conformational changes to crucial functional cysteine residues located on the p65 subunit of p50/p65 abrogating NF-κB DNA-binding capacity (421, 425). The consequences involve decreased levels of inflammatory cytokines such as IL-12 (426), IL-1β (427), IL-6, the chemokine IL-8, and iNOS (428, 429). In addition,

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there is accumulating evidence to suggest that S-nitrosylation inhibits TLR-4 (430, 431) and TLR-2 signalling (432).

There is also in vivo evidence to suggest that S-nitrosylation leads to the inhibition of numerous MAPKs most notably p38/MAPK (433, 434) and Janus kinase (433, 435) which play an essential role in the activation of NFAT, STAT-3 and NF-κB (436). There is also accumulating evidence to suggest that S-nitrosylation is involved in the activation of Nrf2, which appears to be effected via the conformational modification of crucial cysteine thiol groups within the inhibitory Kelch-like ECH-associated protein-1 (Keap1) (437-439).

Hypernitrosylation may also lead to the chronic activation of HIF1α via upregulation and or stabilization of HIF1 (440-442). In addition, irreversible nitrosylation of functional cysteine thiols may also lead to the chronic activation of PI3K/AKT and mTOR signalling (443-446) thereby decreasing the capacity of immune cells to adapt to environmental conditions or changing metabolic needs. There is also evidence that mTOR may be directly activated following inhibitory *S*-nitrosylation of tuberous sclerosis complex 2 (TSC2), which otherwise acts an inhibitor of the enzyme (446). mTOR may also be upregulated by the nitrosylation-mediated activation of the small GTPase which act as a positive regulator of mTOR (447). Prolonged nitrosylation may also compromise immune cell via the chronic upregulation of GSK-3 (448). Finally, nitrosylation-mediated upregulation of GSK-3 and PI3K/AKT signalling activity may introduce a further dimension of metabolic and bioenergetic dysregulation by inhibiting the activity of AMPK (449, 450).

In addition, mTOR may be inactivated by oxidation of Cys1483 by ROS in an environment of chronic oxidative stress (451). mTOR activity may also be inhibited in an environment of oxidative stress as a result of AMPK activation (452) (453). Several other enzymes involved in regulating metabolic reprogramming in immune cells are also activated in an environment of excessive ROS levels most notably PPAR-γ (454, 455).

### 8.2 Detrimental effects on immune cells due to nitro-oxidative stress-mediated mitochondrial dysfunction.

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Chronically elevated ROS/RNS can damage mitochondrial structure and functions via oxidative damage to lipids, proteins, and DNA. The most notable results are damage to the enzymes of the ETC (248, 456-458) and a range of structural and functional phospholipids most notably cardiolipin (459, 460) (461). This ultimately leads to impaired ATP production and accelerated ROS provoking further damage to macromolecules forming the basis of self-amplifying pathology (248, 456-458). Increased NO production by mitochondria in an environment of nitrosative stress may also be a source of dysfunction and damage (462-464). In essence two pathways are involved. The first involves reversible inhibition of ETC enzymes by NO mediated S-nitrosylation (17, 465, 466). The second involves irreversible nitration of functional enzymes and structural proteins by $ONOO^-$ (248, 467). This pattern of pathology leads to ever-increasing levels of mtROS production and bioenergetic failure (468-471).

Clearly compromised mitochondrial function has many direct adverse effects on the activity of immune cells as discussed above. However, mitochondrial dysfunction may also result in numerous indirect adverse effects related to depleted levels of NADPH which results from compromised activity of this organelle (472-474). This is a significant source of metabolic dysfunction in immune cells as the TRX and GSH systems are wholly dependent on the presence of adequate levels of NADPH which acts as an indispensable source of reducing equivalents (475-478). The nuclear encoded nicotinamide nucleotide transhydrogenase (NNT) catalyzes the formation of NADPH from NADP (479, 480) and $NAD^+$ kinases which catalyzes the production of NADP from $NAD^+$ (481, 482) are dependent on mitochondrial respiration and an adequate supply of ATP (472, 473, 483). Mitochondrial dysfunction is associated with depleted levels of NAD + (13) once again due to the fact that the enzyme nicotinamide mononucleotide adenylyltransferase (NMNAT) which catalyses the formation of $NAD^+$ synthesis from nicotinamide mononucleotide (NMN) as part of the salvage pathway (484) is dependent of adequate supplies of ATP (485-487).

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One important adverse consequence of depleted $NAD^+$ levels is compromised mitochondrial NADPH production by isocitrate dehydrogenase (IDH), malic enzyme 2 (ME2), methylenetetrahydrofolate dehydrogenase 2 (MTHFD2). and aldehyde dehydrogenase (ALD), which are all $NAD^+$ dependent (488, 489). The adverse consequences of decreased IDH and ME2 activity extend beyond a shortfall in NADPH production as both enzymes play an essential role in maintaining the activity of the TCA cycle as a whole (490, 491). Depleted $NAD^+$ levels may also compromise NADPH production by the PPP via impaired activity of hexokinase (HK) (492, 493) reviewed (494).

**8.3 Chronic nitro-oxidative stress and the inhibition of antioxidant systems and TCA activity.**

Chronic nitro-oxidative stress may lead to inhibitory nitrosylation and hyperoxidation of crucial functional cysteine residues within TRX and thioredoxin reductase (TRXR) thereby compromising or abrogating the activity of the TRX system (495-498). Chronically elevated levels of ROS/RNS decrease the activity the GSH system (499, 500). Mechanistically, this is achieved via the oxidation and nitrosylation or tyrosine nitration or via inhibiting the activity of GSH, glutathione peroxide, and glutathione reductase (13, 322, 501). Increased production of radical species also increases the activity of multidrug resistance-associated proteins (MRP) resulting in increased extrusion of GSH and GSSH into the intercellular environment and decreased importation of cysteine thereby decreasing the synthesis of replacement GSH (502-505). A state of persistent nitro-oxidative stress may also lead to the inhibition of Nrf2 via several mechanisms including increased activity of MAPK kinase, decreased activity DJ-1 (461, 506) and reduced activity of the TRX system via the mechanisms described above (507, 508).

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Nitrosylation and or oxidation of functional cysteine groups in several TCA enzymes may also exert a number of adverse effects on the metabolism of immune cells. Enzymes so inactivated include a-ketoglutarate dehydrogenase (AKGD), which catalyses the conversion of α-ketoglutarate, $NAD^+$, and coenzyme A to succinyl-CoA, (509-511). Aconitase, which catalyses the conversion of citrate to isocitrate (512, 513), IDH (514-516), ME2 (517, 518), and pyruvate dehydrogenase kinase (519). The importance of IDH and ME2 as sources of NADPH needed in immune cell metabolism has been discussed above and this does not need repetition. However, the adverse consequences of AKGD, aconitase, and pyruvate dehydrogenase kinase are of particular importance. AKGD partial inhibition can dramatically decrease TCA cycle flux and, hence, decrease the concentration of the metabolic intermediates required for NADPH synthesis (520, 521) while aconitase, inactivation results in the accumulation of citrate (521). The inactivation of pyruvate dehydrogenase kinase also results in adverse metabolic consequences by inhibiting the conversion of pyruvate to acetyl-CoA (519).

**8.4 Detrimental effects of chronic nitro-oxidative stress on the HDL complex.**

Chronically elevated ROS/RNS levels are a cause of depleted circulating HDL (522-524), ApoA1 levels (524-526), and PON-1 (527, 528) reviewed(Farid and Horii 2012). Chronic oxidative stress also induces HDL (529-531) and ApoA1 (523, 532, 533) dysfunctions. PON-1 is also rendered dysfunctional in such an environment which appears to be mediated by elevated activity of MPO (527, 528) (534). The mechanisms underpinning the development of a dysfunctional HDL particle and reduced activity of ApoA1 are relatively complex and readers interested in the area are referred to the work of for a detailed consideration of the matter (41).

**8.5 Chronic nitro-oxidative stress and the advent of immunosuppression.**

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Chronic nitro-oxidative stress can induce the development of a phenomenon normally described as endotoxin tolerance by provoking the transcriptional activation of IDO (535, 536). Increased activity of this enzyme results in the upregulation of the tryptophan catabolite (TRYCAT) pathway and aryl hydrocarbon receptor (AhR) activity and upregulated activity of RelB (537, 538), miR-146a (539, 540), TGF-β1 (541, 542), and IL-10 (543, 544) (541). IL-10 and TGF-β1 exert multiple inhibitory effects on TLR signalling by suppressing the translation of vital signalling proteins such as TNF receptor associated factor 6 (TRAF6), interleukin-1 receptor-associated kinase 1 (IRAK1) and reduced activity of NF-κB (545) (reviewed (546). Neutrophils in a state of endotoxin tolerance are characterised by decreased oxidative burst, downregulated TLR4 receptors, and impaired rolling, endothelial cell adhesion and migration to sites of infection (547-549). Macrophages in a state of endotoxin tolerance display significant dysregulation of their activity as APCs due to IL-10 and TGF-β mediated downregulation of the major histocompatibility complex (MHC) class II (550). Impaired antigen presentation is also seen in DCs following IDO activation and the phenomenon is driven by the same mechanism discussed in the context of macrophages above (550). In this state, DC activation of naïve T cells leads to Th-2 polarisation (551, 552). The activity of these DCs may inhibit the activity of memory and effector T cells, encourage the development of CD4 and CD8 T cell anergy, and induce production and the activation of Tregs (553, 554). Prolonged endotoxin tolerance is typified by impaired proliferation and anergy of CD4 T and CD8 T cells and increased number of Tregs (555-557). Readers interested in the mechanisms underpinning these observations are invited to consult the work of (558, 559). Finally endotoxin tolerance is characterised by reduced number and cytolytic function of natural killer cells (560-562).

**Summary and conclusion.**

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The functions, performance, and survival of immune cells is strongly regulated by redox mechanisms, including intracellular and extracellular ROS/RNS and oxidized phospholipids, cellular anti-oxidants such as the glutathione, thioredoxin, and HDL systems, and nuclear factor erythroid 2-related factor 2 (Nrf-2). Hypernitrosylation and chronic nitro-oxidative stress may reduce activity of these antioxidant systems, thereby decreasing the activity levels of the tricarboxylic acid cycle, mitochondrial functions, and immune cell metabolism. As such, redox mechanisms regulate and modulate many different immune functions including but not limited to macrophage and T helper cell polarization, phagocytosis, production of pro- versus anti-inflammatory cytokines, metabolic reprogramming of immune cells, immune training and tolerance, chemotaxis, pathogen sensing, antiviral and antibacterial effects, Toll-like receptor activity, and endotoxin tolerance. ROS/RNS, oxidized phospholipids, and the key antioxidant systems are new drugs targets in the treatment and prevention of immune disorders.

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