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Review

Perturbation in cellular redox homeostasis: Decisive regulator of T cell mediated immune responses

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ABSTRACT

Cellular redox homeostasis plays a pivotal role in generation and maintenance of physiological responses. Perturbation in cellular redox status causes modulation in redox sensitive signaling pathways determining the cell fate. Depending on the extent of generation and spatio-temporal regulation of reactive oxygen species (ROS) generating oxidative stress, it can act as death stimulus or as secondary messenger. Multiple exogenous oxidants or thiol reactive compounds, endogenous oxidants such as NADPH oxidase, superoxide dismutase regulate T cell mediated immune responses. Thus, a meticulous understanding of the coordinated functioning of T cell mediated immune responses in oxidative niche is essential. The present review aims to delineate the effect of cellular redox status on T cell activation and subsequent regulation of redox sensitive immunoregulatory transcription factors such as NF-κB, NFAT and AP-1, which manifests the onset of inflammation associated disorders.

1. Introduction

Redox homeostasis is eminent for physiological processes required for cell survival. Imbalance in redox equilibrium has been iterated as the prime candidate in pathogenesis of several disorders mediated by chronic immune responses like autoimmune and neurodegenerative diseases, allergies and cancer [1]. Importance of oxidative burst in clearance of evading pathogen is very well established; however regulated generation and clearance of reactive oxygen species (ROS) is required for normal immune responses [2]. In the past two decades, the effect of oxidative stress on T cell mediated immune responses playing a role in acute and chronic diseases has been delineated. ROS have been attributed in autoimmunity and antigen specific T cell proliferation. Commitment of T cell to Th1 or Th2 response is regulated by activation of redox sensitive signaling cascades [3].

Antioxidant machinery including intracellular redox couples like GSH/GSSG in T cells governs the endogenous ROS levels and is coupled to the oxidation state of cysteine residues in proteins. Immunoregulatory transcription factors contain redox sensing critical cysteine residues in their active domain that gets modified under oxidative conditions leading to dysregulated execution of immune responses [4]. These domains are being focused as a prime target in developing novel agents to modulate immune responses. Perturbation in cellular redox status is known to play a dual role; mild oxidative stress can enhance the T cell proliferation whereas induction of intermediate and high levels of oxidative stress is known to suppress T cell mediated immune responses. Oxidative stress mediated modification of NF-κB, NFAT and AP-1 leads to aberrant T cell responses in RA, SLE and Type 1 diabetes [5]. The present review aims to highlight the key targets of cellular redox status on activation of T cells, redox sensitive immunoregulatory transcription factors and associated disorders.

2. Redox homeostasis and TCR signalosome

2.1. Cellular redox homeostasis

ROS are consequences of oxidative metabolism which include the superoxide anions (O_2^{-}), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($OH\cdot$). Of the many potential endogenous sources of ROS, membrane bound NADPH oxidase (NOX), lipoxygenase, mitochondrial respiratory chain and xanthine oxidase have been documented as potent inducers [6–8] Superoxide is generated by one-electron reduction of oxygen molecule which is converted into H_2O_2 by superoxide dismutase. H_2O_2, also produced by Fenton reaction, oxidizes macromolecules to induce genomic instability [9]. Redox sensitive molecules playing an eminent role in T cell mediated immune responses are often

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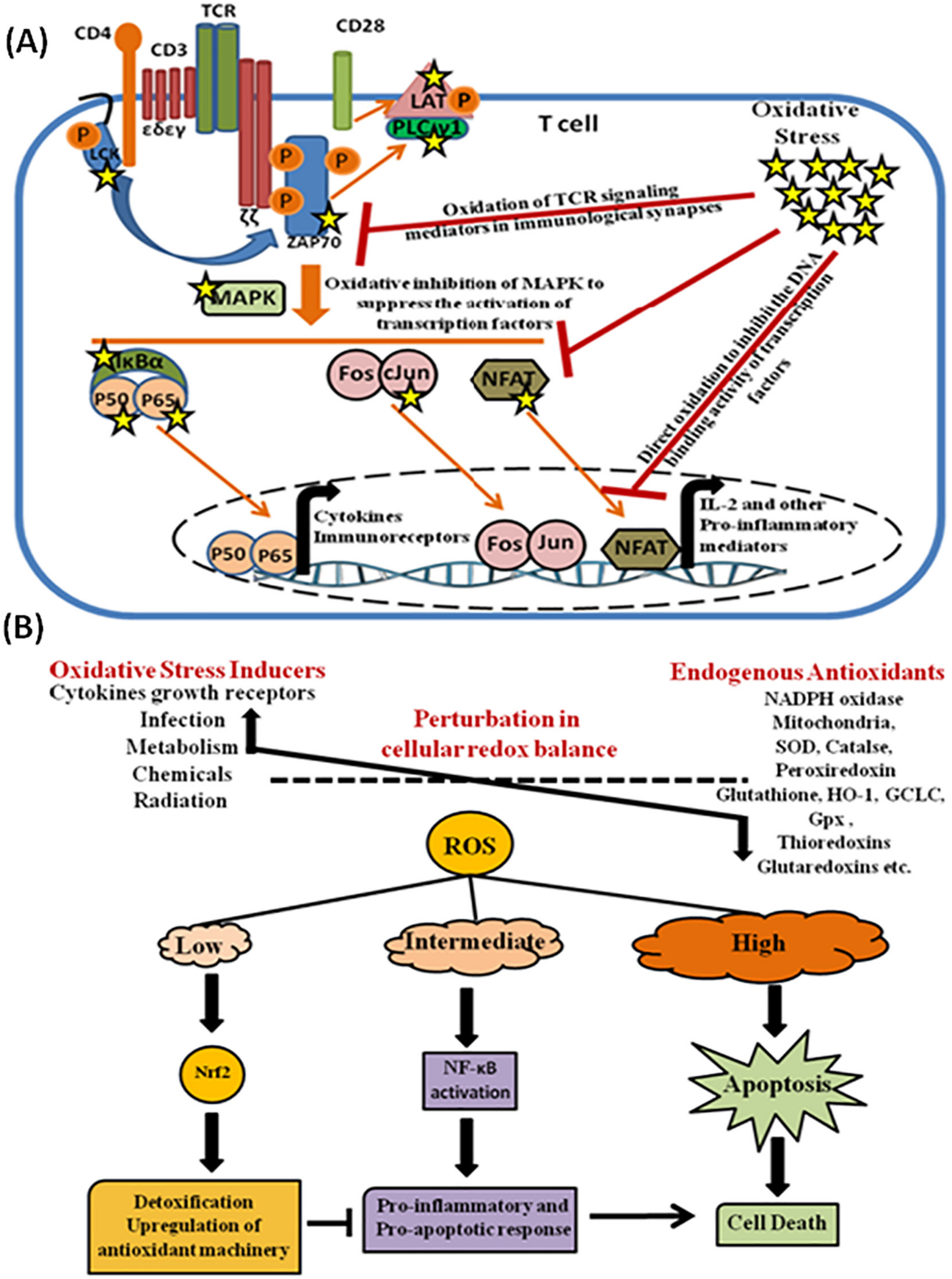

Fig. 1. Perturbation of cellular redox homeostasis regulates the cell fate. (A) Multiple potent exogenous and endogenous oxidants contribute in providing the intracellular oxidative niche. Induction of low level oxidative stress activates the redox sensitive pro-survival pathway Nrf2 that in turn protects cell from oxidative damages. High level of oxidative stress leads to induction of inflammatory responses and apoptosis. (B) Redox modulation of immunoregulatory transcription factors. High ROS levels and importunate exposure to oxidative stress is associated with suppression of TCR mediated signaling leading to inhibition of T cell mediated immune responses. Increased oxidative stress may target multiple molecules in TCR signaling pathway (indicated with yellow star) by inducing oxidation of cysteine residues or oxidation of upstream MAPK. This in turn inhibits the activation of redox sensitive immunoregulatory transcription factors (NF-κB, AP-1 and NFAT). Modulation of redox homeostasis under high oxidative stress further inhibits the DNA binding potential of these transcription factors. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

being modified by ROS (Fig. 1A). H_2O_2 and O_2^{-} have long being documented as to exert diverse effects on the target proteins depending upon the extent and timing of stimulation [10]. Controlled and organised production of ROS underlines its potential to act as signaling molecule in T cell mediated immune responses.

Under stress conditions, expression and temporal distribution of redox couples GSH/GSSG, cys/cyss and thioredoxin oxidised/reduced determines the cellular function and response [11]. Critical cystine residues present in proteins act as redox sensors and are prone to oxidation into sulfenic acids or disulfide formation resulting in the modulation of host immune responses [11,12]. High levels of ROS function as toxin and induce cell death, whereas low levels of ROS acts as second-messengers to induce immunoregulatory pathways by activating redox-sensitive transcription factors, Nuclear Factor-E2-related factor-2 (Nrf2), Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) etc. (Fig. 1B).

2.2. ROS dependent TCR (signalosome) activation

T cell activation and downstream signaling is a highly regulated and coordinated cascade of multiple transducers. Interaction of peptide-MHC with cognate T cell receptor (TCR) is dependent on the threshold stimulus which precisely decides the fate (activation, clonal expansion, differentiation or anergy) of naïve T cells [13–15]. After TCR-peptide-MHC interaction, TCR co-receptor CD4/CD8 assists in localization of Lck in close proximity to the immunoreceptor tyrosine based activation motif (ITAMs) and gets activated by CD45 [16]. Activated Lck in a cascade of events results in activation of LAT and SLP-76 to form nucleation point known as signalosome [17–19]. Phosphorylated LAT and SLP76 serve as adapter proteins for phospholipase Cγ [20]. Activated PLCγ1 hydrolyzes the membrane lipid PI(4,5)P2 (phosphatidylinositol 4,5-bisphosphate) to produce the secondary messengers IP_3 (inositol trisphosphate) and DAG (diacylglycerol). The IP_3 activates Ca^{2+} dependent nuclear factor of activated T cells (NFAT) to induce IL-2 secretion [21,22] whereas DAG results in PKCθ mediated NF-κB stimulation for T cell activation [23].

Griffith et al. showed that exposure to low level of H_2O_2 induced activation of NF-κB and expression of IL-2 in T cell lymphoma [6]. Further, Staal et al. proposed that reduction in the intracellular antioxidant levels, thiol-reactive chemicals like H_2O_2 resulted in inflammatory response due to faulty coupling of T cell receptors mode [24]. NAC inhibited activation of NF-κB, secretion of TNF-α and IL-1 implicating ROS in induction of T cell mediated immune responses [25,26]. At the inflammatory site, T cells are present in an oxidative niche due to release of ROS by neutrophils. Persistent exposure to high levels of ROS can inhibit T cell proliferation and lead to apoptosis [27]. H_2O_2 induced defective TCR dependent phosphorylation of PLCγ1 was abrogated by catalase implicating that ROS is required for normal T cell mediated responses [28]. As mentioned earlier, the indispensable role of LAT in TCR mediated transduction of stimuli, human LAT contains four cysteine residues that act as redox sensors, cys9 and cys26 located in the transmembrane region, cys29 intracellular and cys117 in the cytoplasmic tail [29]. The presence of LAT in the immunological synapse is governed by the palmitoylation of its cys26. ROS induced oxidation of the cys26 hinders in the palmitoylation, causing the displacement of LAT from the plasma membrane, thereby blocking the TCR-mediated signaling pathways [30,31]. Since the membrane localization of LAT is crucial for its function, the hyporesponsiveness of T cells in chronic oxidative stress is believed to occur due to membrane displacement of LAT [29]. Further, ROS were also shown to induce oxidative inactivation of CD45 while thiol antioxidant decreased CD45 regulated Lck kinase phosphorylation [32]. As mentioned above the critical role of PKCθ in regulation of TCR signaling, the catalytic domain of disulfide linked inactive PKCθ contains multiple critical cysteine residues. During T cell activation reduced redox potential, increased GSH concentration and upregulated Trx1 are required to reduce the disulfide linkage in PKCθ [33,34].

Apart from the exogenous ROS or thiol reactive compounds, endogenous NADPH oxidase (Nox) and superoxide dismutase also regulate the T cell mediated immune responses [35]. Nox are membrane bound flavo-cytochrome proteins that transport an electron from NADPH-FAD-cytochrome *b*245-O_2 channel generating superoxide radical [36]. Nox proteins are imperative for immune response by generation of oxidative burst mediated killing of pathogen [35]. Nox has been shown to channelize the lineage commitment of T cells to modulate Th1 whereas Nox deficient cells exhibited Th17 phenotype [37]. Further, Nox was shown to regulate Treg cells mediated suppression of $CD4^+$ T cells and reduced apoptosis was observed in T cells isolated from Nox catalytic subunit [(gp91(phox)] deficient mice compared to wild type T cells [38,39]. Thus, the endogenous oxidant (Nox) plays a crucial role in T cell susceptibility and could serve as a potent target for therapeutic interventions. Mitochondria are another potent endogenous source of ROS which has been eminently embroiled to regulate T cell mediated immune responses. Mitochondrial superoxide is converted to H_2O_2 by Mn-superoxide dismutase (MnSOD) which acts as a major redox signal. Mitochondrial ROS was shown to activate AP-1, NF-κB and inhibition of mitochondrial complex I exhibited reduced production of IL-2 [40]. Murphy and Siegel showed that an increase in mitochondrial respiration is essential for enhanced IL-2 expression [41]. Further, reduction in mitochondrial ROS was shown to reduce the $CD8^+$ T cell responses by regulating cross presentation of dendritic cells [42]. Mitochondria were shown to modulate the Ca^{2+} dependent signals and also increase the ATP gradient required for TCR mediated phosphorylation [43,44].

3. Activation and redox regulation of immunoregulatory transcription factors

3.1. Redox regulation of nuclear factor kappa-light-chain-enhancer of activated B cells pathway

The nuclear factor kappa-B (NF-κB) is a ubiquitous heterodimeric Rel family transcription factor whose activation is controlled by cytoplasmic partitioning. NF-κB was first identified as a transcription factor that binds to the intronic enhancer of the kappa light chain gene (the κB site) in B cells [45]. NF-κB can be activated by an array of stimuli like oxidative stress, ionising radiations, TNF-α, IL-1, MHC-peptide-TCR interaction or CD3/CD28 stimulation [46,47]. Cytoplasmic events in response to these stimuli lead to activation of IKK complex which phosphorylates IκBα at N-terminal region leading to its degradation. NF-κB translocates to the nucleus where further post translational changes govern its activity [48]. Engagement of antigen receptors on B and T lymphocytes also results in activation of IKK and NF-κB (Fig. 2A). A sequential order exists for TCR based NF-κB activation. Activated PKCθ phosphorylates Carma-1, initiating the assembly and recruitment of CBM (Carma-1, Bcl10, MALT-1) complex to the membrane. Once CBM gets phosphorylated, it promotes the generation of lys63 link polyubiquitin chains of NEMO. These polyubiquitin chains are required for the activation of TAK-1, a MAPKKK, responsible for activation of IKKβ [49–51]. The NF-κB/Rel target genes include cytokines, chemokines, cytokine/chemokine receptors, adhesion molecules, survival genes, cell cycle regulators, acute phase proteins and inducible effector enzymes. The majority of proteins encoded by NF-κB target genes participate in the host immune responses.

Ability of ROS to affect multiple factors in a given pathway delimits their defining contributions to redox signaling. Increased Trx1 concentration in the nucleus enhanced NF-κB binding to its consensus sequence in stimulated cells [52,53]. Oxidation of critical cysteine residues at the catalytic site of enzymes and binding pockets of various regulatory proteins affects multiple signaling pathways. Intriguingly, it was shown that oxidative stress mediated glutathionylation of Keap1 inhibits NF-κB activation by degradation of IKKβ [54]. A report by Kaileh M et al., using L929 mouse fibroblast cells, showed inhibition of NF-κB activation by directly suppressing IKKβ kinase activity. Further, they also reported thioalkylation-sensitive redox based inhibition of IKKβ kinase [55]. Cys62 present in the RHD of p50 subunit is known to be imperative for the DNA binding activity of NF-κB. ROS mediated *S*-thiolation of this critical cys residue leads to suppressed NF-κB activity [56,57]. Further, antioxidants were shown to abrogate the DNA binding ability of NF-κB which is dependent on phosphorylation of ser276 of RelA required for its interaction with CBP/300 implicating the regulatory role of ROS in NF-κB activation [58]. An alternate route of NF-

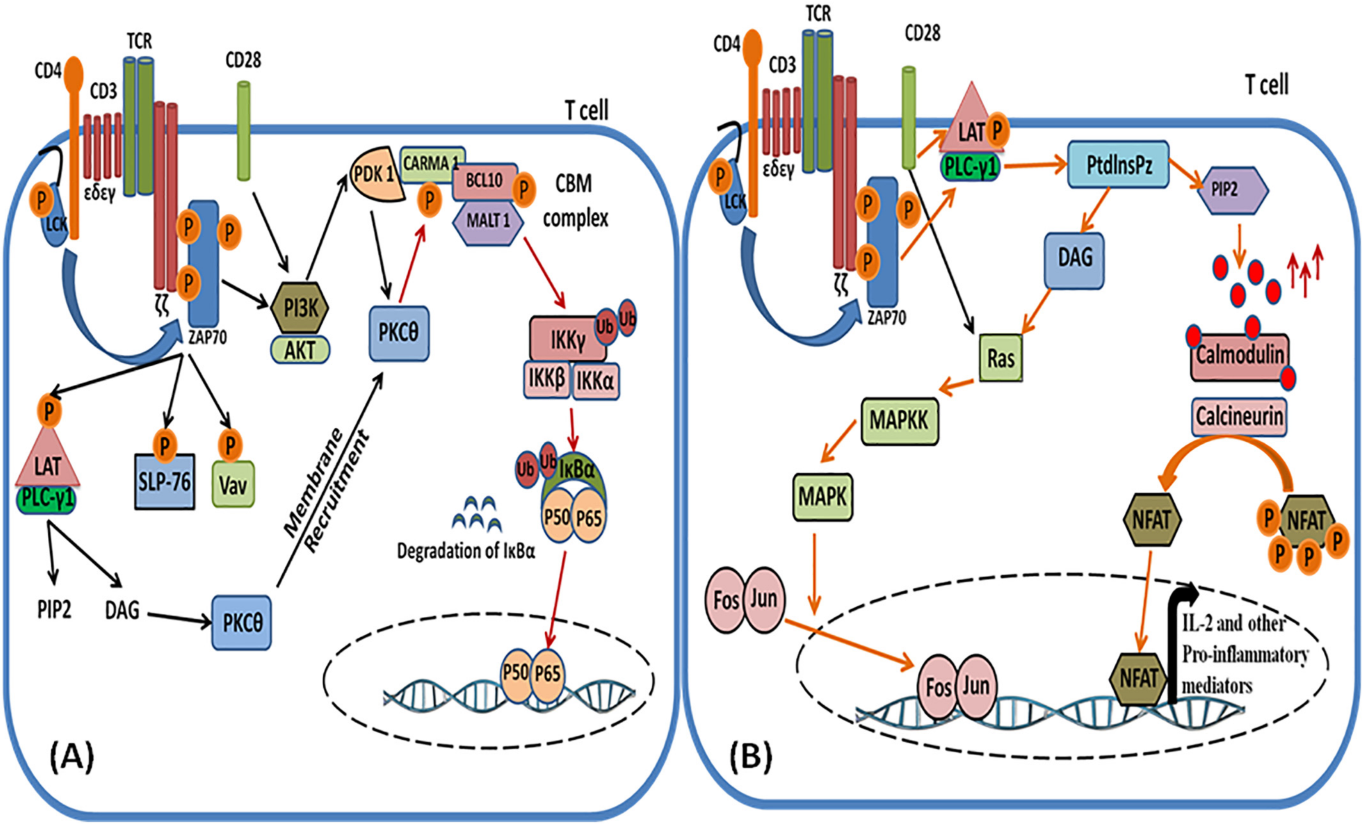

Fig. 2. T cell receptor induced NF-κB, NFAT and AP-1 signaling pathway. (A) Engagement of antigen receptor initiates a signaling cascade resulting in activation of a series of upstream kinases such as IKK, PKC and PI3K which further activate NF-κB by phosphorylation-mediated degradation of IκBα. Activated upstream kinases may also phosphorylate p65, the active subunit of NF-κB. Free activated NF-κB, in the form of p65-p50 heterodimer, translocates to the nucleus and binds to its consensus sequences located in the promoter of a target gene. (B) Activated T cell receptor initiates the signal transduction to activate the Ca^{2+}/calmodulin-dependent phosphatase calcineurin. Calcineurin further dephosphorylates the NFAT to induce its nuclear translocation and activation.

κB regulation by exogenous H_2O_2 exists that involves phosphorylation of IκBα at tyr42, thereby rescuing it from ubiquitin mediated proteasomal degradation [59]. Phosphorylated tyr42 serves as an SH2 domain for binding with PI3K resulting in unmasking of NF-κB and allowing its translocation in nucleus [60]. *S*-thiolation at cys189 results in inhibition of phosphorylation at serine residues and consequent degradation [61]. Another potential target for ROS mediated inhibition of NF-κB is IKK. Oxidative stress mediated by H_2O_2, nitric oxide and arsenite induced *S*-thiolation of cys179 of IKK that led to its inhibition and suppression of NF-κB activation [56,57]. Further, oxidation of cys179 in IKK has been recognized to play a pivotal role in anti-inflammatory action of 15-dPGJ2, prostaglandins [62].

Apart from the endogenous ROS direct action on NF-κB, cross talk with Nrf2 has been shown to inhibit the activation of NF-κB [54]. Nrf2 is a pivotal redox sensitive immunoregulatory transcription factor that conducts the basal expression of downstream cytoprotective, antioxidant and detoxifying genes. Alteration in cellular redox status and generation of mild oxidative stress results in activation and translocation of Nrf2 in nucleus. It further forms heterodimers complex with Maf, a co-transcription factor, which binds to the antioxidant response element sequence to regulate the expression of downstream genes [63]. Mutation in cys151 of KEAP-1 was shown to inhibit sulforaphane and *tert*-butylhydroquinone induced Nrf2 activation [64]. Interestingly, studies employing in vitro alkylation and in vivo site-directed mutagenesis illustrated the pivotal role of cys273 and cys288 for Nrf2 activation. Mutation in these two cysteines resulted in subdued KEAP-1 mediated inhibition of Nrf2 pathway [65]. Activation of Nrf2 was shown to abrogate mitogens induced inflammatory responses. The anti-inflammatory effects have been attributed to HO-1-Nrf2 dependent protein, mediated inhibition of pro-inflammatory cytokine production, leukocyte migration and adhesion [66]. Intriguingly, an alternate route of Nrf2 mediated anti-inflammatory action is mediated via cross talk with NF-κB. Several studies have highlighted the Nrf2 and NF-κB cross talk as primary target for development of novel anti-inflammatory agents. Cinnamaldehyde exhibited suppression of NF-κB pathway by activating Nrf2 and inhibiting IκBα. Polyphenols like curcumin showed activation of Nrf2 that led to modulation of transactivation of NF-κB [67]. KEAP-1 has been shown to bind IKKβ and causes its degradation by acting as an adapter for CUL-3 based E3 ligase [68]. Further, pro-oxidant like 1,4-naphthoquinone has been shown to activate Nrf2 and concomitantly induced KEAP-1 mediated inhibition of NF-κB in murine lymphocytes to suppress mitogens induced inflammatory responses [54]. Therefore, these studies further comfort the role of redox based Nrf2 in modulating the NF-κB pathway.

3.2. Redox regulation of nuclear factor of activated T cell pathway

The nuclear factor of activated T (NFAT) cell is functionally related to Rel A family of proteins. NFAT was first discovered as an inducible transcription factor that regulated the expression and secretion of IL-2 by stimulated T cells [69,70]. On TCR-peptide-MHC engagement, signaling in immunological synapse induces phosphorylation of PLCγ which further hydrolyses PI(4,5)P2 into PIP_2 and DAG. PIP_2 binds to the receptor on endoplasmic reticulum triggering the opening of Ca^{2+} channels thereby increasing its intracellular concentration. Rise in cytoplasmic Ca^{2+} concentration results in activation of calmodulin/calcineurin [71]. Calcineurin dephoshorylates PxIxIT motif at N-terminal region of NFAT resulting in its nuclear translocation. NFAT translocate to the nucleus and binds to its consensus sequence along with some additional transcription factors to regulate gene expression (Fig. 2B)

[33,72,73]. NFAT cooperates with AP-1 to trigger T cell responses, FoxP3 to control immune tolerance, MEF to control muscle development and GATA to control heart development [74].

Since then extensive studies have elucidated its role as signal transducer in regulating T cell mediated immune responses. NFAT plays a key role in eliciting and regulating immune responses by regulating the expression of IL-2, IL-3, IL-10, IL-4, IL-5, IL-13, GM-CSF, TNF-α, IFN-γ, CD25 and Cox-2. It also plays a pivotal role in differentiation of $CD4^+$ T helper cells and Th1 response [71,75]. NFAT regulated by changes in cellular redox which results in impairment of T cell functioning. Oxidative stress has been shown to suppress transcriptional activity of NFAT [76]. Cells cultured in thiol deficient medium having low levels of glutathione showed reduced NFAT:DNA binding, and were unresponsive towards IL-2 and resistant to H_2O_2 induced Fas mediated apoptosis [77,78]. H_2O_2 mediated oxidative stress was shown to inhibit calcineurin and subsequent activation of NFAT in NK cells [79]. Redox sensitive Fe and Zn ions associated to the active domain of calcineurin. Thioredoxin mediated inhibition of calcineurin and reduced calcineurin activity in thiol deprived cells substantiated the pivotal role of cellular redox regulation of NFAT [80,81]. Moreover, thiol moiety in methionine which is regulated by methionine sulfoxide reductases system governs the functioning of NFAT [82]. Conserved Met residues (Met179/Met228 and Met10) residing next to cys residues are present in human calcineurin. ROS mediated oxidation of Met residues may facilitate the oxidation of cys178, cys229 and cys11 residues in vicinity. This leads to loss of conformational integrity of calcineurin which further inhibits NFAT activation [83,84].

Further, reports have highlighted that ROS produced by mitochondrial respiration enhanced the activation of NFAT in T cells. The matrix MnSOD converts superoxide into H_2O_2 that diffuses into the cytoplasm and enhances nuclear localization of NFAT [85]. Interestingly, prooxidants induced oxidative stress inhibited T cell proliferation and cytokine secretion by suppressing mitogen induced activation of NFAT. Antioxidants abrogated the observed anti-inflammatory effects [86]. Quinone derived compounds exhibiting anti inflammatory effects were shown to interact with the −SH of critical cys residues thereby attenuating the functioning of the immunoregulatory protein. Therefore, ROS mediated *S*-thiolation could also play a decisive role in regulating the activation of NFAT [54,87].

3.3. Redox regulation of activator protein 1

Diversity of biological responses like T cell activation, cytokine regulation, leukocyte differentiation, anergy induction, proliferation, survival and apoptosis makes activator protein 1 (AP-1) a key transcription factor. AP-1 is a heterogenous complex composed of two subunits belonging to Fos and Jun, Maf and ATF sub-families, which recognize either 12-*O*-tetradecanoylphorbol-13-acetate (TPA) response elements (5′-TGAG/CTCA-3′) and cAMP response elements (CRE, 5′-TGACGTCA-3′) [88–91]. Both, homodimers of Jun and heterodimers of Fos/Jun, can bind to TPA-responsive elements (TREs). The heterodimers of Fos/Jun results in the higher affinity for DNA-binding. cJun serves as an anchor via DNA binding motif that allows the regulation of gene expression via cFos (Fig. 2B) [92].

Phosphorylation of cJun and de novo synthesis of Fos and Jun governs the functioning of AP-1 [93,94]. Activation of AP-1 and binding to its cognate sequence can be accomplished in mature $CD4^+CD8^-TcR^{high}$ and immature $CD4^-CD8^-TcR^-$ thymocytes, but not in the transitional stages when the cells ($CD4^+CD8^+$ TcR^{low}) are subjected to positive and negative selection [95]. Mutations in AP-1 proximal to the IL-2 promoter decreased the expression of IL-2 indicating the pivotal role of AP-1 in T cell [96]. Diminution in DNA binding and AP-1 activation is critical in the induction of anergy and potential of anergic T cells to respond on re-stimulation [97]. ERK, JNK and p38 MAPK phosphorylate Elk to increase the expression of c-fos leading to the formation of heterodimers and activation of AP-1 in response to oxidative stimuli [98].

Perturbation in cellular redox status is known to modulate the activation and functioning of AP-1 [57]. The intracellular levels of AP-1 are regulated by redox based modulation at transcriptional level and protein turnover. Oxidative stress induced activation of JNK and p38 kinases regulated the activation of c-Jun and ATF2 [57,99]. Induction of oxidative stress inhibited the histone acylation resulting in activation of AP-1. Antioxidants were shown to inhibit binding of AP-1 to its consensus sequence whereas H_2O_2 was shown to increase AP-1 binding to its cognate sequence. The observed increase was dependent upon oxidative stress mediated histone acetylation and reduction in GSH levels [100]. Mitochondrial H_2O_2 can induce oxidation of AP-1 and overexpression of MnSOD that can ameliorate TCR induced activation of AP-1 indicating the regulation of T cell activation by mitochondrial generated oxidative stress [101]. Further, a single conserved cysteine residue present in the DNA binding site of c-Jun act as redox sensor by undergoing reversible oxidation [102]. NO and GSNO were shown to inhibit its DNA binding activity by forming mixed disulfides with the cys269 residue [103]. DNA binding potential of AP-1 was attenuated by depleted intracellular thiols or reduced intracellular levels of Ref-1 or use of oxidised thioredoxin [104,105]. Over-expression of Trx and Ref-1 was shown to potentiate the AP-1 transcriptional activity [106]. Further, Trx mediated oxidation of conserved cysteine residues in AP-1 resulted in altered function [107,108]. Trx induced reduction of conserved cys residue located in the DNA binding domain to enhance the binding of Jun and Fos to the consensus sequence [109,110]. Any perturbation in functioning of immunoregulatory transcription factors may result in dysregulated functioning leading to health impairment.

4. Cellular redox modulation in health and disease

Cellular redox homeostasis is critical for eliciting an efficient immune response. However, prolonged ROS production or dysregulated antioxidant machinery causes imbalance in cellular redox status; which impaired immune responses observed in multiple autoimmune diseases or T cell leukaemia.

4.1. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by production of an array of autoantibodies that induce acute and chronic inflammation in various tissues and organs [111]. Due to the auto-reactive antibody titre elicited self reactive antibody, it was considered to be mediated mainly by B cells that led to inflammation. However, compelling evidences highlight the indispensable role of T cells in stimulating the differentiation, proliferation and maturation of B cell [112,113]. Increased oxidative stress characterized by over production of NOS and dysregulated clearance of ROS was shown in lymphocytes from active lupus patients as a cause of response to cell death signals in SLE [114]. Also, impaired mitochondrial functioning and elevated mitochondrial membrane potential was observed in T cells isolated from SLE patients [115,116]. Along with its impact on T cell signaling, oxidative stress induced modification of self antigens, accumulation of oxidised HDL and generation of autoantibodies cross reactive with DNA, contributes to pathogenesis of SLE [117]. Further, augmentation in intracellular calcium was shown to activate NFAT that altered the expression of CD40L gene of lupus T cells. This led to sustained production of antibodies by B cells. Interestingly, activation of TCR caused hyper-responsive phenotype due to phosphorylation of tyrosine residues present on signaling intermediates in SLE T cells [118]. Aberrant transcription of NF-κB, NFAT and AP-1 results in altered expression of IL-2 characteristic of SLE T cells [119].

4.2. Rheumatoid arthritis

Rheumatoid arthritis (RA) is characterized by accumulation of

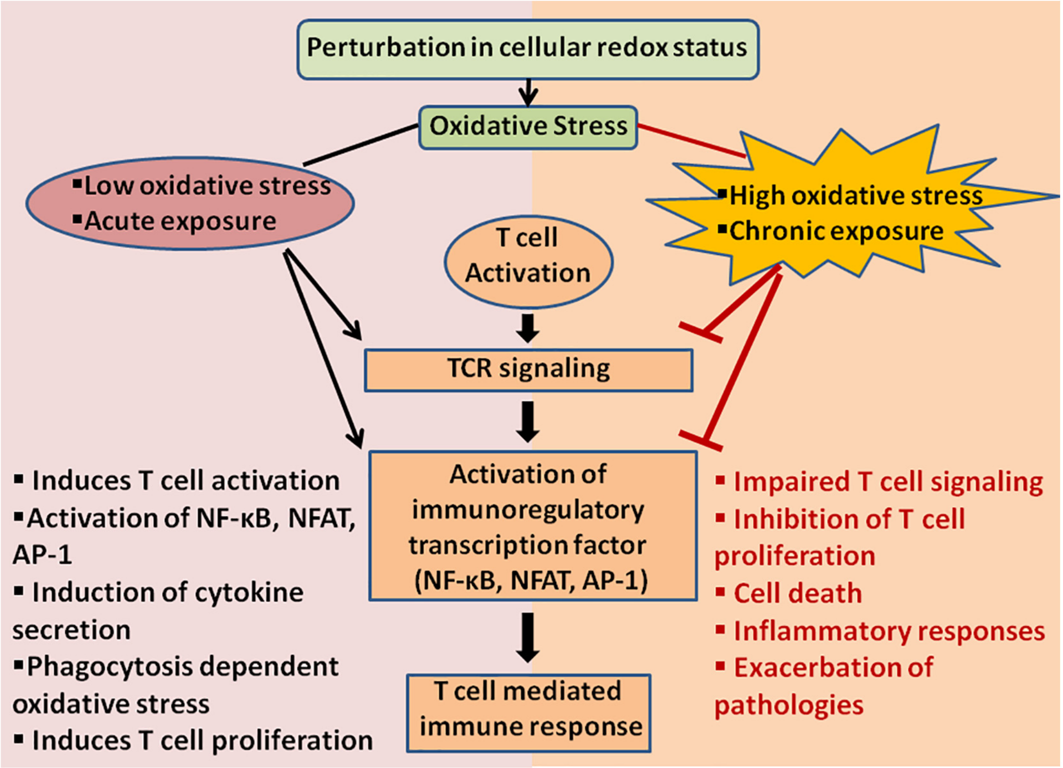

Fig. 3. Cellular redox homeostasis governs the T cell mediated immune responses. Different mode of T cell response occurs under low/acute and high/chronic exposure. ROS plays a dual role in regulating T cell mediated immune responses. Low levels of generated oxidative stress for short duration are required for TCR signaling mediated elicitation of normal T cell response characterized by T cell proliferation, cytokine secretion and clearance of pathogen by phagocytosis. On the other hand, high levels and prolonged exposure of ROS results in impaired TCR signaling pathway that leads to generation of inflammatory response and aggravation of associated disorders.

synovial fluids in joints due to systemic and chronic inflammation [120]. Autoantigens are presented to auto reactive T cells that underline the pathogenesis of RA. Increased activation of T cell was observed to increase the severity of arthritis. Other T cell types including regulatory T cells and γδT cells have been implicated in the progression of RA [121,122]. NOX-2 derived ROS reduced the T cell mediated severity in arthritis in mouse models [123]. Increased oxidative stress, cytokine production and activation of NOX signaling pathways led to degradation of cartilage and bone in synovial joints by leukocytes, macrophages and other inflammatory cells [124]. Intriguingly, compounds that induce an increase in oxidative niche inside the cell are being investigated as the potent therapeutic modules. Hultqvist et al. showed that phytol induced oxidative burst in granulocytes resulted in apoptosis of autoreactive T cells thereby preventing progression of RA in Ncf1DA rats [125]. Further, NF-κB pathway gets activated in RA affected tissues in knockout studies. NF-κB induced hyper proliferation of synovial cells by increasing the expression of FLIP and bcl-2 which are pivotal for pathogenesis of RA [126]. NFAT1 is the regulating transcription factor for osteoclast differentiation and expression of osteoclast-specific genes. Studies using NFAT1 knockout mice and NFAT1/4 double- knockout mice showed an asymmetric oligoarthritis corroborating the crucial role of NFAT in RA [127].

4.3. *Type 1 diabetes*

Type 1 diabetes is an autoimmune disease underlined by leukocyte infiltration due to the recognition of pancreatic β-cell antigen by T cells. Oxidative stress has been implicated in causing the diabetes associated vascular damages leading to cardiopathy, retinopathy and nephropathy [128,129]. NF-κB induced activation and hyperactivity of T cells in antigen presenting cells resulting in altered cytokines secretion which may contributed to the initiation of type 1 diabetes. NF-κB is also activated by a number of pro-inflammatory cytokines to regulate both the survival and death of β-cells [130]. Oxidative stress induced in pancreatic islets led to increased production of TNF-α and IL-1β due to activation of NF-κB [131]. Metalloporphyrin-based SOD mimics were shown to delay the onset of type 1 diabetes induced by adoptive transfer of diabetogenic T cell clone in young NOD-SCID mice. This further highlighted the role of redox modulation in etiology of type 1 diabetes [132]. In an elegant study with a constitutively active mutant mouse model, it was shown that NF-κB activation is a potential trigger of immune-mediated diabetes. Transgenic mice of human IKK2 demonstrated spontaneous development of immune mediated diabetes with insulitis and hyperglycemia. The study involved an array of genes, involved in allergic inflammation and increased MHC class I/II expression by pancreatic β-cells and diabetes development [133]. Further, NFAT pathway was shown to regulate gene promoters in islets. Selective targeting of components of NFAT pathway can enhance insulin production in pancreatic β-cells [134]. Thus, redox modulators used as therapeutics may serve as a beneficial tool for treatment of type 1 diabetes and its complications.

5. Conclusion

Synchronised functioning of multiple immunoregulatory mediators is required to generate an efficient T cell mediated immune response. Response to an antigenic stimulus is mediated via T cell receptor induced signal transduction pathway and activation of immunoregulatory transcription factors. One of the major factors that can modulate the T cell immune responses is the spatio-temporal generation of ROS. Cellular redox balance has been highlighted as a physiological mediator and regulator of multiple cellular processes. High ROS production or chronic oxidative stress severely affects the immune cell functioning leading to inflammation and associated inflammatory disorders (Fig. 3). TCR mediated signaling pathways and transcription factors involved in generation of T cell mediated adaptive responses contains multiple critical cysteine residues. Under conditions of oxidative stress, these cysteine residues are susceptible towards oxidation into sulfenic acids or disulfide formation or *S*-thiolation leading to impaired functioning of immunoregulatory transcription factors. Blocking of NF-κB activation, thereby inhibiting T cell responses, is used as an important strategy for curbing inflammation using small molecules [135,136].

Further, cross talk between mitochondrial metabolism, ROS and Ca^{2+} regulation has been shown to induce T cell activation [137]. Therefore, a better understanding of endogenous oxidative stress induced modulation of T cell dependent adaptive immune responses is of utmost importance. Thus, cellular redox modifiers may serve as an amenable strategy in eliciting the outcome of contemporary immunology which is focused on improving the substandard vaccines and destruction of autoimmune T cells.

Conflict of interest

There are no actual or potential conflicts of interest.

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