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Redox homeostasis, T cells and kidney diseases: three faces in the dark

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Abstract

The redox equilibrium is crucial for the maintenance of immune homeostasis. Here, we summarize recent data showing that oxidation regulates T-cell functions and that alterations of the redox equilibrium may play an important role in the pathogenesis of inflammatory conditions affecting the kidneys. We further discuss potential links between oxidation, T cells and renal diseases such as systemic lupus erythematosus, renal ischaemia/reperfusion injury, end-stage renal disease and hypertension. The basic understanding of oxidation as a means by which diseases are directly affected results in unexpected pathophysiological similarities. Finally, we describe potential therapeutic options targeting redox systems for the treatment of nephropathies affecting humans.

Key words: acute kidney injury, autoimmunity, end-stage kidney disease, systemic lupus erythematosus (SLE), T-cell activation

Introduction

Recently, redox homeostasis has been the focus of intense investigations, especially in inflammatory conditions [1], and most recently in research of regulated necrosis [2–4]. An altered inflammatory response is the basis of many diseases, including allergy and systemic autoimmunity, which often affect the kidneys. Under particular circumstances, which are not yet completely understood, inflammation is not properly terminated, resulting in continuous activation of the immune cells and prolonged inflammation and tissue damage mainly mediated by T cells and macrophages. In this review, we summarize recent advances on how the redox balance regulates T-cell functions and we discuss the possible interplay between oxidation and T cells in inflammatory diseases affecting kidneys.

T-cell activation and differentiation

T cells are key orchestrators of the response against pathogens and are also fundamental in maintaining self-tolerance. A number of clinically important conditions have been described in which T-cell functions are altered, as in AIDS or upon immunosuppression for solid organ transplantation. T-cell progenitors differentiate in the thymus into immature T cells that acquire the expression of the T-cell receptor (TCR), which recognizes antigen peptides from pathogens presented along with major histocompatibility complex (MHC). In addition to the TCR, T cells are characterized by expression of the co-receptor molecules CD4 and CD8 on their cell surface. $CD4^+$ T cells, also called T helper (Th) cells, recognize antigen/MHC-II complexes on antigen presenting cells (APCs) and coordinate the activation of other immune cells including B cells, macrophages, etc.

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Therefore, CD4$^+$ T cells are crucial for coordination of the immune response and for the elimination of invading pathogens. On the other hand, CD8$^+$ T cells, referred to as T cytotoxic cells, recognize antigen/MHC-I complexes and are responsible for the killing of pathogen-infected cells.

Recognition of MHC/peptide complexes by the TCR and the co-receptors results in T-cell activation (for a review, see [5]). Signalling via the TCR is further supported by co-stimulatory (e.g. CD28) and accessory (e.g. integrins) molecules. Upon TCR ligation, members of the Src family kinases Lck and Fyn phosphorylate the immunoreceptor tyrosine-based signalling motifs (ITAMs) located within the TCR-associated CD3 and ζ chains. This event results in the recruitment of the tyrosine kinase ζ chain–associated protein kinase of 70 kDa (ZAP-70) to the receptor. ZAP-70 is in turn activated and further phosphorylates the linker for activation of T cells (LAT), a transmembrane adaptor molecule that further assembles a complex leading to Ca^{2+} flux, Ras and protein kinase C (PKC) activation (Figure 1). These events ultimately culminate in gene transcription, proliferation and differentiation of T cells.

T-cell activation and differentiation depends on APCs such as dendritic cells (DCs), macrophages and B cells. Among them, DCs are highly specialized in antigen presentation and in T-cell priming [6]. DCs act as sentinels in the body where they capture antigens. Danger signals such as microbial products or cytokines from injured tissue activate DCs, which in turn migrate to secondary lymphoid organs, where they allow initiation of the immune response [7]. The nature of the stimulus dictates which kind of immune response will be set in motion [8]. Therefore, depending on the insult affecting a given tissue, different subsets of DCs can be generated that in turn are able to coordinate the differentiation of a particular Th subset.

To date, the following Th subsets have been described: Th1, Th2, Th9, Th17, Th22, Tfh (follicular helper T cells), Tr1 (type 1 regulatory T cells) and Treg (regulatory T cells), each possessing a specific function in the elimination of pathogens. The development, the function and the involvement of Th subsets in human diseases are summarized in Figure 1 (for a review, see [9, 10]).

Redox equilibrium: an emerging new player in the regulation of T-cell differentiation

Reactive oxygen species (ROS) include the superoxide anion radical ($O_2^{\cdot -}$), hydroxyl radical ($HO^{\cdot}$), hydrogen peroxide (H_2O_2) and

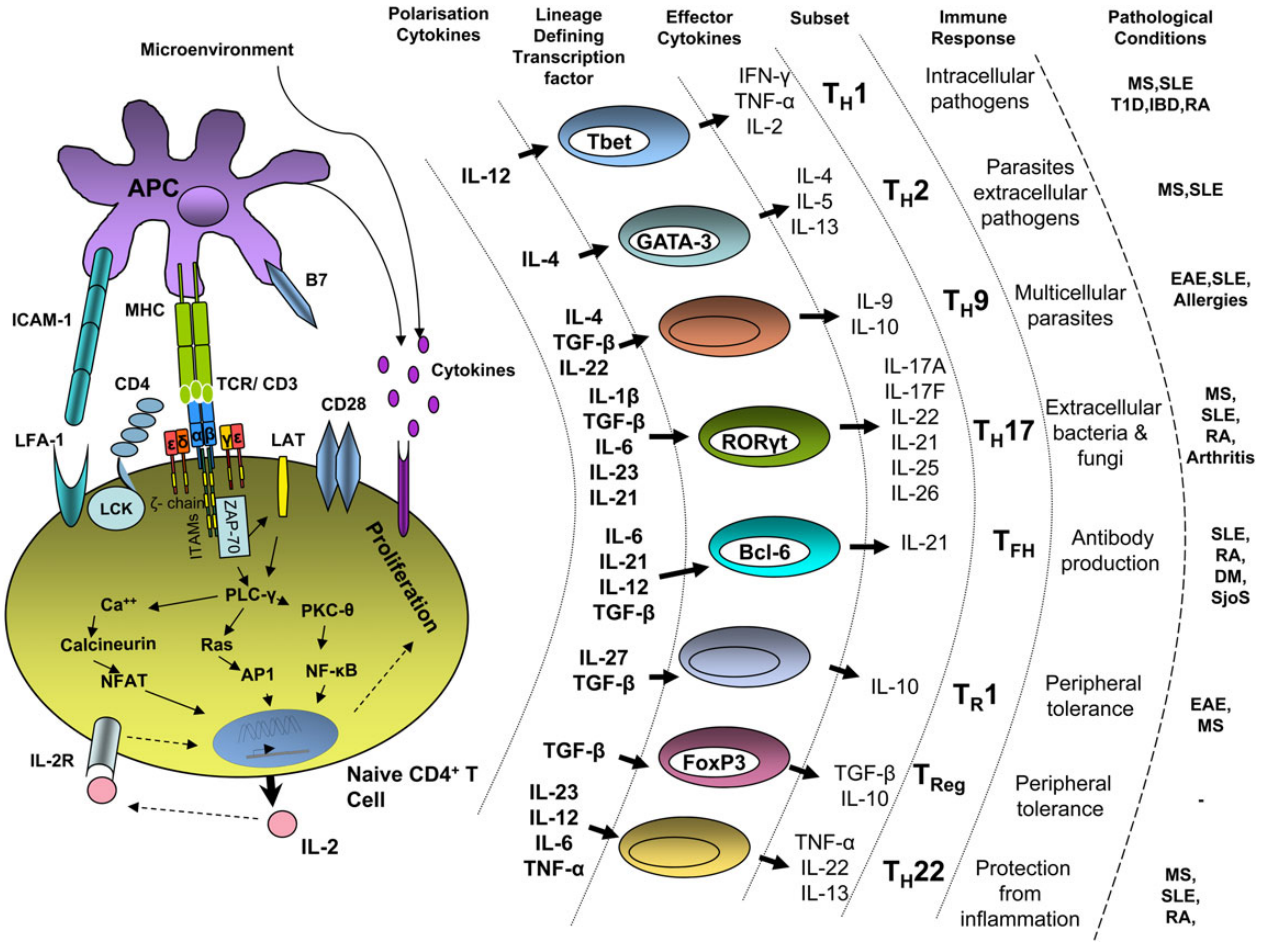

Fig. 1. T-cell activation and T-cell subsets differentiation. Upon TCR ligation by MHC/peptide complexes on APCs, an activating signal is triggered within T cells leading to transcriptional activation, IL-2 production and proliferation. Additional receptors (e.g. CD4, CD28, integrins and cytokine receptors) also participate in this process. The orchestration of these signals results in Th differentiation into various effector and regulatory subsets. Cytokines inducing Th differentiation, lineage-defining transcription factors, effector cytokines, physiological function and implication in pathological conditions are indicated. RA, rheumatoid arthritis; MS, multiple sclerosis; SLE, systemic lupus erythematosus; T1D, diabetes mellitus type 1; IBD, inflammatory bowel disease; DM, juvenile dermatomyositis; SjoS, Sjogren's syndrome; EAE, experimental autoimmune encephalomyelitis.

hypochlorous acid [11]. It has been known for many years that ROS may have, in high concentrations (oxidative stress), deleterious effects on living organisms, as they can damage all major cell constituents, including lipids, proteins and DNA. Conversely, at lower concentrations, ROS participate in the regulation of signalling processes and cellular responses such as proliferation and differentiation [11, 12]. Therefore, in order to maintain the appropriate redox state, cells require a regulation system for the precise generation and elimination of ROS (redox homeostasis).

Superoxide is generated in the mitochondria when electrons 'accidentally' leak from the transport chain and reduce molecular oxygen (Figure 2) [12]. Additionally, cells also possess enzymatic sources of superoxide such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOX) and xanthine oxidase (XO) [11]. Superoxide is highly unstable and rapidly dismutates to H_2O_2, a process mediated by the superoxide dismutase (SOD) (Figure 2). H_2O_2 can further participate in the generation of $HO^{\cdot}$ during Fenton reactions [12].

In order to protect cell constituents from oxidative damage and/or to ensure the appropriate intracellular concentration of ROS required for cell functions, cells have developed a complex defence system comprising a variety of substances (antioxidants), which neutralize the excess ROS (Figure 2). Antioxidants include enzymes such as SOD, glutathione peroxidase, catalase and non-enzymatic agents such as vitamin C, vitamin E, the tripeptide glutathione (γ-L-glutamyl-L-cysteinyl-glycine, GSH), carotenoids, flavonoids and also free amino acids, which can easily react with ROS (e.g. cysteine) [11, 12]. Whereas reduced GSH is one of the major intracellular redox buffers, the cysteine/cystine couple plays an important role in the regulation of extracellular redox homeostasis [13].

It is well established that TCR triggering results in the generation of ROS (for a review, see [14]). Different sources of ROS in T cells have been described, including NOX enzymes and mitochondria. Despite the fact that the mechanisms by which ROS regulate T-cell activation are not yet completely clear, an appropriate redox state is absolutely required for T-cell activation. Alterations in the redox equilibrium induced by TCR-generated ROS may influence the activation of several molecules and support signalling [14]. However, high levels of ROS (oxidative stress) are detrimental for T cells, as they may inhibit signalling or induce apoptosis. In fact, a decrease in intracellular GSH blocks TCR-mediated calcium flux and proliferation in human peripheral T cells [15, 16].

The same regulatory mechanism applies to a variety of cells in which ROS function as signalling molecules by inhibiting phosphatases, modulating the activity of kinases and regulating the activation of transcription factors [1, 11]. Nevertheless, the

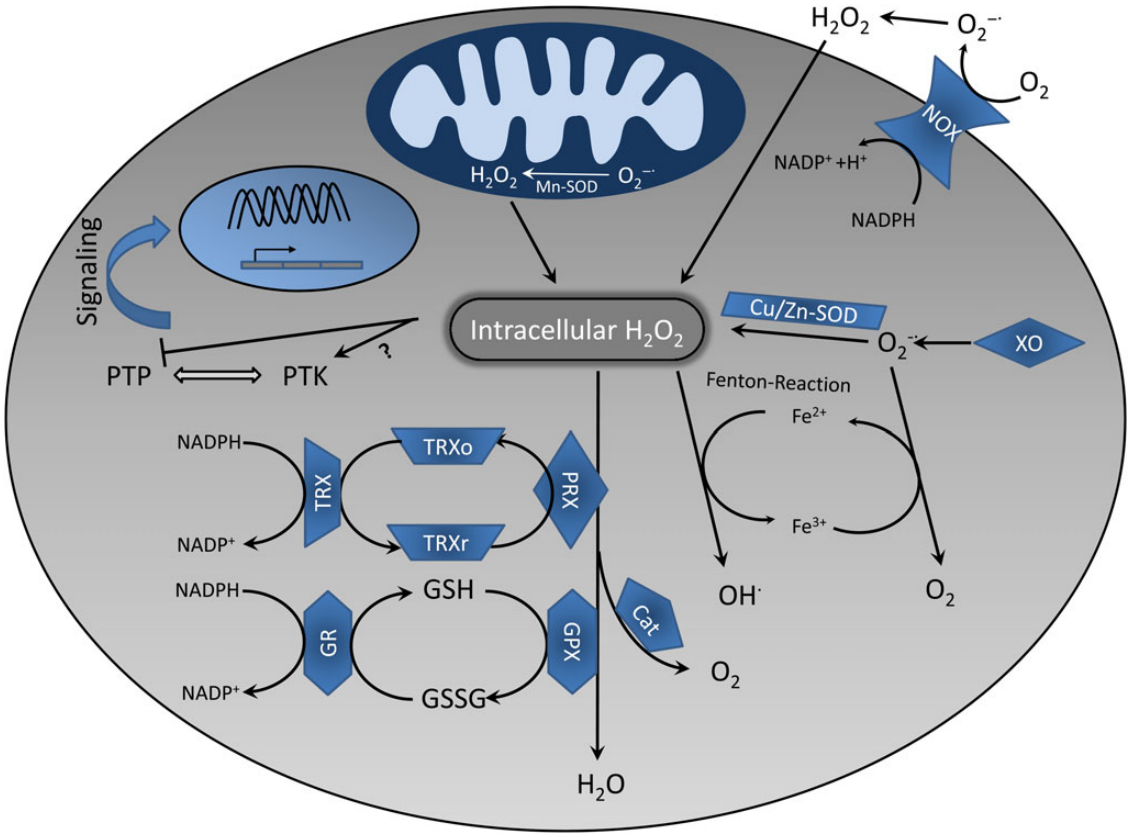

Fig. 2. Redox homeostasis in T cells. The main sources of ROS are the mitochondrial electron transport chain, NOX and XO, which produce $O_2^{\cdot-}$. $O_2^{\cdot-}$ either spontaneously or with the help of specific enzymes (i.e. SOD) is catalysed to H_2O_2. The latter can be further reduced to water by Cat or converted to OH· in the presence of transition metals (Fenton reaction). Different antioxidant systems have also been depicted. GSH is the most important cellular antioxidant. GPX mediates GSH oxidation by H_2O_2, which is converted to GSSG. GSSG is reconverted to GSH by GR via oxidation of NADPH. The TRX system is involved in cellular redox homeostasis as well. In this case, H_2O_2 oxidizes TRXr to TRXo, which is subsequently re-reduced by NADPH. H_2O_2 functions as a regulator of T-cell signalling via inhibition of PTPs or modulating the activity of PTKs. NOX, NADPH oxidase; XO, xanthine oxidase; $O_2^{\cdot-}$, superoxide anion; SOD, superoxide dismutase; Cat, catalase; GSH, glutathione; GSSG, glutathione disulfide; TRX, thioredoxin; PTP, protein tyrosine phosphatase; PTK, protein tyrosine kinase; TRXr, reduced thioredoxin; TRXo, oxidized thioredoxin; PRX, peroxiredoxin, GR, glutathione reductase; GPX, glutathione peroxidase.

exact molecular mechanisms of how ROS regulate signalling are only partially understood, and we are far from understanding these mechanisms in disease settings of stress, sepsis, autoimmunity and acute kidney injury.

Accumulating evidence now suggests that T-cell differentiation is strongly redox dependent. Several *in vitro* experiments performed on isolated T cells have shown that the redox state regulates interleukin 2 (IL-2) and IL-4 production. Antioxidants inhibit IL-2 and IL-4 expression [17–19]. In agreement with these findings, a pro-oxidant situation induces the expression of IL-2 and IL-2R and also enhances proliferation [20–22]. Interestingly, inhibition of mitochondria-generated ROS in T cells isolated from patients suffering from atopic dermatitis also blocked TCR-mediated IL-4 production [17]. Therefore, in recent years, treatment with antioxidant has become a therapeutic option to cure inflammatory diseases (discussed below).

The data reported above suggest that IL-2 and IL-4 production in T cells requires ROS. The molecular mechanisms of ROS-mediated regulation of cytokine production are not yet clear. Although ROS have been directly implicated in the regulation of the activation of transcription factors, it appears that, in T cells, oxidative processes likely regulate proximal TCR signalling, which in turn affects the signal strength and the execution of the transcriptional programme [14].

In addition to the effects on cytokine production, different studies have assessed the role of the redox balance on Th differentiation *in vitro*. It appears that a pro-oxidation state induces T-cell polarization into the Th2 lineage. In fact, an increase in superoxide generation correlates with augmented IL-4, IL-5 and IL-13 production [23]. Importantly, antioxidants inhibit this effect. Similarly, treatment with *N*-acetyl cysteine (NAC), a GSH precursor, or GSH suppresses Th2 differentiation [24, 25]. In agreement with the latter studies, higher free thiol levels correlate with a skewed Th1/Th2 balance towards the Th1 lineage [26]. Also, data from NOX2-deficient mice suggest that naive $CD4^+$ T cells with defective generation of ROS are biased towards the Th1 lineage [27, 28]. In the absence of NOX2, T cells display enhanced T-bet and reduced STAT5 and GATA3 activation and, accordingly, secreted more interferon γ (IFN-γ) but less IL-4 [29].

In addition to Th1/Th2 differentiation, ROS have also been implicated in the generation of Th17 cells. A recent study has shown that T cells from immediate early response gene X-1 (IEX-1)-deficient mice have increased mitochondrial ROS production upon CD3/CD28 stimulation and enhanced generation of Th17 cells [30, 31]. The specific involvement of ROS in the generation of Th17 cells was shown by the treatment with antioxidants that suppress Th17 differentiation in IEX-1-deficient mice. In addition, these mice are highly susceptible to develop collagen-induced arthritis.

Understanding how oxidation regulates Th polarization is an understudied area that needs further investigation. Indeed, recent studies emphasize that reprogramming of Th differentiation may have important therapeutic implications for the treatment of inflammation [32, 33].

Redox-dependent regulation of APC functions: the effects on Th differentiation

T cells are primed in lymphoid tissues and their differentiation depends on cytokines and signals provided by neighbouring cells, in particular APCs. Also APC functions can be regulated in a redox-dependent manner. Therefore, alterations of the redox state of APCs or of the microenvironment may affect the ability of APCs to support T-cell differentiation. In this section, we summarize recent data highlighting the importance of the redox state of APCs for T-cell differentiation and its potential implication in the development of human autoimmune diseases.

The role of GSH

It has been observed that an increase in intracellular GSH levels in LPS-stimulated human monocyte-derived DCs and thymic stromal lymphopoietin-activated myeloid DCs promoted Th1 (IFN-γ) but inhibited Th2 (IL-4, IL-13) responses [34]. When GSH levels are elevated, DCs release more IL-27 and IL-12, which in turn support Th1 differentiation. Indeed, blocking IL-12 by the addition of neutralizing anti-IL-12 monoclonal antibody or suppressing IL-27 by siRNA results in suppressed production of the Th1 cytokine IFN-γ. In addition, GSH levels are critical for the regulation of IL-12 production by APCs such as DCs and macrophages [35–38]. Collectively, these studies suggest that an oxidized intracellular milieu in APCs decreases the secretion of IL-12, thus skewing Th polarization to the Th2 lineage, whereas a reduced intracellular state in APCs favours Th1 differentiation.

Analysis of the molecular mechanisms involved in the expression of IL-12 revealed that GSH regulates IL-12 expression by inducing p38-MAPK but suppressing JNK-MAPK activation [39, 40]. GSH is not only involved in the regulation of redox homeostasis, but it also appears to control other aspects of cellular functions, including gene transcription and proliferation [40]. Therefore, it is not yet clear whether GSH regulates cytokine release in a redox-dependent manner. However, a study suggests that ROS produced upon LPS stimulation of human monocyte-derived DCs is required for cytokine production by DCs [41].

Altered GSH levels have been found in a variety of autoimmune diseases [42]. A correlation between decreased GSH levels and anti-thyroperoxidase antibodies has been found in Hashimoto's thyroiditis [43]. Moreover, a mutation in glutathione S-transferase, an enzyme facilitating the elimination of ROS by catalysing their conjugation to GSH, has been found to correlate with an elevated risk of developing anti-citrullinated protein antibody and rheumatoid arthritis (RA) [44]. Therefore, reduced GSH levels in autoimmunity may skew Th differentiation to the Th2 subset or even to the Th17 lineage [45], thus favouring autoantibody production.

The role of NOX2

ROS have also been directly implicated in antigen processing and in the generation of the MHC-II-restricted peptide repertoire in APCs. NOX2 appears to be involved in this process [46–48]. NOX2-mediated ROS inactivate cysteine cathepsines in the phagosome, thus modulating their activity. In the absence of ROS, cysteine cathepsines have altered substrate specificity that affects the processing of proteins. It has been shown that in myelin oligodendrocyte glycoprotein (MOG)-induced experimental autoimmune encephalomyelitis (EAE), NOX2-deficient APCs are unable to prime Th cells because of inefficient presentation of the MOG immunodominant epitope [46]. Consequently, NOX2-deficient mice are protected from EAE. However, these effects appear to be specific for certain proteins and for EAE. In fact, NOX2 deficiency results in the development of inflammatory diseases in both humans and mice (for a review, see [49–51]). As ROS production is strongly decreased in cells lacking a functional NOX2, the above findings contradicted the general idea that ROS promote inflammation. It is now clear that ROS have different effects depending on their levels, their source and when they

are produced and, hence, under particular conditions, may promote hyperinflammatory responses, whereas in other cases they suppress autoimmunity. The molecular mechanisms regulating these two different outcomes remain unclear, but a necro-inflammatory auto-amplification loop may contribute to the pathogenesis [3]. One study has shown that NOX2-generated ROS are required to activate p38-MAPK signalling in IFN-γ/LPS-stimulated murine DCs [52]. This pathway in turn suppresses IL-12 expression. NOX2-deficient DCs secrete more IL-12 and skew $CD4^+$ T-cell differentiation to the Th1 subset. It also appears that NOX2-generated ROS in Tregs is required for their suppression function [53]. In the absence of a functional NOX2 or upon antioxidant treatment, Tregs are less efficient in the suppression of effector cells. These data demonstrate that NOX2-derived ROS may regulate tolerance at different levels.

The role of oxidized lipids

Recent data have clearly highlighted that oxidation of low-density lipoproteins (LDLs) influences DC functions and plays a crucial role in atherosclerosis and autoimmunity. Atherosclerosis is a chronic inflammatory disease affecting the functionality of blood vessels [54]. It is also established that a correlation exists between autoimmunity [e.g. RA and systemic lupus erythematosus (SLE)] and the risk of developing cardiovascular disease [55]. Now possible links between atherosclerosis and autoimmunity have been proposed [56, 57]. LDLs function as lipid carriers in the blood [58]. When LDLs diffuse into the subendothelial area of the artery, they can undergo ROS-mediated oxidation. Oxidized LDLs (oxLDLs) function as inflammatory mediators via different pathways [59]. It is now evident that oxLDLs regulate DC function and Th polarization. In fact, oxLDLs stimulate DCs to polarize T cells into the Th1 lineage in both humans and mice [56]. Th1 cells in turn support and promote the disease, likely via IFN-γ [60]. In addition to promoting Th1 differentiation, new findings suggest that oxLDLs also support Th17 polarization both *in vitro* and *in vivo* [61]. oxLDLs induce IL-6 secretion by DCs upon binding to CD36 and TLR4 via MyD88, thus in turn favouring Th17-cell differentiation. Furthermore, this study demonstrates that oxLDLs enhance the pathogenicity of MOG-specific T cells and the severity of EAE. What is the exact temporal relation between atherosclerosis and autoimmunity is still unclear. It has been proposed that elevated levels of inflammatory cytokines in autoimmunity promote atherosclerosis [55]. However, on the basis of the above data, it is possible to speculate that increased levels of oxLDLs under atherosclerosis conditions may favour Th1 or Th17 differentiation, thus driving the progression of autoimmunity. How oxLDLs promote both Th1 and Th17 cells is not yet clear. It is possible that the discrimination between Th1 versus Th17 may depend on the chemical composition of the oxLDLs. DCs are able to recognize different species of modified lipids via different receptors (e.g. CD36, LOX-1) [56, 58]. Therefore, the integration of different signals downstream of these receptors will likely dictate the outcome of the DC-mediated Th developmental programme.

An additional study further emphasizes the importance of lipid oxidation in DC maturation and in turn on Th differentiation [62]. Mice lacking lipoxygenase (LO), an enzyme oxygenating free and esterified polyunsaturated fatty acids, show enhanced DC maturation and increased Th17 differentiation. Moreover, these mice also display a more severe EAE, thus indicating the importance of LO and LO-derived oxidized lipids in autoimmunity. Mechanistically, LO participates in regulation of the activation of the transcription factor NRF2, which in turn inhibits DC maturation. LO also seems to inhibit IL-23 transcription, which is required for Th17 polarization.

On top of these molecularly defined pathways, cell death in a form of regulated necrosis, referred to as ferroptosis, has recently been associated with a defined lipid peroxidation signature [63] that depends on glutathione peroxidase 4 activity and GSH levels [64]. Since regulated necrosis triggers necroinflammation [65], it is conceivable that also these processes of ROS-driven parenchymal damage may contribute to overall organ damage, obviously with a predominantly important function in the kidney [3, 63]. Very recently, ferroptosis has also been described in T cells in immunity to infection [66]. Therefore, pharmacological targeting of ROS differentiation and ferroptosis by means of the same compounds, e.g. ferrostatins, may provide a promising therapeutic option. Today, however, broad clinical application of such inhibitors is precluded by the lack of mechanistic insights.

The interplay between oxidation, Th cells and kidney diseases

The aetiology of many kidney diseases is still largely not well understood. In particular, little is known about the interplay between oxidation, Th cells and tissue damage. As mentioned in the section "T-cell activation and differentiation", under some inflammatory conditions, alteration of Th differentiation is one of the factors contributing to disease development or progression. In this paragraph, we summarize recent data in which a link between oxidation, alterations of T-cell function and renal disease has been proposed and we also discuss potential therapeutic implications (see Table 1).

SLE is one of the most well-known kidney diseases in which oxidative stress is increased [93, 94]. Recent data point out that oxidation inhibits T-cell signalling, leading to Erk activation and DNA methyltransferase expression, thus in turn resulting in DNA demethylation, overexpression of immune genes and autoimmunity [95]. Additional studies have shown that oxidation of PKCδ, which results in its inactivation, is responsible for the defective Erk activation and lupus development in mice [96, 97]. Therefore, antioxidants may represent beneficial co-adjuvants for the treatment of SLE. Indeed, a study has shown that non-enzymatic antioxidants (e.g. NAC and cysteamine) improve survival in a mouse model of SLE [68]. An important advance in the therapy of SLE using dietary supplements has been recently provided. It has been shown that a diet rich in transmethylation micronutrients can ameliorate SLE in a lupus mouse model [70]. This study has further shown that the dietary methyl donor content directly correlates with increased methylation and decreased expression of the *CD40lg* gene. CD40L is expressed on T cells and contributes to disease pathogenesis by stimulating antibody production upon engagement with CD40 expressed on B cells [98].

The sources of ROS in SLE are not known. Nevertheless, a possible involvement of mitochondria in the generation of ROS in T cells from SLE patients has been previously proposed [99]. T cells from SLE patients exhibit mitochondrial dysfunctions such as elevated mitochondrial transmembrane potential, reduced ATP production and enhanced generation of ROS. It is believed that these alterations diminish activation-induced apoptosis and sensitize T cells for necrosis, a process that may contribute to the establishment of the inflammatory milieu in SLE. Recently, it has been shown that these alterations in the mitochondrial functions activate mechanistic target of rapamycin (mTOR), which in turn drives IL-4 production and necrotic T-cell death

Table 1. Potential therapeutic approaches targeting redox homeostasis in kidney diseases

Disease	Treatment	Effects	Species	Ref.
SLE lupus nephritis	Rapamycin	Restores T-cell activation, ameliorates disease	Human	[67]
	NAC	Suppresses anti-DNA antibody, modestly improves survival	Mouse	[68]
	Cysteamine	Inhibits renal insufficiency, markedly improves survival	Mouse	[68]
	NAC	Blocks mTOR, restores T-cell functions, ameliorates disease	Human	[69]
	Transmethylation micronutrients	Reduce CD40L expression on T cells, ameliorate disease	Mouse	[70]
	Antroquinonol	Inhibits conventional T-cell activation, enhances Treg suppression, reduces inflammation	Mouse	[71]
	Epigallocatechin-3-gallate	Reduces oxidative stress, enhances Treg suppression activity, prevents renal disease	Mouse	[72]
	Curcumin	Reduces immune complex deposition, decreases inflammation	Mouse	[73]
IRI	Ligustrazine	Reduces oxidative stress, reduces immune cell infiltration, protects from kidney injury	Mouse	[74]
	β-Carotene	Protects from oxidative stress	Rat	[75]
	NAC/ebselen	Reduce oxidation, prevent kidney damage	Rat	[76]
	EPC-K1	Reduces oxidative stress, attenuates disease	Rat	[77]
	Green tea polyphenols	Reduce oxidative stress, reduce infiltration of $CD8^+$ T cells, reduce apoptosis, reduce renal injury	Rabbit	[78, 79]
	Ferrostatins	Reduce lipid peroxidation in IRI in epithelial and immune cells	Mouse	[3, 63]
ESRD	Zinc	Reduces oxidative stress, decreases inflammation, improve immune status	Human	[80, 81]
	Ginkgo biloba extract	Partially reverse thrombogenic coagulation	Human	[82]
Renal diseases mediated by oxLDLs	Quercetin	Reduces NOX2 and NOX4 activation and oxidative stress	*In vitro*	[83]
	Coenzyme Q10	Reduces NOX2 activation and ROS generation	*In vitro*	[84]
	Ubiquinol	Reduces ROS production, ameliorates renal function	Rat	[85]
	Ellagic acid	Inhibits NOX2-mediated superoxide production, enhances antioxidant defences	*In vitro*	[86]
	Ginkgo biloba extract	Inhibits NOX2 activation, the expression of inflammatory genes and protein nitrosylation	*In vitro*	[87]
	Epigallocatechin-3-gallate	Inhibits NOX2 activation, ROS generation and the expression of inflammatory genes	*In vitro*	[88]
	Resveratrol	Protects from oxidative damage	*In vitro*	[89]
Lithiasis	Coenzyme Q10	Improves renal function	Human	[90]
Hypertension	NAC	Enhances reduced GSH level, improves renal functions	Rat	[91]
	Epoxyeicosatrienoic acid analogue	Reduces oxidative stress and inflammation, protects kidneys	Rat	[92]

in SLE [100]. According to the data presented above, inhibition of mTOR using rapamycin reduces disease activity and restores T-cell activation in SLE patients [67]. Interestingly, a more recent work has demonstrated that the antioxidant NAC blocks mTOR activation in lupus patients, restores T-cell functions and ameliorates disease [69]. How NAC affects mTOR activation is not yet clear. It is possible that NAC neutralizes excessive ROS or may influence mitochondrial functions.

The effects of other antioxidants, such as vitamins A, C and E, were also tested in SLE patients [101]. In these studies, it appears that the nutrient intake of regular antioxidants is not associated with a decreased risk of developing SLE [101]. Thus, NAC and rapamycin, perhaps also used in combination, are promising therapeutic interventions to reduce oxidative stress and restore T-cell functions in SLE patients. Other compounds displaying antioxidant and anti-inflammatory activities showed efficacy in the treatment of glomerulonephritis in mouse models. For example, antroquinonol inhibited the activation of conventional T cells but enhanced the suppressive capability of Tregs and also reduced renal inflammation [71]. Similarly, epigallocatechin-3-gallate treatment reduced oxidative stress in the kidney and enhanced Treg function, thus preventing lupus nephritis [72]. Finally, treatment with the well-known plant antioxidant compound curcumin decreased renal inflammation and immune complex deposition in the glomeruli via a mechanism likely involving Tregs [73].

Ischaemia/reperfusion kidney injury (IRI) is another well-known disease leading to kidney failure. ROS also play an important role in the pathogenesis of this disease. Recent data suggest that stanniocalcin-1 (STC1), an intracrine protein crucial for tubular epithelial survival [102], inhibits IRI by regulating the expression of mitochondrial uncoupling protein 2 by negatively regulating superoxide generation and by reducing the infiltration of macrophages and T cells in the kidney [103]. Thus, in addition to superoxide scavengers such as SOD, which protects from IRI [104], targeting STC1 may represent a therapeutic option for this disease. Also, several antioxidants such as ligustrazine, β-carotene, NAC/ebselen, EPC-K1 and green tea polyphenols have been shown to be effective in attenuating IRI in different animal models [74–79]. Long-term dialysis is a procedure required for the treatment of patients suffering from end-stage renal disease (ESRD). It is known that ESRD patients undergoing long-term dialysis display increased oxidative stress [105]. Recent studies have found an association between oxidative stress and altered levels of essential trace elements in long-term dialysis patients [80, 106]. In particular, an elevated Cu/Zn ratio was observed in

these patients. Zn has antioxidants and anti-inflammatory properties and thus zinc supplementation may represent a therapeutic tool for the treatment of dialysis patients. Indeed, clinical studies have shown that zinc supplementation intake ameliorates oxidative stress, inflammation and immune status in dialysis patients [80, 81]. Among immune cells, Tregs isolated from long-term dialysis display reduced suppressive capacity, cell-cycle arrest and undergo apoptosis [107]. These alterations appear to be mediated by increased levels of oxLDL in ESRD patients. oxLDLs strongly contribute to endothelial dysfunctions and are responsible for secondary cardiovascular defects associated with a variety of diseases characterized by oxidative stress, including renal diseases [108]. As mentioned in the paragraph above, oxLDLs induce alterations in Th differentiation and thus oxLDLs may further contribute to autoimmunity and tissue damage. A number of *in vitro* studies have shown that different compounds, including quercetin, coenzyme Q10, ellagic acid, gingko biloba extract, epigallocatechin-3-gallate and resveratrol, are capable of counteracting or attenuating oxLDL-mediated dysfunctions *in vitro* [83, 84, 86–89]. Some data regarding the *in vivo* efficacy of these compounds are also available. For example, it has been demonstrated that coenzyme Q10 administration improves renal function in patients with lithiasis undergoing extracorporeal shockwave lithotripsy [90]. Similarly, reduced coenzyme Q10 ameliorates renal function in animal models [85]. Moreover, gingko biloba extract also exerted beneficial effects on the thrombogenic coagulation profile in ERSD patients [82].

It has been shown that in both animal models and humans, T cells also participate in the pathogenesis of kidney disease induced during hypertension (reviewed in [109]). In an animal model of hypertension, T cells infiltrate the kidney where they contribute to tissue damage, likely by releasing ROS (via NOX2) and other inflammatory mediators [110]. Compounds with antioxidant and anti-inflammatory properties such as NAC and an epoxyeicosatrienoic acid analogue attenuate kidney damage and hypertension in animal models [91, 92].

Future perspective

Changing the redox homeostasis of the microenvironment or modulating more selectively the T cell and APC redox state may represent a therapeutic approach for the treatment of inflammatory diseases. During recent years, studies have been undertaken in an attempt to modulate DC functions or to reprogramme Th differentiation [111–113]. It will be important for the future to assess whether reprogramming of DCs or Th cells upon modulation of the redox equilibrium *in vitro* will be helpful in the treatment of inflammatory kidney diseases. As reported above, alterations of redox homeostasis affect DC functions, thus in turn altering the adaptive immune response. Surprisingly, little is known about redox-mediated alterations affecting DCs in kidney diseases. Therefore, further steps aimed at dissecting the role of DCs in renal pathologies are required for the development of new pharmacological strategies.

A number of studies, summarized in Table 1, have also assessed the efficacy of different antioxidants and anti-inflammatory compounds as potential therapeutic agents in the prevention and cure of inflammatory kidney diseases. To date, the question remains open as to whether available compounds, especially those having antioxidant activity, are beneficial or not for patients suffering from nephropathies. We hope that by improving the limited bioavailability of these compounds, it will be possible to enhance their efficacy and their therapeutic effects.

Of crucial importance will be identification of the molecular targets of ROS in T cells and DCs. This will reveal important new insights into ROS-regulated pathways and will lead to the identification of oxidation targets. The aim of this avenue of research is the development of immunomodulatory compounds for the treatment of inflammation. During the last decade, advances in the field of proteomics have led to the development of new tools to analyse protein thiol oxidation [114–116]. These new methods have been shown to be useful for the identification of oxidation targets in cell lines [117–119].

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Conflict of interest statement

None declared.

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