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COMMENTARY

REDOX SIGNALLING BY TRANSCRIPTION FACTORS NF-κB AND AP-1 IN LYMPHOCYTES

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When molecular oxygen accumulated in our atmosphere more than 2 billion years ago, aerobic organisms adapted using using oxygen as an electron acceptor in respiration. Although respiration is, by far, one of the most efficient ways of generating energy in biological systems, it has one harmful side-effect: incomplete reduction of dioxygen results in the formation of ROIs.§ These include the superoxide anion ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), and the hydroxyl radical (OH·). Superoxide anions originate from a single electron transfer on dioxygen [1]. This ROI has a short diffusion radius inside the cell, but it is eventually converted by SODs into H_2O_2, the most stable and diffusible ROI. Transition metals, such as iron or copper ions, convert $O_2^{\cdot-}$ and H_2O_2 to an extremely reactive hydroxyl radical via the Fenton or Haber/Weiss reaction.

While low amounts of ROIs can be considered as physiological side-products of various electron transfer reactions and are tolerated by the cell, increased levels of ROIs, referred to as oxidative stress, are linked to pathophysiological phenomena. Many adverse conditions, including ionizing and UV irradiation, heat shock, viral and bacterial infections, as well as environmental pollutants cause oxidative stress. In principle, ROIs can react with all classes of biological macromolecules, resulting in lipid peroxidation, inactivation of proteins, and strand breakage in nucleic acids [1].

During evolution, cells of the immune system, in particular, have learned to utilize ROIs in two ways: first, as chemical weapons and, second, as signalling molecules triggering a variety of biological processes, such as gene expression and proliferation control. How macrophages and neutrophils produce high amounts of ROIs as a first line of defense against invading microorganisms has been reviewed extensively [2, 3]. However, the roles of ROIs as signalling molecules are just beginning to be discovered. On the one hand, immune cells but also many other types of cells can transiently produce low levels of ROIs in response to distinct extracellular stimuli. These ROI levels do not suffice to kill other cells, but may have a hormone-like function. On the other hand, cells can respond to slightly enhanced ROI levels and use them as second messengers in signal transduction processes. ROIs can trigger the activation of protein kinases and phosphatases, regulate gene expression, and control cell proliferation and death. In this commentary, we will review very recent studies showing that ROIs and oxidation/reduction (redox) processes are critically involved in controlling cellular functions, particularly in T cells.

Mechanisms protecting from ROIs

With the use of dioxygen as electron acceptor in respiration, it was mandatory to coevolve mechanisms protecting aerobic life from the detrimental effects of ROIs. A first line of defense was the development of effective antioxidative molecules, that either detoxify ROIs (GSH, SODs, catalase, thioredoxin), block free radical chain reactions (tocopherol, ascorbate) or bind transition metals (transferrin, coeruloplasmin). Among the most important antioxidants is GSH (L-γ-glutamyl-L-cysteinyl-glycine). GSH reduces peroxides by the action of glutathione peroxidase and is regenerated by NADPH-dependent glutathione reductase [4, 5]. Inside the cell, millimolar amounts of GSH are present mainly in the reduced form, although even small changes in the ratio of GSH to GSSG may have significant biological effects. GSH/GSSG ratios can vary enormously between intracellular compartments, being the highest (100:1) in the nucleus and the lowest (2:1) in the endoplasmic reticulum [6]. Cytoplasmic GSH levels are determined largely by the availability of its precursor, L-cysteine. The most important source of L-cysteine in the blood plasma is L-cystine, the disulfide-linked oxidized dimer. In contrast to most other cell types, T lymphocytes have a very low transport activity for L-cystine and, hence, a low baseline supply with the GSH precursor [7, 8]. As a consequence, T cells are highly susceptible toward changes in the intracellular redox state.

Another important antioxidative molecule, whose role in immunoregulatory processes is becoming increasingly elucidated, is thioredoxin [9–11]. Thioredoxin is a relatively small protein with two redox active sulfhydryl groups. It is largely cytoplasmic, but it can be secreted and taken back up into the cytosol by lymphocytes under certain conditions. Although both the GSH and thioredoxin systems catalyze the reduction of disulfides, there

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§ Abbreviations: AP-1, activator protein-1; ATL, adult T cell leukemia; EGF, epidermal growth factor; GSH, glutathione; GSSG, glutathione disulfide; IL, interleukin; HIV, human immunodeficiency virus; LPS, lipopolysaccharide; LTR, long terminal repeat; MHC, major histocompatibility complex; NF-AT, nuclear factor activated T cells; NF-κB, nuclear factor-κB; PDTC, pyrrolidine dithiocarbamate; ROI, reactive oxygen intermediate; SOD, superoxide dismutase; SRE, serum response element; SRF, serum response factor; TCF, ternary complex factor; TCR, T cell receptor; and TNF, tumor necrosis factor.

is one significant difference. GSH is more effective in reducing small disulfides, whereas thioredoxin is more efficient in reducing (poly)peptides with exposed disulfides. The principal role of thioredoxin appears to be its protein oxidoreductase activity.

The oxidant stress response

When cells are treated with H_2O_2, they become resistant toward subsequent higher amounts of ROIs that would be lethal without pretreatment [12]. This observation indicates that cells can activate an adaptive genetic program against oxidative stress [13]. The genetic response to oxidative stress has been studied intensively in bacteria [reviewed in Refs. 14–16]. In *Escherichia coli,* the synthesis of some 80 proteins is induced upon exposure to H_2O_2 or $O_2^{\cdot-}$-generating chemicals. Two transcription factor systems, OxyR and SoxR/S, have been identified that activate expression of genes whose products are involved in either the protection from oxidative stress or the repair of ROI-mediated damages. Intriguingly, the two transcription factors respond to different ROI species. OxyR is activated by H_2O_2, whereas SoxR/S is selectively induced by superoxide anions. Transcription factors that sense changes in dioxygen or ROI concentration have also been found in yeast and plants. In *Saccharomyces cerevisiae,* binding of a heme group, whose synthesis requires oxygen, activates the transcription factor HAP-1, which controls transcription of the catalase and SOD gene [17]. In plants, salicylic acid (SA) is known as a mediator for systemic acquired resistance, an equivalent of the vertebrate immune response. Recently, the SA-binding protein has been shown to contain catalase activity, which decreases significantly upon ligand binding and thereby results in the accumulation of H_2O_2 [18]. Hence, the plant immune response involves generation of ROI messengers by ligand-induced inhibition of an ROI-eliminating enzyme.

In mammalian cells, the mechanisms by which ROIs are sensed or inducibly produced are less well understood, and transcription factors that are exclusively activated by ROIs or that selectively control expression of ROI-protective and repair enzymes have not been identified. In T lymphocytes, most of the genes induced by oxidative stress can be equally activated by more biological signals, such as cytokines or T cell mitogens. The overlapping effect of both chemical and biological signals may be explained by the fact that some cytokines and T cell mitogens seem to initiate ROI production themselves and utilize ROIs as intracellular signalling molecules. In the past years, increasing evidence has suggested that ROI-induced gene expression plays a widespread role in inflammation, injury and infection.

NF-κB: A redox effector of the immune system

NF-κB was the first eukaryotic transcription factor shown to respond directly to oxidative stress [19]. NF-κB plays a key role in the regulation of numerous genes involved in pathogen responses and cellular defense mechanisms. Many immunologically relevant genes, in particular those encoding cytokines and cytokine receptors, growth factors, and cell adhesion molecules, contain functional NF-κB binding sites in their promoter and enhancer regions [for actual lists, see Refs. 20 and 21]. In T lymphocytes, gene expression of IL-2 and the IL-2 receptor α chain have been shown to be controlled by NF-κB. Furthermore, some retroviruses, such as HIV-1, contain κB binding sites in their regulatory LTR region and thus employ the transcriptional activity of this host factor for induction of proviral expression and viral replication [22].

NF-κB activation does not require new protein synthesis. A great variety of mainly pathogenic or pro-inflammatory stimuli, such as LPS, viral infection, UV and γ-irradiation, and the cytokines IL-1 and TNF, activate the transcription factor within minutes. In addition, virtually all inducers of T cell activation, such as ligation of CD3, CD2, and CD28 and infection with T cell lymphotropic viruses, such as HTLV-1 and HIV-1 and -2, activate NF-κB [21].

By measurement of ROI production, GSH depletion, and other indicators of oxidative stress, it has been shown that basically all inducers of NF-κB also induce a transient ROI formation. These observations indicated that ROIs are presumably a common messenger required for NF-κB activation. Indeed, several studies have reported that activation of NF-κB by all stimuli known to date is blocked by various antioxidants, including GSH precursors (*N*-acetylcysteine, L-cysteine), metal chelators, thiols, dithiocarbamates, and vitamin E and derivatives [reviewed in Ref. 13]. Further evidence for an essential role of ROIs came from experiments using exogenously added prooxidants. In Jurkat and other T cell lines, addition of 100–300 μM H_2O_2 or butylperoxide resulted in the rapid activation of NF-κB [19, 23]. Incubation with various superoxide, hydroxyl radical, or NO-generating compounds, however, failed to induce activation, suggesting that, like the bacterial transcription factor OxyR, NF-κB activation is selectively mediated by peroxides. Compelling genetic evidence for an involvement of H_2O_2 came from a recent study with catalase- and Cu/Zn superoxide dismutase (Cu/Zn-SOD)-overexpressing cell lines. In a catalase-overexpressing cell line, NF-κB activation was substantially suppressed compared with the parental cell line, whereas it was superinduced in a Cu/Zn-SOD-overexpressing cell line [24]. Likewise, overexpression of thioredoxin or addition of recombinant thioredoxin to the cell culture medium prevented NF-κB activation by the protein kinase C activator phorbol 12-myristate 13-acetate [25].

Inducible ROI production

How do the diverse stimuli of NF-κB activation induce ROI formation? Since a great variety of agents activate the transcription factor, it is very likely that oxidative stress is elicited by more than one means. In the case of TNF, a very potent activator of NF-κB, it has been suggested that the respiratory chain of mitochondria is the site of ROI formation, which is important for the cytotoxicity as well as NF-κB activation by TNF [26, 27]. In cells lacking a functional mitochondrial respiratory chain as the result of drug action or organelle depletion, NF-κB activation was suppressed significantly.

In T cells, a potent NF-κB activation usually requires two signals, one triggering the TCR and another one, a co-stimulatory molecule [28]. It was observed recently that triggering CD28, a major co-stimulatory molecule, causes the rapid decrease of GSH within minutes and enhances ROI formation, which is maintained for 16–24 hr after cell stimulation [29, 30]. This long-lasting prooxidant stimulus may explain why, in contrast to many other cell types, NF-κB activation in T cells is

generally observed for a rather prolonged period. Inhibitor studies have demonstrated that the dioxygenase activity of 5-lipoxygenase is involved in inducing the prooxidant signal observed upon CD28 ligation [30].

Another principle of ROI formation has been demonstrated for the Tat protein, a major transactivating factor of HIV-1. The potentiation of NF-κB activation by Tat has been attributed to an increased ROI formation by Tat-mediated transcriptional inhibition of the manganese-dependent SOD gene [31]. This situation is reminiscent of the plant system where a redox signal is produced by inhibition of catalase, another ROI-detoxifying enzyme.

ROI-induced intracellular signal transduction

Some steps in the signal transduction pathway of NF-κB activation were elucidated recently, but the precise mode of how ROIs activate NF-κB is still largely unknown. Activated nuclear NF-κB is frequently a heterodimer of a 50 kDa DNA-binding (p50) and a 65 kDa DNA-binding and transactivating subunit (p65 or RelA). In activated T cells, NF-κB complexes are often composed of a p50/c-Rel heterodimer, whereas in unstimulated cells a transcriptionally inactive p50 homodimer can be found that occupies κB sites and thus may inhibit access of active complexes to DNA [32]. In most cell types, NF-κB is present in the cytoplasm as an inactive complex bound to a third inhibitory subunit, called IκB. Activation of cells results in the rapid release of IκB, which allows NF-κB to translocate to the nucleus and to bind to its cognate DNA sequences. It has been demonstrated that NF-κB activation coincides with the rapid proteolytic loss of IκB. The degradation of IκB is absolutely necessary because various protease inhibitors prevent NF-κB activation [33–35]. The degradation of IκB-α is preceded by phosphorylation on serines 32 and 36 [36]. This modification is not sufficient to release IκB from NF-κB but dramatically increases the turnover of IκB, presumably by enhancing the conjugation with ubiquitin [37].

Where in these steps of NF-κB activation do ROIs play a role? Unlike the bacterial peroxide sensor OxyR that can be activated by oxidation *in vitro*, oxidation of purified NF-κB–IκB does not activate but even causes a loss of DNA-binding activity [38]. A conserved cysteine residue in the DNA-binding domain of NF-κB subunits seems to be responsible for this oxidative inhibition [39]. However, since GSH is highly reduced in the nucleus, the physiological significance of this mechanism remains unclear.

A recent study demonstrated that the phosphorylation of IκB-α is blocked by the antioxidant PDTC [35]. This hinted at the possibility that either an IκB kinase was activated or that an IκB phosphatase, which constantly counteracts a constitutive IκB phosphorylation, was inactivated. In light of the observation that serines 32 and 36 constitute sites for the constitutive casein kinase type II, the latter scenario appears more likely. It is very possible that the kinase or phosphatase sensing changes in ROI levels is not directly involved in modifying IκB but is an upstream component of a more complex signaling pathway. There are several kinases that have been reported to be activated by H_2O_2 and other inducers of oxidative stress, including the MAP kinase-related Jun kinases (JNKs) or the tyrosine kinases LTK, EGF receptor and Src kinases [40–45].

Various studies indicated that NF-κB activation involves a cascade of membrane-bound and cytoplasmic protein kinases. For instance, UV irradiation rapidly activates the tyrosine kinase activity of c-Src, an event followed by the activation of the membrane-bound GTP binding protein H-Ras and the Ser/Thr-specific Raf-1 kinase [45]. Overexpression of transdominant negative mutants of these molecules inhibited UV-induced NF-κB activation. Likewise, overexpression of v-Src activated NF-κB in a T cell line [46].

In T lymphocytes, treatment with H_2O_2 results in the rapid and extensive tyrosine phosphorylation of multiple proteins. At least two Src kinases, $p56^{lck}$ and $p59^{fyn}$, are activated by oxidizing agents [43, 44]. Although it is unclear how these kinases are coupled to the NF-κB pathway, they may provide a useful model for ROI-induced signal transduction. We have observed recently that, similar to NF-κB, $p56^{lck}$ and $p59^{fyn}$ are not directly activated by H_2O_2 in a cell-free system or using recombinant kinases. Strong activation, however, could be seen by the addition of GSSG, indicating that, presumably, the formation of a mixed disulfide, a reaction called S-thiolation, may be involved in oxidant-induced kinase activation (Schenk H, Dröge W and Schulze-Osthoff K, unpublished results). Since several inducers of T cell activation lead to an accumulation of GSSG, S-thiolation of a critical cysteine residue may be a physiological mechanism controlling activation of Src-related kinases and other kinases or phosphatases.

Direct redox regulation of transcription factors

NF-κB is not the only transcription factor responding to changes in ROI concentrations. As seen with NF-κB, several unrelated factors with different DNA-binding domains contain also cysteine residues whose oxidation state affects DNA binding. Such redox-sensitive cysteines have been found in the basic leucine zipper proteins c-Fos and c-Jun, the helix-loop-helix transcription factor USF, the zinc finger protein Egr-1, and other factors, such as c-Myb and p53 [reviewed in Ref. 13]. These proteins are inactivated by oxidation *in vitro*, and mutation of the critical cysteine residue to a serine residue creates proteins that are resistant toward oxidative inactivation. Since the reduced state of the conserved cysteines is critical for DNA binding, it has been speculated that redox modification of the DNA-binding domain may be a secondary mechanism of controlling transcriptional activity. However, all present data concerning the direct modification of transcription factors by cysteine oxidation rely on cell-free experiments, and there are only vague hints supporting a physiological role. A ubiquitous nuclear protein, called Ref-1, has been identified, which restores the DNA-binding activity of oxidized Fos and Jun proteins *in vitro* [47]. Ref-1 catalyzes the reduction of thiol groups in these proteins, using thioredoxin as a cofactor.

Antioxidant-induced signal transduction

Heterodimers of members of the Jun and Fos transcription factor family constitute the transcription factor AP-1, for which DNA-binding motifs (consensus sequence: 5′-TGANTCA-3′) can be found in several cytokine genes [48]. Many conditions inducing oxidative stress result in the increased transcription of the c-*fos* and c-*jun* genes. In contrast, however, only a very moderate induction of AP-1 DNA-binding and transactiva-

tion activity is usually observed [49, 50]. Thus, the appearance of mRNAs for Jun and Fos does not necessarily correlate with the activation of AP-1 DNA binding. Exposure of some T cell lines to H_2O_2 results in virtually no change of AP-1 DNA binding activity, while NF-κB is strongly activated [23]. Surprisingly, a strong activation of AP-1 could be observed after treatment of cells with several structurally unrelated antioxidants, including PDTC, *N*-acetyl cysteine, and butylated hydroxyanisole [25, 50]. A significant increase in AP-1 DNA-binding and transactivating activity was also detected after transient overexpression or addition of recombinant thioredoxin, while NF-κB activation was inhibited under the same conditions. The physiological equivalent to the antioxidant treatment may be hypoxia. We* and others [51] have observed that HeLa cells strongly activate AP-1 in a biphasic response under reduced oxygen pressure. In contrast to a previous report [52], this does activate NF-κB. We have observed a very strong activation of NF-κB only upon subsequent reoxygenation of cell cultures.

The induction of AP-1 by antioxidant treatments requires *de novo* protein synthesis of the c-Jun and c-Fos proteins, indicating that yet other transcription factors are responsible for the activation of AP-1 in response to cellular redox changes. In the case of the c-*fos* gene, this pre-existing factor is TCF/Elk-1; in the case of the c-*jun* gene, it is a c-Jun homodimer or a c-Jun/ATF-2 heterodimer. TCF/Elk-1 forms a ternary complex with the SRF on the SRE [53, 54]. Phosphorylation of the transactivation domain of TCF/Elk-1 by mitogen-activated kinases (MAPKs or ERKs) induces the transactivating potential of the complex and leads to c-*fos* gene expression. We have found that the SRE is responsible for the activation of c-*fos* expression in response to both antioxidant and prooxidant stimulation of cells [50]. Such treatments cause an increased TCF/Elk-1 phosphorylation in the cell nucleus, which is preceded by novel phosphorylation and activation of MAP kinases.† TCF/Elk-1 can be considered as a nuclear sensor of the cellular redox imbalance. It is currently unknown which kinases (or phosphatases) in the cascade cause phosphorylation of MAP kinases in response to antioxidants or oxidants. One candidate for an H_2O_2-responsive upstream kinase is the EGF receptor tyrosine kinase [42].

Preexisting homodimers of c-Jun and heterodimers of c-Jun and ATF-2, which induce the c-*jun* gene in response to prooxidant stimuli and other stresses, are activated by *de novo* phosphorylation of c-Jun in its N-terminal domain [55]. One important kinase is JNK, which activates c-Jun in response to UV light, presumably, depending on redox changes [40]. It is currently unknown what activates c-*jun* transcription in response to antioxidant stimuli. A candidate factor is NF-Jun [56]. Since strong AP-1 activation is observed under antioxidant but not under prooxidant conditions, additional posttranscriptional control steps seem to be involved.

The expression of most genes is controlled by the concerted action of multiple distinct transcription factors. For instance, the promoter of the IL-2 gene contains DNA-binding sites for at least four distinct factors: NF-κB, AP-1, NF-AT, and Oct factors [28, 57]. Some of these factors can physically interact among each other when bound to DNA and thereby synergistically promote their DNA-binding and transactivating activity. NF-κB was found to interact directly with AP-1 subunits [58]. NF-ATp, an NF-κB/Rel-related transcription factor activated by the calcium-dependent phosphatase calcineurin, also binds AP-1 and recruits the factor to DNA [59]. These physical interactions with redox-controlled factors will also engage other transcription factors in redox regulation.

Redox-sensitive T cell functions

Since the redox-controlled transcription factors NF-κB and AP-1 are used extensively for signalling and gene induction in immune cells, it is mandatory that various T cell functions are redox dependent. Indeed, while processes occurring early during T cell activation are facilitated by mild or transient prooxidant conditions, late events appear to require reducing or antioxidant conditions. In contrast to bacteria, the ROI response in T cells does not primarily involve cellular defense or repair mechanisms but is associated with more physiological processes, such as signal transduction, proliferation, cytokine synthesis, and other immune regulatory processes. This indicates that during evolution T cells did not only acquire the capability to sense the redox state of the environment but also to use it for the control of specific cellular responses.

The role of ROIs in early T cell activation was studied by the regulation of cytokine and cytokine receptor gene expression. Many gene products produced by activated T cells, including IL-2, GM-CSF, TNF-α, IL-6, IL-2R α chain, and MHC class I genes, require NF-κB for their inducible transcriptional control [reviewed in Ref. 21]. It has been reported that micromolar concentrations of H_2O_2 potently activate NF-κB in T cell lines [19], as well as the transcription of the IL-2 and IL-2R α chain genes, which is conferred by κB regulatory sites in these genes [23, 60]. Since neutrophils and macrophages secrete large amounts of ROIs in inflamed tissues, exogenously produced ROIs are likely to play a hormone- or mediator-like role in early T cell activation. Furthermore, activation of cultured T cells by stimulation of the TCR or co-stimulatory molecules rapidly induces an intracellular production of ROIs, as measured by the induction of H_2O_2 production or GSH depletion [23, 29, 30]. The regulatory role of this ROI production is shown by the strong inhibitory effect of distinct antioxidants on the expression of cytokine genes following T cell activation. IL-2 and the IL-2R α chain are examples of genes inhibited by antioxidants in peripheral blood lymphocytes [60, 61]. Antioxidants also have been reported to cause the arrest of thymocyte differentiation, an event associated with a profound decrease of NF-κB and TCF-1 activation [62]. The requirement of ROIs for the expression of NF-κB-regulated cytokine and other genes is not restricted to T cells. It was also observed for endothelial cells, various tumor cell lines, fibroblasts, keratinocytes, macrophages, and pre-B cells.

ROIs seem to be further involved in early IL-2-independent steps of T cell proliferation. Studies of mixed lymphocyte cultures have revealed that several agents that inhibit the effects of ROIs also suppress lymphocyte proliferation [63, 64]. In some T cell lines, a short ex-

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posure to low amounts of H_2O_2 causes a marked increase in DNA synthesis [23, 65]. The mitogenic effect of ROIs is activation dependent and only observed in the absence of TCR stimulation. This indicates that a strong mitogenic stimulus either bypasses the requirement of ROIs or induces ROI formation by itself.

ROIs seem to be required only for the early phases of the T cell cycle. Antioxidants strongly inhibit the proliferation of mitogenically activated PBLs in the first 2 hr but not at later time points after mitogenic stimulation, indicating that preferentially the transition from the G_0 to the G_1 phase is blocked by these agents [66]. Moreover, prolonged prooxidant treatment is lethal to T cells. In fact, the most optimal mitogenic stimulation by H_2O_2 is achieved by the subsequent addition of catalase [23].

Later stages of the T cell cycle are promoted by reducing/antioxidant conditions. Thiols, such as 2-mercaptoethanol, increase proliferation in response to T cell mitogens and are therefore routinely added to the culture medium. Thioredoxin, also called "ATL-derived factor," has been identified as an autocrine growth factor produced by ATL cells [11]. Thioredoxin exerts co-stimulatory activity and increases cytokine expression in response to phorbol esters or TCR stimulation. Experiments using GSH depletion have shown that a number of T cell functions are correlated with their thiol levels. Even a partial depletion of the intracellular GSH pool has been found to inhibit IL-2-dependent cytotoxic T cell activity and the generation of lymphokine-activated killer (LAK) cells [67–69]. Therefore, administration of antioxidants may provide a measure to increase the antitumor efficiency in IL-2/LAK cell therapy.

Conclusions

Changes in the cellular redox state toward either prooxidant or antioxidant conditions have profound effects on cellular functions. T lymphocytes are particularly well-studied in this respect. It appears that early T cell functions with a proinflammatory character (such as cytokine gene induction) are promoted by prooxidant conditions, whereas later functions, such as proliferation and maintained expression of genes, are inhibited by prooxidant but promoted by antioxidant conditions. This suggests that there is a requirement of delicate cellular redox shifts for effective T cell activation. Given our detailed knowledge about the roles and characteristics of transcription factors NF-κB and AP-1 (in conjunction with NF-AT) in T cell function, the following scenario emerges. Immediate-early T cell functions require a transient production of ROIs in response to stimulation of TCR and co-stimulatory molecules. This condition is required to activate transcription factor NF-κB, which will initiate the transcription of cytokine (IL-2, TNF) and receptor genes (IL-2R α chain). For progression to later T cell functions, it seems mandatory that the potentially harmful prooxidant phase is only transient and restored to normoxic or even antioxidant conditions. It is under these latter conditions that the transcription factor AP-1 becomes activated by new synthesis. AP-1 is composed of proto-oncogene products and is involved in the positive control of proliferation. It is thus tempting to speculate that the requirement of reducing conditions for later T cell functions is partly due to the optimal activation of AP-1 under these conditions. An interesting possibility is that generally inflammatory processes rely on prooxidant conditions and NF-κB, whereas proliferative processes depend on antioxidant conditions and AP-1.

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