Chapter 13
Oxidative Stress in Infectious Diseases

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Abstract The "big three" infectious diseases HIV/AIDS, tuberculosis, and malaria were collectively responsible for nearly 260 million infected people in 2010. HIV, *Mycobacterium tuberculosis*, and *Plasmodium falciparum*, the causative agents of AIDS, tuberculosis, and malaria, are continuously exposed to reactive oxygen and nitrogen species endogenously produced or derived from the host immune system in response to infection. Oxidative stress has a key function in the pathogenesis of many infectious diseases, and represents moreover a promising strategy for chemotherapeutic development. Understanding the redox interactions and redox signaling mechanisms of pathogens and their hosts is crucial for developing (1) drugs that support the host antioxidant defense in order to protect cells from oxidative damage, (2) drugs that enhance specific reactive oxygen or nitrogen species to improve the host defense against pathogens, and (3) drugs that interfere with the redox system of the pathogen in order to block its growth and survival.

Keywords Antioxidants • HIV/AIDS • Malaria • Tuberculosis • Redox system

Abbreviations

AhpC	alkyl hydroperoxide reductase
AIDS	acquired immunodeficiency syndrome
AOP	antioxidant protein
ASK	apoptosis signal-regulating kinase
G6PD	glucose 6-phosphate dehydrogenase
GR	glutathione reductase

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GST	glutathione S-transferase
gp120	glycoprotein 120
Grx	glutaredoxin
GSH	reduced glutathione
GSSG	oxidized glutathione
HAART	highly active anti-retroviral therapy
HIV	human immunodeficiency virus
KatG	catalase-peroxidase
iNOS	nitric oxide synthase
LTR	long terminal repeat
Mca	mycothiol *S*-conjugate amidase
MscR	mycothiol-*S*-nitrosoreductase/-formaldehyde reductase
MSH	mycothiol
MSNO	*S*-nitrosomycothiol
MSSM	mycothiol disulfide
Msr	methionine sulfoxide reductases
Mtr	mycothiol reductase
NAC	N-acetylcysteine
NFκB	nuclear factor κB
NO	nitric oxide
NOX	NADPH oxidase
nPrx	nuclear peroxiredoxin
Plrx	plasmoredoxin
Prx	peroxiredoxin
RNS	reactive nitrogen species
ROS	reactive oxygen species
SOD	superoxide dismutase
Tat	transactivator protein
TNF	tumor necrosis factor
TPx	thioredoxin peroxidase
Trx	thioredoxin
TrxR	thioredoxin reductase

13.1 Introduction

Oxidative stress is not a disease, but an unspecific pathological state that can be worsened by depletion of antioxidants, immunosuppressants, zinc and selenium deficiency, xenobiotics, and infections, thus being involved in the pathogenesis of a variety of diseases (Stehbens 2004). Mammalian cells of the immune system use the production of reactive oxygen and nitrogen species (ROS, RNS) to control and defend themselves against infections with bacterial pathogens, parasites, or viruses. Infectious agents counteract oxidative stress derived from the host immune system by highly efficient antioxidant defense systems. Inhibiting the antioxidant

defense of parasites, bacteria, and viruses is an intensely studied strategy in order to develop effective anti-infectious drugs. AIDS (HIV), tuberculosis (*Mycobacterium tuberculosis*), and malaria (*Plasmodium falciparum*) are the three leading infectious diseases worldwide. In their pathogenesis, oxidative stress plays a major role, which will be comprehensively discussed in this review.

13.2 Oxidative Stress in HIV/AIDS

According to the WHO, 2.7 million people were newly infected and 34 million people were living with the human immunodeficiency virus (HIV) in 2010 (WHO 2011a). HIV infection leads to a complex disease with broad clinical symptoms and complex pathogenic mechanisms. Dysregulation of the immune system is caused by a constant decline of $CD4^+$ T cells (Pantaleo et al. 1993), which has been intensely studied. ROS and oxidative stress are critically involved in the pathogenesis of HIV infection, with the most important aspects being discussed in the following paragraphs.

13.2.1 Mechanisms of Oxidative Stress in the Pathogenesis of HIV Infection

A role of ROS in viral infections had already been described in 1970 (Belding et al. 1970) and has been intensely investigated since that time. Oxidative stress, ROS, and antioxidant defense systems appear to be implicated in many aspects of HIV infection and AIDS such as immune function, inflammatory response, virus replication, and apoptosis. Humans infected with HIV show chronically increased levels of oxidative stress, decreased concentrations of antioxidants, and perturbations in the antioxidant systems (Gil et al. 2010). Furthermore, high plasma concentrations of hydroperoxides and malondialdehyde were found in HIV patients, indicating increased lipid peroxidation (Suresh et al. 2009). The activation of $CD4^+$ T cells and monocytes/macrophages upon HIV infection is triggered by hydrogen peroxide, superoxide anion, and peroxynitrite. Moreover, HIV infection of macrophages results in enhanced production of peroxynitrite and superoxide (Elbim et al. 1999). Oxidative stress upon HIV infection can be induced by the HIV transactivator protein (Tat) and the envelope glycoprotein gp120 (Price et al. 2005). However, the mechanisms of oxidative stress induction have not been completely unraveled.

13.2.1.1 Viral Replication

Redox signaling has an important function in the regulation of viral gene transcription and replication. Oxidative stress has been found to increase HIV replication

in vitro, while antioxidants show the opposite effect and reduce virus replication (Schreck et al. 1991; Roederer et al. 1990). The promoter of HIV-1 is located in the long terminal repeat (LTR) at the 5′-end and contains binding sites for different transcription factors, including NFκB that mediate the activation of viral transcription in complex interplay with both viral and host factors (for review please see Hiscott et al. 2001). Reactive oxygen intermediates such as H_2O_2 and oxygen radicals disturb the redox balance towards oxidizing conditions and thereby activate the translocation of NFκB into the nucleus, where it binds to the HIV LTR in order to increase the expression of viral genes and replication (Schreck et al. 1991). Moreover, peroxynitrite was shown to play a major role in virus replication, since a synthetic peroxynitrite decomposition catalyst (MnTBAP) had a strong inhibitory effect on virus replication. Peroxynitrite is suggested to also mediate its effects via the NFκB pathway (Aquaro et al. 2007). Overexpression of peroxiredoxin IV in T cells deactivated HIV LTR and thus inhibited HIV transcription by regulating hydrogen peroxide-mediated activation of NFκB (Jin et al. 1997). Both degradation of IκB and binding of NFκB to the LTR are suggested to be redox-controlled. Furthermore, the HIV LTR contains binding sites for the transcription factors p53 and AP-1, which are also sensitive to redox regulation (Pereira et al. 2000).

An HIV-encoded protein required for efficient viral transcription is Tat, a transactivator protein activated upon oxidizing conditions and inhibited upon reduction, thus functioning as a redox sensor (Koken et al. 1994; Washington et al. 2010). Dysfunction of Tat leads to disturbed transcription with the formation of prematurely terminated short transcripts (Kao et al. 1987). HIV Tat protein contains a cysteine-rich domain with several CxxC motifs that form intramolecular disulfide bonds required for the transactivation activity (Koken et al. 1994). *In vitro* inhibition of HIV expression by N-acetylcysteine (NAC) might at least in part be mediated by reduction and deactivation of Tat (Washington et al. 2010). Similarly, thioredoxin reductase has been shown to act as a negative regulator of Tat transactivation activity by reducing critical disulfide bonds (Fig. 13.1) (Kalantari et al. 2008). Moreover, Tat itself enhances oxidative stress by increasing the expression of tumor necrosis factor (TNF α/β) and by repressing the expression of antioxidant defense enzymes such as manganese superoxide dismutase, glutathione peroxidase, and γ-glutamylcysteine synthetase (Romani et al. 2010; Buonaguro et al. 1994; Flores et al. 1993; Richard et al. 2001; Choi et al. 2000). Therefore, Tat contributes to the oxidizing environment during HIV infection by decreasing the levels of several antioxidant enzymes.

13.2.1.2 Apoptosis

HIV manipulates apoptotic pathways of host cells by multiple factors in order to kill non-infected inflammatory or immune cells and infected $CD4^+$ T cells by apoptosis (reviewed in (Gougeon 2005)). Balancing of ROS and redox signaling are suggested to be critically involved in HIV-induced apoptosis (Agrawal et al. 2007; Romero-Alvira and Roche 1998; Buccigrossi et al. 2011; Banki et al. 1998). HIV infection

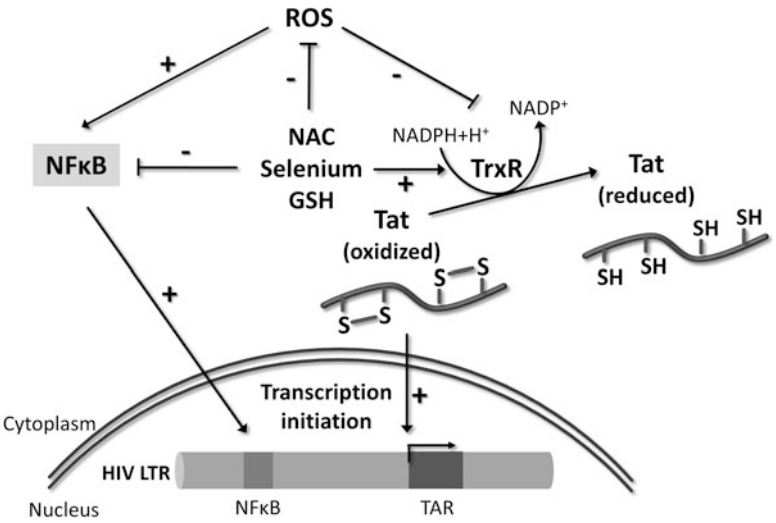

Fig. 13.1 Scheme of the influence of reactive oxygen species on HIV transcription and replication. Increased cellular concentrations of reduced glutathione (GSH) and supplementation with selenium or N-acetylcysteine (NAC) decrease the concentrations of reactive oxygen species (ROS) and activate antioxidant enzymes such as thioredoxin reductase (TrxR). ROS activate NFκB-dependent gene expression, which is decreased under reducing conditions. HIV transactivator protein (Tat) is inhibited by reduction of critical disulfide bonds. TrxR has been shown to reduce Tat and thereby inhibits Tat-mediated HIV transcription (modified after Kalantari et al. 2008)

leads to an increase in mitochondrial ROS that subsequently trigger apoptosis together with other agents such as viral proteins (Tat, gp120) and cytokines (TNFα). Moreover, caspases are cysteine-dependent enzymes and are thus sensitive towards the redox status of the cell (Hampton and Orrenius 1998).

Members of the thioredoxin (Trx) family including Trx itself, glutaredoxin (Grx), and peroxiredoxins have been discussed in the context of apoptotic signaling during HIV infection (Masutani et al. 2005). Trx is upregulated in the plasma of HIV-infected patients (Nakamura et al. 1996), and is known to inhibit the activity of apoptosis signal-regulating kinase 1 (ASK1) under reducing conditions, and thereby blocks induction of apoptosis, an effect that is reversed under oxidative stress and subsequent oxidation of Trx (Saitoh et al. 1998). In contrast, thioredoxin-dependent peroxidases, peroxiredoxins, are able to inhibit apoptosis by scavenging hydrogen peroxide (Kim et al. 2000).

Recently, it has been reported that HIV Tat protein can directly mediate apoptosis in enterocytes via a redox-dependent mechanism, leading to damage of the intestinal mucosa (Buccigrossi et al. 2011). Similarly, ROS have been shown to be crucial for HIV Tat-induced apoptosis in neurons (Agrawal et al. 2007). Tat-induced apoptotic signaling is suggested to be based on an increase in intracellular ROS concentrations and an imbalance in the GSH/GSSG ratio (Buccigrossi et al. 2011; Agrawal et al. 2007; Choi et al. 2000). Moreover, NAC not only prevents oxidative stress by

balancing ROS and GSSG concentrations, but also appears to inhibit Tat-induced apoptosis (Buccigrossi et al. 2011).

13.2.2 Antioxidant Systems During HIV Infection

Several clinical studies showed that the redox balance in HIV-infected patients without highly active anti-retroviral therapy (HAART) is severely disturbed, with perturbations affecting almost all components of the antioxidant defense system including glutathione, tocopherol, ascorbate, selenium, the thioredoxin system, superoxide dismutase, and glutathione peroxidase (Gil et al. 2010), as summarized in the following paragraphs.

13.2.2.1 Thioredoxin Family

In order to enter host cells, HIV requires the viral glycoprotein gp120, which undergoes conformational changes depending on the reduction of disulfides. Reduction of gp120 can be catalyzed by Trx1, Grx1, and protein disulfide isomerase, thus demonstrating that the host redox system is required for virus entry into host cells (Reiser et al. 2012; Azimi et al. 2010; Auwerx et al. 2009).

Dysregulation of the Trx system appears to be involved in apoptosis in HIV-infected cells as outlined above. *In vitro*, HIV infection of T cell lines decreased the expression of Trx3 shortly after infection (Masutani et al. 2005). Similarly, Trx levels were decreased in monocytes from asymptomatic untreated patients, while Trx expression in cells from AIDS patients was shown to be at a higher level when compared to uninfected cells, which has been suggested to limit ROS levels and apoptosis at later disease stages (Elbim et al. 1999). Thioredoxin reductase 1 (TrxR1) negatively regulates the activity of Tat and thereby Tat-dependent transcription in human macrophages by reducing two disulfide bonds within the cysteine-rich motif of Tat (Kalantari et al. 2008). Inhibition of Grx1 activity by anti-Grx antibodies blocks HIV replication *in vitro*, most likely by inhibiting HIV entry into $CD4^+$ T cells (Auwerx et al. 2009).

Peroxiredoxins reduce hydrogen peroxide by using Trx as an electron donor. In HIV-infected T cell lines, peroxiredoxin IV is downregulated, while T cells overexpressing peroxiredoxin IV show a decreased HIV transcription (Jin et al. 1997). Altogether, these results show that the Trx system is intriguingly involved in HIV infection.

13.2.2.2 Glutathione

In HIV-infected patients, reduced levels of glutathione were found in the plasma, lymphocytes, monocytes, as well as in $CD4^+$ and $CD8^+$ T cells (Eck et al. 1989;

de Quay et al. 1992; Roederer et al. 1991; Buhl et al. 1989). Low levels of reduced glutathione (GSH) are associated with a poor survival of HIV-infected patients (Herzenberg et al. 1997). The mechanisms responsible for impaired GSH production and GSSG reduction upon HIV infection are unclear. Depletion in GSH is accompanied by increased concentrations of oxidized glutathione, indicating a shift in the GSH:GSSG ratio (Aukrust et al. 1995), which has been confirmed in infected macrophages (Morris et al. 2012). Progressively depleted intracellular GSH levels are at least partially mediated by reduced GSH synthesis, since HIV Tat protein decreases transcription and protein levels of γ-glutamylcysteinyl synthetase (Choi et al. 2000). This was supported by a recent study showing that expression of GSH biosynthesis enzymes is decreased in HIV patients, which was attributed to chronically enhanced production of inflammatory cytokines (IL-1, IL-17, and TNF-α) that might interfere with GSH biosynthesis (Morris et al. 2012).

13.2.2.3 Superoxide Dismutase and Catalase

The first enzyme in the defense against superoxide anions is superoxide dismutase (SOD), which converts superoxide anions into hydrogen peroxide, which is subsequently reduced by catalase. The expression of mitochondrial manganese superoxide dismutase (MnSOD) is decreased in HIV-infected patients, with the effect being mediated by HIV Tat protein followed by increased oxidative stress with enhanced protein carbonylation and lipid peroxidation (Flores et al. 1993). In contrast, the expression of cytosolic CuZnSOD in macrophages is increased during HIV infection *in vitro*, most likely to counteract elevated superoxide anion concentrations (Delmas-Beauvieux et al. 1996). Hydrogen peroxide produced by SOD is scavenged by catalase, which shows an increasing activity with progressing HIV infection, and most likely compensates GSH deficiency in HIV-infected cells (Leff et al. 1992).

13.2.3 Antioxidants in the Treatment of AIDS

Decreased concentrations of antioxidants observed in HIV-positive patients are associated with deficiencies of micronutrients with antioxidant properties such as vitamins C and E, thiamine, selenium, and zinc. There are many indications that supplementation with antioxidants can have a beneficial therapeutic effect for HIV-infected patients (reviewed e.g. in Lanzillotti and Tang 2005; Singhal and Austin 2002).

13.2.3.1 N-Acetylcysteine

Enhancing cysteine bioavailability in order to increase GSH concentrations is most likely the major effect of the antioxidant NAC. Oral supplementation with NAC was reported to increase the glutathione pool in plasma and muscle (Atkuri et al. 2007).

NAC has been found to efficiently inhibit HIV replication. NAC is a potent inhibitor of NFκB by counteracting the effect of ROS (Staal et al. 1990), but has also been shown to block the TNFα-stimulated replication of HIV-1 (Roederer et al. 1990). Moreover, treatment with NAC can prevent Tat-induced apoptosis by restoring the GSH:GSSG ratio *in vitro* and *ex vivo*, and thereby protects the intestinal mucosa (Buccigrossi et al. 2011). An increase in GSH can be achieved by both NAC and glutamine supplementation, with NAC supplying cysteine and glutamine by delivering glycine (Borges-Santos et al. 2012). Similar to NAC, glutamine supplementation enhances plasma GSH levels and significantly increases lean body mass in patients with HIV infection (Borges-Santos et al. 2012).

13.2.3.2 Selenium

Selenium deficiency is strongly associated with disease progression and mortality in HIV-infected patients. Selenium supplementation of HIV-infected individuals improves the CD4 count, suppresses the virus load, decreases anxiety, and reduces the need for hospitalization (Hurwitz et al. 2007; Shor-Posner et al. 2003; McDermid et al. 2002). However, information on how selenium influences HIV infection is limited. The effect is most likely mediated via selenoproteins such as TrxR and glutathione peroxidase that shift the redox balance towards a reducing environment and thereby inhibit Tat and thus HIV transcription as explained above (Kalantari et al. 2008).

13.3 Oxidative Stress in Tuberculosis

Tuberculosis infected 8.8 million and killed 1.4 million people in 2010 and is after HIV the second leading cause of death from an infectious disease worldwide (WHO 2011b). *Mycobacterium tuberculosis*, its causative agent in humans, infects and multiplies in lung macrophages of the host. In immunodeficient individuals (e.g., HIV-positive individuals), *M. tuberculosis* can multiply to high numbers and induce an active disease. In contrast, the immune system of immunocompetent individuals is in most cases able to control the infection, and more than 90% of the infected remain asymptomatic (Lawn and Zumla 2011). Despite the bactericidal environment, *M. tuberculosis* is able to survive in macrophages, a fact that demonstrates the adaptation of the pathogen to the oxidant burden in the host.

13.3.1 *Mechanisms of Oxidative Stress in the Pathogenesis of Tuberculosis*

The host immune system is able to influence the virulence of *M. tuberculosis* by producing ROS and RNS. As a reaction towards phagocytosis of *M. tuberculosis*, macrophages can induce the expression of NADPH oxidase (NOX) and nitric oxide synthase 2 (iNOS, NOS2) and thereby increase the oxidative burden. NOX generates superoxide by catalyzing the one-electron reduction of O_2 (Leto and Geiszt 2006). iNOS produces $NO^{\bullet}$, which can react with superoxide to form highly reactive peroxynitrite and can kill mycobacteria (Shiloh and Nathan 2000). iNOS expression and release of RNS are suggested to be important for controlling the virulence of *M. tuberculosis* in humans. A range of studies based on murine models of tuberculosis using iNOS inhibitors and iNOS-deficient mice show that iNOS and RNS are required in order to control tuberculosis infection (MacMicking et al. 1997; Chan et al. 1995; Scanga et al. 2001). Moreover, NO appears to be important for latent tuberculosis infection in mice and prevents reactivation together with RNS-independent mechanisms (Flynn et al. 1998). Contrarily, another study reported no influence of a lack of iNOS on tuberculosis infection (Jung et al. 2002). Similarly, the function of ROS produced by NADPH oxidase in controlling *M. tuberculosis* is controversially discussed. Experiments using NOX-deficient mice models showed that the absence of NOX-produced superoxide increased bacterial growth during an early infection stage (Cooper et al. 2000; Adams et al. 1997). In contrast, another study did not show any differences between a murine knockout model lacking NOX and wildtype mice in ability to control *M. tuberculosis* infection (Jung et al. 2002). However, clear experimental evidence on the ROS/RNS-based mechanisms of infection control in humans is rare. Alveolar macrophages from *M. tuberculosis*-infected patients show increased concentrations of iNOS compared to non-infected individuals (Nicholson et al. 1996). Several single nucleotide polymorphisms of the *nos2a* gene in African Americans show associations with susceptibility to tuberculosis, thus supporting the role of iNOS for pathogenesis of tuberculosis in humans (Velez et al. 2009; Gomez et al. 2007).

13.3.2 *Antioxidant Defense Systems of* Mycobacterium tuberculosis

Several studies reported a remarkable resistance of *M. tuberculosis* towards oxidative stress both *in vitro* and *in vivo*; the bacterium can tolerate H_2O_2 concentrations up to 10 mM (Voskuil et al. 2011). In contrast to enteric bacteria, *M. tuberculosis* shows very low but differential transcriptional responses after exposure to a range of H_2O_2 and NO concentrations, and is resistant to DNA damage-mediated killing by H_2O_2 (Voskuil et al. 2011; Garbe et al. 1996). Low H_2O_2 or NO concentrations lead to an induction of few H_2O_2-/NO-responsive genes such as those encoding proteins

involved in H_2O_2 scavenging, repair mechanisms, and iron acquisition (Voskuil et al. 2011). Similarly, treatment with cumene hydroperoxide also did not have a major impact on gene transcription (Garbe et al. 1996). Interestingly, the expression of many genes involved in antioxidant defense did not show major changes after H_2O_2 or NO exposition indicating that they are constitutively expressed at a high level (Voskuil et al. 2011). Several antimycobacterial drugs, such as ethionamide, isoniazid, and the nitroimidazopyran PA-824, have to be reduced for activation and thus depend on the intracellular redox state. Moreover, an increased NADH/NAD^+ ratio, mutations in NADH dehydrogenase, and mutations in mycothiol biosynthesis have been related to resistance against isoniazid (Vilcheze et al. 2005; Xu et al. 2011; Miesel et al. 1998). Therefore, understanding the redox homeostasis of *M. tuberculosis* is important for drug identification strategies. As an intracellular pathogen, *M. tuberculosis* employs different antioxidant systems to counteract oxidative stress of the host defense system, as discussed in the following paragraphs.

13.3.2.1 Response Towards Oxidative Stress

M. tuberculosis shows an unusually low transcriptional response towards oxidative and nitrosative stress when compared to other enteric bacteria (Garbe et al. 1996). In different bacteria, transcriptional response towards oxidative stress is regulated by the transcription factors OxyR and SoxR, which modulate transcription in response to peroxide and superoxide, respectively. Both regulate the expression of a variety of genes, including a range of redox-active proteins (summarized in (Zahrt and Deretic 2002)). OxyR from *M. tuberculosis* is nonfunctional and is not able to sense peroxide stress. Several mutations (deletions and frameshifts) in the *oxyR* gene render the transcription factor inactive, which impairs the oxidative and nitrosative stress response in *M. tuberculosis* (Deretic et al. 1995; Sherman et al. 1995). Moreover, the *soxRS* regulon is missing in the genome of mycobacteria (Cole et al. 1998).

In *M. tuberculosis*, oxidative stress response can be mediated by the regulator *furA* and catalase-peroxidase KatG, which are mutated and dysfunctional in human pathogenic *M. leprae*. *furA* is located upstream of the catalase-peroxidase *katG*, and is supposed to act as a negative regulator of *katG* expression (Zahrt et al. 2001; Pym et al. 2001). This regulation was suggested to be important for virulence of *M. tuberculosis*, since *M. tuberculosis* mutants lacking *katG* showed a severely impaired persistence in mice and guinea pigs (Li et al. 1998). Moreover, KatG is required for the conversion of the prodrug isoniazid into its active form (Zhang et al. 1992).

The expression of *katG* can also be negatively regulated in a FurA-independent manner by the transcriptional regulator OxyS. Via a cysteine residue in its DNA-binding domain, OxyS binds directly to the katG promoter region, with the DNA-binding capacity being diminished upon oxidation of OxyS. Mycobacteria overexpressing OxyS show an increased susceptibility towards oxidative stress, thereby indicating that OxyS functions as a redox sensor (Li and He 2012).

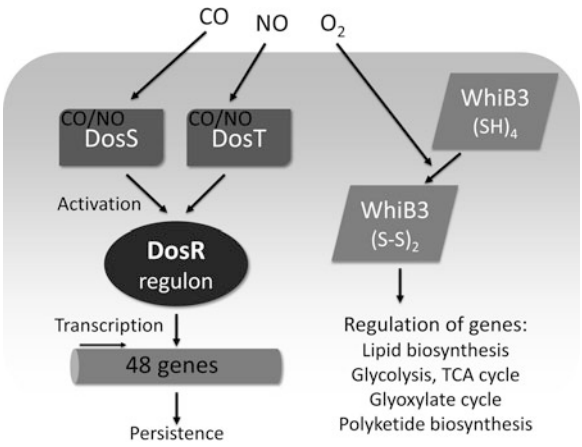

Fig. 13.2 Regulation of oxidative stress response in *Mycobacterium tuberculosis*. The DosR regulon is modulated by the histidine kinases DosS and DosT that sense NO, CO, and O_2. The DosR regulon comprises 48 genes with functions for persistence and stress adaptation. On the basis of a redox switch mechanism, WhiB3 regulates lipid biosynthesis and other central metabolic pathways involved in virulence, persistence, and redox homeostasis in response to oxidative stress (modified after Kumar et al. 2011 and Singh et al. 2009)

The DosR/S/T system (also called DevR system) is a redox-sensing system involved in virulence and persistence of *M. tuberculosis* (Leistikow et al. 2010; Shiloh et al. 2008; Park et al. 2003). The DosR regulon is controlled by DosR (DevR), a response regulator, and DosS and DosT, two sensor histidine kinases. The DosR regulon is induced by conditions that inhibit aerobic respiration, since the heme proteins DosS and DosT can sense NO, O_2, and CO by binding them to iron in their heme group (Shiloh et al. 2008). Subsequently, the DosR dormancy regulon is induced, which includes at least 48 genes suggested to play a role in persistence, latent infection, and stress adaptation (Fig. 13.2) (Park et al. 2003). The DosR regulon enables *M. tuberculosis* to follow and respond to conditions that do not allow aerobic respiration and is required for maintaining the redox balance and energy levels under anaerobic conditions (Leistikow et al. 2010).

Another redox signaling pathway in *M. tuberculosis* is controlled by WhiB3, a redox regulator that senses NO and O_2 from the host and is involved in virulence and pathogenesis of mycobacteria (Fig. 13.2) (Steyn et al. 2002). WhiB3 from *M. tuberculosis* contains four cysteine residues coordinating an iron-sulfur cluster that can specifically bind NO and O_2 (Singh et al. 2007). DNA binding of WhiB3 occurs independently of its iron-sulfur cluster but depends on the oxidation state of its four cysteines: oxidation stimulates DNA binding, while reduction diminishes it (Singh et al. 2009). Oxidation of WhiB3 stimulates DNA binding to several lipid biosynthetic genes and directly regulates production of lipids including poly- and diacyltrehaloses, sulfolipids, and triacylglycerol. WhiB3 is regarded as a redox sensor that connects host redox signals with its intermediary metabolism,

since it induces a metabolic shift to fatty acids by regulating lipid anabolism in response to oxidative stress during tuberculosis infection (Singh et al. 2009). Thus, WhiB3 maintains the intracellular redox homeostasis in part by channeling reducing equivalents into *M. tuberculosis* lipid synthesis, which modulate inflammatory cytokine production (Singh et al. 2009).

13.3.2.2 Thioredoxin System

Intracellular redox homeostasis can be maintained by the Trx family, which can catalyze thiol/disulfide exchange reactions and comprises TrxR, Trx, and thioredoxin peroxidases (TPx). *M. tuberculosis* encodes one TrxR and three Trx (A, B, and C) (Akif et al. 2008). However, no mRNA transcripts of *trxA* have been observed. This is supported by the finding that recombinant TrxA cannot be reduced by TrxR. Thus, *trxA* was suggested to be a cryptic gene in *M. tuberculosis* and is most likely not involved in antioxidant defense (Akif et al. 2008). The TrxR/Trx couple from *M. tuberculosis* is able to reduce peroxides and dinitrobenzenes, while cumene hydroperoxide can only be reduced by TrxR and not by Trx *in vitro* (Zhang et al. 1999). Moreover, TrxC is able to reduce mycothiol, GSSG, and *S*-nitrosoglutathione *in vitro*, which was suggested to be important for defense against host-derived oxidative stress (Attarian et al. 2009). The crystal structure of *M. tuberculosis* TrxC, both oxidized and in complex with an inhibitor, has been solved and can be exploited for structure-based inhibitor development (Hall et al. 2006, 2011)

Thioredoxin peroxidase (TPx) from *M. tuberculosis* shows homology to atypical 2-cys peroxiredoxins but has been characterized as a 1-cys peroxiredoxin with Cys60 being the peroxidatic cysteine (Trujillo et al. 2006). TPx can use TrxB and C as electron donors to efficiently reduce hydrogen peroxide, *t*-butyl hydroperoxide, cumene hydroperoxide, and peroxynitrite (Trujillo et al. 2006; Jaeger et al. 2004). The crystal structure of dimeric TPx revealed a Trx fold similar to that of other peroxiredoxin family members (Rho et al. 2006). *M. tuberculosis* mutants lacking TPx show an increased sensitivity towards hydrogen peroxide and nitric oxide. Moreover, they are unable to survive and grow in macrophages, cannot establish acute infections or maintain persistent infections in murine tuberculosis models, and show an attenuated virulence. This indicates that TPx is an essential component of the antioxidant defense of *M. tuberculosis* (Hu and Coates 2009).

13.3.2.3 Mycothiol

Like other actinomycetes, *M. tuberculosis* lacks detectable levels of glutathione and glutathione peroxidases and employs mycothiol (MSH, AcCys-GlcN-Ins) as its major low molecular weight thiol. MSH is a cysteinyl pseudo-disaccharide consisting of N-acetylcysteine, glucosamine, and *myo*-inositol, and was discovered in 1993 (Newton et al. 1993). In *M. smegmatis* and *M. tuberculosis*, MSH concentrations are in a low millimolar range, comparable to the concentrations of glutathione in

eukaryotes (Newton et al. 1996). MSH is required for the survival of *M. tuberculosis* (Sareen et al. 2003), but not for *M. smegmatis* (Rawat et al. 2002).

The biosynthetic pathway of MSH consists of five steps catalyzed by four enzymes, which cannot be found in eukaryotes or eubacteria and are thus discussed as highly feasible targets for chemotherapeutic interventions against mycobacteria. MshA is an N-acetylglucosamine transferase that forms 3-phospho-GlcNAc-Ins, which is converted into GlcNAc-Ins by dephosphorylation catalyzed by a phosphatase termed MshA2. The deacetylase MshB deacetylates GlcNAc-Ins to form Gln-Ins, which is then ligated to cysteine by MshC, a mycothiol ligase. Cys-Gln-Ins is subsequently acetylated by mycothiol synthase MshD generating MSH (for detailed reviews of MSH biosynthesis please see (Jothivasan and Hamilton 2008; Fan et al. 2009)).

The functions of MshA-D have been intensely investigated by gene knockout studies in *M. smegmatis* and *M. tuberculosis*. MshA and C are indeed essential for growth and survival of *M. tuberculosis* (Buchmeier and Fahey 2006; Sareen et al. 2003), while mutants lacking MshB and D are still viable (Buchmeier et al. 2006). These studies show that only the absence of MshA or C leads to complete depletion of MSH, while still 10 and 2% of normal MSH levels could be detected in the mutants lacking MshC or MshD, respectively (Sareen et al. 2003; Buchmeier and Fahey 2006; Buchmeier et al. 2003, 2006). Moreover, disruption of the MshD gene in *M. tuberculosis* results in high levels of the MshD substrate Cys-GlcN-Ins and N-formyl-Cys-GlcN-Ins, with the latter being maintained in a reduced state. Thus, N-formyl-Cys-GlcN-Ins might function as a surrogate for MSH under normal conditions, but is not sufficient under increased oxidative stress (Buchmeier et al. 2006). These studies indicate that MshA and C might be more feasible as targets for anti-mycobacterial drug development (Fan et al. 2009).

MSH exerts a range of protective functions in mycobacteria by serving as an intracellular redox buffer as a functional analog of GSH and by maintaining the redox balance. Low MSH levels in *M. smegmatis* result in a remarkably increased sensitivity towards free radicals, oxidants, alkylating agents, and antibiotics including erythromycin, rifamycin, and penicillin G (Rawat et al. 2002; Buchmeier et al. 2006). Thus, MSH is involved in protection against oxidative stress and antibiotics. In contrast, MSH-depleted mutants show a 200-fold increased resistance towards isoniazid, demonstrating a function of MSH in the drug mechanism of isoniazid (Rawat et al. 2002). Furthermore, MSH protects against electrophilic xenobiotics by forming MSH-toxin conjugates (Rawat et al. 2004).

MSH-dependent enzymes are involved in several cellular processes, including defense against ROS and RNS and detoxification of electrophilic xenobiotics (Fig. 13.3). Mycothiol disulfide (MSSM) can be reduced by the NADPH-dependent flavoenzyme mycothiol disulfide reductase (Mtr, mycothione reductase), which maintains a high MSH:MSSM ratio by the same disulfide reducing mechanism found in glutathione reductase (Argyrou et al. 2004; Argyrou and Blanchard 2004). MSH-toxin conjugates can be hydrolyzed by mycothiol *S*-conjugate amidase (Mca) forming a mercapturic acid and GlcN-Ins. While the mercapturic acid derivative can be exported from the cell, GlcN-Ins is recycled for re-synthesis of MSH (Newton

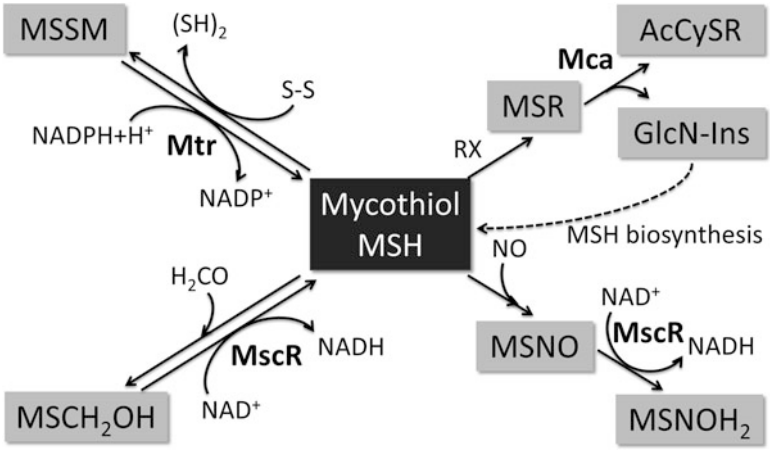

Fig. 13.3 Functions of mycothiol, the major low molecular weight thiol in *Mycobacterium tuberculosis*. Mycothiol (MSH) can reduce proteins and oxidants and is thereby oxidized to mycothiol disulfide (MSSM). MSSM is recycled by mycothiol reductase (Mtr) under consumption of NADPH + H^+. *S*-nitrosomycothiol (MSNO) can be reduced by mycothiol-*S*-nitrosoreductase/-formaldehyde reductase (MscR) to MSH sulfonamide ($MSNOH_2$). MSH can react with formaldehyde (HCOOH) to form the hemothioacetal formylmycothiol ($MSCH_2OH$), which is reduced by MscR. Thiol-reactive reagents (RX) form MSH-toxin conjugates that are hydrolyzed by mycothiol *S*-conjugate amidase (Mca) yielding a mercapturic acid and GlcN-Ins. The latter can enter the MSH biosynthesis pathway to be recycled to MSH (modified after Newton et al. 2008)

et al. 2000). *M. tuberculosis* Mca has a crucial function in drug resistance, a fact that directed interest towards the development of inhibitors against Mca (Nicholas et al. 2003). MSH can rapidly react with formaldehyde forming a hemithioacetal, which is a substrate of mycothiol-*S*-nitrosoreductase/-formaldehyde reductase (MscR) (Vogt et al. 2003). Moreover, MscR can reduce *S*-nitrosomycothiol (Vogt et al. 2003) and is required for growth of *M. tuberculosis* (Sassetti et al. 2003).

13.3.2.4 Further Enzymes of Antioxidant Defense

M. tuberculosis encodes a catalase peroxidase (KatG) that exhibits catalase, peroxidase, and peroxynitritase activity and can therefore detoxify ROS and RNS (Rouse et al. 1996; Manca et al. 1999; Wengenack et al. 1999). Experiments using transgenic murine models indicated that the major role of KatG is the defense against the oxidative burden in the host by metabolizing peroxides generated by the host phagocyte NADPH oxidase (Ng et al. 2004). In order to exhibit its antimycobacterial activity, the most effective and specific antimycobacterial drug isoniazid has to be converted from a prodrug form into its active form by KatG (Zhang et al. 1992). Mutations in the mycobacterial *katG* gene are associated with resistance to isoniazid. At least 130 known mutations of *katG* are characterized by a

decreased or diminished activity of KatG and thus reduced formation of the adduct INH-NAD (reviewed in Vilcheze and Jacobs 2007).

The peroxiredoxin-type alkyl hydroperoxide reductase (AhpC) can directly detoxify hydroperoxides and peroxynitrite (Bryk et al. 2000; Master et al. 2002). Although AhpC is considered to be a 2-cys peroxiredoxin, it involves a third cysteine in catalysis (Koshkin et al. 2004). AhpC employs the Trx-like protein AhpD, a protein with a low alkylhydroperoxidase activity of its own, as an electron donor but cannot be reduced by Trx (Hillas et al. 2000; Bryk et al. 2002). Moreover, *M. tuberculosis* codes for a 1-cys peroxiredoxin named alkyl hydroperoxide reductase E (AhpE), which is involved in peroxide and peroxynitrite detoxification (Hugo et al. 2009). In order to detoxify superoxide radicals, *M. tuberculosis* encodes two SODs, an iron-dependent SOD, and a Cu and Zn-dependent one (Zhang et al. 1991; D'Orazio et al. 2009). Two methionine sulfoxide reductases (MsrA and B) are supposed to reduce methionine sulfoxide to methionine in *M. tuberculosis*. MsrA and B appear to have redundant functions, since only a mutant lacking both genes would be more sensitive to nitrite and hypochlorite compare to wildtype (Lee et al. 2009).

13.4 Oxidative Stress in Malaria

Besides HIV/AIDS and tuberculosis, malaria is one of the world's most devastating diseases. Although the number of reported malaria cases was reduced by more than 50% between 2000 and 2010, the estimated number of malaria-related deaths is with 665,000–1,133,000 people in 2010 still high (WHO 2011c; Murray et al. 2012). Approximately 86% of malaria deaths globally were of children under 5 years of age, and 91% of the deaths were in Africa (WHO 2011c). Tropical malaria is caused by *Plasmodium falciparum*, a unicellular eukaryotic parasite that lives and multiplies both in *Anopheles* mosquitoes and humans. An infected *Anopheles* mosquito injects sporozoites into the subcutaneous tissue of the human host. The sporozoites migrate to the liver, where they develop into merozoites, which subsequently can invade red blood cells. There, the parasites undergo asexual replication until merozoites are formed and released by rupture of the red blood cell membrane. Most merozoites infect new red blood cells and thus restart the intraerythrocytic cycle leading to the typical symptoms of tropical malaria. Some parasites differentiate into the sexual forms required for transmission into the mosquito vector (for review please see Tuteja 2007; Kappe et al. 2010).

13.4.1 Sources of Oxidative Stress in Malaria Parasites

During their intraerythrocytic development, malaria parasites face high concentrations of oxygen and iron and are exposed to intense oxidative stress derived

from different sources. *Plasmodium* parasites degrade host hemoglobin as their major source of nutrients for protein synthesis, which is at the same time also a major source of oxidative stress. Hemoglobin is taken up from the erythrocyte cytoplasm into the acidic food vacuole and is systematically degraded by proteases into free heme and amino acids (Francis et al. 1997). Most of the highly toxic free heme (ferriprotoporphyrin IX) aggregates to crystalline hemozoin, the so-called malaria pigment (Stiebler et al. 2011). Alternative detoxification pathways of heme comprise heme degradation and binding to glutathione or heme-binding proteins (Loria et al. 1999; Ginsburg et al. 1998). However, small amounts of heme escape from the detoxification mechanisms and cause major oxidative damage including lipid peroxidation and DNA damage (reviewed in Kumar and Bandyopadhyay 2005). In the acidic food vacuole, free heme is oxidized from Fe(II) to Fe(III) with concomitant production of superoxide and H_2O_2 (Atamna and Ginsburg 1993). Additionally, malaria parasites have to counteract ROS released by the host immune system in order to fight the infection (Becker et al. 2004).

13.4.2 Oxidative Stress in the Pathogenesis of Malaria

Oxidative stress has been implicated in different aspects of malaria pathogenesis (reviewed in Becker et al. 2004; Hunt and Stocker 1990). Human glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzymopathy and confers resistance to infection and/or the development of severe clinical symptoms of malaria (Ruwende and Hill 1998). Protection from malaria is thought to be based on a lack of reducing equivalents in the form of NADPH, leading to oxidation of hemoglobin to membrane-associated hemochromes, which finally lead to early IgG-based detection and degradation of G6PD-deficient parasitized erythrocytes (Cappadoro et al. 1998). Moreover, a reduced multiplication rate was attributed to an intracellular accumulation of toxic oxidized molecules such as oxidized glutathione and hemozoin. Similar protection mechanisms were proposed for glutathione reductase-deficient erythrocytes (Gallo et al. 2009).

During disease manifestation, the redox balance of the patient is disturbed. The levels of glutathione, tocopherol, catalase, and superoxide dismutase in the erythrocyte and the concentrations of ascorbate and albumin in the plasma are significantly decreased in patients with malaria when compared to uninfected erythrocytes (Das and Nanda 1999; Pabon et al. 2003; Narsaria et al. 2011). Reduced α-tocopherol content in the erythrocyte membrane was associated with malaria and may contribute to erythrocyte loss and anemia in severe malaria (Griffiths et al. 2001). Moreover, increased lipid peroxidation has been reported in patients infected with *falciparum* or *vivax* malaria (Polat et al. 2002; Das et al. 1990; Pabon et al. 2003; Narsaria et al. 2011). Micronutrients including vitamins A, E, and zinc may have a beneficial effect on the severity of malaria by modulating immune response and decreasing oxidative stress (Nussenblatt and Semba 2002; Zeba et al. 2008).

The role of macrophage-derived ROS in controlling malaria infection has been controversially discussed. It has been hypothesized that phagocyte-derived ROS are involved in host immunity against malaria infections (Hunt and Stocker 1990). Superoxide produced by NADPH oxidase was reported to be involved in malaria transmission and gametocyte development but not in parasitemia patterns, as shown in murine malaria models lacking NADPH oxidase (Harada et al. 2001). Similarly, another study did not show any effect of the absence of functional NADPH oxidase and thus of phagocyte-derived ROS on parasitemia and parasite burden in murine malaria models. This indicates that ROS generated by phagocytes are not involved in controlling malaria infection (Potter et al. 2005). Furthermore, phagocyte-derived ROS are not associated with the pathogenesis of cerebral malaria in mice malaria models (Sanni et al. 1999) but have been implicated in neuronal damage in humans (Becker et al. 2004).

In uncomplicated and severe malaria, low levels of nitric oxide (NO) were detected and are associated with increased disease severity and mortality. Plasma levels of IL-10, a cytokine that suppresses NO synthesis, were increased with severity, while levels of NOS2 were decreased in cerebral malaria (Anstey et al. 1996). Moreover, severe malaria is associated with depletion of arginine, the precursor of NO, and elevated levels of plasma arginase, which catabolizes arginine (Weinberg et al. 2008). Therefore, suppression of NO was suggested to protect against severe disease rather than to contribute to malaria pathogenesis (Anstey et al. 1996).

A beneficial role of antioxidants as an adjunctive treatment of severe malaria has been discussed. Treatment of adults with NAC increased the rate of normalization of plasma lactate by a TNF-independent mechanism that was attributed to improved red cell deformability or increased GSH levels (Watt et al. 2002). However, NAC as an adjunctive treatment with artesunate did not influence the disease outcome in patients with severe *falciparum* malaria (Charunwatthana et al. 2009). The effect of NAC appears to be concentration-dependent: low doses of NAC decrease H_2O_2 levels and lipid peroxidation by increasing GSH concentrations, while supplementation with high doses of NAC had the opposite effect *in vitro* (Fitri et al. 2011). Thus, putative beneficial effects of NAC treatment remain controversial.

As explained above, NO is supposed to have a significant function in controlling malaria infection (Weinberg et al. 2008). Supplementation with L-arginine, the substrate of NO synthase and precursor of NO, leads to recovery of arginine levels and improvement of endothelial function in patients with severe malaria as shown in a Phase I trial (Yeo et al. 2008).

13.4.3 Antioxidant Defense System

In order to avoid oxidative damage and maintain a redox balance, malaria parasites employ an efficient combination of antioxidant systems based on GSH and Trx as outlined in the following paragraphs. Moreover, *Plasmodium* codes for two SODs,

which convert superoxide radicals to hydrogen peroxide (Gratepanche et al. 2002; Sienkiewicz et al. 2004). However, enzymes with major antioxidant functions in other organisms such as catalase, glutathione peroxidase, and methionine sulfoxide reductase are missing in *Plasmodium* (Sztajer et al. 2001; Clarebout et al. 1998).

13.4.3.1 The Glutathione System

Glutathione is the major low molecular weight thiol in malaria parasites and functions as a thiol redox buffer by cycling between a reduced and an oxidized form (Becker et al. 2003b). GSH is a cofactor for detoxification of electrophilic compounds and methylglyoxal (Harwaldt et al. 2002; Iozef et al. 2003), reduces the dithiol glutaredoxin (Rahlfs et al. 2001), and directly reduces a range of ROS, RNS, protein disulfides, and sulfenates (Becker et al. 2003b). GSH is synthesized by the consecutive activity of γ-glutamyl-cysteine synthetase and glutathione synthetase. A lack of the glutathione biosynthesis pathway leads to decreased GSH levels and a significant growth delay during the intraerythrocytic stage but completely blocks oocyte development in the *Anopheles* vector (Vega-Rodriguez et al. 2009). During the intraerythrocytic stage, the parasites depend on either GSH *de novo* synthesis or efficient reduction of GSSG by glutathione reductase, since a knockout of both enzymes is lethal for the parasites (Pastrana-Mena et al. 2010).

High intracellular concentrations of GSH in malaria parasites are maintained by an NADPH-dependent reaction catalyzed by the flavoenzyme glutathione reductase (GR). A range of studies examined the kinetic mechanism of GR in detail and developed selective inhibitors of the parasite enzymes (e.g. Bohme et al. 2000; Krauth-Siegel et al. 1996; Sarma et al. 2003). As a consequence of its central position in antioxidant defense, *P. falciparum* GR was regarded as a highly attractive drug target (Becker et al. 2003b, 2004). However, recent studies demonstrated that *P. berghei* GR is not essential during the intraerythrocytic stage but is required for sporogony in the *Anopheles* vector (Buchholz et al. 2010; Pastrana-Mena et al. 2010). High functional redundancy in the antioxidant network of *P. falciparum* allows reduction of GSSG by several GR-independent pathways such as direct reduction by Trx, reduction by protein *S*-glutathionylation, and by dihydrolipoamide-dependent reactions catalyzed by Grx (Becker et al. 2003b, 2004; Kanzok et al. 2000). In order to maintain low intracellular GSSG concentrations, the parasite exports GSSG into the erythrocyte cytosol (Atamna and Ginsburg 1997).

A major function of glutathione is the non-enzymatic reduction of Grx, a dithiol protein that catalyzes the reduction of a variety of proteins on the basis of a dithiol exchange mechanism (Holmgren 1989). *Plasmodium* encodes one classic dithiol Grx (i.e., PfGrx) and three monothiol Grx (Rahlfs et al. 2001; Deponte et al. 2005). PfGrx can serve as a hydrogen donor for ribonucleotide reductase (Rahlfs et al. 2001), interacts with several proteins from different metabolic pathways in *Plasmodium* (Sturm et al. 2009), and catalyzes the deglutathionylation of proteins *in vitro* (Kehr et al. 2011).

GSH is a cofactor of glutathione *S*-transferase, an enzyme that catalyzes the conjugation of electrophiles with GSH for detoxification of xenobiotics (reviewed in Eaton and Bammler 1999). *P. falciparum* GST cannot be assigned to any of the described GST classes and has been investigated in detail (Harwaldt et al. 2002; Fritz-Wolf et al. 2003).

13.4.3.2 The Thioredoxin System

Thioredoxins are central proteins in redox homeostasis and reduce a large variety of protein and non-protein substrates. Trx are directly involved in antioxidant defense and furthermore contribute to redox signaling and regulation by modulating the structure and/or activity of many proteins in response to the intracellular redox state (Arner and Holmgren 2000; Holmgren 1989). *Plasmodium* employs three Trx and two Trx-like proteins with distinct subcellular localization (Nickel et al. 2006). Cytosolic Trx1, the most intensely studied *P. falciparum* Trx, detoxifies hydroperoxides and glutathione disulfide directly, functions as an electron donor for peroxiredoxins and plasmoredoxin (see below), and regulates a variety of proteins (Nickel et al. 2006; Sturm et al. 2009; Jortzik et al. 2010).

Thioredoxin reductase (TrxR) maintains Trx in a reduced state in an NADPH-dependent reaction. TrxR regulates antioxidant defense and cell growth either indirectly by reducing Trx or directly by reducing other substrates including hydrogen and lipid peroxides, dehydroascorbate, selenium compounds, Grx, protein disulfide isomerase, and ubiquinone (reviewed in Becker et al. 2000). *P. falciparum* TrxR contains two catalytic centers each consisting of two cysteine residues, while mammalian TrxR contains a selenocysteine-cysteine in its C-terminal active site (Gladyshev et al. 1996; Williams et al. 2000). By using alternative translation initiation, *P. falciparum* expresses two isoforms of TrxR, which are located in the cytosol and in the mitochondrion (Kehr et al. 2010). *P. falciparum* TrxR was discussed as an excellent drug target (Becker et al. 2000; Nickel et al. 2006). Knockout studies demonstrated that TrxR is indeed essential for *P. falciparum* (Krnajski et al. 2002) but not for the rodent malaria parasite *P. berghei* (Buchholz et al. 2010). Whether the discrepancy is due to *in vitro* culture conditions, technical aspects, or indeed major differences in the redox metabolism of *P. falciparum* and *P. berghei* remains to be studied. However, high redundancies in the Trx and GSH systems might allow compensation for the loss of single components. Simultaneous inhibition of the two *Plasmodium* disulfide reductases GR and TrxR provides a good strategy for the development of antimalarial chemotherapeutic interventions (Buchholz et al. 2010).

Trx protects from oxidative damage by serving as an electron donor for Trx-dependent peroxidases, which catalyze the reduction of different peroxides including hydrogen peroxide, peroxynitrite, cumene hydroperoxide, and *tert*-butylhydroperoxide. According to the number of catalytic cysteines, the enzymes are clustered into 1-cys and 2-cys peroxiredoxins (Wood et al. 2003). *Plasmodium* harbors six peroxidases (recently reviewed in Gretes et al. 2012): Prx1a (TPx1) and

Prx1m (TPx2) (Nickel et al. 2005; Komaki-Yasuda et al. 2003), Prx5 (antioxidant protein, AOP) (Sarma et al. 2005), and Prx6 (1-cys peroxiredoxin) (Nickel et al. 2006) are classic peroxiredoxins. Additionally, a glutathione peroxidase-like TPx and a nuclear peroxiredoxin (PrxQ, nPrx) associated with chromatin have been described (Sztajer et al. 2001; Richard et al. 2011). Except for nPrx (Richard et al. 2011), all *P. falciparum* peroxidases prefer Trx as a reducing substrate. Additionally, malaria parasites import human peroxiredoxin 2 as an enzymatic scavenger of hydroperoxides into their cytosol (Koncarevic et al. 2009).

A *Plasmodium*-specific oxidoreductase is plasmoredoxin (Plrx), a dithiol protein belonging to the thioredoxin superfamily. Plrx can be reduced by glutathione but more effectively by Trx and Grx *in vitro*; it transfers electrons to ribonucleotide reductase and glutathione disulfide and interacts with several enzymes involved in different cellular pathways (Becker et al. 2003a; Nickel et al. 2005; Sturm et al. 2009). In *P. berghei*, Plrx is dispensable under unstressed conditions, indicating a high functional redundancy with other redox-active proteins (Buchholz et al. 2008).

References

Adams LB, Dinauer MC, Morgenstern DE, Krahenbuhl JL (1997) Comparison of the roles of reactive oxygen and nitrogen intermediates in the host response to Mycobacterium tuberculosis using transgenic mice. Tuber Lung Dis 78:237–246

Agrawal L, Louboutin JP, Strayer DS (2007) Preventing HIV-1 Tat-induced neuronal apoptosis using antioxidant enzymes: mechanistic and therapeutic implications. Virology 363:462–472

Akif M, Khare G, Tyagi AK, Mande SC, Sardesai AA (2008) Functional studies of multiple thioredoxins from Mycobacterium tuberculosis. J Bacteriol 190:7087–7095

Anstey NM, Weinberg JB, Hassanali MY, Mwaikambo ED, Manyenga D, Misukonis MA, Arnelle DR, Hollis D, McDonald MI, Granger DL (1996) Nitric oxide in Tanzanian children with malaria: inverse relationship between malaria severity and nitric oxide production/nitric oxide synthase type 2 expression. J Exp Med 184:557–567

Aquaro S, Muscoli C, Ranazzi A, Pollicita M, Granato T, Masuelli L, Modesti A, Perno CF, Mollace V (2007) The contribution of peroxynitrite generation in HIV replication in human primary macrophages. Retrovirology 4:76

Argyrou A, Blanchard JS (2004) Flavoprotein disulfide reductases: advances in chemistry and function. Prog Nucleic Acid Res Mol Biol 78:89–142

Argyrou A, Vetting MW, Blanchard JS (2004) Characterization of a new member of the flavoprotein disulfide reductase family of enzymes from Mycobacterium tuberculosis. J Biol Chem 279:52694–52702

Arner ES, Holmgren A (2000) Physiological functions of thioredoxin and thioredoxin reductase. Eur J Biochem 267:6102–6109

Atamna H, Ginsburg H (1993) Origin of reactive oxygen species in erythrocytes infected with Plasmodium falciparum. Mol Biochem Parasitol 61:231–241

Atamna H, Ginsburg H (1997) The malaria parasite supplies glutathione to its host cell–investigation of glutathione transport and metabolism in human erythrocytes infected with Plasmodium falciparum. Eur J Biochem 250:670–679

Atkuri KR, Mantovani JJ, Herzenberg LA, Herzenberg LA (2007) N-Acetylcysteine – a safe antidote for cysteine/glutathione deficiency. Curr Opin Pharmacol 7:355–359

Attarian R, Bennie C, Bach H, Av-Gay Y (2009) Glutathione disulfide and S-nitrosoglutathione detoxification by Mycobacterium tuberculosis thioredoxin system. FEBS Lett 583:3215–3220

Aukrust P, Svardal AM, Muller F, Lunden B, Berge RK, Ueland PM, Froland SS (1995) Increased levels of oxidized glutathione in CD4+ lymphocytes associated with disturbed intracellular redox balance in human immunodeficiency virus type 1 infection. Blood 86:258–267

Auwerx J, Isacsson O, Soderlund J, Balzarini J, Johansson M, Lundberg M (2009) Human glutaredoxin-1 catalyzes the reduction of HIV-1 gp120 and CD4 disulfides and its inhibition reduces HIV-1 replication. Int J Biochem Cell Biol 41:1269–1275

Azimi I, Matthias LJ, Center RJ, Wong JW, Hogg PJ (2010) Disulfide bond that constrains the HIV-1 gp120 V3 domain is cleaved by thioredoxin. J Biol Chem 285:40072–40080

Banki K, Hutter E, Gonchoroff NJ, Perl A (1998) Molecular ordering in HIV-induced apoptosis. Oxidative stress, activation of caspases, and cell survival are regulated by transaldolase. J Biol Chem 273:11944–11953

Becker K, Gromer S, Schirmer RH, Muller S (2000) Thioredoxin reductase as a pathophysiological factor and drug target. Eur J Biochem 267:6118–6125

Becker K, Kanzok SM, Iozef R, Fischer M, Schirmer RH, Rahlfs S (2003a) Plasmoredoxin, a novel redox-active protein unique for malarial parasites. Eur J Biochem 270:1057–1064

Becker K, Rahlfs S, Nickel C, Schirmer RH (2003b) Glutathione – functions and metabolism in the malarial parasite Plasmodium falciparum. Biol Chem 384:551–566

Becker K, Tilley L, Vennerstrom JL, Roberts D, Rogerson S, Ginsburg H (2004) Oxidative stress in malaria parasite-infected erythrocytes: host-parasite interactions. Int J Parasitol 34:163–189

Belding ME, Klebanoff SJ, Ray CG (1970) Peroxidase-mediated virucidal systems. Science 167:195–196

Bohme CC, Arscott LD, Becker K, Schirmer RH, Williams CH Jr (2000) Kinetic characterization of glutathione reductase from the malarial parasite Plasmodium falciparum. Comparison with the human enzyme. J Biol Chem 275:37317–37323

Borges-Santos MD, Moreto F, Pereira PC, Ming-Yu Y, Burini RC (2012) Plasma glutathione of HIV(+) patients responded positively and differently to dietary supplementation with cysteine or glutamine. Nutrition 28(7–8):753–756

Bryk R, Griffin P, Nathan C (2000) Peroxynitrite reductase activity of bacterial peroxiredoxins. Nature 407:211–215

Bryk R, Lima CD, Erdjument-Bromage H, Tempst P, Nathan C (2002) Metabolic enzymes of mycobacteria linked to antioxidant defense by a thioredoxin-like protein. Science 295:1073–1077

Buccigrossi V, Laudiero G, Nicastro E, Miele E, Esposito F, Guarino A (2011) The HIV-1 transactivator factor (Tat) induces enterocyte apoptosis through a redox-mediated mechanism. PLOS One 6:e29436

Buchholz K, Rahlfs S, Schirmer RH, Becker K, Matuschewski K (2008) Depletion of Plasmodium berghei plasmoredoxin reveals a non-essential role for life cycle progression of the malaria parasite. PLOS One 3:e2474

Buchholz K, Putrianti ED, Rahlfs S, Schirmer RH, Becker K, Matuschewski K (2010) Molecular genetics evidence for the in vivo roles of the two major NADPH-dependent disulfide reductases in the malaria parasite. J Biol Chem 285:37388–37395

Buchmeier N, Fahey RC (2006) The mshA gene encoding the glycosyltransferase of mycothiol biosynthesis is essential in Mycobacterium tuberculosis Erdman. FEMS Microbiol Lett 264:74–79

Buchmeier NA, Newton GL, Koledin T, Fahey RC (2003) Association of mycothiol with protection of Mycobacterium tuberculosis from toxic oxidants and antibiotics. Mol Microbiol 47: 1723–1732

Buchmeier NA, Newton GL, Fahey RC (2006) A mycothiol synthase mutant of Mycobacterium tuberculosis has an altered thiol-disulfide content and limited tolerance to stress. J Bacteriol 188:6245–6252

Buhl R, Jaffe HA, Holroyd KJ, Wells FB, Mastrangeli A, Saltini C, Cantin AM, Crystal RG (1989) Systemic glutathione deficiency in symptom-free HIV-seropositive individuals. Lancet 2: 1294–1298

Buonaguro L, Buonaguro FM, Giraldo G, Ensoli B (1994) The human immunodeficiency virus type 1 Tat protein transactivates tumor necrosis factor beta gene expression through a TAR-like structure. J Virol 68:2677–2682

Cappadoro M, Giribaldi G, O'Brien E, Turrini F, Mannu F, Ulliers D, Simula G, Luzzatto L, Arese P (1998) Early phagocytosis of glucose-6-phosphate dehydrogenase (G6PD)-deficient erythrocytes parasitized by Plasmodium falciparum may explain malaria protection in G6PD deficiency. Blood 92:2527–2534

Chan J, Tanaka K, Carroll D, Flynn J, Bloom BR (1995) Effects of nitric oxide synthase inhibitors on murine infection with Mycobacterium tuberculosis. Infect Immun 63:736–740

Charunwatthana P, Abul Faiz M, Ruangveerayut R, Maude RJ, Rahman MR, Roberts LJ 2nd, Moore K, Bin Yunus E, Hoque MG, Hasan MU, Lee SJ, Pukrittayakamee S, Newton PN, White NJ, Day NP, Dondorp AM (2009) N-acetylcysteine as adjunctive treatment in severe malaria: a randomized, double-blinded placebo-controlled clinical trial. Crit Care Med 37:516–522

Choi J, Liu RM, Kundu RK, Sangiorgi F, Wu W, Maxson R, Forman HJ (2000) Molecular mechanism of decreased glutathione content in human immunodeficiency virus type 1 Tat-transgenic mice. J Biol Chem 275:3693–3698

Clarebout G, Slomianny C, Delcourt P, Leu B, Masset A, Camus D, Dive D (1998) Status of Plasmodium falciparum towards catalase. Br J Haematol 103:52–59

Cole ST, Brosch R, Parkhill J, Garnier T, Churcher C, Harris D, Gordon SV, Eiglmeier K, Gas S, Barry CE 3rd, Tekaia F, Badcock K, Basham D, Brown D, Chillingworth T, Connor R, Davies R, Devlin K, Feltwell T, Gentles S, Hamlin N, Holroyd S, Hornsby T, Jagels K, Krogh A, McLean J, Moule S, Murphy L, Oliver K, Osborne J, Quail MA, Rajandream MA, Rogers J, Rutter S, Seeger K, Skelton J, Squares R, Squares S, Sulston JE, Taylor K, Whitehead S, Barrell BG (1998) Deciphering the biology of Mycobacterium tuberculosis from the complete genome sequence. Nature 393:537–544

Cooper AM, Segal BH, Frank AA, Holland SM, Orme IM (2000) Transient loss of resistance to pulmonary tuberculosis in p47(phox−/−) mice. Infect Immun 68:1231–1234

D'Orazio M, Cervoni L, Giartosio A, Rotilio G, Battistoni A (2009) Thermal stability and redox properties of M. tuberculosis CuSOD. Arch Biochem Biophys 486:119–124

Das BS, Nanda NK (1999) Evidence for erythrocyte lipid peroxidation in acute falciparum malaria. Trans R Soc Trop Med Hyg 93:58–62

Das BS, Thurnham DI, Patnaik JK, Das DB, Satpathy R, Bose TK (1990) Increased plasma lipid peroxidation in riboflavin-deficient, malaria-infected children. Am J Clin Nutr 51:859–863

de Quay B, Malinverni R, Lauterburg BH (1992) Glutathione depletion in HIV-infected patients: role of cysteine deficiency and effect of oral N-acetylcysteine. AIDS 6:815–819

Delmas-Beauvieux MC, Peuchant E, Couchouron A, Constans J, Sergeant C, Simonoff M, Pellegrin JL, Leng B, Conri C, Clerc M (1996) The enzymatic antioxidant system in blood and glutathione status in human immunodeficiency virus (HIV)-infected patients: effects of supplementation with selenium or beta-carotene. Am J Clin Nutr 64:101–107

Deponte M, Becker K, Rahlfs S (2005) Plasmodium falciparum glutaredoxin-like proteins. Biol Chem 386:33–40

Deretic V, Philipp W, Dhandayuthapani S, Mudd MH, Curcic R, Garbe T, Heym B, Via LE, Cole ST (1995) Mycobacterium tuberculosis is a natural mutant with an inactivated oxidative-stress regulatory gene: implications for sensitivity to isoniazid. Mol Microbiol 17:889–900

Eaton DL, Bammler TK (1999) Concise review of the glutathione S-transferases and their significance to toxicology. Toxicol Sci 49:156–164

Eck HP, Gmunder H, Hartmann M, Petzoldt D, Daniel V, Droge W (1989) Low concentrations of acid-soluble thiol (cysteine) in the blood plasma of HIV-1-infected patients. Biol Chem Hoppe Seyler 370:101–108

Elbim C, Pillet S, Prevost MH, Preira A, Girard PM, Rogine N, Matusani H, Hakim J, Israel N, Gougerot-Pocidalo MA (1999) Redox and activation status of monocytes from human immunodeficiency virus-infected patients: relationship with viral load. J Virol 73:4561–4566

Fan F, Vetting MW, Frantom PA, Blanchard JS (2009) Structures and mechanisms of the mycothiol biosynthetic enzymes. Curr Opin Chem Biol 13:451–459

Fitri LE, Sardjono TW, Simamora D, Sumarno RP, Setyawati SK (2011) High dose of N-acetylcysteine increase HO and MDA levels and decrease GSH level of HUVECs exposed with malaria serum. Trop Biomed 28:7–15

Flores SC, Marecki JC, Harper KP, Bose SK, Nelson SK, McCord JM (1993) Tat protein of human immunodeficiency virus type 1 represses expression of manganese superoxide dismutase in HeLa cells. Proc Natl Acad Sci USA 90:7632–7636

Flynn JL, Scanga CA, Tanaka KE, Chan J (1998) Effects of aminoguanidine on latent murine tuberculosis. J Immunol 160:1796–1803

Francis SE, Sullivan DJ Jr, Goldberg DE (1997) Hemoglobin metabolism in the malaria parasite Plasmodium falciparum. Annu Rev Microbiol 51:97–123

Fritz-Wolf K, Becker A, Rahlfs S, Harwaldt P, Schirmer RH, Kabsch W, Becker K (2003) X-ray structure of glutathione S-transferase from the malarial parasite Plasmodium falciparum. Proc Natl Acad Sci USA 100:13821–13826

Gallo V, Schwarzer E, Rahlfs S, Schirmer RH, van Zwieten R, Roos D, Arese P, Becker K (2009) Inherited glutathione reductase deficiency and Plasmodium falciparum malaria–a case study. PLOS One 4:e7303

Garbe TR, Hibler NS, Deretic V (1996) Response of Mycobacterium tuberculosis to reactive oxygen and nitrogen intermediates. Mol Med 2:134–142

Gil L, Tarinas A, Hernandez D, Riveron BV, Perez D, Tapanes R, Capo V, Perez J (2010) Altered oxidative stress indexes related to disease progression marker in human immunodeficiency virus infected patients with antiretroviral therapy. Biomed Pharmacother 1(1):8–15

Ginsburg H, Famin O, Zhang J, Krugliak M (1998) Inhibition of glutathione-dependent degradation of heme by chloroquine and amodiaquine as a possible basis for their antimalarial mode of action. Biochem Pharmacol 56:1305–1313

Gladyshev VN, Jeang KT, Stadtman TC (1996) Selenocysteine, identified as the penultimate C-terminal residue in human T-cell thioredoxin reductase, corresponds to TGA in the human placental gene. Proc Natl Acad Sci USA 93:6146–6151

Gomez LM, Anaya JM, Vilchez JR, Cadena J, Hinojosa R, Velez L, Lopez-Nevot MA, Martin J (2007) A polymorphism in the inducible nitric oxide synthase gene is associated with tuberculosis. Tuberculosis (Edinb) 87:288–294

Gougeon ML (2005) To kill or be killed: how HIV exhausts the immune system. Cell Death Differ 12(Suppl 1):845–854

Gratepanche S, Menage S, Touati D, Wintjens R, Delplace P, Fontecave M, Masset A, Camus D, Dive D (2002) Biochemical and electron paramagnetic resonance study of the iron superoxide dismutase from Plasmodium falciparum. Mol Biochem Parasitol 120:237–246

Gretes MC, Poole LB, Karplus PA (2012) Peroxiredoxins in parasites. Antioxid Redox Signal 17(4):608–633

Griffiths MJ, Ndungu F, Baird KL, Muller DP, Marsh K, Newton CR (2001) Oxidative stress and erythrocyte damage in Kenyan children with severe Plasmodium falciparum malaria. Br J Haematol 113:486–491

Hall G, Shah M, McEwan PA, Laughton C, Stevens M, Westwell A, Emsley J (2006) Structure of Mycobacterium tuberculosis thioredoxin C. Acta Crystallogr D Biol Crystallogr 62:1453–1457

Hall G, Bradshaw TD, Laughton CA, Stevens MF, Emsley J (2011) Structure of Mycobacterium tuberculosis thioredoxin in complex with quinol inhibitor PMX464. Protein Sci 20:210–215

Hampton MB, Orrenius S (1998) Redox regulation of apoptotic cell death. Biofactors 8:1–5

Harada M, Owhashi M, Suguri S, Kumatori A, Nakamura M, Kanbara H, Matsuoka H, Ishii A (2001) Superoxide-dependent and -independent pathways are involved in the transmission blocking of malaria. Parasitol Res 87:605–608

Harwaldt P, Rahlfs S, Becker K (2002) Glutathione S-transferase of the malarial parasite Plasmodium falciparum: characterization of a potential drug target. Biol Chem 383:821–830

Herzenberg LA, de Rosa SC, Dubs JG, Roederer M, Anderson MT, Ela SW, Deresinski SC, Herzenberg LA (1997) Glutathione deficiency is associated with impaired survival in HIV disease. Proc Natl Acad Sci USA 94:1967–1972

Hillas PJ, del Alba FS, Oyarzabal J, Wilks A, Ortiz De Montellano PR (2000) The AhpC and AhpD antioxidant defense system of Mycobacterium tuberculosis. J Biol Chem 275:18801–18809

Hiscott J, Kwon H, Genin P (2001) Hostile takeovers: viral appropriation of the NF-kappaB pathway. J Clin Invest 107:143–151

Holmgren A (1989) Thioredoxin and glutaredoxin systems. J Biol Chem 264:13963–13966

Hu Y, Coates AR (2009) Acute and persistent Mycobacterium tuberculosis infections depend on the thiol peroxidase TpX. PLOS One 4:e5150

Hugo M, Turell L, Manta B, Botti H, Monteiro G, Netto LE, Alvarez B, Radi R, Trujillo M (2009) Thiol and sulfenic acid oxidation of AhpE, the one-cysteine peroxiredoxin from Mycobacterium tuberculosis: kinetics, acidity constants, and conformational dynamics. Biochemistry 48:9416–9426

Hunt NH, Stocker R (1990) Oxidative stress and the redox status of malaria-infected erythrocytes. Blood Cells 16:499–526; discussion 527–530

Hurwitz BE, Klaus JR, Llabre MM, Gonzalez A, Lawrence PJ, Maher KJ, Greeson JM, Baum MK, Shor-Posner G, Skyler JS, Schneiderman N (2007) Suppression of human immunodeficiency virus type 1 viral load with selenium supplementation: a randomized controlled trial. Arch Intern Med 167:148–154

Iozef R, Rahlfs S, Chang T, Schirmer H, Becker K (2003) Glyoxalase I of the malarial parasite Plasmodium falciparum: evidence for subunit fusion. FEBS Lett 554:284–288

Jaeger T, Budde H, Flohe L, Menge U, Singh M, Trujillo M, Radi R (2004) Multiple thioredoxin-mediated routes to detoxify hydroperoxides in Mycobacterium tuberculosis. Arch Biochem Biophys 423:182–191

Jin DY, Chae HZ, Rhee SG, Jeang KT (1997) Regulatory role for a novel human thioredoxin peroxidase in NF-kappaB activation. J Biol Chem 272:30952–30961

Jortzik E, Fritz-Wolf K, Sturm N, Hipp M, Rahlfs S, Becker K (2010) Redox regulation of Plasmodium falciparum ornithine delta-aminotransferase. J Mol Biol 402:445–459

Jothivasan VK, Hamilton CJ (2008) Mycothiol: synthesis, biosynthesis and biological functions of the major low molecular weight thiol in actinomycetes. Nat Prod Rep 25:1091–1117

Jung YJ, Lacourse R, Ryan L, North RJ (2002) Virulent but not avirulent Mycobacterium tuberculosis can evade the growth inhibitory action of a T helper 1-dependent, nitric oxide Synthase 2-independent defense in mice. J Exp Med 196:991–998

Kalantari P, Narayan V, Natarajan SK, Muralidhar K, Gandhi UH, Vunta H, Henderson AJ, Prabhu KS (2008) Thioredoxin reductase-1 negatively regulates HIV-1 transactivating protein Tat-dependent transcription in human macrophages. J Biol Chem 283:33183–33190

Kanzok SM, Schirmer RH, Turbachova I, Iozef R, Becker K (2000) The thioredoxin system of the malaria parasite Plasmodium falciparum. Glutathione reduction revisited. J Biol Chem 275:40180–40186

Kao SY, Calman AF, Luciw PA, Peterlin BM (1987) Anti-termination of transcription within the long terminal repeat of HIV-1 by tat gene product. Nature 330:489–493

Kappe SH, Vaughan AM, Boddey JA, Cowman AF (2010) That was then but this is now: malaria research in the time of an eradication agenda. Science 328:862–866

Kehr S, Sturm N, Rahlfs S, Przyborski JM, Becker K (2010) Compartmentation of redox metabolism in malaria parasites. PLOS Pathog 6:e1001242

Kehr S, Jortzik E, Delahunty C, Yates JR 3rd, Rahlfs S, Becker K (2011) Protein s-glutathionylation in malaria parasites. Antioxid Redox Signal 15:2855–2865

Kim H, Lee TH, Park ES, Suh JM, Park SJ, Chung HK, Kwon OY, Kim YK, Ro HK, Shong M (2000) Role of peroxiredoxins in regulating intracellular hydrogen peroxide and hydrogen peroxide-induced apoptosis in thyroid cells. J Biol Chem 275:18266–18270

Koken SE, Greijer AE, Verhoef K, van Wamel J, Bukrinskaya AG, Berkhout B (1994) Intracellular analysis of in vitro modified HIV Tat protein. J Biol Chem 269:8366–8375

Komaki-Yasuda K, Kawazu S, Kano S (2003) Disruption of the Plasmodium falciparum 2-Cys peroxiredoxin gene renders parasites hypersensitive to reactive oxygen and nitrogen species. FEBS Lett 547:140–144

Koncarevic S, Rohrbach P, Deponte M, Krohne G, Prieto JH, Yates J 3rd, Rahlfs S, Becker K (2009) The malarial parasite Plasmodium falciparum imports the human protein peroxiredoxin 2 for peroxide detoxification. Proc Natl Acad Sci USA 106:13323–13328

Koshkin A, Knudsen GM, Ortiz De Montellano PR (2004) Intermolecular interactions in the AhpC/AhpD antioxidant defense system of Mycobacterium tuberculosis. Arch Biochem Biophys 427:41–47

Krauth-Siegel RL, Muller JG, Lottspeich F, Schirmer RH (1996) Glutathione reductase and glutamate dehydrogenase of Plasmodium falciparum, the causative agent of tropical malaria. Eur J Biochem 235:345–350

Krnajski Z, Gilberger TW, Walter RD, Cowman AF, Muller S (2002) Thioredoxin reductase is essential for the survival of Plasmodium falciparum erythrocytic stages. J Biol Chem 277:25970–25975

Kumar S, Bandyopadhyay U (2005) Free heme toxicity and its detoxification systems in human. Toxicol Lett 157:175–188

Kumar A, Farhana A, Guidry L, Saini V, Hondalus M, Steyn AJ (2011) Redox homeostasis in mycobacteria: the key to tuberculosis control? Expert Rev Mol Med 13:e39

Lanzillotti JS, Tang AM (2005) Micronutrients and HIV disease: a review pre- and post-HAART. Nutr Clin Care 8:16–23

Lawn SD, Zumla AI (2011) Tuberculosis. Lancet 378:57–72

Lee WL, Gold B, Darby C, Brot N, Jiang X, de Carvalho LP, Wellner D, St John G, Jacobs WR Jr, Nathan C (2009) Mycobacterium tuberculosis expresses methionine sulphoxide reductases A and B that protect from killing by nitrite and hypochlorite. Mol Microbiol 71:583–593

Leff JA, Oppegard MA, Curiel TJ, Brown KS, Schooley RT, Repine JE (1992) Progressive increases in serum catalase activity in advancing human immunodeficiency virus infection. Free Radic Biol Med 13:143–149

Leistikow RL, Morton RA, Bartek IL, Frimpong I, Wagner K, Voskuil MI (2010) The Mycobacterium tuberculosis DosR regulon assists in metabolic homeostasis and enables rapid recovery from nonrespiring dormancy. J Bacteriol 192:1662–1670

Leto TL, Geiszt M (2006) Role of Nox family NADPH oxidases in host defense. Antioxid Redox Signal 8:1549–1561

Li Y, He ZG (2012) The mycobacterial LysR-type regulator OxyS responds to oxidative stress and negatively regulates expression of the catalase-peroxidase gene. PLOS One 7:e30186

Li Z, Kelley C, Collins F, Rouse D, Morris S (1998) Expression of katG in Mycobacterium tuberculosis is associated with its growth and persistence in mice and guinea pigs. J Infect Dis 177:1030–1035

Loria P, Miller S, Foley M, Tilley L (1999) Inhibition of the peroxidative degradation of haem as the basis of action of chloroquine and other quinoline antimalarials. Biochem J 339(Pt 2): 363–370

Macmicking JD, North RJ, Lacourse R, Mudgett JS, Shah SK, Nathan CF (1997) Identification of nitric oxide synthase as a protective locus against tuberculosis. Proc Natl Acad Sci USA 94:5243–5248

Manca C, Paul S, Barry CE 3rd, Freedman VH, Kaplan G (1999) Mycobacterium tuberculosis catalase and peroxidase activities and resistance to oxidative killing in human monocytes in vitro. Infect Immun 67:74–79

Master SS, Springer B, Sander P, Boettger EC, Deretic V, Timmins GS (2002) Oxidative stress response genes in Mycobacterium tuberculosis: role of ahpC in resistance to peroxynitrite and stage-specific survival in macrophages. Microbiology 148:3139–3144

Masutani H, Ueda S, Yodoi J (2005) The thioredoxin system in retroviral infection and apoptosis. Cell Death Differ 12(Suppl 1):991–998

McDermid JM, Lalonde RG, Gray-Donald K, Baruchel S, Kubow S (2002) Associations between dietary antioxidant intake and oxidative stress in HIV-seropositive and HIV-seronegative men and women. J Acquir Immune Defic Syndr 29:158–164

Miesel L, Weisbrod TR, Marcinkeviciene JA, Bittman R, Jacobs WR Jr (1998) NADH dehydrogenase defects confer isoniazid resistance and conditional lethality in Mycobacterium smegmatis. J Bacteriol 180:2459–2467

Morris D, Guerra C, Donohue C, Oh H, Khurasany M, Venketaraman V (2012) Unveiling the mechanisms for decreased glutathione in individuals with HIV infection. Clin Dev Immunol 2012:734125

Murray CJ, Rosenfeld LC, Lim SS, Andrews KG, Foreman KJ, Haring D, Fullman N, Naghavi M, Lozano R, Lopez AD (2012) Global malaria mortality between 1980 and 2010: a systematic analysis. Lancet 379:413–431

Nakamura H, de Rosa S, Roederer M, Anderson MT, Dubs JG, Yodoi J, Holmgren A, Herzenberg LA (1996) Elevation of plasma thioredoxin levels in HIV-infected individuals. Int Immunol 8:603–611

Narsaria N, Mohanty C, Das BK, Mishra SP, Prasad R (2011) Oxidative stress in children with severe malaria. J Trop Pediatr 58(2):147–150

Newton GL, Fahey RC, Cohen G, Aharonowitz Y (1993) Low-molecular-weight thiols in streptomycetes and their potential role as antioxidants. J Bacteriol 175:2734–2742

Newton GL, Arnold K, Price MS, Sherrill C, Delcardayre SB, Aharonowitz Y, Cohen G, Davies J, Fahey RC, Davis C (1996) Distribution of thiols in microorganisms: mycothiol is a major thiol in most actinomycetes. J Bacteriol 178:1990–1995

Newton GL, Av-Gay Y, Fahey RC (2000) A novel mycothiol-dependent detoxification pathway in mycobacteria involving mycothiol S-conjugate amidase. Biochemistry 39:10739–10746

Newton GL, Buchmeier N, Fahey RC (2008) Biosynthesis and functions of mycothiol, the unique protective thiol of Actinobacteria. Microbiol Mol Biol Rev 72:471–494

Ng VH, Cox JS, Sousa AO, Macmicking JD, McKinney JD (2004) Role of KatG catalase-peroxidase in mycobacterial pathogenesis: countering the phagocyte oxidative burst. Mol Microbiol 52:1291–1302

Nicholas GM, Eckman LL, Newton GL, Fahey RC, Ray S, Bewley CA (2003) Inhibition and kinetics of mycobacterium tuberculosis and mycobacterium smegmatis mycothiol-S-conjugate amidase by natural product inhibitors. Bioorg Med Chem 11:601–608

Nicholson S, Bonecini-Almeida Mda G, Lapa E Silva JR, Nathan C, Xie QW, Mumford R, Weidner JR, Calaycay J, Geng J, Boechat N, Linhares C, Rom W, Ho JL (1996) Inducible nitric oxide synthase in pulmonary alveolar macrophages from patients with tuberculosis. J Exp Med 183:2293–2302

Nickel C, Trujillo M, Rahlfs S, Deponte M, Radi R, Becker K (2005) Plasmodium falciparum 2-Cys peroxiredoxin reacts with plasmoredoxin and peroxynitrite. Biol Chem 386:1129–1136

Nickel C, Rahlfs S, Deponte M, Koncarevic S, Becker K (2006) Thioredoxin networks in the malarial parasite Plasmodium falciparum. Antioxid Redox Signal 8:1227–1239

Nussenblatt V, Semba RD (2002) Micronutrient malnutrition and the pathogenesis of malarial anemia. Acta Trop 82:321–337

Pabon A, Carmona J, Burgos LC, Blair S (2003) Oxidative stress in patients with non-complicated malaria. Clin Biochem 36:71–78

Pantaleo G, Graziosi C, Fauci AS (1993) New concepts in the immunopathogenesis of human immunodeficiency virus infection. N Engl J Med 328:327–335

Park HD, Guinn KM, Harrell MI, Liao R, Voskuil MI, Tompa M, Schoolnik GK, Sherman DR (2003) Rv3133c/dosR is a transcription factor that mediates the hypoxic response of Mycobacterium tuberculosis. Mol Microbiol 48:833–843

Pastrana-Mena R, Dinglasan RR, Franke-Fayard B, Vega-Rodriguez J, Fuentes-Caraballo M, Baerga-Ortiz A, Coppens I, Jacobs-Lorena M, Janse CJ, Serrano AE (2010) Glutathione reductase-null malaria parasites have normal blood stage growth but arrest during development in the mosquito. J Biol Chem 285:27045–27056

Pereira LA, Bentley K, Peeters A, Churchill MJ, Deacon NJ (2000) A compilation of cellular transcription factor interactions with the HIV-1 LTR promoter. Nucleic Acids Res 28:663–668

Polat G, Aslan G, Eskandari GH, Delialioglu N, Bagdatoglu O, Atik U (2002) The role of nitric oxide and lipid peroxidation in patients with Plasmodium vivax malaria. Parasite 9:371–374

Potter SM, Mitchell AJ, Cowden WB, Sanni LA, Dinauer M, de Haan JB, Hunt NH (2005) Phagocyte-derived reactive oxygen species do not influence the progression of murine blood-stage malaria infections. Infect Immun 73:4941–4947

Price TO, Ercal N, Nakaoke R, Banks WA (2005) HIV-1 viral proteins gp120 and Tat induce oxidative stress in brain endothelial cells. Brain Res 1045:57–63

Pym AS, Domenech P, Honore N, Song J, Deretic V, Cole ST (2001) Regulation of catalase-peroxidase (KatG) expression, isoniazid sensitivity and virulence by furA of Mycobacterium tuberculosis. Mol Microbiol 40:879–889

Rahlfs S, Fischer M, Becker K (2001) Plasmodium falciparum possesses a classical glutaredoxin and a second, glutaredoxin-like protein with a PICOT homology domain. J Biol Chem 276:37133–37140

Rawat M, Newton GL, Ko M, Martinez GJ, Fahey RC, Av-Gay Y (2002) Mycothiol-deficient Mycobacterium smegmatis mutants are hypersensitive to alkylating agents, free radicals, and antibiotics. Antimicrob Agents Chemother 46:3348–3355

Rawat M, Uppal M, Newton G, Steffek M, Fahey RC, Av-Gay Y (2004) Targeted mutagenesis of the Mycobacterium smegmatis mca gene, encoding a mycothiol-dependent detoxification protein. J Bacteriol 186:6050–6058

Reiser K, Francois KO, Schols D, Bergman T, Jornvall H, Balzarini J, Karlsson A, Lundberg M (2012) Thioredoxin-1 and protein disulfide isomerase catalyze the reduction of similar disulfides in HIV gp120. Int J Biochem Cell Biol 44(3):556–562

Rho BS, Hung LW, Holton JM, Vigil D, Kim SI, Park MS, Terwilliger TC, Pedelacq JD (2006) Functional and structural characterization of a thiol peroxidase from Mycobacterium tuberculosis. J Mol Biol 361:850–863

Richard MJ, Guiraud P, Didier C, Seve M, Flores SC, Favier A (2001) Human immunodeficiency virus type 1 Tat protein impairs selenoglutathione peroxidase expression and activity by a mechanism independent of cellular selenium uptake: consequences on cellular resistance to UV-A radiation. Arch Biochem Biophys 386:213–220

Richard D, Bartfai R, Volz J, Ralph SA, Muller S, Stunnenberg HG, Cowman AF (2011) A genome-wide chromatin-associated nuclear peroxiredoxin from the malaria parasite Plasmodium falciparum. J Biol Chem 286:11746–11755

Roederer M, Staal FJ, Raju PA, Ela SW, Herzenberg LA (1990) Cytokine-stimulated human immunodeficiency virus replication is inhibited by N-acetyl-L-cysteine. Proc Natl Acad Sci USA 87:4884–4888

Roederer M, Staal FJ, Osada H, Herzenberg LA (1991) CD4 and CD8 T cells with high intracellular glutathione levels are selectively lost as the HIV infection progresses. Int Immunol 3:933–937

Romani B, Engelbrecht S, Glashoff RH (2010) Functions of Tat: the versatile protein of human immunodeficiency virus type 1. J Gen Virol 91:1–12

Romero-Alvira D, Roche E (1998) The keys of oxidative stress in acquired immune deficiency syndrome apoptosis. Med Hypotheses 51:169–173

Rouse DA, Devito JA, Li Z, Byer H, Morris SL (1996) Site-directed mutagenesis of the katG gene of Mycobacterium tuberculosis: effects on catalase-peroxidase activities and isoniazid resistance. Mol Microbiol 22:583–592

Ruwende C, Hill A (1998) Glucose-6-phosphate dehydrogenase deficiency and malaria. J Mol Med (Berl) 76:581–588

Saitoh M, Nishitoh H, Fujii M, Takeda K, Tobiume K, Sawada Y, Kawabata M, Miyazono K, Ichijo H (1998) Mammalian thioredoxin is a direct inhibitor of apoptosis signal-regulating kinase (ASK) 1. EMBO J 17:2596–2606

Sanni LA, Fu S, Dean RT, Bloomfield G, Stocker R, Chaudhri G, Dinauer MC, Hunt NH (1999) Are reactive oxygen species involved in the pathogenesis of murine cerebral malaria? J Infect Dis 179:217–222

Sareen D, Newton GL, Fahey RC, Buchmeier NA (2003) Mycothiol is essential for growth of Mycobacterium tuberculosis Erdman. J Bacteriol 185:6736–6740

Sarma GN, Savvides SN, Becker K, Schirmer M, Schirmer RH, Karplus PA (2003) Glutathione reductase of the malarial parasite Plasmodium falciparum: crystal structure and inhibitor development. J Mol Biol 328:893–907

Sarma GN, Nickel C, Rahlfs S, Fischer M, Becker K, Karplus PA (2005) Crystal structure of a novel Plasmodium falciparum 1-Cys peroxiredoxin. J Mol Biol 346:1021–1034

Sassetti CM, Boyd DH, Rubin EJ (2003) Genes required for mycobacterial growth defined by high density mutagenesis. Mol Microbiol 48:77–84

Scanga CA, Mohan VP, Tanaka K, Alland D, Flynn JL, Chan J (2001) The inducible nitric oxide synthase locus confers protection against aerogenic challenge of both clinical and laboratory strains of Mycobacterium tuberculosis in mice. Infect Immun 69:7711–7717

Schreck R, Rieber P, Baeuerle PA (1991) Reactive oxygen intermediates as apparently widely used messengers in the activation of the NF-kappa B transcription factor and HIV-1. EMBO J 10:2247–2258

Sherman DR, Sabo PJ, Hickey MJ, Arain TM, Mahairas GG, Yuan Y, Barry CE 3rd, Stover CK (1995) Disparate responses to oxidative stress in saprophytic and pathogenic mycobacteria. Proc Natl Acad Sci USA 92:6625–6629

Shiloh MU, Nathan CF (2000) Reactive nitrogen intermediates and the pathogenesis of Salmonella and mycobacteria. Curr Opin Microbiol 3:35–42

Shiloh MU, Manzanillo P, Cox JS (2008) Mycobacterium tuberculosis senses host-derived carbon monoxide during macrophage infection. Cell Host Microbe 3:323–330

Shor-Posner G, Lecusay R, Miguez MJ, Moreno-Black G, Zhang G, Rodriguez N, Burbano X, Baum M, Wilkie F (2003) Psychological burden in the era of HAART: impact of selenium therapy. Int J Psychiatry Med 33:55–69

Sienkiewicz N, Daher W, Dive D, Wrenger C, Viscogliosi E, Wintjens R, Jouin H, Capron M, Muller S, Khalife J (2004) Identification of a mitochondrial superoxide dismutase with an unusual targeting sequence in Plasmodium falciparum. Mol Biochem Parasitol 137:121–132

Singh A, Guidry L, Narasimhulu KV, Mai D, Trombley J, Redding KE, Giles GI, Lancaster JR Jr, Steyn AJ (2007) Mycobacterium tuberculosis WhiB3 responds to O2 and nitric oxide via its [4Fe-4S] cluster and is essential for nutrient starvation survival. Proc Natl Acad Sci USA 104:11562–11567

Singh A, Crossman DK, Mai D, Guidry L, Voskuil MI, Renfrow MB, Steyn AJ (2009) Mycobacterium tuberculosis WhiB3 maintains redox homeostasis by regulating virulence lipid anabolism to modulate macrophage response. PLOS Pathog 5:e1000545

Singhal N, Austin J (2002) A clinical review of micronutrients in HIV infection. J Int Assoc Physicians AIDS Care (Chic) 1:63–75

Staal FJ, Roederer M, Herzenberg LA (1990) Intracellular thiols regulate activation of nuclear factor kappa B and transcription of human immunodeficiency virus. Proc Natl Acad Sci USA 87:9943–9947

Stehbens WE (2004) Oxidative stress in viral hepatitis and AIDS. Exp Mol Pathol 77:121–132

Steyn AJ, Collins DM, Hondalus MK, Jacobs WR Jr, Kawakami RP, Bloom BR (2002) Mycobacterium tuberculosis WhiB3 interacts with RpoV to affect host survival but is dispensable for in vivo growth. Proc Natl Acad Sci USA 99:3147–3152

Stiebler R, Soares JB, Timm BL, Silva JR, Mury FB, Dansa-Petretski M, Oliveira MF (2011) On the mechanisms involved in biological heme crystallization. J Bioenerg Biomembr 43:93–99

Sturm N, Jortzik E, Mailu BM, Koncarevic S, Deponte M, Forchhammer K, Rahlfs S, Becker K (2009) Identification of proteins targeted by the thioredoxin superfamily in Plasmodium falciparum. PLOS Pathog 5:e1000383

Suresh DR, Annam V, Pratibha K, Prasad BV (2009) Total antioxidant capacity–a novel early bio-chemical marker of oxidative stress in HIV infected individuals. J Biomed Sci 16:61

Sztajer H, Gamain B, Aumann KD, Slomianny C, Becker K, Brigelius-Flohe R, Flohe L (2001) The putative glutathione peroxidase gene of Plasmodium falciparum codes for a thioredoxin peroxidase. J Biol Chem 276:7397–7403

Trujillo M, Mauri P, Benazzi L, Comini M, de Palma A, Flohe L, Radi R, Stehr M, Singh M, Ursini F, Jaeger T (2006) The mycobacterial thioredoxin peroxidase can act as a one-cysteine peroxiredoxin. J Biol Chem 281:20555–20566

Tuteja R (2007) Malaria – an overview. FEBS J 274:4670–4679

Vega-Rodriguez J, Franke-Fayard B, Dinglasan RR, Janse CJ, Pastrana-Mena R, Waters AP, Coppens I, Rodriguez-Orengo JF, Srinivasan P, Jacobs-Lorena M, Serrano AE (2009) The glutathione biosynthetic pathway of Plasmodium is essential for mosquito transmission. PLOS Pathog 5:e1000302

Velez DR, Hulme WF, Myers JL, Weinberg JB, Levesque MC, Stryjewski ME, Abbate E, Estevan R, Patillo SG, Gilbert JR, Hamilton CD, Scott WK (2009) NOS2A, TLR4, and IFNGR1 interactions influence pulmonary tuberculosis susceptibility in African-Americans. Hum Genet 126:643–653

Vilcheze C, Jacobs WR Jr (2007) The mechanism of isoniazid killing: clarity through the scope of genetics. Annu Rev Microbiol 61:35–50

Vilcheze C, Weisbrod TR, Chen B, Kremer L, Hazbon MH, Wang F, Alland D, Sacchettini JC, Jacobs WR Jr (2005) Altered NADH/NAD+ ratio mediates coresistance to isoniazid and ethionamide in mycobacteria. Antimicrob Agents Chemother 49:708–720

Vogt RN, Steenkamp DJ, Zheng R, Blanchard JS (2003) The metabolism of nitrosothiols in the Mycobacteria: identification and characterization of S-nitrosomycothiol reductase. Biochem J 374:657–666

Voskuil MI, Bartek IL, Visconti K, Schoolnik GK (2011) The response of mycobacterium tuberculosis to reactive oxygen and nitrogen species. Front Microbiol 2:105

Washington AT, Singh G, Aiyar A (2010) Diametrically opposed effects of hypoxia and oxidative stress on two viral transactivators. Virol J 7:93

Watt G, Jongsakul K, Ruangvirayuth R (2002) A pilot study of N-acetylcysteine as adjunctive therapy for severe malaria. QJM 95:285–290

Weinberg JB, Lopansri BK, Mwaikambo E, Granger DL (2008) Arginine, nitric oxide, carbon monoxide, and endothelial function in severe malaria. Curr Opin Infect Dis 21:468–475

Wengenack NL, Jensen MP, Rusnak F, Stern MK (1999) Mycobacterium tuberculosis KatG is a peroxynitritase. Biochem Biophys Res Commun 256:485–487

WHO (2011a) Global HIV/AIDS response. Progress Report 2011. Available http://whqlibdoc.who.int/publications/2011/9789241502986_eng.pdf

WHO (2011b) Global tuberculosis control 2011 [Online]. Available http://www.who.int/tb/publications/global_report/en/. Accessed 10 Feb 2012

WHO (2011c) World malaria report 2011 [Online]. Available http://www.who.int/malaria/world_malaria_report_2011/en/. Accessed 14 Feb 2012

Williams CH, Arscott LD, Muller S, Lennon BW, Ludwig ML, Wang PF, Veine DM, Becker K, Schirmer RH (2000) Thioredoxin reductase two modes of catalysis have evolved. Eur J Biochem 267:6110–6117

Wood ZA, Schroder E, Robin Harris J, Poole LB (2003) Structure, mechanism and regulation of peroxiredoxins. Trends Biochem Sci 28:32–40

Xu X, Vilcheze C, Av-Gay Y, Gomez-Velasco A, Jacobs WR Jr (2011) Precise null deletion mutations of the mycothiol synthesis genes reveal their role in isoniazid and ethionamide resistance in Mycobacterium smegmatis. Antimicrob Agents Chemother 55:3133–3139

Yeo TW, Lampah DA, Gitawati R, Tjitra E, Kenangalem E, McNeil YR, Darcy CJ, Granger DL, Weinberg JB, Lopansri BK, Price RN, Duffull SB, Celermajer DS, Anstey NM (2008) Recovery of endothelial function in severe falciparum malaria: relationship with improvement in plasma L-arginine and blood lactate concentrations. J Infect Dis 198:602–608

Zahrt TC, Deretic V (2002) Reactive nitrogen and oxygen intermediates and bacterial defenses: unusual adaptations in Mycobacterium tuberculosis. Antioxid Redox Signal 4:141–159

Zahrt TC, Song J, Siple J, Deretic V (2001) Mycobacterial FurA is a negative regulator of catalase-peroxidase gene katG. Mol Microbiol 39:1174–1185

Zeba AN, Sorgho H, Rouamba N, Zongo I, Rouamba J, Guiguemde RT, Hamer DH, Mokhtar N, Ouedraogo JB (2008) Major reduction of malaria morbidity with combined vitamin A and zinc supplementation in young children in Burkina Faso: a randomized double blind trial. Nutr J 7:7

Zhang Y, Lathigra R, Garbe T, Catty D, Young D (1991) Genetic analysis of superoxide dismutase, the 23 kilodalton antigen of Mycobacterium tuberculosis. Mol Microbiol 5:381–391

Zhang Y, Heym B, Allen B, Young D, Cole S (1992) The catalase-peroxidase gene and isoniazid resistance of Mycobacterium tuberculosis. Nature 358:591–593

Zhang Z, Hillas PJ, Ortiz De Montellano PR (1999) Reduction of peroxides and dinitrobenzenes by Mycobacterium tuberculosis thioredoxin and thioredoxin reductase. Arch Biochem Biophys 363:19–26