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Unusual thiol-based redox metabolism of parasitic flukes

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ABSTRACT

Parasitic flukes are exposed to free radicals and, to a greater extent, reactive oxygen species (ROS) during their life cycle. Despite being relentlessly exposed to ROS released by activated immune cells, these parasites can survive for many years in the host. Cellular thiol-based redox metabolism plays a crucial role in parasite survival within their hosts. Evidence shows that oxidative stress and redox homeostasis maintenance are important clinical and pathobiochemical as well as effective therapeutic principles in various diseases. The characterization of redox and antioxidant enzymes is likely to yield good target candidates for novel drugs and vaccines. The absence of active catalase in fluke parasites offers great potential for the development of chemotherapeutic agents that act by perturbing the redox equilibrium of the cell. One of the redox-sensitive enzymes, thioredoxin glutathione reductase (TGR), has been accepted as a drug target against blood fluke infections, and related clinical trials are in progress. TGR is the sole enzyme responsible for Trx and GSH reduction in parasitic flukes. The availability of helminth genomes has accelerated the research on redox metabolism of flukes; however, significant achievements have yet to be attained. The present review summarizes current knowledge on the redox and antioxidant system of the parasitic flukes.

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1. Liver flukes

Liver fluke diseases due to infections by digenetic trematodes such as *Fasciola* spp., *Opisthorchis* spp., and *Clonorchis sinensis* are major parasitic problems worldwide. *Fasciola hepatica* and/or *Fasciola gigantica* infection of domestic ruminants (sheep, cattle, buffalo, and goats) causes major economic losses (>US$3 billion p.a.) in livestock production, infecting over 600 million animals globally [1–3]. Fascioliasis has been recognized as a major helminth infection in cattle in the tropics; it affects 25–100% of cattle in Africa, the Middle East, and Southeast Asia. *F. hepatica* is more widespread in temperate countries, with a prevalence of up to 70%. In humans, fascioliasis is also an important zoonotic disease that has infected 2.4–17 million people and has put approximately 180 million people at risk globally [4,5]. However, due to the asymptomatic nature of human fascioliasis, the number of infected people worldwide may be even higher [6]. Major human fascioliasis endemic areas include Africa, Europe, the Middle East (including Egypt), Southeast Asia, and Latin America, with the highest prevalence at 72–100% in the Bolivian Altiplano [7]. WHO recommends triclabendazole for the treatment of fascioliasis; the drug is active against both parasite stages, i.e., the metacercariae and adult stages. However, recent studies have suggested that the endoparasites have gained resistance to triclabendazole in several countries [8–10].

The small liver flukes, *Opisthorchis viverrini*, *Opisthorchis felineus*, and *C. sinensis*, also cause major public health problems worldwide. *C. sinensis* is widespread in China, Korea, and northern Vietnam, while *O. viverrini* is endemic in Southeast Asia, including Thailand, Lao People's Democratic Republic (Lao PDR), Cambodia, and southern Vietnam. *O. felineus* is endemic in western Siberia and Eastern Europe. Reports suggest that about 35 million people are infected with *C. sinensis* globally, with up to 15 million human infections in China alone. About 8–10 million individuals are infected with *O. viverrini* in Thailand, Lao PDR, and Vietnam [11]. More than 600 million people worldwide, particularly in Asia, are at a risk of infection with these two liver flukes. These infections are acquired when raw or undercooked freshwater fish harboring the infective stage (metacercaria) of the parasite are consumed. Ingested metacercariae excyst in the duodenum and juvenile flukes migrate into the biliary tree, where

Abbreviations: DTNB, 5,5′-diothiobis(2-nitrobenzoic acid); FAD, Flavin adenine dinucleotide; GSH, Reduced glutathione; GSSG, Oxidized glutathione; GR, Glutathione reductase; Grx, Glutaredoxin; ROS, Reactive oxygen species; TGR, Thioredoxin glutathione reductase; TMX, Trx-transmembrane-related protein; Trx, Thioredoxin; TrxR, Thioredoxin reductase.

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they grow to their adult stage. These infections are associated with hepatobiliary diseases, including hepatomegaly, cholangitis, fibrosis of the periportal system, cholecystitis, and gallstones, and are major etiological agents of cholangiocarcinoma. *O. viverrini* and *C. sinensis* have been classified as Group 1 carcinogens, i.e., metazoan parasites that are carcinogenic to humans, by the WHO's International Agency for Research on Cancer [12,13]. However, these infections can be treated using only the antihelminthic drug praziquantel, which raises the concern of drug-resistant flukes. Thus, there is a need for other alternative drugs or vaccines. In addition, these liver flukes have a long life span; *C. sinensis* has been reported to survive in humans for up to 26 years. Increasing economic losses due to livestock mortality and development of resistance to the available drugs against these liver flukes throughout the world suggest the need for identification and characterization of novel drug targets against these parasites.

2. Thiol-based redox metabolism

2.1. Overview

All aerobic organisms are exposed to reactive oxygen species (ROS) such as H_2O_2, superoxide anions, and hydroxyl radicals during normal aerobic metabolism or after exposure to radical-generating compounds. When released in high quantities, ROS can cause severe damage to molecules such as lipids, proteins, DNA, and RNA, leading to the induction of apoptosis or even necrosis [14]. Therefore, the production as well as removal of ROS must be strictly controlled in order to sustain favored cellular functions and avoid harmful overproduction [15]. In order to preserve this crucial reducing milieu, aerobes have evolved efficient redox and antioxidant systems [15–19]. Increasing evidence indicates that cellular redox status regulates various aspects of cellular functions and oxidative stress. Thus, to maintain the redox balance, cells have developed several ways to protect themselves against oxidative stress. These include many small non-enzymatic antioxidative compounds such as vitamins A, C, and E, and glutathione, as well as a number of enzymatic systems.

Living cells experience redox chemistry in their normal environment, which involves the threat of oxygen. Even under the influence of this highly oxidizing compound, the cytosol of living cells provides a reducing environment that is essential for its proper function. The only significantly redox-active component of generic proteins is the amino acid cysteine (Cys), which oxidizes to form a disulfide bond under normal atmospheric conditions. Cys is a key amino acid for protein folding, metal coordination, and enzyme catalysis because of to the redox properties of the thiol group [20–22]. In the cell, the redox state of the Cys thiols is regulated by the thioredoxin (Trx) and glutathione (GSH) systems [21,23–26].

Due to the economic and health significances of these liver flukes, numerous studies have focused on the various aspects of the diseases. However, there are several research areas, including the biochemistry of the liver flukes, specifically the redox metabolism, that still need to be studied. This redox reaction is vital for the liver flukes to survive under oxidative stress conditions from host inflammatory responses, and it may link to the identification of novel protein drug targets for liver flukes.

2.2. Classical Trx and GSH system

In almost all organisms, including the mammalian hosts of parasitic flukes, the intracellular redox milieu is maintained by two parallel systems, namely Trx and GSH systems. The Trx system consists of a) Trx and b) a Trx reductase (TrxR) utilizing NADPH. Trxs are small ubiquitous thiol-disulfide oxidoreductases whose key function involves reduction of disulfide bonds of the target proteins. After the target reduction, Trx is brought back to its reduced state by TrxR, which acquires the electrons from NADPH. The GSH system consists of a) GSH, b) an NADPH-dependent glutathione reductase (GR), and c) many glutaredoxin isoforms (Grxs). Grxs transfer electrons from GSH to an inter- or intramolecular disulfide and then to their oxidizing substrate, liberating the native functional protein. These systems also play a key role in various cellular processes, including DNA synthesis, defense against oxidative stress, detoxification, protein folding, cellular signaling, and repair. The enzymes of redox metabolism have been identified as a promising target development of novel drugs [27–30]. Fig. 1 shows the outline of the Trx and GSH systems. For more detailed mechanisms of the classical Trx and GSH systems, see previous reviews [23–26,31–39].

2.3. Linked Trx-GSH system in parasitic flukes

The Trx and GSH pathways differ in parasitic and free-living flatworms. The classical enzymes were lost in the parasitic lineage during evolution [40]. In contrast to all other organisms, including the free-living forms, parasitic flukes lack the conventional TrxR and GR proteins and are substituted by a single enzyme, thioredoxin glutathione reductase (TGR) [41–44]. TGR was originally discovered in *Schistosoma mansoni*, which showed the presence of a fused Trx-and-GSH system centered on TGR (Fig. 1c) [45–48]. Since then, this system has been reported in a number of parasites, including *Schistosoma japonicum* [49,50], *Echinococcus granulosus* [51], *Taenia crassiceps* [52], *Taenia solium* [53], *F. hepatica* [54], and *F. gigantica* [55,56]. An absorption spectrum of flavin-saturated SmTGR has an $A_{280/460}$ ratio of 7.61, which is typical of flavoenzymes, thereby suggesting that TGR is a flavin-containing enzyme [45]. In the absence of catalase, the cellular redox homeostasis of these parasites relies completely on the flavoenzyme—TGR, which supplies electrons to both GSSG and Trx [43]. TGR has broad substrate

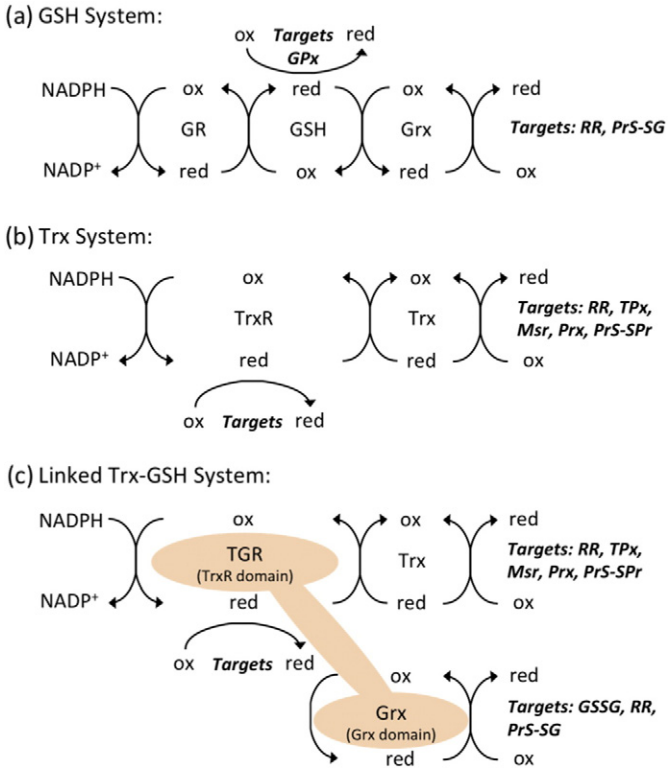

Fig. 1. GSH, Trx and linked Trx–GSH systems. Electron-flow in the Trx, GSH and linked Trx–GSH systems are shown. The GSH system (a) comprises GR, GSH, NADPH and Grx, whereas the Trx system (b) comprises TrxR and Trx. In linked Trx-GSH systems (c), TGR replaces TrxR, GR and Grx, and provides reducing equivalents to proteins of both systems. The fusion between Grx and TrxR domains in TGR is highlighted in red colour. GSH, glutathione; GSSG, oxidized glutathione; Msr, methionine sulfoxide reductase; PrS-SG, glutathione-protein mixed disulfide; PrS-SPr, protein disulfide; Prx, peroxiredoxin; RR, ribonucleotide reductase; Trx, thioredoxin.

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