The Nervous System: An Ideal Therapeutic Target for Anti-Schistosomal Drug Discovery

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Schistosomiasis is a parasitic disease that afflicts over 200 million people worldwide, causing visceral organ disturbance, and impairing growth and cognitive development in children [1]. The etiological agents of human schistosomiasis are the blood flukes of the genus Schistosoma, including S. mansoni, S. haematobium, and S. japonicum. S. mansoni is blamed for over 90% of all human schistosomiasis [2]. Epidemiological evidence reveals that schistosomiasis is typically endemic in tropical countries in Africa, the Caribbean, South America, Southeastern Asia and Middle East, especially in the regions where the intermediate snail host that carries the parasite. Because no vaccine is available for Schistosoma, chemotherapeutic intervention is still the primary option for schistosomiasis treatment. The treatment of human schistosomiasis relies solely on Praziquantel which has been widely used for over three decades. However, emergence of drug resistance in the worms has ignited enthusiasm to search for alternative drug candidates.

To date, there have been numerous candidate molecules that were proposed as potential chemotherapeutic targets for treating schistosomiasis. These molecules are involved in a variety of survival-related machineries of the worm, including redox metabolism (e.g. thioredoxin glutathione reductase) [3,4], ion channels (e.g. calcium channel subunits) [5], chromatin modification (e.g. histone acetyltransferases and deacetylase) [6], metal homeostasis (e.g. phytochelatin synthase) [7,8], protein maturation (e.g. methionine aminopeptidase) [9], and cell signaling (e.g. cAMP-dependent protein kinase and cyclophilin) [10,11]. In contrast to these potential therapeutic strategies, the nervous system of the helminth parasites has been successfully employed as a target by anthelmintics currently in use, including ivermectin, levamisole and monepantel [1]. All of these drugs act on neuroreceptors in the neuromuscular system of the worm, which results in disrupting the neural and neuromuscular transmission, and consequently paralyzing and killing the worm. Ivermectin not only eliminates nematodes, but also trematodes (Fasciola spp., Schistosoma spp.) as well [1].

Schistosoma has a well developed nervous system that consists of a simple brain and several pairs of longitudinal nerve cords (the central nervous system) and a peripheral network that innervates almost all body tissues, especially the tegument, the somatic musculature and the suckers [1,2]. Biogenic amines, including serotonin, dopamine and 5-hydroxytryptamine, are the major neurotransmitters in the nervous system of schistosomes and function as pivotal modulators of neuromuscular transmission, regulating locomotion, attachment to the host and many other behaviors that are essential to the parasite survival in the host [1]. Thus, Biosynthetic enzymes, receptors and transporters of biogenic amines may be aimed as the targets for the development of chemotherapeutic agents against schistosomes. Drug screens have revealed that blockers for serotoningic and dopaminergic receptors and serotonin transporter are the potent disruptors that inhibit schistosome motility [1]. Serotonergic and dopaminergic receptors belong to the members of the super family of G Protein-Coupled Receptors (GPCRs). Recently, Ribeiro et al. have cloned a novel Schistosoma mansoni G protein-coupled receptor (SmGPR-3) [2]. SmGPR-3 was activated by dopamine and other catecholamines, resulting in a strong effect on the motility of larval schistosomes [2]. Immuno staining showed the localization of SmGPR-3 in the central nervous system and the peripheral plexuses innervating the musculature, the caecum, the tubercles and the male reproductive system of Schistosoma mansoni [2]. Since SmGPR-3 is substantially different from dopamine receptor of the mammalian host, this novel protein may be employed as a potential target for developing new schistosome-specific drugs. However, which G protein is recruited by SmGPR-3, how SmGPR-3 undergoes trafficking, endocytosis and degradation, and how SmGPR-3 signals remain yet to be investigated.

GPCRs constitute the largest family of cell surface receptors which share a common topology of seven transmembrane domains and modulate a variety of cell activities [12]. GPCRs are the targets of nearly half drugs currently in use and for the development of new therapeutics that treat a wide range of human diseases [12]. Regulation of surface expression, endocytosis, recycling and degradation of GPCRs involves a number of machineries that spatiotemporally mediate GPCRs-promoted cell signaling [13,14]. Thus, all these machineries could be targeted for drug development. Moreover, the significant evolutionary difference in the structures of GPCRs between schistosome and the host allows developing drugs that specifically kill schistosome but cause less side-effect in the host [1]. To date, most of anthelmintic drugs currently in use act on the nervous system of helminth parasites [1]. Likewise, GPCRs in the nervous system of schistosome is a promising therapeutic target for anti-schistosomal drug discovery.

References


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Received January 02, 2013; Accepted January 05, 2013; Published January 28, 2013


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