International Journal for Parasitology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

International Journal for Parasitology

journal homepage: www.elsevier.com/locate/ijpara

Review Article

The Tao survivorship of schistosomes: implications for schistosomiasis control

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ARTICLE INFO

Article history:
Received 27 November 2015
Received in revised form 6 January 2016
Accepted 6 January 2016
Available online xxxx

Keywords:
Schistosomiasis
Host-schistosome interface
Immunomodulation
microRNAs
Epigenetic control
Transmission blocking vaccine
Drug target identification
CRISPR-Cas system

ABSTRACT

Schistosomiasis, caused by blood flukes of the genus *Schistosoma*, is a major public health problem which contributes substantially to the economic and financial burdens of many nations in the developing world. An array of survival strategies, such as the unique structure of the tegument which acts as a major host-parasite interface, immune modulation mechanisms, gene regulation, and apoptosis and self-renewal have been adopted by schistosome parasites over the course of long-term evolution with their mammalian definitive hosts. Recent generation of complete schistosome genomes together with numerous biological, immunological, high-throughput "-omics" and gene function studies have revealed the Tao or strategies that schistosomes employ not only to promote long-term survival, but also to ensure effective life cycle transmission. New scenarios for the future control of this important neglected tropical disease will present themselves as our understanding of these Tao increases.

1. Introduction

Schistosomiasis remains one of the most serious public health issues in the developing world, afflicting more than 240 million people, with close to 800 million at risk (Steinmann et al., 2006; Weerakoon et al., 2015). This neglected tropical disease is caused by infection with blood fluke (trematode) worms of the genus *Schistosoma*. The three main species of clinical relevance are *Schistosoma mansoni*, *Schistosoma japonicum* and *Schistosoma haematobium*. The annual number of disability-adjusted life years (DALYs) lost due to schistosomiasis was estimated to be 3.3 million in 2010, ranking it as third in the list of global neglected diseases (Hotez et al., 2014). Infection with *S. mansoni* and *S. japonicum* results in hepatic and intestinal schistosomiasis, associated with the formation of granulomas and fibrosis around trapped eggs lodged in the liver or intestinal wall. *Schistosoma haematobium* infections result in urogenital schistosomiasis and the associated pathologies include fibrosis of the bladder and bladder cancer, and there is an increased risk of HIV infection and infertility in women with urogenital schistosomiasis (Brindley and Hotez, 2013). The chronic and debilitating symptoms associated with schistosomiasis contribute significantly to the current cycle of poverty existing in many developing countries in the tropics and subtropics.

Schistosomes are dioecious and have a complex lifecycle involving an aquatic snail as an intermediate host and a mammalian definitive host (Weerakoon et al., 2015). Eggs produced by the female adult worm are released from the definitive host and hatch in freshwater. The released miracidia then penetrate the snail host and develop asexually into mother and then daughter sporocysts, within which cercariae are produced that are in turn released into water. The schistosome lifecycle continues when the free-swimming cercariae infect a mammalian host. After skin penetration, the larvae transform into schistosomula which migrate via a route involving the epidermis, the epidermal-dermal basement membrane, and dermis (Mountford and Trottein, 2004). Once in the dermis, the schistosomula rapidly exit after locating capillaries or lymphatic vessels in which they are carried to the heart and lungs, and finally arrive at the hepatic portal system, where the juveniles pair up and mature sexually. Schistosomes in copula then migrate to the mesenteric veins (*S. mansoni* and *S. japonicum*) or the pelvic venous plexus (*S. haematobium*), where the female worms lay eggs intravascularly, with patency periods varying between species. In contrast to *S. haematobium* and *S. mansoni*, which both generally only infect humans, *S. japonicum* is parasitic in humans and more than 40 other species of mammals which act as reservoir hosts. The adult parasites can survive in the harsh

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http://dx.doi.org/10.1016/j.ijpara.2016.01.002
0020-7519/

Please cite this article in press as: Cai, P., et al. The Tao survivorship of schistosomes: implications for schistosomiasis control. Int. J. Parasitol. (2016), http://dx.doi.org/10.1016/j.ijpara.2016.01.002

microenvironment of the blood vessels of the definitive hosts for several decades. The schistosome lifecycle is shown in Fig. 1.

Currently, praziquantel (PZQ)-based chemotherapy, combined with morbidity management, are the predominant strategies adopted for the treatment and control of schistosomiasis (Mutapi et al., 2011b; Chen, 2014). This strategy reflects the fact that no effective vaccine is available to prevent schistosomiasis, despite a large panel of antigen candidates having been tested over the past decades (McManus and Loukas, 2008). Theoretically, schistosomiasis should be manageable since multiple stages of its causative agents can be targeted for control and even for elimination, but this contrasts with the long-lasting prevalence of the disease in many

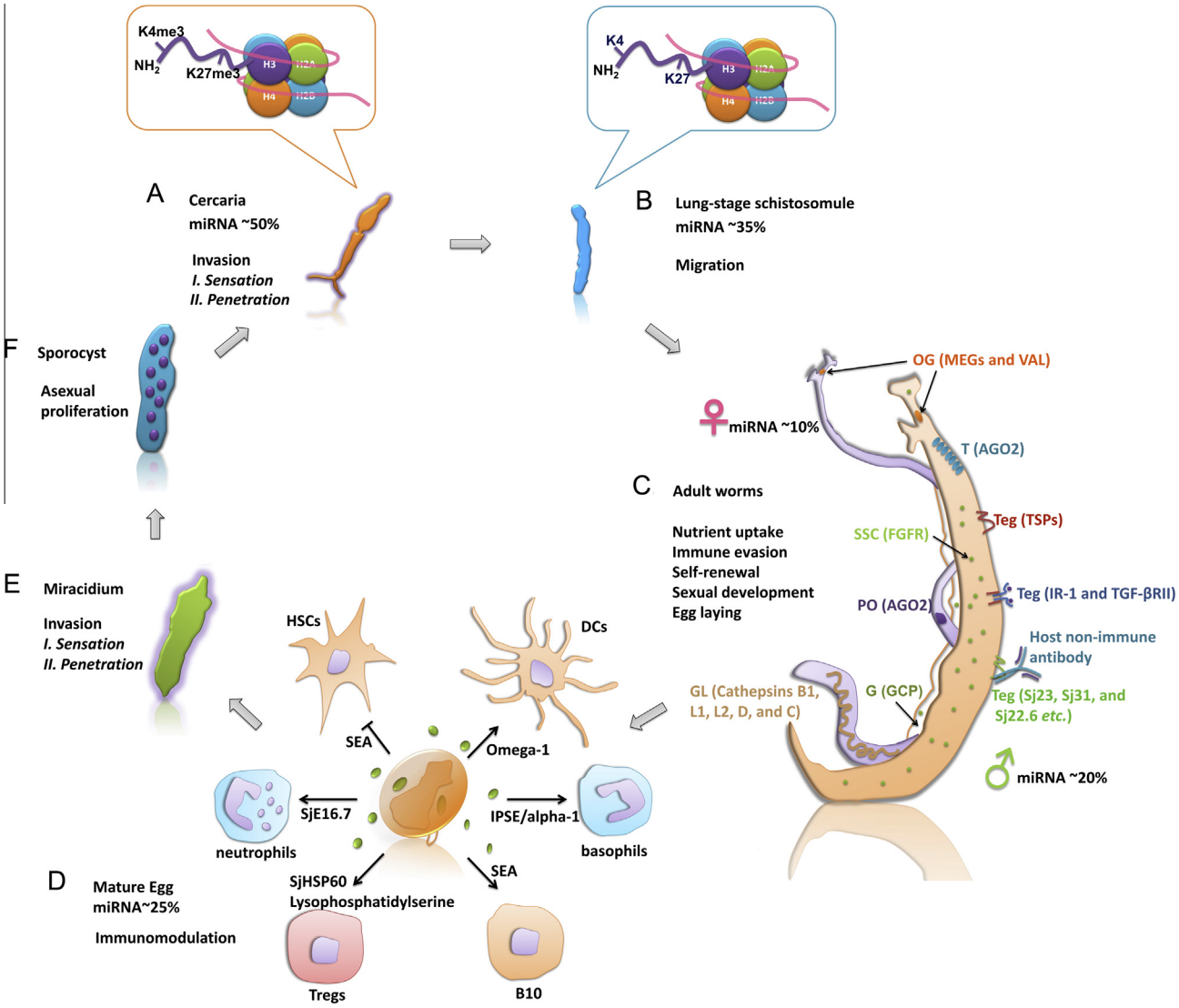

Fig. 1. Diagram illustrating the key survival strategies adopted by schistosomes throughout the life cycle. Cercariae sense environmental stimuli and invasion is further mediated by protein kinase signalling pathways at the initial step of penetration. Different histolytic enzymes are employed by *Schistosoma mansoni* and *Schistosoma japonicum* (SmCE and SjB2, respectively) as the major invasive peptidase to facilitate penetration after the cercariae adhere to mammalian skin. Schistosomula use a wide variety of neurotransmitters to control their motility via interacting with neurotransmitter receptors or transporters, important factors for their migration. The tegument and digestive tract are two important host-parasite interfaces crucial for the survival of schistosomes. In the tegument (Teg), antigenic variation (Sj-tetraspanin (TSP)-2, -5, -18 and -22) and mimicry (a covered with host non-immune antibodies and complement components) commonly take place. Also, the worms utilise receptors (e.g., insulin receptor (IR) I and transforming growth factor-beta (TGF-β) II receptor) to facilitate their development and fecundity through interaction with host-derived ligands. The schistosome digestive tract is responsible for nutrient acquisition and waste disposal. The oesophageal gland (OG) initiates the digestion of host blood, and several members of the schistosome micro-exon gene (MEG) and venom allergen-like (VAL) families may be involved in this process. A number of proteases (e.g., cathepsin B1, L1, L2, D and C) continue the process in the gut lumen. The excreted/secreted protein (ESP) of mature schistosome eggs is recognised as the main mediator in the triggering and manipulation of the host immune response by orchestrating a range of immune cells, particularly dendritic cells (DCs), regulatory T (Treg) cells and neutrophils. The asexual reproduction of a sporocyst produces a large number of cercariae, a process which greatly increases the chance for infection of definitive hosts. Gene regulatory mechanisms are crucial for schistosomes with their complex life cycle stage transitions For example, bivalent histone H3 methylation (at position K4 and K27 at the N-terminus) only occurs in the cercarial stage, and this process has been suggested to trigger the transcription of approximately 120 genes in *S. mansoni*. The microRNA (miRNA) content in total small RNAs varies in different developmental stages and a set of miRNAs has been confirmed to be associated with the development and sexual maturation of these parasites, highlighting their pivotal roles in gene regulation during transit of the developmental stages. In schistosome germline cells (posterior ovary (PO) and testes (T)), Argonaute 2 (AGO2) – associated endo-siRNAs suppress transposable element (TE) activity, acting as a guardian for genome stability. An intrinsic apoptosis pathway and a population of neoblast-like cells have been identified in schistosomes, suggesting that a self-renewal mechanism contributes to the vitality of the parasite within the blood vessels of the definitive host. Crucial genes expressed in different stages and tissues/cells are denoted in brackets, while the miRNA content (%) in the total small RNA population is shown in the different developmental stages. FGFR, fibroblast growth factor receptor orthologue; G, gynaecophoric canal; GCP, Gynaecophoral canal protein; GL, gut lumen; HSC, hepatic stellate cells; HSP, heat shock protein; SEA, soluble egg antigen; SSC, stem somatic cells. (Modified from Fig. 1, Cai et al., 2016.)

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