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Schistosomiasis as a disease of stem cells

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Schistosomiasis is a devastating parasitic disease caused by flatworms of the genus *Schistosoma*. The complex life cycles and developmental plasticity of these parasites have captured the attention of parsitologists for decades, yet little is known on the molecular level about the developmental underpinnings that have allowed these worms to thrive as obligate parasites. Here, we describe basic schistosome biology and highlight how understanding the functions of stem cells in these worms will transform our understanding of these parasites. Indeed, we propose that schistosomiasis is fundamentally as disease of stem cells. We hope this review will attract new interest in the basic developmental biology of these important organisms.

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Introduction

Schistosomes infect more than 200 million of the world's poorest people [1]. These parasites claim the lives of 250,000 people annually [2], but the chronic disability associated with infection robs millions more of the ability to live healthy and productive lives, effectively condemning infected individuals to a life of poverty [3]. To put the scope of this problem into perspective, some estimates suggest that the global morbidity due to schistosome infection may reach levels rivaling diseases including malaria, TB, and perhaps even HIV/AIDS [4]. Further, treatment of schistosomiasis relies upon a single drug (praziquantel) and it remains unclear how effective this drug will be in eradicating this disease in the developing world [5].

While the effects of the schistosome infection are horrific and new therapeutics are urgently needed, the rich, fascinating, and virtually unexplored biology of these parasites should not be ignored. In fact, recent years have seen important advances in schistosome biology, setting the stage for major progress in understanding both the organism and the disease. These advances include the publication of the genomes of the schistosome species that are major human pathogens [6–8], the development of genetic tools to map mutations in the genome [9], methods for RNA interference (RNAi) [10–12], tools for robust whole-mount *in situ* hybridization [13,14••], a growing set of tissue specific markers [14••,15], and promising developments in the generation of transgenic parasites [16,17]. There is even a National Institutes of Health-supported Schistosomiasis Resource Center that provides schistosome material and training to investigators free of charge [18]. Given these resources, basic studies of these unique parasites are poised for a renaissance. Here we detail one emerging area of investigation in these parasites: the biology of stem cells. Although few molecular details about schistosome stem cells exist, there is a great deal of evidence to suggest that these cells are critical for the success of this organism as a parasite. As such, we believe that schistosomes present a fantastic model organism to ask basic questions about stem cell behavior and regulation while simultaneously addressing fundamental aspects of an important disease.

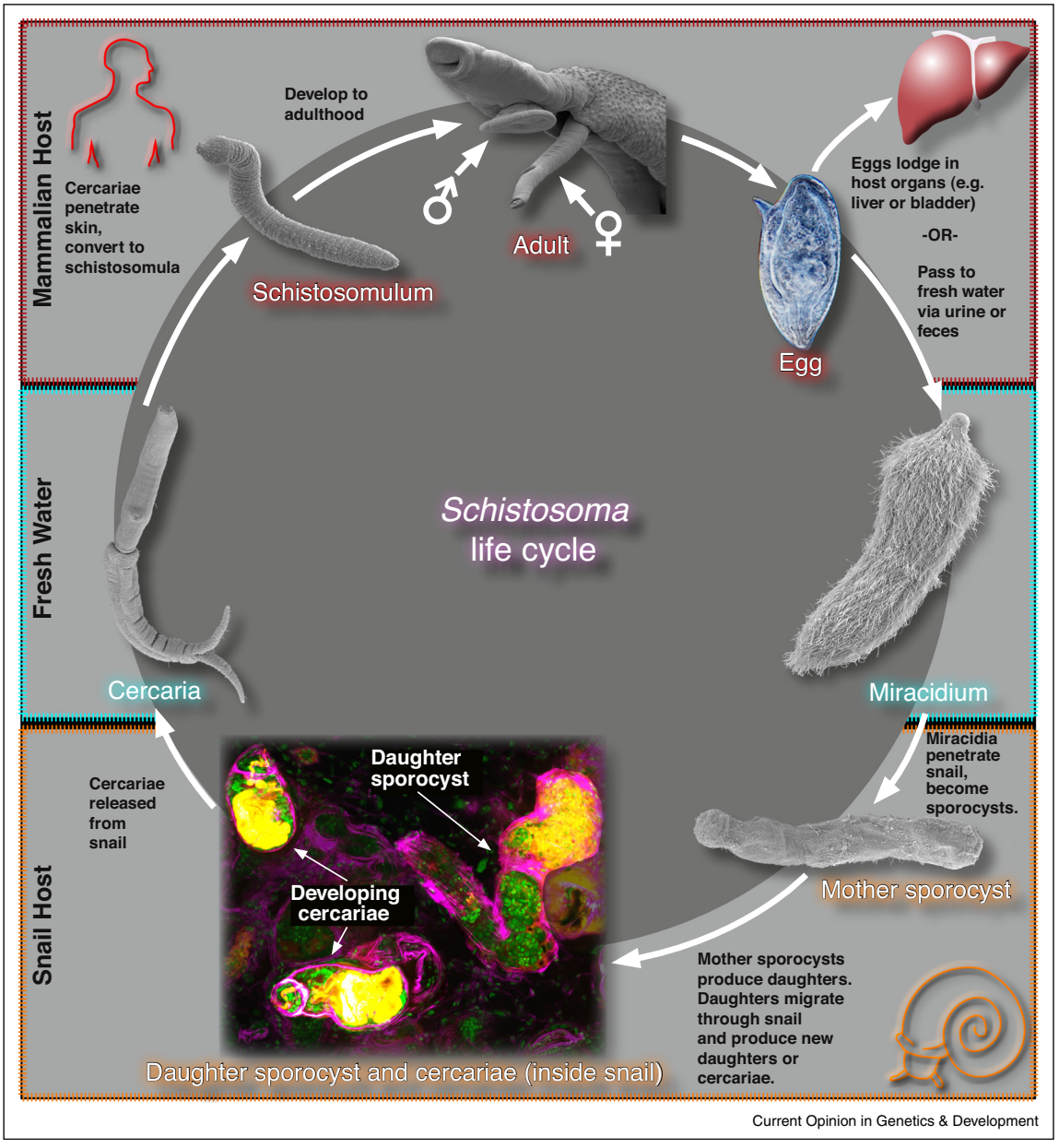
A primer on schistosome biology

Schistosomes are members of the phylum Platyhelminthes (flatworms) which includes a myriad of free-living and parasitic taxa that inhabit most aquatic and some humid terrestrial environments [19]. Perhaps the most well-known flatworms are the free-living freshwater planarians. Capable of regenerating following nearly every type of injury, planarians employ a population of pluripotent stem cells known as neoblasts that fuel not only regeneration but also worm growth and tissue homeostasis [20–22]. Studies of planarians date back over one hundred years and with recent advances in molecular tools, these worms have enjoyed a resurgence in their use as model organisms for the study of regeneration and stem cell biology [20]. Though planarians represent a fascinating model for regenerative and developmental biology, the planarian's parasitic relatives, the Neodermata, should not be ignored. The Neodermata represent a monophyletic clade that includes all three groups of parasitic flatworms: the monogeneans, the cestodes and the trematodes [23•,24]. The ability the Neodermata to parasitize nearly every vertebrate on earth is due in large part to their extreme developmental strategies. Monogeneans can develop like 'Russian Dolls,' with multiple generations of worms developing inside a single mother

[25]. Cestodes (tapeworms) can grow tens of meters inside their host by perpetually adding new segments to their body, with each segment possessing sexually mature reproductive organs [19]. However, there are few developmental feats that can eclipse the remarkable life cycles exhibited by the trematodes.

Like all trematodes, the schistosome life cycle includes both intermediate (snail) and definitive (mammalian) hosts [19] (Figure 1). The life cycle begins when the eggs shed *via* urine or feces from an infected human reach fresh water. These eggs hatch to release free-living ciliated larvae, known as a miracidia, that proceed to locate and invade a snail intermediate host. Once the miracidium enters the snail, it undergoes a dramatic developmental conversion, becoming another larval stage known as the mother sporocyst. Each mother sporocyst gives rise to hundreds of larvae, termed daughter sporocysts. These daughter sporocysts eventually leave the mother sporocyst and migrate to distal regions of the snail.

Figure 1



The schistosome life-cycle. See text for details.
Adapted from [52].