Booming Omics in Schistosoma

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Abstract :

Efforts to eliminate schistosomiasis are hindered by incomplete efficacy of the only FDA-approved antischistosomal drug, praziquantel. By using postgenomic technologies, Wendt et al. and Wang et al. deciphered the function of several genes required for worm survival and pathogenesis, which opens the way for the development of innovative parasite-targeted therapies.

Keywords : schistosomiasis, RNA interference, scRNA-seq, praziquantel proteasome, blood feeding

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Schistosomiasis — also known as bilharziasis — is one of the most devastating world's neglected tropical disease responsible for considerable human morbidity. The etiological agents, schistosomes, are dioecious flatworms that reside permanently *in copula* within the host blood vessels. While blood feeding, the females lay eggs of which the majority becomes encysted in surrounding host tissues and organs (especially the liver), causing pathology [1]. Despite increased efforts to eradicate schistosomiasis over the past five decades, more than 200 000 people still die each year from schistosome-associated complications [2]. This apparent failure to control disease transmission is in part due to the incomplete parasitocidal efficacy of praziquantel, which is ineffective on immature worms, does not prevent reinfection or the emergence of drug-resistant parasites. Accordingly, in its recently published roadmap aiming at eliminating schistosomiasis by 2030, the World Health Organization (WHO) highlights that new anti-schistosomal treatments are urgently needed [3].

Hitherto, the development of innovative therapies has been hampered by the paucity of molecular and genetic tools for exploring schistosome biology. In their two enlightening articles, [Wang *et al.*](#) [4] and [Wendt *et al.*](#) [5] provide new insights into the functional biology of schistosomes that will undoubtedly unleash the discovery of new potential drug targets.

Indeed, despite tremendous advances in both genome resources and genetics in the past few years (Figure 1), much of the molecular and cellular processes that underpin the tissue maintenance and survival of adult schistosomes remain poorly

understood. To gain a better insight into these processes, Wendt and colleagues joining FACS (Fluorescence-Activated Cell Sorting), single-cell transcriptomics and in-situ hybridization successfully generate an unbiased classification of cellular subtypes in *S. mansoni* male, mature and immature female worms. This approach enabled to produce a precious atlas of ~43,000 high-quality cells (freely available at <http://www.collinslab.org/schistocyte/>), representing 68 transcriptionally distinct cell categories [5]. These clusters notably included neoblasts, which are motile stem cells involved in tissue turnover and regeneration [6]. Although previous studies indicate that neoblasts of schistosomes predominantly serve for tegument maintenance, there is evidence that other flatworms (*e.g.*, Planarians) also possess 'specialized' neoblasts that are progenitors for specific differentiated tissues [7]. Here, [Wendt *et al.*](#) pointed out the existence of a previously undescribed sub-population of neoblasts that cluster with gut cells, the latter being required for digestion of host blood. By combining RNA interference (RNAi) and parasitological analyses, it was shown that this neoblast 'gut lineage' expresses a homologue of *hepatocyte nuclear factor 4 (hnf4)*, a gut marker in planarians, which is required for gut preservation and hematophagous behavior. Indeed, RNA silencing of *hnf4* resulted in a sizeable drop in the number of luminal microvilli, leading to morphological abnormalities of the gut and subsequent parasites' inability to digest red blood cells and absorb nutrients. Considering the importance of blood feeding for the production of eggs, which are the hallmarks of schistosomiasis pathology, [Wendt *et al.*](#) further evaluated the pathogenicity of worms whose *hnf4* gene was knocked-down through RNAi. In a striking *in vivo* experiment, it was demonstrated that the loss of *hnf4* confers reduced pathology (*i.e.*, egg-induced granulomas) following surgical transplantation into *Schistosoma*-naive mice.

Moreover, RNAi-treated parasites were significantly shorter than non-treated controls, indicating that *hnf4* is also required for normal growth. Taken together, these data suggest that targeting the blood feeding machinery may constitute a relevant alternative strategy to praziquantel.

Another study conducted by the same research group has successfully used high-throughput RNAi screening for profiling the essential gene landscape, and the identification of novel therapeutic targets in *S. mansoni* [4]. By this approach, Wang and colleagues present a dataset of over 2000 genes (~ 20% of the protein-coding genes), of which 261 were assigned to the parasite's critical gene repertoire. From the list of top candidates, a couple of serine/threonine kinases (TAO and STK25) were found to be essential in maintaining neuromuscular function. Indeed, RNA silencing of either of these kinase encoding genes resulted in impaired locomotion, tetanic contraction of the body of the worm, and detachment from the culture substrate. Most importantly, loss of *tao* or *stk25* gene expression impedes schistosome capacity to reside within the host blood vessels, resulting in an attenuated schistosome egg-induced pathology. Another noteworthy feature of this work is the elegant approach used to characterize a large portion of the 195 genes designated as essential for parasite attachment. Indeed, the transcriptomic analysis revealed substantial amounts of genes related to the ubiquitin-proteasome pathway (UPP), which maintains protein homeostasis and normal cellular functions in eukaryotes [8]. Strikingly, RNA silencing of virtually all UPP elements led to tissue degeneration *in vitro*, worm immobilization and even death [4]. This underscores a central role of UPP in the maintenance of tegument integrity and survival in schistosomes. Considering the importance of UPP in both larval and adult worm

stages [9,10], Wang *et al.* then sought to evaluate its druggability. By filtering databases and chemical libraries, a series of compounds were therefore selected upon their potential to inhibit UPP components. This last and most exciting approach allowed identifying p97, a central component in the UPP, as a novel target for drug development. In sum, this article sheds light on the usefulness of large-scale RNAi for unravelling complex cellular pathways and exploring their potential benefit in the field of schistosomiasis.

Altogether, these two illuminating articles provide unprecedented foundation for better understanding multiple aspects of schistosome biology and subsequently unveil hidden drug targets. These findings notably allowed putting in foreground some pre-existing pharmacological agents, thus accelerating the discovery of unexpected highly effective anthelmintic compounds. It is also important to underline the considerable value of the state-of-the-art methods employed here, in order to identify other clinical drug candidates with selective activity on worm (and thus with limited side-effects). One future investigation avenue may concern reproductive biology (*i.e.*, egg production) of schistosomes, because such therapeutic intervention would combine the advantage of reducing the pathology while limiting the transmission. The latest exciting developments in functional genomic technologies (especially CRISPR-Cas9) will undoubtedly stimulate further fruitful research into this important area of schistosome biology and greatly help for disease control and development of innovative therapeutic strategies.

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Figure 1. Timeline of omics milestones and tendencies for *Schistosoma* research.

Functional genomics

High throughput screening

Computational drug repurposing