Booming Omics in Schistosoma

Yohann Le Govic, Benjamin Gourbal, Jérôme Boissier

TRENDS IN PARASITOLOGY 2021 vol 37 num 1 pp 6-8

Booming Omics in Schistosoma

Yohann Le Govic,[1,2] Benjamin Gourbal,[3] and Jérôme Boissier[3,*]

1-Department of Medical Parasitology and Mycology, Amiens University Hospital, Amiens, France
2-Host–Pathogen Interaction Study Group (GEIHP, EA 3142), UNIV Angers, UNIV Brest, Federative Structure of Research
'-Cellular Interactions and Therapeutic Applications', SFR 4208 ICAT, Angers, France
3-IHPE, University of Montpellier, CNRS, Ifremer, University of Perpignan Via Domitia, Perpignan, France
*Correspondence: boissier@univ-perp.fr (J. Boissier). https://doi.org/10.1016/j.pt.2020.10.010

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.

Schistosomiasis — also known as bilharziasis — is one of the most devastating of the world's neglected tropical diseases that is responsible for considerable human morbidity. The etiological agents, schistosomes, are dioecious flatworms that reside permanently in copula within the host's blood vessels. While blood feeding, the females lay eggs of which the majority become 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 schistosomeassociated complications [2].

This apparent failure to control disease transmission is, in part, due to the incomplete parasiticidal efficacy of praziquantel, which is ineffective on immature worms and does not prevent reinfection or the emergence of drugresistant parasites. Accordingly, in the recently published roadmap, aiming at eliminating schistosomiasis by 2030, the World Health Organization (WHO) highlights that new antischistosomal 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 recent 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 fluorescence-activated cell sorting (FACS), single-cell transcriptomics, and in situ hybridization – successfully generate an unbiased classification of cellular subtypes in Schistosoma mansoni male, mature and immature female worms. This approach enabled them to produce a precious atlas of ~43 000 high-quality cells (freely available at SchistoCyte Atlas[i]), 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 indicated that neoblasts of schistosomes predominantly serve for tegument maintenance, there is evidence that other flatworms (e.g., planarians) also have 'specialized' neoblasts that are progenitors for specific differentiated tissues [7]. Here, Wendt et al. pointed out the existence of a previously undescribed subpopulation 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 homolog 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 inability of the parasites 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 the 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, RNAitreated parasites were significantly shorter than nontreated 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 highthroughput RNAi screening for profiling the essential gene landscape and 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 impeded 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 numbers 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 for 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 by their potential to inhibit UPP components. This last and most exciting approach allowed the identification of 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 unraveling complex cellular pathways and exploring their potential benefit in the field of schistosomiasis.

Altogether, these two illuminating articles provide an unprecedented foundation for a better understanding of multiple aspects of schistosome biology and, as a consequence, unveil hidden drug targets. Notably, these findings have highlighted 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 used here in order to identify other clinical drug candidates with selective activity on these worms (and thus with limited side effects). One future avenue for investigation may concern reproductive biology (i.e., egg production) of schistosomes because such therapeutic intervention would combine the advantage of reducing the pathology with a limitation in 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 disease control and the development of innovative therapeutic strategies

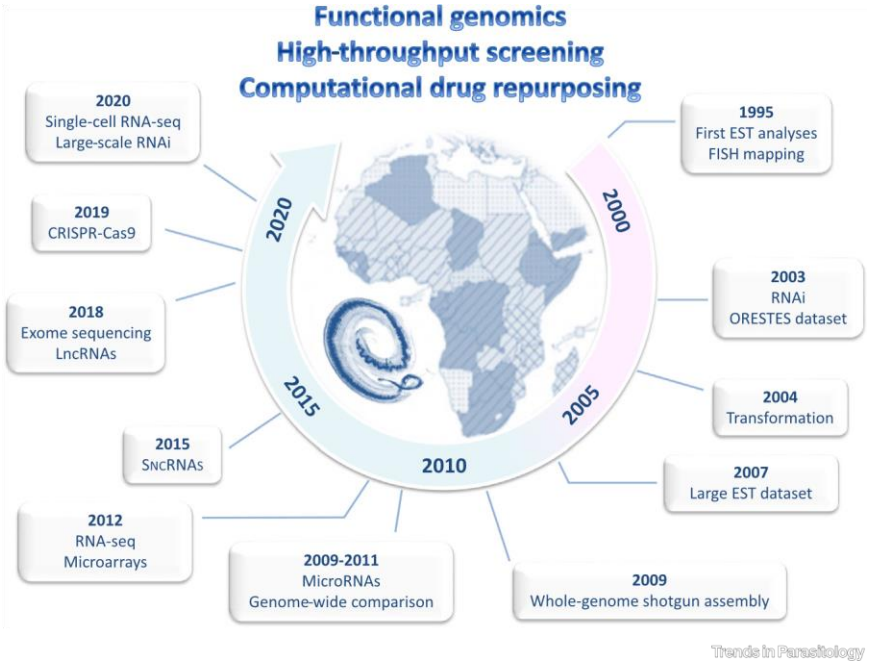

Figure 1. Timeline of Omics Milestones and Tendencies for Schistosoma Research.
Abbeviations: EST, expressed sequence tag; FISH, fluorescent in situ hybridization; ORESTS, open reading frame expressed sequence tags.

Resources
I www.collinslab.org/schistocyte/

References

1. Colley, D.G. et al. (2014) Human schistosomiasis. Lancet 383, 2253–2264
2. Chitsulo, L. et al. (2004) Schistosomiasis. Nat. Rev. Microbiol. 2, 12–13
3. WHO/Department of Control of Neglected Tropical Diseases (2020) Ending the Neglect to Attain the Sustainable Development Goals – A Road Map for Neglected Tropical Diseases 2021–2030, WHO/UCN/NTD/2020.01.
4. Wang, J. et al. (2020) Large-scale RNAi screening uncovers therapeutic targets in the parasite Schistosoma mansoni. Science 369, 1649–1653
5. Wendt, G. et al. (2020) A single-cell RNA-seq atlas of Schistosoma mansoni identifies a key regulator of blood feeding. Science 369, 1644–1649
6. Collins, J.J. et al. (2013) Adult somatic stem cells in the human parasite Schistosoma mansoni. Nature 494, 476–479
7. Reddien, P.W. (2018) The cellular and molecular basis for planarian regeneration. Cell 175, 327–345
8. Collins, G.A. and Goldberg, A.L. (2017) The logic of the 26S proteasome. Cell 169, 792–806
9. Bibo-Verdugo, B. et al. (2019) The proteasome as a drug target in the metazoan pathogen, Schistosoma mansoni. ACS Infect. Dis. 5, 1802–1812
10. Nabhan, J.F. et al. (2007) The 26S proteasome in Schistosoma mansoni: bioinformatics analysis, developmental expression, and RNA interference (RNAi) studies. Exp. Parasitol. 117, 337–347