Schistosome dipeptide of love

Yohann Le Govic, Jérôme Boissier, Nicolas Papon

Spotlight

Schistosome dipeptide of love

Yohann Le Govic [1,2,*], Jérome Boissier [3,*], Nicolas Papon [4]

[1] Infectious Agents, Resistance and Chemotherapy (AGIR), UR 4294, University of Picardy Jules Verne, Amiens, France
[2] Parasitology-Mycology Department, Center for Human Biology, University Hospital of Amiens-Picardie, Amiens, France
[3] IHPE, Univ. Montpellier, CNRS, Ifremer, Univ. Perpignan Via Domitia, Perpignan, France
[4] Univ Angers, Univ Brest, IRF, SFR ICAT, Angers, France

*Correspondence: LeGovic.Yohann@chu-amiens.fr; boissier@univ-perp.fr

Authors' ORCID
Jérôme BOISSIER | https://orcid.org/0000-0002-0793-3108
Yohann LE GOVIC | https://orcid.org/0000-0001-7686-4612
Nicolas PAPON | https://orcid.org/0000-0001-6265-7321

Keywords: Parasites, flatworm, schistosome, nonribosomal peptide, secondary metabolism

---

Abstract

The female schistosome's dependence on the male to reach sexual maturity has puzzled scientists for decades. Using various molecular techniques, Chen et al. dissect the synthesis pathway of the dipeptide BATT produced by the male which emitted into its environment, induces sexual maturation and egg-laying in the female.

Schistosomiasis (also known as bilharzia) remains one of the most life-threatening neglected tropical diseases in the poorest countries, affecting several hundred million people and responsible for more than 200,000 deaths each year [**1**]. Schistosomiasis is caused by dioecious parasitic flatworms (blood flukes) of the genus *Schistosoma*, and the considerable morbidity of the disease mostly relies on chronic intestinal, hepato-splenic or urogenital damages deriving from inflammatory immune responses developed toward the entrapment in host tissues of eggs laid by female worms [**2**]. Considering the large parasitic burden in infected individuals, long-term investment in research is critical to better understand the pathophysiology of these infections, with the aim of developing new strategies for efficient prevention, diagnosis, and therapeutic interventions [3]. In this regard, the identification of molecular processes governing egg production in female schistosomes could throw light on new targets for disrupting the prolificacy of these parasites and preventing the egg-mediated disease [**4**]. It has been known for a long time that the female schistosome must mate with a male prior being able to produce eggs (**Figure 1A**) [**5**]. Male-female pairing in *Schistosoma* is among the most spectacular processes observed in the field of parasitology: the muscular male worm grasps the frail female in a large ventral groove called the gynaecophoral canal [**6**]. This enterlacing stage is primarily used by the male for female insemination and, importantly, this process was initially thought to stimulate female sexual development. However, recent advances provided evidence that continuous and direct interactions with a male worm, and not sperm transfer, are mandatory for triggering female maturation and subsequent egg production. However, the molecular events orchestrating the stimulation of female sexual organ development during male:female pairing remained hitherto unknown. In such a perspective, unprecedented insights into the molecular interplay underlying this process in *Schistosoma mansoni* [**7**], the causative agent of intestinal schistosomiasis, were gained recently through a remarkable report by the research group of James J. Collins III published in *Cell* [**8**].

In a series of preliminary experiments and taking advantage of recent advancement in both schistosome *in vitro* culture and RNAi-mediated gene silencing procedures [**9**,**10**], Chen and colleagues first identified *gli1* as an essential gene required in male worms for female sexual maturation. Importantly, the Gli1 predicted protein shares high homologies with animal zinc finger transcription factors involved in the Hedgehog-GLI signaling pathway, which is well documented for its critical role in controlling cell specification, cell-cell interaction and tissue patterning in animals. *gli1* mRNA is precisely expressed among the male ventral part, a zone that is in contact with the female (**Figure 1B**). Because of its putative function of master regulator of gene expression, the research group then compared the global transcriptional reprogramming that occurred during wild-type male:female and *gli1*-silenced male:female pairing. While only a restricted number of genes were found to be up-regulated in male after pairing, a single of these (Smp_158480) was strongly overexpressed in a *gli1*-dependent manner. Interestingly, this gene was predicted to encode a multidomain protein similar to Ebony, a well-characterized nonribosomal peptide synthetase (NRPS) responsible for biosynthesis of a dipeptide secondary metabolite in *Drosophila melanogaster*. Based on sequence homology, this new schistosome gene was named *Schistosoma mansoni nonribosomal peptide synthetase* (*Sm-nrps*). The physiological relevance was nicely provided by RNAi experiments confirming that *Sm-nrps* is essential in *S. mansoni* male worms

for female sexual maturation. Interestingly, *in situ* hybridization analysis revealed that *Sm-nrps* mRNA is expressed in very few cells in the head of virgin male but when male mates the transcripts abundantly accumulate in a particular cell type, the ciliated sensory neurons, located throughout the gynecophoral canal (**Figure 1B**) [**11**]. This unique tissue localization of *Sm-nrps* mRNA obviously corroborates a prominent role of the corresponding protein in driving male:female interactions. Whatever *gli1* or *Sm-nrps* RNA silenced males this impairs their ability to induce female sexual maturity. Further biochemical characterizations have highlighted the NRPS activity of the SmNRPS recombinant protein, which catalyzes selective coupling of the decarboxylation product of tryptophan, tryptamine, and β-alanine to yield the β-alanyl-tryptamine dipeptide (abbreviated BATT) (**Figure 1C**). Finally, Chen and colleagues conducted a relevant series of *in vitro* experiments suggesting that BATT is secreted from paired male schistosomes throughout their gynecophoral canal by ciliated sensory neurons, this compound being sufficient to induce molecular pathways for female to become sexually mature and subsequent egg laying behavior. However, pairing experiments and egg-laying analysis also indicated that BATT alone is important but insufficient for the development and maintenance of sexual maturity in female worms, suggesting that additional factors may help into these processes.

Overall, this excellent new report by James J. Collins group throws light on the central role of the specialized metabolite BATT in governing the pairing process in *S. mansoni*. It is now well engrailed in the literature that secondary metabolism is widely developed in bacteria, fungi and plants for regulating a plethora of intra- and inter-specific interactions. In this respect, secondary metabolites are primarily known in microorganisms for their toxic properties in mediating the chemical warfare engaged between distinct species colonizing a common niche, while other specialized volatile compounds are produced by some flowering plants for attracting specific insect pollinators. However, a restricted number of examples concerning the occurrence of secondary biosynthetic pathway in animals are currently available. Thus, at a basic level and beyond the breakthrough this stunning study represents in the field of parasitology, the regulation of female schistosome sexual development by a male nonribosomal peptide teaches us how much secondary metabolisms and the specialized molecules they produce orchestrate multiple facets of biotic interactions in the tree of life. On a mechanistic point of view, it would be of course exciting to move forward with this outstanding story by investigating the potential critical function of ciliated sensory neurons located on the male's ventral surface in detecting the presence of the female for promoting the biosynthesis of the love drug BATT through SmNRPS activity. In such a perspective, while SmNRPS already represents a relevant new worm target, deciphering the early molecular events involved in female perception by male worms could provide unprecedented opportunities for identifying innovative routes for future therapeutic developments.

In conclusion, Chen and colleagues cements secondary metabolism as a new field of science in parasitology that is ripe for future progress. It also propels antimetabolite-based treatments as potential strategies for preventing morbidity of schistosomiasis and opens new avenues for developing adjunctive antiparasitic therapies against other debilitating worm infections. As such, there is considerable excitement that new love elixir could be discovered in other dioecious helminth species in the near future.

References

1. McManus, D.P. *et al.* (2018) Schistosomiasis. *Nat. Rev. Dis. Primers*. 4, 13
2. Grzych, J.M. *et al.* (1991) Egg deposition is the major stimulus for the production of Th2 cytokines in murine Schistosomiasis mansoni. *J. Immunol.* 146, 1322-1327
3. Mäder, P. et al. (2018) Chemotherapy for fighting Schistosomiasis: Past, Present and Future. *ChemMedChem*. 13, 2374-2389
4. Langenberg, M.C.C. et al. (2020) A controlled human *Schistosoma mansoni* infection model to advance novel drugs, vaccines and diagnostics. *Nat. Med.* 26, 326-332
5. Severinghaus, A.E. (1928) Sex studies on *Schistosoma japonicum*. *J. Microsc. Sci*. 71, 653–702
6. Beltran, S., Boissier, J. (2008) Schistosome monogamy: who, how, and why? *Trends Parasitol*. 24, 386-391
7. Anderson T.J.C., Enabulele, E.E. (2021) *Schistosoma mansoni*. *Trends Parasitol*. 37, 176-177
8. Chen, R. et al. (2022) A male-derived nonribosomal peptide pheromone controls female schistosome development. *Cell* 31, S0092-8674(22)00327-0.
9. Wang, J. et al. (2020) Large-scale RNAi screening uncovers therapeutic targets in the parasite *Schistosoma mansoni*. *Science* 369, 1649-1653
10. Wang, J., Chen, R., Collins, J.J. 3rd. (2019) Systematically improved in vitro culture conditions reveal new insights into the reproductive biology of the human parasite *Schistosoma mansoni*. *PLoS Biol*. 17, e3000254
11. 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.

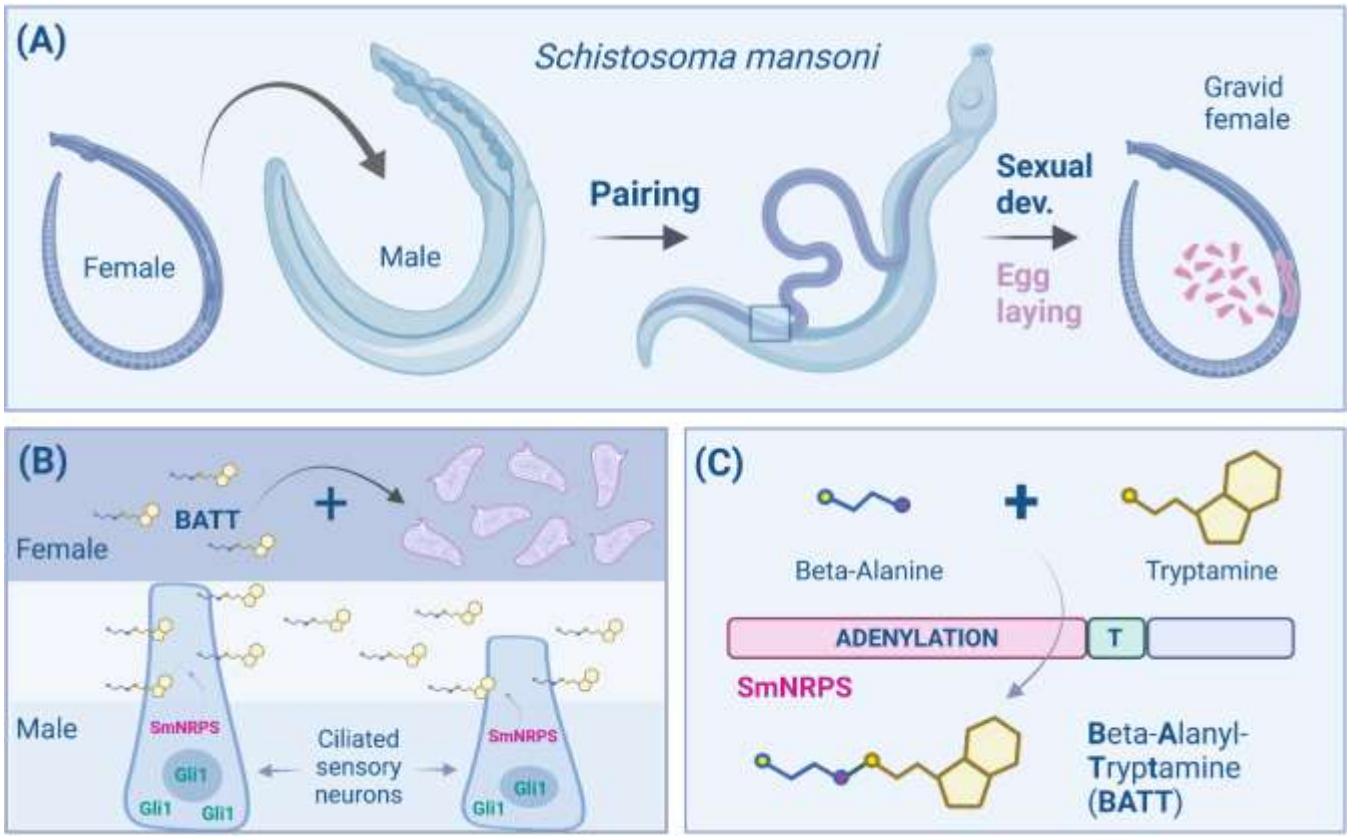

Figure 1. A male-derived dipeptide pheromone controls female schistosome development. **(A)** The female schistosome depends on the continued pairing of male both to achieve sexual development and to produce eggs.. **(B)** The research group of James J. Collins III recently provided unprecedented insights into the molecular pathway orchestrating the initiation and maintenance of female sexual maturity. They showed that *gli1* mRNA expressed in male, precisely in the zone in contact with the female, is essential for female maturation. This latter transcript induces the expression of a new *Sm-nrps* gene located in the ciliated sensory neuros of the male gynecophoral canal. **(C)** Further biochemical analysis revealed that SmNRPS protein catalyzes selective coupling of the decarboxylation product of tryptophan, tryptamine, and β-alanine to yield the β-alanyl-tryptamine dipeptide (abbreviated BATT).