Epigenetic Modulation of Schistosome Eggshell Formation is a Novel Target for reducing Transmission and Pathology of Schistosomiasis

Vitor Coutinho Carneiro², Isabel de Abreu da Silva¹, Eduardo Torres³, Stephany Caby², Julien Lancelot², Mathieu Vanderstraete², Silviya Furdas⁴, Manfred Jung⁴, Raymond Pierce²* and Marcelo Fantappié¹*

¹Universidade Federal do Rio de Janeiro; ²Institut Pasteur de Lille, France; ³Universidade do Estado do Rio de Janeiro; ⁴Albert-Ludwigs-University of Freiburg, Germany.

INTRODUCTION: Inhibitors of histone modifying enzymes are under investigation as treatments for a variety of pathologies, including parasitic diseases. Egg production is required for the transmission and immunopathology of schistosomiasis and females worms lay 300 eggs daily. A large fraction of the female total mRNA encodes one eggshell protein, Smp14. OBJECTIVES: In this respect, we focused on reveal the molecular mechanism involved on Smp14 expression. METHODS: Gene reporter assay, ChIP, dsRNAi and qRT-PCR. RESULTS AND DISCUSSION: We report that the nuclear receptors SmRXR1 and SmNR1 regulate Smp14 transcription through the recruitment of the histone acetyltransferases SmGCN5 and SmCBP1. The treatment of HEK293 cells with histone deacetylase (HDAC) inhibitors (NaB or TSA) produced an activation of the SmRXR1/SmNR1-mediated Smp14 promoter activity. Incubation with synthetic HAT inhibitors, including PU139, significantly impaired the Smp14 promoter activity. Worm pairs cultivated with PU139 exhibited limited expression of Smp14 mRNA and protein. ChIP analysis demonstrated chromatin condensation at the Smp14 promoter site in worms treated with PU139. ChIP also revealed the presence of H3K27me3 and the absence of RNA Pol II at the Smp14 promoter region. Significantly, the PU139-mediated inhibition of Smp14 expression resulted in a significant number of abnormal and defective eggs within the ootype. In addition, scanning electron microscopy revealed structural defects and unformed eggshells, and vitelline leakage was apparent. The RNAi-targeting of SmGCN5 or SmCBP1 significantly decreased Smp14 transcription and protein synthesis, which compromised the reproductive system of mature female worms, egg-laying and egg morphology. CONCLUSION Our data strongly suggest that the inhibition of Smp14 expression targeting SmGCN5 and/or SmCBP1 represents a novel and effective strategy for schistosomiasis control.

Keywords: Schistosomiasis, Smp14, acetylation.