First Insights into the Autophagy Machinery and its Induction by Imatinib in *Schistosoma mansoni*

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Schistosomiasis is a neglected tropical disease caused by blood flukes (schistosomes) of the genus *Schistosoma*. This debilitating and chronic disease is a significant veterinary and public health problem with > 200 million people infected. The main pathogenicity is caused by eggs laid by the female worm, which requires the female to be in a constant pairing with a male partner. We hypothesize a role for a fundamental cellular process, autophagy, in the regulation of key processes in schistosome biology.

Autophagy is activated during starvation or cellular stress and contributes to maintain homeostasis. Although autophagy is known as essential pathway involved in regulating cell survival, reproduction, organ and body reshaping in various organisms, autophagy has been basically neglected in schistosome research. Here, for the first time, we shed light on the autophagy machinery, its involvement in reproduction of *Schistosoma mansoni*, and its suitability as antischistosomal therapeutic target. We identified autophagy genes by *in-silico* analyses and quantified their transcript level by qRT-PCR in female and male worms prior and after *in vitro* culture. Furthermore, worms were treated with autophagy inhibitors (bafilomycin A1, wortmannin and spautin-1) or an autophagy inducer (rapamycin) to evaluate effects on worm vitality and reproduction as well as autophagy protein expression. Among the identified autophagy genes were Beclin, Ambra1, Vps34, Dram, DAP1, and LC3B. The damage-regulated autophagy modulator DRAM was significantly higher transcribed in males compared to females, while for the death-associated protein DAP1 it was the opposite. The conversion of the autophagy protein LC3B, a key marker for autophagic activity, was impaired by bafilomycin A1 but induced by rapamycin. All autophagy inhibitors negatively affected worm fitness and egg production as well as the morphology of gonads and intestine.

An anticancer drug, imatinib (Gleevec), drastically affected intestinal morphology and caused death of adult worms within 3-4 days *in vitro* (already published). We present first evidence that imatinib induces autophagy in adult *S. mansoni*, which was evident from significant increase of LC3B. Interestingly, the drastic effects induced by imatinib on pairing stability, egg production, and gut dilatation were mitigated by autophagy inhibition using bafilomycin A1.

Our study demonstrates that autophagy genes in *S. mansoni* not only show an interesting sex-dependent expression pattern, which might point to developmental or reproductive roles, but when disrupted by chemical inhibition, can affect parasite viability and reproduction.