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Invited Review

Epigenetic modulation, stress and plasticity in susceptibility of the snail host, *Biomphalaria glabrata*, to *Schistosoma mansoni* infection

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ABSTRACT

Blood flukes are the causative agent of schistosomiasis – a major neglected tropical disease that remains endemic in numerous countries of the tropics and sub-tropics. During the past decade, a concerted effort has been made to control the spread of schistosomiasis, using a drug intervention program aimed at curtailing transmission. These efforts notwithstanding, schistosomiasis has re-emerged in southern Europe, raising concerns that global warming could contribute to the spread of this disease to higher latitude countries where transmission presently does not take place. Vaccines against schistosomiasis are not currently available and reducing transmission by drug intervention programs alone does not prevent reinfection in treated populations. These challenges have spurred awareness that new interventions to control schistosomiasis are needed, especially since the World Health Organization hopes to eradicate the disease by 2025. For one of the major species of human schistosomes, *Schistosoma mansoni*, the causative agent of hepatointestinal schistosomiasis in Africa and the Western Hemisphere, freshwater snails of the genus *Biomphalaria* serve as the obligate intermediate host of this parasite. To determine mechanisms that underlie parasitism by *S. mansoni* of *Biomphalaria glabrata*, which might be manipulated to block the development of intramolluscan larval stages of the parasite, we focused effort on the impact of schistosome infection on the epigenome of the snail. Results to date reveal a complex relationship, manifested by the ability of the schistosome to manipulate the snail genome, including the expression of specific genes. Notably, the parasite subverts the stress response of the host to ensure productive parasitism. Indeed, in isolates of *B. glabrata* native to central and South America, susceptible to infection with *S. mansoni*, the heat shock protein 70 (*Bg*-HSP70) gene of this snail is rapidly relocated in the nucleus and transcribed to express HSP70. Concurrently, hypomethylation of the CpG sites, within the *Bg*-HSP70 intergenic DNA region, proceeds by conveying epigenetic and spatio-epigenetic mechanisms in temporal concordance. It is notable that this is only the second example reported where a pathogen has been shown to control host cell spatio-epigenetics for its own advantage. Nonetheless, the remarkable mechanisms through which genes become activated i.e. DNA and chromatin remodeling and relocation to a nuclear compartment conducive to gene expression may represent novel intervention targets.

1. Introduction

Schistosomiasis is a major neglected tropical disease and is considered the most important helminthic disease of humanity in terms of morbidity and mortality (Colley, 2014; Hotez et al., 2008). Moreover, schistosomiasis is ranked second only to malaria for causing long-term chronic human morbidity that has been shown to contribute to stagnation of economic growth in the developing world (Bonds, 2012). Major advances have been made in recent years to reduce schistosomiasis by a mass drug administration (MDA) program with the drug praziquantel (PZQ) that targets the adult worm but not larval stages of the parasite (King et al., 2011). Advocacy for effective control of schistosomiasis is growing, especially since reinfection in treated populations makes sustaining long-term reduction of disease transmission challenging (Colley and Secor, 2014; Lelo et al., 2014). Furthermore, schistosomiasis has re-emerged in Europe, raising concerns that global warming may be contributing to the spread of the disease

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into countries hitherto beyond the present endemic range (Boissier et al., 2015). The World Health Organization (WHO) has projected the year 2025 for the global eradication of schistosomiasis, http://www.who.int/tdr/news/2016/key_challenges_identified_elim_ntd/en/. However, without an effective vaccine, no new drugs and poor access to clean water and sanitation in endemic areas, there is a growing awareness that alternative tools to control schistosomiasis, based on blocking parasite development in the snail host, have to be explored (King and Bertsch, 2015). There is an ongoing debate to return to the 'gold-standard' method of using molluscicides to reduce snail populations (King and Bertsch, 2015). Other, more ecologically acceptable approaches involving prawns and other predators, and bacterial pathogens, to control snail populations in contaminated freshwater have clear utility, at least in some regions (Duval et al., 2015; Sokolow et al., 2015). Indeed, the concept of biologically based control was proposed more than 60 years ago (Hubendick, 1958). As proof of principle, incompatible snails have been used in endemic areas to reduce transmission of schistosomiasis (Pointier, 1993; Marques et al., 2014).

The life cycle of schistosomes is complex, with snails serving as the intermediate host and humans as the definitive host. Whereas in most cases not every snail that encounters a parasite becomes infected, the human host, on the other hand, is always susceptible to infection once the infective cercaria (released from an infected snail) penetrates the human skin. This difference in the dynamics of infection outcome between the snail and human host is thought to reflect that the snail, rather than the human host, shapes the genetic make-up of the schistosome. Co-evolution of this snail/parasite interplay, resulting either in successful parasite development in a susceptible/compatible snail, but destruction in a resistant/incompatible one, is enigmatic and worthy of deeper investigation.

During the past two decades, however, more studies on the snail/schistosome relationship have been undertaken (Knight et al., 2014; Mutuku et al., 2014; Yoshino et al., 2014). These studies showed that several factors play a role in what determines the outcome of the snail/schistosome interaction. The focus of our work in this area has been to begin to examine the role of epigenetics in modulating snail host susceptibility to schistosome infection (Knight et al., 2014). Epigenetic mechanisms in a host-parasite relationship generate plasticity that drives adaptability/co-evolution between the host and parasite. Epigenetics is defined as covalent modification (methylation and acetylation, and others) of the chromatin that regulates gene expression without any alteration in underlying DNA sequence. These changes confer an inheritable trait and in a host-pathogen interaction provides a selective pressure that shapes parasite survival versus destruction in the host. An instructive example, in the snail host and schistosome interaction, is the epigenetic control that has been shown to link snail compatibility and incompatibility to the transcription of diverse parasite mucin (SmPoMuC) genes for productive parasitism (Perrin et al., 2013). A recent study has also shown the epigenetic control of transcription regulation in the infective form of the parasite, the cercaria (Roquis et al., 2015). The significance of epigenetics in regulating gene expression in the host-pathogen interaction of invertebrates is understudied. However, a recent workshop showed there exists a growing interest in elucidating the role of epigenetic regulation and phenotypic plasticity in marine and fresh water molluscs (http://ihpe.univ-perp.fr/2-fevrier-workshop-on-mollusk-epigenetic/).

A genomic response to an external stimulus such as an infection requires signaling through to the nucleus and the genome via the cytoplasm, through the nuclear membrane, into the nucleus, where the response is transmitted to the chromatin. The nucleus is a highly organized organelle with numerous, diverse structures that interact with and influence the genome. These structures include the nuclear lamina, nucleoli and other nuclear bodies. We have shown that a number of these exist in *Biomphalaria glabrata*, using antibodies that recognize the human versions of antigens within these structures (Knight et al., 2014). These structures look remarkably similar to nuclear structures found in human cells that we were hoping to identify in the snail cells (Knight et al., 2014). We also revealed that the mollusk *B. glabrata* has chromosome territories (Odoemelam et al., 2009) very similar in shape and organization to more complex species such as human, pig and mouse (Odoemelam et al., 2009). Further studies with *B. glabrata* interphase chromosome territories demonstrated that they did not have a Rabl-type configuration in the nucleus but a radial distribution with individual chromosomes sitting in non-random locations, also in common with higher eukaryotes. Chromosomes have been found to be comparatively static at interphase (Chubb et al., 2002), not showing much movement after the early G1 phase due to becoming tethered to nuclear structures. This territorial organization of chromosomes leads to spaces between chromosomes into which RNA is transcribed (Lampel et al., 1997; Bridger et al., 2005) and genes can move within (Kosak and Groudine, 2004a,b), as they come out on chromatin loops away from the main body of the chromosome territory, to be activated or silenced. Having chromosomes and genes spatially organized in such a way requires signaling, chromatin modeling, protein modification and energy, and thus spatial organization and positioning must convey an advantage to the organism. Furthermore, this specific positioning of genomic elements to different compartments within interphase nuclei gives a further level of regulation and control over the genome, over and above linear DNA sequence and epigenetics via chromatin remodeling, by bringing the genome into association with specific nuclear areas and structures that are involved in expression or repression of genes – such that the nuclear structure field understand this organization as some type of spatio-epigenetics.

The ability to assess non-random gene positioning in nuclei by a variety of methods is permitting more knowledge concerning how the genome behaves in health and disease but also responds to external stimuli. Interestingly, interphase gene positioning is even being developed as a cancer diagnostic and prognostic tool (Meaburn et al., 2009). It seems that many genes, but not all, move towards the nuclear interior and associate with nuclear structures such as transcription factories, splicing speckles or nuclear bodies, in order to be transcribed. Indeed, in porcine mesenchymal stem cells induced to differentiate into adipocytes, genes activated in the adipogenesis pathway relocate to a new nuclear compartment more interiorly positioned in the cell nuclei (Szczerbal et al., 2009). Interestingly, these activated genes were found out on chromatin loops, and even though they were from different chromosomes they were often co-localized at a single splicing speckle concomitantly with their up-regulation (Szczerbal and Bridger, 2010). Activated genes can also relocate to transcription factories (Sexton et al., 2007). In order for the specific regions of chromatin to be moved, a change in chromatin status through epigenetics is likely necessary, such that the locus becomes remodeled and is subjected to quite rapid directional movement to the new compartment, possibly through nuclear motor activity (Bridger, 2011).

Here we review the *Schistosoma mansoni-B. glabrata* interaction and the capacity of schistosomes to influence host genome behavior. Through gene position analysis using labeled probes and fluorescence *in situ* hybridization (FISH) we demonstrated that spatio-epigenetics is activated in the snail soon after exposure to the parasite. Schistosomes have the ability to stimulate the expression of snail genes within 2 h of penetration by the miracidium of the snail. Non-random movement of gene loci occurs within the same time frame as the hypomethylation of the heat shock protein (HSP) 70 locus – a processes that turns on this stress protein at both RNA and protein levels (Arican-Goktas et al., 2014; Knight et al., 2015). Aside from one study of infection with Epstein-Barr virus, which

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induces the movement of chromosome 17 in infected human cells (Li et al., 2010), other pathogens have not been reported to orchestrate changes in the host they occupy to alter the host genome behavior in such a profound manner. Unraveling the mechanism(s) behind these novel results should provide opportunities to develop tools that can be utilized to block schistosome transmission in the snail host.

2. *Schistosoma mansoni* miracidia induce stress upon early infection of the *B. glabrata* snail host

Miracidia, the short-lived, free-living stage of the parasite, hatch in freshwater once the eggs in human urine and feces are released in endemic foci such as rivers, lakes and streams. Miracidia infect compatible snail hosts by penetrating soft body parts (headfoot or the tentacles). In laboratory reared *B. glabrata* infected with *S. mansoni* that are maintained in the experimental mouse model, Richards and Shade (1987) showed that snail susceptibility was variable but dependent on whether or not the parasite and snail were genetically compatible. Genetic crosses between susceptible (e.g. NMRI strain) and resistant (e.g. BS-90 strain) snails revealed that resistance is a complex trait in juvenile snails but a Mendelian single-gene character in the adult snails (Knight et al., 1999; Ittiprasert et al., 2013). In recent studies we showed that susceptibility in the *S. mansoni*/*B. glabrata* relationship can be modulated by whether or not stress-encoding transcripts (e.g. HSP 70, HSP 90) are induced early and significantly within the early phase of miracidia penetrating the snail. Whereas stress genes are induced early in susceptible/-compatible snails, up-regulation of these genes fails to occur until later during infection in the resistant snail. Intriguingly, neither irradiated attenuated (Ittiprasert et al., 2009) miracidia nor incompatible heterologous schistosome spp. (*Schistosoma haematobium*, *Schistosoma japonicum*) induce an early stress response in the *B. glabrata* susceptible snail (Adema et al., unpublished data).

3. Non- lethal heat shock renders the resistant BS-90 snail host susceptible to infection, and geldanamycin treatment of susceptible snails before infection renders them non-susceptible

To further investigate the role of stress in *B. glabrata* susceptibility to *S. mansoni*, the resistant BS-90 snail was subjected to mild heat shock (32 °C) to induce HSP 70 and HSP 90 prior to infection. Surprisingly, resistant snails treated in this manner were found to shed cercariae at 4 weeks post-exposure while the susceptible NMRI snail treated with geldanamycin, an HSP 90 inhibitor, before infection were rendered non-susceptible (Fig. 1) (Ittiprasert and Knight, 2012). Expression of HSP70 protein occurs in susceptible but not resistant adult and juvenile snails exposed to wild-type but not to irradiated miracidia (Knight et al., 2015). Importantly, progeny as early as the first filial generation of resistant BS-90 snails maintained at 32 °C become susceptible when infected and kept at 25 °C – a temperature at which they are normally resistant to the parasite.

Clearly, these findings revealed that early stress induction (within 2 h) after miracidia penetration of the snail is an important step that enables the parasite to establish itself in the snail host, although we do not yet understand the signaling pathways involved in this unprecedented rapid upregulation of stress in the early parasite-infected susceptible snail. Until we identify which snail proteins interact with these schistosome-induced heat shock proteins it will be difficult to determine how this early stress induction directly or indirectly affects parasite infectivity in the susceptible/compatible snail host. To begin to identify candidate proteins associated with stress in the early schistosome-infected snail from a working hypothesis that these proteins directly facilitate early stage parasite development/differentiation in the snail host, we are comparing transcriptomes between BS-90 snails exposed to parasites for 2 h cultured either at 25 °C (resistant) or at the permissive temperature (32 °C) by using an RNA sequencing (RNAseq) approach (unpublished data).

4. Spatio-epigenetics and early modulation of transcription occurs in the schistosome-infected *B. glabrata* snail host

Strikingly, we have shown that *B. glabrata* genes that are upregulated after an infection, such as *HSP70*, *actin* and *ferritin*, relocate in the cell nuclei from a non-random position to a new non-random site within interphase nuclei. This spatial reorganization of specific regions of the snail genome has been revealed in embryonic *B. glabrata* tissue culture cells (Bge) co-cultured with parasite (Knight et al., 2011) and in intact snails (from somatic ovotestis nuclei) undergoing infection with schistosomes (Arican-Goktas et al., 2014). These studies revealed that a gamma irradiated, and hence

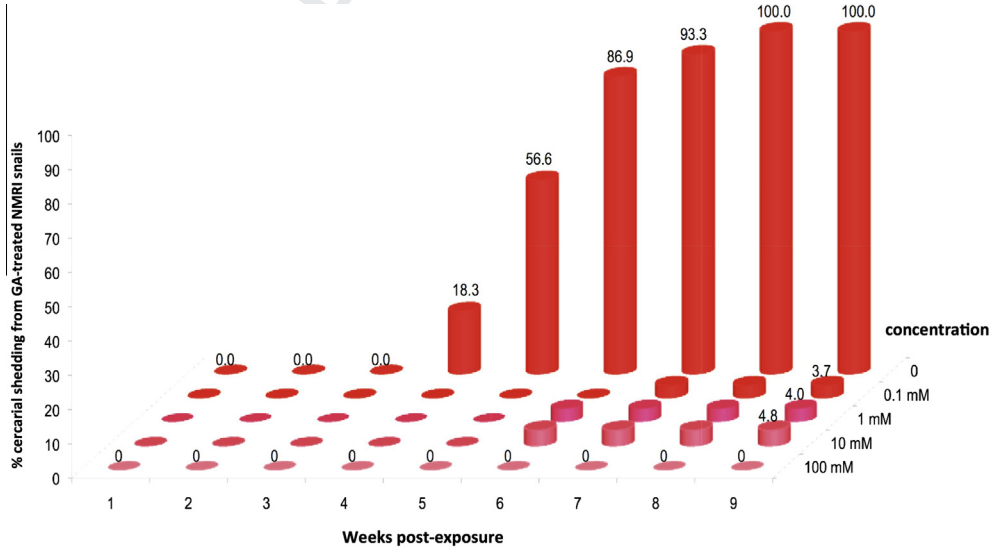

Fig. 1. Treatment of susceptible NMRI strain *Biomphalaria glabrata* snails with geldanamycin, an inhibitor of heat shock protein, before exposure to *Schistosoma mansoni* miracidia renders snails non-susceptible to infection. The histogram shows the percentage of cercariae shedding from the susceptible NMRI snails pre-treated with increasing concentrations of the heat shock protein 90 inhibitor before exposure to miracidia. Note that at 9 weeks post-exposure, 100% of untreated NMRI snails shed cercariae compared with snails treated with 100 mM geldanamycin that failed to shed cercariae. Modified with permission from Fig. 6B of Ittiprasert and Knight, 2012.

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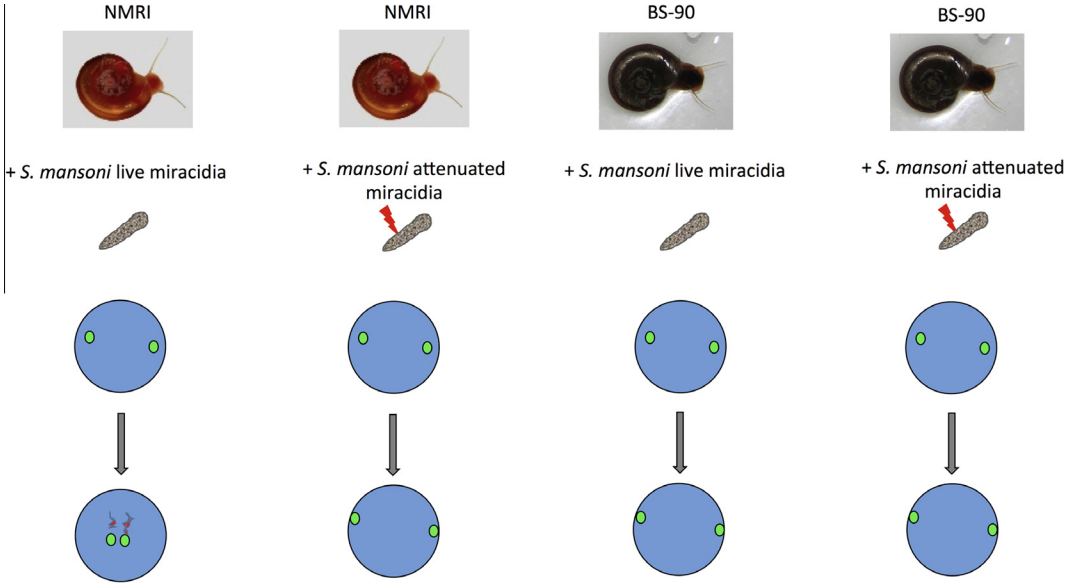

Fig. 2. This cartoon represents the findings of Arican-Goktas et al. (2014) whereby heat shock protein (HSP) 70 gene loci (green), which become upregulated after an infection with live *Schistosoma mansoni* miracidia in susceptible *Biomphalaria glabrata* snails (NMRI and BS-90 strains), move from an intermediate nuclear location (blue) to a new interior nuclear location, to become transcribed and release mRNA (red). This movement of the HSP70 loci was not detected when the miracidia were attenuated or resistant snails were employed. This publication also revealed the gene loci moving to a new location prior to expression, supporting the hypothesis that the gene moves to be transcribed not the other way around.

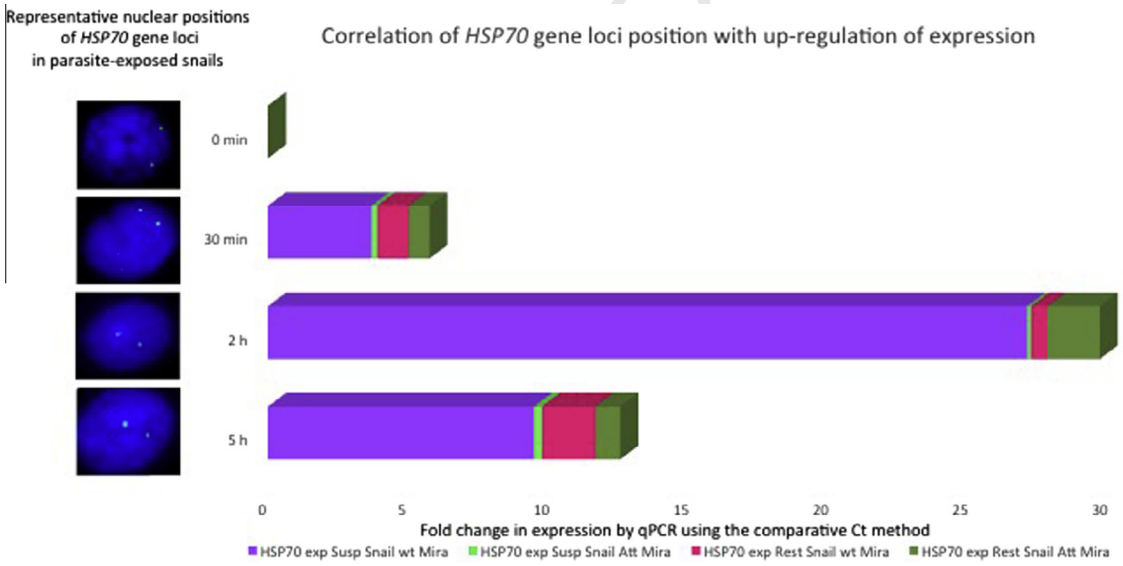

Fig. 3. Chart displaying the fold change in the expression of the *Biomphalaria glabrata* HSP70 gene in the interphase nuclei of cells derived from the susceptible (NMRI) and resistant (BS-90) snail strains, pre- and post-exposure to *Schistosoma mansoni* miracidia, as measured by quantitative PCR. *Biomphalaria glabrata* snails were infected with wild type or irradiated attenuated miracidia, dissected, fixed and subjected fluorescent *in situ* hybridization (FISH). Fifty images were collected for each time point (0, 0.5, 2, 5 h) and analyzed by an erosion analysis. In the susceptible snails the *hsp70* gene was repositioned after infection from an intermediate position to an internal location within interphase nuclei. Representative images of these positions are shown columns. This repositioning was temporally correlated with upregulation of gene expression 2 h p.i. No repositioning or any significant change in expression is observed in the resistant strain snails. Further, there was no nuclear relocation of the *hsp70* gene loci and no real HSP70 expression was detected by quantitative PCR when the two snail lines were infected with irradiated miracidia.

attenuated, parasite fails to elicit the same spatial relocation of these gene loci both in vitro and in vivo (Fig. 2). Indeed, the actin gene has been the most interesting of the genes moving, as it reveals for the first time that gene loci move ~30 min before transcription is detected by quantitative PCR. This is an important aspect of genome behavior where the hypothesis that gene loci move to a new area within the nucleus to be expressed has yet to be substantially proven. Our studies have provided the first evidence that a gene moves prior to activation (Knight et al., 2014) (Fig. 2). Our data also revealed that the parasite is orchestrating the behavior of specific genes, specifically HSP 70, for its own advantage, since the movement and expression of HSP 70 gene loci is not seen in snails resistant to the schistosome infection (Fig. 3). We have yet to show how the parasite elicits such changes in the host genome but we have some preliminary evidence that nuclear motor proteins are indeed involved in the relocation of gene loci.

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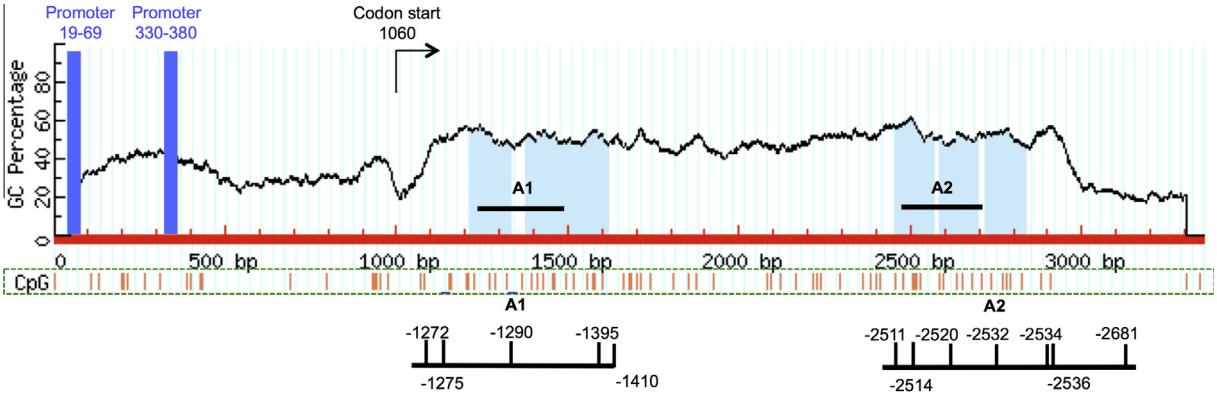

Fig. 4. Schematic of predicted CpG islands and promoters in the *Biomphalaria glabrata hsp70* gene (~3 Kb) region. The light blue regions denotes the CpG islands of *B. glabrata hsp70* gene, the black lines marked by A1 and A2 indicate methylation sites. The red vertical lines in the green dashed outlined box indicate the CpG sites and the two promoters (locations 19–69 and 330–380) that did not contain CpG sites. Reproduced with permission from Fig. 1A of Ittiprasert et al., 2015.

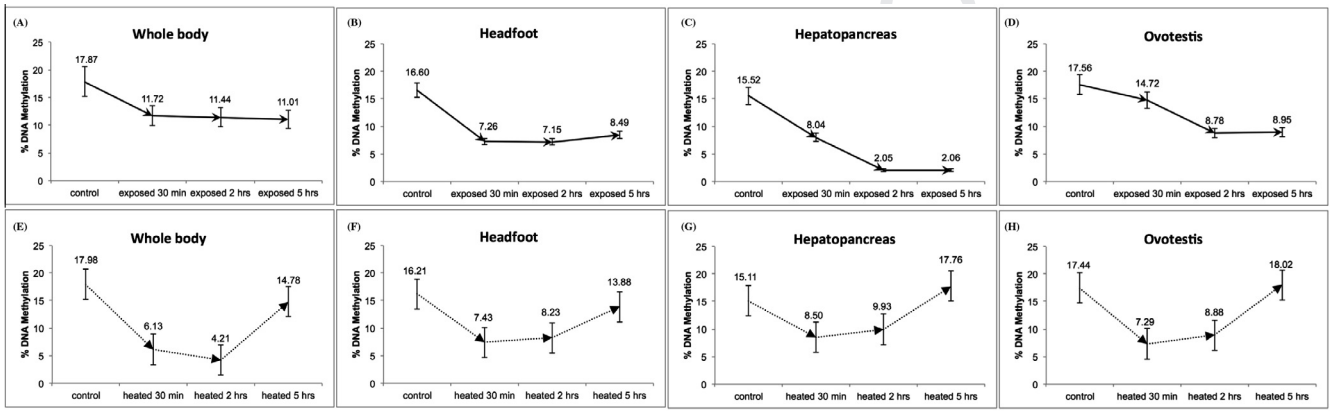

Fig. 5. 5-Methylcytosine levels of the *Biomphalaria glabrata* HSP 70 in various organs. Cytosine DNA methylation levels in *B. glabrata* whole body tissue, headfoot hepatopancreas and ovotestis after exposure to miracidia of *Schistosoma mansoni* (10 miracidia/snail) (A–D) and heat shock treatment (E–H), respectively. DNA methylation percentages were calculated from individual samples that were run in triplicate, and from four independent experiments. The average of delta Cycle threshold (Ct) by quantitative PCR with SYTO-9 fluorescent dye was used for the methylation level calculation. Percentage values are expressed as means ± S.D. Reproduced with permission from Fig. 2 of Ittiprasert et al., 2015.

5. Hypomethylation of CpG islands of the HSP 70 locus negatively correlates with upregulation of the transcript in susceptible snail organs after schistosome infection

To determine more closely whether epigenetic modifications at the HSP 70 locus influence *B. glabrata* susceptibility to *S. mansoni*, the methylation of cytosine residues, specifically CpG dinucleotides in the HSP 70 region (Fig. 4) was evaluated in the NMRI strain susceptible snail undergoing stress from either heat shock (abiotic stress at 32 °C) or *S. mansoni* infection (biotic stress) (Ittiprasert et al., 2015). Methylation of CpG residues in the genome has been shown to modify gene expression without any underlying change to the DNA sequence. Two percent of the DNA of *B. glabrata* may be methylated (Fneich et al., 2013). Thus, to quantify differences in DNA methylation between normal and stressed snails, levels of DNA methylation were measured in snail tissues (whole body, headfoot, hepatopancreas and ovotestis), following infection or heat shock. Both stressors led to decreased levels of methylation of HSP 70, in a time-dependent manner, concurrently with increases in transcription of HSP 70 (Fig. 5). Temporal hypomethylation of the locus differed, depending on whether the snail was responding to abiotic or biotic stress, and was also more dramatic and longer lasting in the DNA from the hepatopancreas of infected snails, reflecting the upregulation of transcription of HSP 70 in this snail organ. These results remain to be further investigated by more profiling of the methylome of the susceptible snail while responding to various stressful conditions. To date, we have also shown that as has previously been reported for other invertebrates, DNA methylation of the HSP 70 locus occurs within the gene body but not the promotor region (Gavery and Roberts, 2013). Promotor region DNA methylation in a mollusk has, however, been recently reported (Saint-Carlier and Riviere, 2015).

6. Closing remarks

The role of epigenetics and susceptibility of the snail host to schistosome infection is a new frontier in the search to uncover mechanisms of parasitism that can be blocked to disrupt transmission of this tropical disease. To date we have shown that the incoming parasite has the ability to regulate expression of stress genes in the snail host via spatio-epigenetics and change in DNA methylation patterns in snail organs. Importantly, these epigenetic modulations take place within a short time frame post-schistosome exposure of the snail host and underscores a phenotype that either leads to resistance or susceptibility to infection. The factor(s) released from the parasite excretory secretory products (ESPs) signaling via the stress pathway to reprogram chromatin in order to modify transcriptional regulation in the snail host genome for its own gain remains to be identified. The proteome of ESPs from

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S. mansoni developmentally transforming miracidia has been reported (Wu et al., 2009), facilitating comparison of ESPs with products released from irradiated attenuated miracidia, so we can search for candidate proteins present only in wild type miracidia. With the recent release of a draft genome of *B. glabrata* (Adema et al., unpublished data) and the advent of better genome editing tools such as the CRISPR-Cas9 system (Mali et al., 2013; Pennisi, 2013) that also is active in mollusks (Perry and Henry, 2015), we can envision that a knock-out snail deplete of heat shock transcription factor can be utilized to further investigate the role of early stress, epigenetic control and plasticity in snail susceptibility in the *B. glabrata/S. mansoni* host/pathogen model system.

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