Schistosoma haematobium and host hormones

Mónica Botelho
08/11/2017
• What is schistosomiasis?
Hormones

1. Eggs hatch releasing miracidia
2. Eggs of S. mansoni released in feces, S. japonicum released in urine
3. Miracidia penetrate snail tissue
4. Sporocysts in snail (successive generations)
5. Cercariae released by snail into water and free-swimming
6. Cercariae lose tails during penetration and become Schistosomulae
7. Schistosomulae penetrate skin
8. Circulation
9. Migrate to portal blood in liver and mature into adults
10. Paired adult worms migrate to:
   - Mesenteric venules of bowel/rectum (laying eggs that circulate to the liver and shed in stools)
   - Venous plexus of bladder

S. mansoni
S. japonicum
S. haematobium

= Infective Stage
= Diagnostic Stage
BEWARE
BILHARZIA
ERECTED BY ASSOCIATION FOR BILHARZIA
CONTROL  •  P.O. BOX 2171 BULAWAYO
Schistosomiasis: facts and figures

- Human schistosomes currently infect more than 200 million people in 76 countries worldwide in the endemic areas of Africa, the Caribbean, Central America, South America, East Asia, and the Middle East.
Global distribution of Schistosomiasis

Senegal
An epidemic of schistosomiasis along the Senegal River basin caused by water-resource development schemes continues unabated.

Egypt
Praziquantel chemotherapy coupled to a vigorous media campaign has resulted in a significant decrease in the morbidity and prevalence of schistosomiasis infection.

Iran, Morocco, and Saudi Arabia
Schistosomiasis control has been successful in those areas with elimination of the infection contemplated.

China
Schistosoma continues to be a major public health problem in the lake and marshy regions despite successful control in other endemic areas.

Lao People's Democratic Republic
Schistosoma mekongi control has been successful around Khong Island with prevalence reduced from 42% to < 2%.

North-east Brazil
Urban schistosomiasis now present in and around many major cities.

Ghana
Intestinal schistosomiasis has increased due to the construction of the Akosombo Dam and other much smaller dams.

sub-Saharan Africa
More than 85% of the estimated 200 million people globally with schistosomiasis and the majority of patients with severe disease live on this continent.

Indonesia
Schistosomiasis has been controlled in the Lindu region of Sulawesi such that the prevalence of infection is lower than 2%.
• Is there a role for *S. haematobium* in bladder cancer?
S. haematobium and bladder cancer

• A causal association between the parasite and bladder cancer was postulated in 1911 by Fergusson, but so far proof of this association has remained elusive.
S. haematobium and bladder cancer

Squamous cell carcinoma of the urinary bladder has been associated with *Schistosoma haematobium* infection in many parts of Africa.

A parasite-tumor linkage is further suggested by the predominance of squamous cell (as opposed to transitional cell) morphology of bladder carcinomas seen in *S. haematobium*-endemic areas.
• What about host endocrine system?
Schistosomiasis and host hormones

It has been shown that schistosomes synthesizes steroid hormones (Nirde et al, FEBS Letters, 1983).

Schistosomes produce hormone-like signals (Mendonça et al, Parasitology Today, 2000).

Existence of receptors able to bind the molecules of estradiol (Barrabes, Ann Parasitol Hum Comp, 1986; Mendonça et al, Parasitology Today, 2000).
Schistosomiasis and host hormones

Recent experimental evidence suggests that schistosomes can not only evade immune responses actively but also exploit the hormonal microenvironment within the host to favor their establishment, growth and reproduction (Escobedo et al, Trends in Parasitology, 2005).
Shistosoma haematobium produces an estradiol-related molecule
**Shistosoma haematobium** produces an estradiol-related molecule

Botelho et al. Exp Parasitol 2009

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (years)</th>
<th>E2</th>
<th>Range</th>
<th>Testosterone</th>
<th>Range</th>
<th>LH</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>4</td>
<td>62,8</td>
<td>0-22</td>
<td>&lt;15,0</td>
<td>2-10</td>
<td>0,114</td>
<td>&lt;2,5</td>
</tr>
<tr>
<td>Male</td>
<td>12</td>
<td>30,8</td>
<td>0-25</td>
<td>77,5</td>
<td>5-500</td>
<td>1,79</td>
<td>0,2-8,0</td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>79,8</td>
<td>0-25</td>
<td>363</td>
<td>5-500</td>
<td>1,89</td>
<td>0,2-8,0</td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
<td>45,7</td>
<td>0-25</td>
<td>724</td>
<td>&gt;200</td>
<td>5,89</td>
<td>1,4-7,7</td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
<td>31,9</td>
<td>0-25</td>
<td>535</td>
<td>&gt;200</td>
<td>7,65</td>
<td>1,4-7,7</td>
</tr>
<tr>
<td>Male</td>
<td>20</td>
<td>68,3</td>
<td>&lt;56,0</td>
<td>982</td>
<td>262-1593</td>
<td>2,87</td>
<td>1,4-7,7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antigenic preparations</th>
<th>E2 (pg/ml) ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. haematobium</td>
<td>14,8±0,14</td>
</tr>
<tr>
<td>S. mansoni</td>
<td>12,6±0,27</td>
</tr>
<tr>
<td>F. haepatica</td>
<td>&lt;10</td>
</tr>
<tr>
<td>H₂Od</td>
<td>&lt;10</td>
</tr>
<tr>
<td>10 nM E2</td>
<td>1632,9±2,5</td>
</tr>
</tbody>
</table>
*S. haematobium* produces estrogenic molecules that are able to down-regulate ER alpha and ER beta and repress ER transcriptional activity.
Methodological Strategy

Gene expression Real-Time PCR
Methodological Strategy

Transfection  pERE-Luc
Methodological Strategy

Mass spectrometry LC-ESI-MS
*S. haematobium* produces estrogenic molecules that are able to down-regulate ER alpha and ER beta and repress ER transcriptional activity.
*S. haematobium* produces estrogenic molecules that are able to down-regulate ER alpha and ER beta and repress ER transcriptional activity.

Botelho et al. Exp Parasitol 2010
*S. haematobium* produces estrogenic molecules that are able to down-regulate ER alpha and ER beta and repress ER transcriptional activity.
Schistosomiasis, bladder cancer and host hormones
*Schistosoma haematobium* total antigen down-regulates ER alpha and ER beta in HCV29 normal urothelial cells and down-regulates ER expression in the bladders of CD1 mice

**Gene Expression**

![Gene Expression Chart](chart.png)

- **C**: Control
- **E2**: Estrogen
- **ICI**: ICI 182,780
- **E2+ICI**: Estrogen + ICI 182,780
- **Sh**: Shox2
- **Sh+E2**: Shox2 + Estrogen
- **Sh+ICI**: Shox2 + ICI 182,780
- **Sh+E2+ICI**: Shox2 + Estrogen + ICI 182,780

**Fold increase**

- ER alpha
- ER beta

Botelho et al. *Oncol Rep.* 2011
Conclusions

*S. haematobium* and hormones

*S. haematobium* total antigen expresses estradiol-related molecules that down regulate Estrogen Receptor alpha and beta in estrogen responsive cells. These estrogens are also present in the sera of *Schistosoma*-infected individuals, and they have the ability to repress Estrogen Receptor transcriptional activity.

The estrogenic molecules present in *S. haematobium* extracts could have a carcinogenic effect possibly through estrogen adduct-mediated pathway and could further explain the link between this parasite and squamous cell carcinoma of the bladder.
Overall

Therefore, these results may open potential new strategies for cancer diagnosis by using these estrogens as biomarkers in schistosomiasis-associated bladder cancer.