Immune Response and Vaccine Development in Schistosomiasis

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The Lifecycle

Schistosomiasis

1. Infective Stage
2. Diagnostic Stage

1. Sponges in snail (successive generations)
2. Miracidia penetrate snail tissue
3. Eggs hatch releasing miracidia
4. In feces
5. Cercariae released by snail into water and free-swimming
6. Cercariae lose tails during penetration and become schistosomulae
7. 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)

S. mansoni
S. japonicum
S. haematobium

venous plexus of bladder
Schistosomiasis – The Numbers

750 million exposed to infection in 74 endemic countries, 200 million infected

20 million with serious morbidity, ~280,000 deaths annually

One fifth of the world's population harbours at least one species of intestinal dwelling nematode

This equates to approximately 39 million Disability Adjusted Life Years (DALYS)

Tuberculosis gives a figure of 46 million DALYS

This is an important infection with a real cost to human productivity
To understand the epidemiology of these infections, you need to recognise that the population dynamics of these parasites are fundamentally different from those of other infectious agents.

They do not multiply within an individual host, and they can live in the host for up to 7 years (!)

The number of worms in a host is due to the number of infection events and is related to the degree of exposure.

It is the number of worms in an individual that is important in the transmission of the disease.

It is the intensity of infection that is important – not prevalence.
Age Intensity Curve

Egg output

Circulating antigen

Age (yrs)

Naus et al., Infect Immun, 1999
Typically, more than 70% of the worms in a population are found within less than 15% of the host individuals.

The most heavily infected individuals are at greatest risk of morbidity and are also the major source of infective stages.

The same pattern is seen regardless of environmental or cultural differences.
Age Intensity Curve

Egg output

Circulating antigen

Resident Cohort

Immigrant Cohort

Naus et al., Infect Immun, 1999
A Word of Caution…

When conducting human studies, be careful about potential bias

Males frequently have heavier infections than females
Hormone-related differences in immune response?
Behaviour, socio-cultural differences?
What are the immune correlates of protection?

Eosinophils

Antibodies (IgE/IgG4)

Cytokines (IL-4, and IL-5)
Eosinophils

Peripheral eosinophilia is a characteristic feature of helminth infections

In vitro - cytotoxic to schistosomula in the presence of parasite specific antibodies

In Kenya\(^1\), children with eosinophil counts > 400,000/ml had significantly reduced rates of *S.mansoni* re-infection

Gambian children\(^2\) with elevated eosinophil counts were less susceptible to *S. haematobium* re-infection

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\(^1\)Sturrock *et al*., *Trans R Soc Trop Med Hyg*, 1987

\(^2\)Hagan *et al*., *Parasite Immunol*, 1985
Resistance to re-infection is correlated with percentage of whole blood eosinophils

IoS/R
Index of susceptibility/resistance

number of time re-infected x 100
weeks in project x cars per week

Ganley-Leal et al., Infect Immun, 2006
A Correlate of Protection: IgE

Treatment and re-infection study in The Gambia

Water contact - adults and children were as exposed to infection

Re-infection measured 15 months after treatment

Multiple linear regression used to assess the contribution of age, Ab and exposure to re-infection

Negative relationship between IgE and re-infection

A Correlate of Susceptibility: IgG4

Treatment re-infection study in 118 people in Brazil
Tested relationship between re-infection and anti-schistosome larvae antibodies
Re-infection showed a negative correlation with IgE and a positive one with IgG4

High IgE:IgG4 ratio was associated with low re-infection

18 months after treatment

Demeure et al., J Infect Dis, 1993
The IgE/IgG4 Axis

IL-4 and IL-5 both drive IgG4 and IgE class switching (hence their role in helminth immunity)

But IgG4 and IgE are functionally antagonistic

IgG4 competes for antigens with IgE

Thus, IgG4 blocks IgE-mediated basophil and mast cell degranulation (also likely to block IgE-mediated eosinophil function)

A simple measure of immunity to Schistosomiasis:

IgE:IgG4
What about Regulation?

Regulation is a key element in our response to infection

Too little regulation leads to uncontrolled immune responses, pathology and organ failure

Too much regulation leads to poor immune responses and uncontrolled infection

Helminth infections are chronic infections

To survive in the host, they must regulate the immune system to stay in balance with it

Many researchers in the field are trying to understand the regulatory response, and identify the helminth proteins that generate Tregs

We may be able to use these proteins to modulate unwanted immune responses
Can Worms Tame the Immune System?

Researchers are investigating the use of parasites as remedies for inflammatory bowel disease and other disorders of hyperimmunity.

In a stunt reminiscent of the TV reality show Fear Factor, dozens of unpaid volunteers have recently been gulping Cannedade faced with 2500 live eggs from parasitic worms. The host, so to speak, of this experiment was gastroenterologist Joel Weinstock of the University of Iowa in Iowa City. The hope-for reward for the participants was remission of the disruptive and painful symptoms of inflammatory bowel disease (IBD). Weinstock is among a small but growing group of researchers who believe that parasitic worms, or substances derived from them, could provide effective treatments for not only IBD but also a range of autoimmune disorders.

The idea may sound crazy, but it is buttressed by studies showing that treating mice with eggs, larvae, or extracts of helminths—parasitic worms such as flukes, flatworms, tapeworms, and pinworms—can dampen, and perhaps prevent, allergic reactions, reduce the severity of multiple sclerosis (MS)-like disease, and block the development of type 1 diabetes (see sidebar). Recent data indicate that helminths may protect against disease by triggering so-called regulatory T cells, which function as the immune system's brake on overactive immune responses.

A new approach to therapy for ulcerative colitis and Crohn's disease?

Drs. Mainsel and Weinstock propose that treating patients with such parasites could offer a new treatment option. "We are opening up the possibility of whole new classes of drugs," says Weinstock. "It's a new and different approach to treating these diseases."
Immunity to Schistosomiasis

Cercariae → Schistosomula → Adult worms → Eggs

- **Th1**
  - IFN-γ
  - TNF-α
  - NO

- **Th2**
  - IL-4
  - IL-13
  - IL-5

- **Treg**
  - IL-10
  - TGF-β
  - Arginase

**Immune response**

- **Dunne & Cooke**, Nat Rev Immunol, 2005
Quick Question!

Should we treat helminth infections by mass drug administration?
Another Cautionary Tale…

All the immune components associated with human immunity to schistosomiasis (and other helminths) are exactly the same as those associated with allergic disease

- Eosinophils
- Basophils
- Mast Cells
- IgE
- Histamine release

Our immune system has evolved with continual helminth infection – they are not new to us
There is now good evidence that helminth proteins very closely resemble allergens

**Example**

*S. Mansoni* Tegument Allergen Like Proteins (SmTAL1-13)

SmTAL1 is the dominant IgE antigen in *S. mansoni*

IgE to SmTAL1 is correlated with resistance to reinfection

Increases with age

Will MDA give rise to allergic sensitivities in the absence of helminths?

What is the cost of treating allergies versus the cost treating helminths?

Should we be mass administering antihelmintics?


Pinot de Moira *et al.*, Infect Immun, 2013
Vaccines! And another Word of Caution…

There are quite a number of vaccines for a number of different helminth parasites

### S. mansoni

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Stage(s)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SmSynt</td>
<td>Schistosomula and Adult</td>
<td>Figueiredo, PLoS NTD 2014; 8:e3107</td>
</tr>
<tr>
<td>SmTSP-2, Sm29</td>
<td>Adult worms and lung-stage schistosomula</td>
<td>Pinheiro, Parasite Immunol 2014; 36: 303</td>
</tr>
<tr>
<td>Sm10.3</td>
<td>All stages</td>
<td>Martins, PLoS NTD, 2014; 8: e2750.</td>
</tr>
<tr>
<td>SG3PDH</td>
<td>Larvae</td>
<td>El Ridi, J Parasitol, 2013; 99: 194</td>
</tr>
<tr>
<td>Smteg</td>
<td>Schistosomula</td>
<td>Araujo, Acta tropica, 2012; 124: 140</td>
</tr>
<tr>
<td>SmStoLP</td>
<td>Adults and 7-day-old schistosomula</td>
<td>Farias, PLoS NTD, 2010; 4: e597</td>
</tr>
</tbody>
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### S. japonicum

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<tr>
<th>Vaccine</th>
<th>Stage(s)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SjTP22.4</td>
<td>Adult, Schistosomulum and cercaria</td>
<td>Zhang, Vaccine, 2012; 30:5141</td>
</tr>
<tr>
<td>SjEsRRBL1S</td>
<td>Highly expressed in 14-28 day old schistosomes</td>
<td>Wu, Exp Parasitology. 2012; 131:383</td>
</tr>
<tr>
<td>SjMLP/Hsp70</td>
<td>Eggs, cercariae, schistosomula and adult</td>
<td>He, Parasitol Res, 2010; 107</td>
</tr>
<tr>
<td>SjPSMA5</td>
<td>Up-regulated in 18-day and 32-day schistosomes</td>
<td>Hong Y, Exp Parasitol, 2010; 126: 517</td>
</tr>
</tbody>
</table>
Generalized urticaria induced by the Na-ASP-2 hookworm vaccine: Implications for the development of vaccines against helminths

David J. Diemert, MD, FRCP(C), a,b,c Antonio G. Pinto, MD, c Janaina Freire, MD, c Amar Jariwala, MD, a Helton Santiago, MD, PhD, b,c Robert G. Hamilton, PhD, d Maria Victoria Periago, PhD, e Alex Loukas, PhD, e Leon Tribolet, BSc, e Jason Mulvenna, PhD, e,f Rodrigo Correa-Oliveira, PhD, e Peter J. Hotez, MD, PhD, a,g and Jeffrey M. Bethony, PhD b,c Washington, DC, Belo Horizonte, Brazil, Baltimore, Md, Cairns and Brisbane, Australia, and Houston, Tex

This vaccine candidate was safe and immunogenic in a US trial
But it failed in Brazil

Why?

Diemert et al., J Allergy Clin Immunol, 2012
Schistosome Vaccines – what should we do?

Generate an IgE response?
Need to avoid allergic responses

Vaccinate adults who have preexisting immunity, and probable current infection?
Lessons from the hookworm trial

Vaccinate children without preexisting immunity?
Role of \textit{in utero} environment
Rise in allergies in absence of schistosomiasis

Think of something else?
Targeting the Schistosomula

Can generate IgG responses to Schistosomula
Avoid allergic responses

Work at the skin stage
Prevent infection and transmission

Susceptible to innate and adaptive responses
Conclusions – more questions than answers

Protective immunity to schistosomiasis is developed over time and with continual exposure

Protective immunity correlates with

- High eosinophil counts
- High IgE
- Th2 responses (IL-4/5)

Chronic infection means you must modulate immune system

- Tregs

Can we generate a vaccine?

- Allergic reactions

Effect of immunity in uninfected hosts – will it drive the emergence of allergies?

- Effect of MDA?
Reduced transmission of human schistosomiasis after restoration of a native river prawn that preys on the snail intermediate host

Susanne H. Sokolow, Elizabeth Huttinger, Nicolas Jouanard, Michael H. Hsieh, Kevin D. Lafferty, Armand M. Kuris, Gilles Riveau, Simon Senghor, Cheikh Thiam, Alassane N’Diaye, Djibril Sarr Faye, and Giulio A. De Leo

Completion of the Diama Dam in Senegal in 1986

No prawns above the dam after 1986

Schisto prevalence

1986 – 0%
1992 – 70%
1997 – 100%
Acknowledgements

I nicked a few slides from: