Immunopathology of schistosomiasis mansoni in mice and men

Padraic Fallon recently presented an excellent summary of cytokine responses and immunopathology in infected mice and humans1. We wish to take issue with several points, including Fallon’s implication that morbidity and death in immunodeficient mice caused by type 1 cytokine responses is relevant to human schistosomiasis. In this model, hepatocellular toxicity12 is apparently caused by Schistosoma mansoni egg antigens that are neutralized in immunologically intact mice2,3. Fallon et al. recently presented a detailed description of this response2. In considering the varied causes of morbidity and mortality in humans and mice (Table 1) this toxicity, termed ‘cytokine shock’ in the table, has no apparent counterpart in infected humans.

Symmers’ piperstrem periportal fibrosis is the characteristic hepatic lesion of severe schistosomiasis mansoni4,5. As noted by Fallon, Henderson et al. described liver fibrosis in mice that was strikingly similar morphologically to the human disease6. Modulatory anti-egg idiotypes were absent from both mice and humans with Symmers’ fibrosis but were present in those without Symmers’ fibrosis2,7. Limited data from mice and humans suggest that T helper 1 (Th1) pathways are involved in the pathogenesis of Symmers’ fibrosis8,9, although another study found that mice producing idiotypes stimulating interferon γ (IFN-γ) were those that did not develop Symmers’ fibrosis. In our studies in patients with Symmers’ fibrosis we found IFN-γ production only when interleukin 10 (IL-10) was neutralized9. These findings suggest, in contrast to the interpretation of Fallon, that type 1 responses are not necessarily linked to hepatosplenic disease.

Vaccination of mice before infection with S. mansoni eggs and IL-12 results in a predominantly Th1 response, compared with the Th2 response in unvaccinated mice. Fibrosis is markedly reduced, granuloma size is decreased, and ‘cytokine shock’ is not seen10. Present information is inadequate to indicate whether such immune deviation towards a Th1-type reaction might be helpful or inadvisable in humans. In mice, our findings indicate that both extreme Th2 and Th1 immune polarization is potentially harmful and that Th2 polarization augments fibrosis11. The Th1 reaction associated with cytokine shock in mice, in our opinion, is not relevant. Conceivably, cytokine shock might develop in patients with immunodepression such as that associated with AIDS, but the very low levels of infection in humans compared with those in mice would suggest that egg-mediated cytokine shock should seldom, if ever, occur even in these patients.

S. japonicum and S. haematobium infections differ markedly from S. mansoni infections in both humans and mice. Notably, the egg-mediated hepatotoxicity does not occur in S. haematobium- or S. japonicum-infected T-cell depleted mice12,13 or in S. japonicum-infected nude or severely combined immunodeficiency (SCID) mice14. Thus, this unusual pathology might be restricted to S. mansoni infection in immunodeficient mice.

In summary, our areas of agreement with Fallon are much greater than the areas of disagreement. We particularly consider that, interesting as it is in its own right, hepatotoxicity in immunodeficient mice lacks relevance to human schistosomiasis. Better definition of the pathogenesis of both acute toxemic disease and chronic schistosomiasis in humans remains a high priority.

Allen W. Cheever
The Biomedical Research Institute, 12111 Parklawn Drive, Rockville, MD 20852-1709, USA.

Karl F. Hoffmann
Thomas A. Wynn
T Wynn@atlas.niaid.nih.gov
The Immunobiology Section, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA.

References
9 Mwatha, J.K. et al. (1998) High levels of TNF, soluble TNF receptors, soluble ICAM-1 and IFN-γ, but low levels of IL-5, are associated with hepatosplenic disease in human schistosomiasis mansoni. J. Immunol. 160, 3992–3999
### Table 1. Schistosomiasis mansoni infection: comparison of human and murine disease and causes of death.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Human morbidity and mortality</th>
<th>Murine morbidity and mortality</th>
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<tbody>
<tr>
<td>Acute toxemic disease</td>
<td>Fever, high eosinophilia, allergic cutaneous and pulmonary symptoms in some, may begin before S. mansoni egg laying (5 weeks) but is exacerbated by egg laying. Immune complex related. Resolves spontaneously in weeks. Granulomas are unusually large and destructive compared to later infections. Th0 after treatment. Perhaps predominantly Th2 before treatment. Rarely fatal.</td>
<td>High eosinophilia, mice look ruffled, relatively inactive. In moderate infections appearance improves by 10–12 weeks of infection, eosinophilia decreases, granulomas downregulate size. Th0 progresses rapidly to Th2 dominance after S. mansoni egg laying begins.</td>
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<tr>
<td>Symmers’ periportal fibrosis of the liver</td>
<td>Death is most frequently from blood loss from ruptured submucosal esophageal varices. Terminally, hepatocellular failure may result in jaundice and coma similar to that seen in cirrhosis but unlike the hepatocellular necrosis seen in murine cytokine shock. Portal hypertension occurs exclusively in patients with Symmers’ fibrosis and is not related to granulomas.</td>
<td>Death most frequently from bleeding from small mucosal lesions in gut. Not from varices, which are on serosal surface of the esophagus. Probably unrelated to human variceal bleeding. Portal hypertension related to number and size of granulomas and not to Symmers’-like fibrosis</td>
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<tr>
<td>Related syndromes present almost only in patients with Symmers’ fibrosis</td>
<td>Morbidity or death from pulmonary hypertension related to schistosomal pulmonary arteritis caused by granulomas around eggs shunted from portal system. Morbidity or death from glomerulonephritis producing nephrotic syndrome or renal failure.</td>
<td>Pulmonary arteritis exists in chronic infections and can be augmented by constructing portocaval shunts surgically. Only subtle glomerular lesions, no nephrotic syndrome or renal failure.</td>
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<tr>
<td>Ectopic lesions</td>
<td>Ectopic eggs may produce lesions in brain, skin etc.</td>
<td>Occurs, morbidity not described.</td>
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<tr>
<td>Colonic polyposis</td>
<td>An uncommon lesion particularly described in Egyptian patients and associated with extreme diarrhea, which may be fatal.</td>
<td>No similar lesions.</td>
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<tr>
<td>Diarrhea</td>
<td>Related to intensity of chronic infection.</td>
<td>Occurs in acute infections. Virtually unstudied.</td>
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<tr>
<td>Cytokine shock</td>
<td>Not described. It is possible that this murine syndrome is not homogeneous, i.e. hepatic damage may cause death with or without the influence of intestinal lesions and detailed descriptions of pathogenesis in mice, such as that of Fallon et al., are uncommon.</td>
<td>Occurs in mice unable to ‘neutralize’ egg toxin by granuloma or antibody. Necrosis of individual hepatocytes resembling viral hepatitis and resulting in elevated serum enzymes such as glutamic transaminase released oxalacetic from damaged hepatocytes.</td>
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<tr>
<td>Other</td>
<td>Numerous other features of infection have been modeled in mice, e.g. anemia, associations with salmonella and other infections.</td>
<td>Apart from models of human schistosomiasis, murine infections are useful for the study of immunoregulation etc.</td>
</tr>
</tbody>
</table>

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16 Cheever, A.W. et al. (1999) Egg laying is delayed but worm fecundity is normal in SCID mice infected with Schistosoma japonicum and S. mansoni with or without recombinant tumor necrosis factor alpha treatment. Infect. Immun. 67, 2201–2208