Malaria Pathogenesis: An Outline of a UBM Project at ASU

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1 Project Background

The precise cause of morbidity and mortality from malaria is varied and not completely understood. Clark and his colleagues [2, 3] emphasize similarities between malaria pathogenesis and bacterial sepsis and other conditions leading to general inflammation. In particular, they note that both *Plasmodium falciparum* and *P. vivax* infection correlates with increases in plasma concentration of proinflammatory cytokines, including tumor necrosis factor (TNF), interleukin 1 (IL-1) and lymphotoxin (LT) among others. The resulting inflammatory response is thought to generate oxygen-derived free radicals (ODFRs) important in clearing intraerythrocytic parasites, among other clinically relevant responses. However, the inflammation also appears to contribute significantly to morbidity and mortality—roughly speaking, a significant fraction of malaria patients suffer from their own immune response to the parasites rather than from direct effects of the parasites themselves.

Central to this problem is nitric oxide (NO), which is a double-edged sword. On one hand, NO acts as an anti-inflammatory agent, perhaps calming the pathogenic inflammation. On the other hand, NO may be directly cytotoxic to cells. Here are the details of Clark et al.'s hypothesis:

1. Malaria, probably malarial glycosylphosphatidylinositols (GPIs, proteins that anchor surface antigens to the parasite's plasma membrane), initiate an inflammatory response, causing release of TNF, LT, IL-1 and maybe IL-6 in the short term, and maintained chronically by high mobility group box 1 (HMGB1) proteins released from necrotic cells.

2. The resulting inflammatory response combats the disease in various ways, including

   (a) increasing production of ODFRs, which as mentioned above attack intracellular parasites;

   (b) priming cell mediated immunity, in particular enhancing cytotoxic T cell memory.

3. Concurrently, some of these pro-inflammatory cytokines—TNF at least—activate inducible nitric oxide synthase (iNOS) and, via IL-10, heme oxygenase-1 (HO-1).

4. iNOS and HO-1 generate NO and CO, both of which are anti-inflammatory agents, generating negative feedback (perhaps to modulate the response).

5. However, NO also produces peroxynitrite, which nicks DNA. To repair the damage, cells activate a single-strand DNA repair enzyme called poly (ADP-Ribose) polymerase family member 1 (PARP-1). In effecting the repair PARP-1 irreversibly destroys NAD^+, and replenishment of the lost NAD^+ requires ATP hydrolysis. At pathogenic concentrations of NO, hyperactive PARP-1 can deplete NAD^+, and therefore ATP, enough to impair the activity of the membrane-bound Na^+/K^+ ATPase pump, which in turn causes loss of cell volume regulation, hyponatremia and hyperkalemia.

6. In addition, NO has direct toxic effects on the Na^+/K^+-ATPase pump. In erythrocytes, this toxicity can cause them to swell, increasing erythrocyte clearance by the spleen. The resulting anemia then exacerbates the systemic depletion of ATP.

7. Intracellular ionic disruption caused by ATP rundown can also erode muscle contractility to the point where ventilatory blowoff of CO_2 is impaired. The resulting acidification of the blood further degrades its ability to carry oxygen, in turn exacerbating the anemia.

2 Specific Aims

This research team plans to do the following:

1. Develop a mathematical model of the innate immune response to *Plasmodium* infection, focusing specifically on the beneficial and pathological effects of NO.

2. Use the model to address the following questions:

   (a) Can the balance between therapeutic and pathological effects of NO explain, at least in part, the enormous difference in case fatality between *P. falciparum* and *P. vivax*?

   (b) What is the most effective vaccination strategy for vaccines against malarial GPIs? As pointed out by Clark et al., the answer to this question is not obvious. On one hand, elimination of parasitic GPIs will decrease serum parasite loads and the resulting pathogenic inflammation. On the other hand, it also will inhibit the attack on intraerythrocytic parasites and CMI priming.

   (c) In a more general sense, we will use the model to assess the efficacy of treatment strategies that relieve symptoms without eliminating the parasite. Malaria in the context of overly dramatic immunosuppression may ultimately expose the patient to massive infection, either from the original *Plasmodium* infection or an opportunistic one. We plan to use the model to shed light on the conditions in which such treatment failure can occur.

   (d) We will also use the model to explore another hypothesis of Clark et al. In parts of Africa, aspirin is still commonly used to treat fever in children. Aspirin appears to prolong the activation of INF-γ, which also produces NO by activating iNOS. Clark et al. suggest that giving aspirin to children with

malarial fever—and therefore high serum INF-γ concentrations—may amplify the pathogenic effects of NO, thereby exposing the children to increased risk of mortality.

3 Activities Completed to Date

1. First we studied basic dynamical systems theory in preparation for studying and building the required models.

2. So far we have studied models of malaria infection currently in the literature in search of a foundational model of within-host parasite dynamics. We have identified one reasonable candidate—based on the parasite model of Anderson et al. [1, 4]—upon which we can build our model of the innate immune response to infection.

3. We have begun consolidating our results from a review of the biomedical literature on a wiki set up and managed by one of the team members (Michael Crusoe).

4. We have established parameter values from the literature for ranges of parasitemia density, erythrocyte production rate in the marrow, mean number of ciruculating erythrocytes and spleenic clearance of erythrocytes.

4 Goals for Spring Semester, 2009

1. Identify relevant parameters and variables required in the model.

2. Nail down ranges for parameter values from existing literature when possible.

3. Construct a model or family of models pursuant to our first specific aim.

4. "Test run" the models and continue to revise until we are comfortable with the product.

5. Begin numerical analysis of full model.

6. Identify simpler, more analytically tractable versions of the model and begin their analysis.

5 Team Organization and Membership

1. Biology specialists: Megan McCaughan, Tannaz Farahani

2. Computational specialists: Ian Linday, Michael Crusoe

3. Mathematical specialists: Ivana Malenica, Tatiana Moyer

4. Crossover: R.J. Austerman

References

[1] Anderson, R.M., R.M. May and S. Gupta. 1989. Non-linear phenomena in host-parasite interactions. *Parisitology* **99**:59-79.

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[4] Iggidr, A., J.-C. Kamgang, G. Sallet and J.-J. Tewa. 2006. Global analysis of new intrahost malaria models with a competitive exclusion principle. *SIAM J. Appl. Math.* **67**:260-278.