Dissection of the Host-Parasite Interactions Between *Anopheles stephensi* and *Plasmodium berghei* in the Midgut Epithelium

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The basic biology of vectorparasite interactions during the transit of the parasite in the midgut is still limited, although anopheline mosquitoes play a central role in transmission of the malaria parasite. Detailed analysis of the cell biology of the interactions between *Anopheles stephensi* midgut epithelial cells and *Plasmodium berghei* ookinetes during invasion of the mosquito by the parasite led our laboratory to propose the time-bomb model. In *An. stephensi*, *P. berghei* ookinetes inflict severe damage to cells during invasion. Invaded cells protrude towards the midgut lumen and show some characteristic changes, including induction of nitric oxide synthase (NOS) expression, a substantial loss of microvilli and genomic DNA fragmentation. Recent studies from our group indicate that there is a delay between NOS induction and protein nitration, as revealed by anti-nitrotyrosine monoclonal antibody. A similar delay has recently been reported in activated macrophages and it has been proposed that protein tyrosine nitration in activated macrophages is mediated through a nitrite-dependent peroxidase reaction rather than peroxynitrite generated by direct reaction of nitric oxide (NO) with superoxide anion (O^{2-}). Histochemical staining of malaria-infected midguts revealed that the pattern of peroxidase activity is similar to that of nitro-tyrosine, suggesting that this enzyme may be required for protein nitration in the invaded cells. Similar responses are also observed in *An. gambiae-P. berghei* model. Furthermore, an *in vitro* assay has demonstrated that *Plasmodium* induces peroxidase activity in the midgut that catalyzes protein nitration. A new version of the Time bomb model will be discussed.