Molecular Interactions Between *Plasmodium berghei* and Midgut Epithelium from the Human Malaria Vector Mosquito

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The basic cell biology of vector-parasite interactions during the transit of the parasite in the midgut is still largely unknown, although anopheline mosquitoes play a critical role in transmitting malaria parasite. A detailed analysis of the interactions between *Anopheles stephensi* midgut epithelial cells and *Plasmodium berghei* ookinetes during invasion of the mosquito by the parasite was conducted. In this mosquito, *P. berghei* ookinetes invade polarized columnar epithelial cells with microvilli, which do not express high levels of vesicular ATPase. The invaded cells are damaged, protrude towards the midgut lumen and suffer other characteristic changes, including induction of nitric oxide synthase (NOS) expression, a substantial loss of microvilli and genomic DNA fragmentation. Our results indicate that the parasite inflicts extensive damage leading to subsequent death of the invaded cell. Ookinetes were found to be remarkably plastic, to secrete a subtilisin-like serine protease and the GPI-anchored surface protein Pbs21 into the cytoplasm of invaded cells, and to be capable of extensive lateral movement between cells. The epithelial damage inflicted is repaired efficiently by an actin purse-string-mediated restitution mechanism, which allows the epithelium to 'bud off' the damaged cells without losing its integrity. A new model, the time bomb theory of ookinete invasion, is proposed and its implications with some of the new findings will be discussed.