

Local Epithelial Responses during *Plasmodium* Invasion of the Mosquito Midgut.

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The malaria parasite *Plasmodium* must complete a complex developmental life cycle within *Anopheles* mosquitoes before it can be transmitted into the human host. We profiled on a genomic scale the transcriptional responses of the *A. gambiae* midgut to *P. berghei*, and showed that more than 7% of the assessed mosquito transcriptome is differentially regulated during invasion. The profiles suggested that actin and microtubule cytoskeleton remodeling is a major response of the epithelium to ookinete penetration. Other responses encompass components of innate immunity, extracellular matrix remodelling and apoptosis. These results complement previous cell biological studies that documented major morphological changes of the epithelial cells, including directional lamellipodia/filopodia protrusions beneath the invaded apoptotic cells and formation of cytoplasmic lamellar protrusions (ookinete "hood"), in the invaded cells, tightly embracing the parasite as it exits into the basal subepithelial space. RNAi-dependent gene silencing identified both parasite antagonists and agonists amongst regulators of actin dynamics, and revealed that actin polymerization is inhibitory to the invading parasite. Combined transcriptional and reverse genetic analysis further identified an unexpected dual role of the lipid trafficking machinery of the haemolymph, for both parasite and mosquito egg development.

We conclude that the determinants of malaria parasite development in *Anopheles* include components not only of systemic humoral immunity, but also of intracellular, local epithelial reactions. These results provide novel mechanistic insights for understanding malaria transmission in the mosquito vector.

REFERENCES:

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