Commentary

A complete molecular understanding of malaria parasite invasion of the human erythrocyte: Are we there yet?

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Invited Commentary on 'Semaphorin-7A Is an Erythrocyte Receptor for P. falciparum Merozoite-Specific TRAP Homolog, MTRAP', Bartholdson et al., PLoS Pathogens' 2012.

As a pathogen constantly on the move, the malaria parasite faces several ongoing challenges. Foremost, it must target specific host cells required by each lifecycle stage (whether in mosquito or human host) and, once identified, rapidly traverse the target cell's defences to get inside. For blood-stage merozoite invasion of the erythrocyte (as the best-characterised invasion event in the lifecycle) this complex process appears at first glance to be relatively simple, with the parasite gracefully turning to its apex before entering with little fuss.¹ Looks can, however, be deceiving. In recent years the number of components involved in merozoite invasion has exploded. This includes tens of merozoite surface molecules characterised as binding the erythrocyte, identification of several proteins that comprise the invasion aperture (or tight junction),² a greater understanding of proteins that regulate the parasite's actomyosin motor complex to drive invasion, and an expanding repertoire of erythrocyte receptors targeted for binding/entry.¹ With such growth in molecular detail, are we any nearer to understanding how the merozoite identifies an erythrocyte for invasion and then gets in?

Conceptually, by dividing our understanding into these two events, tropism and the mechanics of entry, it would appear at first that the answer is yes. For example, the known half-dozen or so adhesin-receptor partnerships would appear to determine a large portion of how circulating merozoites identify erythrocytes as an attractive invasion target.¹ Similarly, the parasite-derived tight junction complex (the window through which the parasite passes during invasion) provides a clear site for actomyosin motor traction that the

merozoite can bare on during entry.² The link between these processes is, however, not as clear. How does the parasite at once hold onto the stage-specific cell, form an otherwise conserved invasion aperture, and actively pull on this junction to drive invasion? For many years, the TRAP (thrombospondin-related anonymous protein) family of proteins was touted as the missing link between tropism and the mechanics of invasion, given that different lifecycle stages express different TRAP family members but each appears to link to the common actomyosin invasion motor.³ Two problems with this model remained. To date, no stage specific receptor for a TRAP family member has been identified and no TRAP protein has been linked to the junction. A recent study testing *in vitro* interactions between recombinant parasite and erythrocyte surface proteins from Bartholdson and colleagues fills the first of these gaps by providing substantial evidence that the merozoite-specific TRAP protein, MTRAP, binds the erythrocyte Semaphorin-7A receptor.⁴ Thus MTRAP can now fulfill its role in stage-specific host cell tropism and provide a solid connection with the conserved actomyosin motor. All that stands in the way of a complete molecular model for the processes of adhesion, junction formation and invasion would be a link between MTRAP and the junction. If this final linkage is indentified, will we be there yet? Keen readers of the literature will note the recent conditional knockout of the TRAP family protein (MIC2) and actomyosin motor of the related apicomplexan parasite *Toxoplasma gondii*, which remarkably was still able to invade host cells, albeit with a greatly reduced efficiency.⁵

Thus, ironically, as our description of each step of invasion falls into place our understanding of the process in its entirety might be on the verge of a complete rewrite. It therefore seems that the journey might only just be beginning.

References

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