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The intracellular parasite *Theileria annulata* modulates host cell actin dynamics to control cell-matrix interaction and motility

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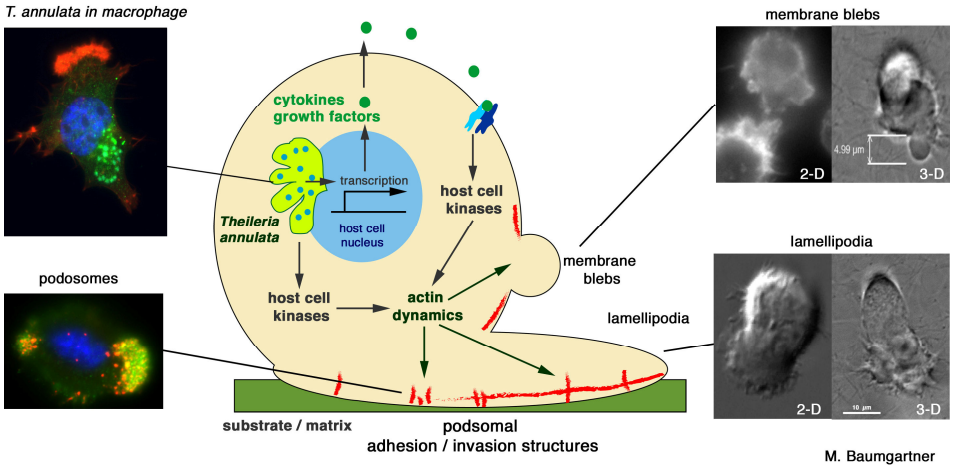
Macrophages infected by the intracellular, protozoan parasite *Theileria annulata* are transformed and display altered motility and invasiveness. This work addresses how *T. annulata* manipulates host cell actin dynamics to modulate motility and invasiveness. Host cell transformation by *Theileria* is reversible because the parasite can be eliminated by drug treatment. Therefore, this work links modulation of actin dynamics by the parasite to host cell transformation.

This work shows that *T. annulata* modulates cell-matrix adhesion, motility and invasiveness of macrophages. Fluorescence time-lapse video microscopy revealed that *T. annulata* does so by targeting actin dynamics in podosomes and lamellipodia, structures that co-ordinate adhesion and motility in macrophages. Hck and other Src kinases are activated in parasitized cells and here it is shown that they stimulate the formation of podosomes and lamellipodia. Elimination of the parasite or interference with Src kinase activity leads to the remodelling of the actin cytoskeleton in lamellipodia and podosomes and to the reversal of the transformation-dependent motility phenotype. The effect of Src family kinases on podosomal reorganisation is the result of their capability to promote recruitment of Ezrin-Radixin-Moesin-family proteins into these structures.

It is furthermore shown that infected macrophages can traverse low rigidity collagen as well as high rigidity matrigel matrices. Motility of infected cells in collagen relies on membrane blebbing and amoeboid motility, whereas in matrigel, amoeboid motility is supported by proteolytic activity. Motility in these three-dimensional environments is enhanced by parasite-induced cytokine secretion and controlled by Src kinases and the Rho-kinase.

Thus, *Theileria* exploits host cell mechanisms that normally control cell motility in varying extracellular environments. By interfering with kinases that regulate motility pathways, *Theileria* adjusts the behaviour of the host cell to its specific needs, namely the propagation of the parasite within the host organism.

Regulation of macrophage actin dynamics and motility by *T. annulata*:



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