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Host Players Involved in the Interaction Between Spotted Fever Group *Rickettsia* and Macrophage-Like Cells

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Members of the spotted fever group (SFG) Rickettsia are obligate intracellular Gram-negative bacteria that are typically transmitted to a mammal during the blood meal acquisition of a feeding tick. While endothelial cells have long been considered the main target cells for rickettsiae during initial stages of infection, several studies have demonstrated parasitism of circulating monocytes, resident macrophages, neutrophils, lymphocytes and hepatocytes in vitro and in vivo by various pathogenic rickettsial species. Interestingly, our group recently reported that two SFG Rickettsia, R. conorii (the etiologic agent of Mediterranean spotted fever) and R. montanensis, (a species not associated with disease in mammals) are both able to proliferate within non-phagocytic mammalian cell lines. However, these two rickettsial species have completely distinct intracellular fates in human THP-1-derived macrophages (Curto P. et al. (2016) Front. Cell. Infect. Microbiol. 6:80). Numerous intact R. conorii cells can be found in the cytoplasm of PMA-differentiated THP-1 cells and are able to effectively grow within these macrophage-like cells similarly to growth kinetics observed in endothelial (EAhy.926) and epithelial (Vero) cell lines. In sharp contrast, R. montanenesis cells are rapidly destroyed within differentiated THP-1 cells in compartments resembling a phago-lysosome. These studies suggested that the ability of Rickettsia species to cause disease in mammals may be correlated in part with the ability of a particular species to proliferate in phagocytes. To further test this hypothesis, we performed growth studies of a panel of *Rickettsia* species including known human pathogens (*R. australis, R. sibirica, R. rickettsii, R. akari*) and species not associated with human disease (*R. amblyomatis* and *R. bellii*) using PMA-differentiated THP-1 cells and the Eahy.926 human endothelial-like cell line. As was previously reported for *R. conorii*, *SFG Rickettsia* species that are associated with human disease were able to efficiently proliferate within non-phagocytic and phagocytic human cell lines. In contrast, *Rickettsia* species not generally associated with recognized diseases in mammals were able to proliferate within endothelial-like cells, but were unable to effectively grow within THP-1 macrophage-like cells. Preliminary comparative genomic studies of these species revealed the presence of cohorts of genes in the recognized pathogens that are either absent or disrupted in so-called "non-pathogenic" species of *Rickettsia*. Together, these results, and our ongoing work may provide for the development of a phenotypic diagnostic tool to assess the pathogenic potential of new *Rickettsia* isolates and species. More importantly, these studies may shed insight into the genetic determinants of *Rickettsia* pathogenicity in mammals and the strategies that pathogenic members of this genus utilize to disseminate within the infected mammalian host.