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Mycobacterial granuloma formation and innate host defense in zebrafish embryos

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In recent years the zebrafish has been shown to be an excellent model for studying the mechanisms of the innate immune defense against pathogens. We have shown that transcriptome responses towards bacterial pathogens including *Mycobacterium* and *Salmonella* species are very similar to responses in mammalian systems. Using combinations of transcriptomic deep sequencing, morpholino knockdown and transgenic reporter fish technologies we have obtained new insights in the functions of key players of the innate immune system. We use both embryo and adult zebrafish models for *Mycobacterium marinum* infection where bacteria evade host immunity and induce granuloma formation similar as in human tuberculosis. We found that a large set of mycobacterium-responsive genes overlapped between the expression signatures of infected zebrafish adults and embryos at different stages of granuloma formation. Since adult zebrafish possess an adaptive immune system similar to mammals and zebrafish embryos rely solely on innate immunity, this overlap indicates a major contribution of the innate component of the immune system in the response to mycobacterial infection. Currently we are using a MyD88 knockout mutant to investigate the role of the innate immune system during early stages of mycobacterial granuloma formation. The use of the zebrafish embryo model will allow *in vivo* screening for anti-mycobacterial drugs at a high-throughput level. Another important strength of the zebrafish model is that the transparency of embryos allows detailed real-time imaging of infection processes *in vivo*. To facilitate these real-time analyses we are developing novel transgenic reporter lines for the macrophage lineage. A knock-down approach targeting the conserved transcription factor Pu.1 resulted in the identification of novel macrophage-specific markers, including a signal transducer pivotal for the migration of macrophages during the innate immune response of zebrafish embryos to bacterial infection.

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