The pathological manifestation of tuberculosis is very typical in terms of the presence of granulomas, or cellular aggregates, that form around infection foci. Besides the host-protective role of containment of infection, granulomas have a host-detrimental role, as they provide a niche for bacterial persistence, contribute to the sequestration of bacteria from drugs and promote bacilli to adopt a persister state [1-3]. In approximately 90% of the individuals infected with *Mycobacterium tuberculosis*, a dynamic balance between host and pathogen maintains the disease in a subclinical stage, where bacilli reside in a latent state within granulomas. However, the bacilli can remain in the host for a lifetime and in roughly 10% of the cases reactivation and initiation of clinical disease occurs at some point in life [4]. Although this proportion of reactivation might seem low, 10% of the estimated 2 billion infected individuals represents a gigantic reservoir of renascent active bacilli that sustains disease and transmission [5]. Eradication of *M. tuberculosis* will only become realistic when a strategy is found to prevent granuloma formation or to kill bacilli within granulomas. To reach this goal, it is crucial to understand the mechanisms involved in the granuloma response. In this thesis, the *Mycobacterium marinum* zebrafish embryo model was used to investigate the effect of mycobacterial genes on the initial stages of granuloma formation. This led to the identification of mycobacterial factors that are required for the initiation of the granuloma response. This knowledge might be instrumental to the success of new therapeutic strategies directed against tuberculosis.