Restoration of pattern recognition receptor costimulation to treat chromoblastomycosis, a chronic fungal infection of the skin.

Chromoblastomycosis is a chronic skin infection caused by the fungus Fonsecaea pedrosoi. Exploring the reasons underlying the chronic nature of F. pedrosoi infection in a murine model of chromoblastomycosis, we find that chronicity develops due to a lack of pattern recognition receptor (PRR) costimulation. F. pedrosoi was recognized primarily by C-type lectin receptors (CLRs), but not by Toll-like receptors (TLRs), which resulted in the defective induction of proinflammatory cytokines. Inflammatory responses to F. pedrosoi could be reinstated by TLR costimulation, but also required the CLR Mincle and signaling via the Syk/CARD9 pathway. Importantly, exogenously administering TLR ligands helped clear F. pedrosoi infection in vivo. These results demonstrate how a failure in innate recognition can result in chronic infection, highlight the importance of coordinated PRR signaling, and provide proof of the principle that exogenously applied PRR agonists can be used therapeutically.