TLR4 IS ESSENTIAL FOR *PSEUDALLESCHERIA BOYDII*-INDUCED ACTIVATION OF MURINE MACROPHAGES

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Pseudallescheria boydii is an emerging opportunistic filamentous fungus that causes localized and disseminated infections in both immunocompetent and immunocompromised patients. We demonstrated the involvement of an α-(1$\rightarrow$4) glucan from the fungal cell wall in the recognizing of the fungus by the immune system (1). In this study, production of cytokines by peritoneal macrophages of mice deficient in TLR-associated adaptor protein MyD88, CD14, TLR2 and TLR4, were analyzed in order to investigate the contribution of TLRs and CD14 to host cells interaction with conidial and mycelial forms of *P.boydii*. *P. boydii* conidia were able to stimulate release of TNF-a, IL-6 and IL-10 by macrophages. TNF-a was released in response to conidial forms of *P. boydii*, but not in response to the hyphae. MyD88 -/- macrophages were impaired in the ability to release TNF-a in response to *P. boydii* conidia. Cellular activation induced by *P. boydii* conidia required TLR4 and CD14 signaling, but not TLR2. Dendritic cell maturation induced by *P. boydii* conidia was dependent of TLR4 as observed by reduced TNF-a release. *In vivo* experiments comparing wild-type and TLR4 deficient mice infected with conidia showed a decreasing in the neutrophil recruitment. Altogether these results imply that TLR4 recognizes *P. boydii* conidia and that TLR4 mediated signaling is required to an optimal immune response against *P. boydii*.

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1- Bittencourt V.C. *et al*. 2006. J. Biol. Chem. (32):22614-23