



Microbes and Infection 17 (2015) 285–294



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Original article

## Dok proteins are recruited to the phagosome and degraded in a GP63-dependent manner during *Leishmania major* infection

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Received 26 August 2014; accepted 19 December 2014

Available online 30 December 2014

### Abstract

Three adaptor molecules of the Dok family, Dok-1, Dok-2 and Dok-3 are expressed in macrophages and are involved in the negative regulation of signaling in response to lipopolysaccharide and various cytokines and growth factors. We investigated the role and the fate of these proteins following infection with *Leishmania major* promastigotes in macrophages. The protozoan parasite *L. major* causes cutaneous leishmaniasis and is known for its capacity to alter host-cell signaling and function. *Dok-1/Dok-2*<sup>-/-</sup> bone marrow-derived macrophages displayed normal uptake of *L. major* promastigotes. Following *Leishmania* infection, Dok-1 was barely detectable by confocal microscopy. By contrast, phagocytosis of latex beads or zymosan led to the recruitment of Dok-1 to phagosomes. In the absence of the *Leishmania* pathogenesis-associated metalloprotease GP63, Dok-1 was also, partially, recruited to phagosomes containing *L. major* promastigotes. Further biochemical analyses revealed that similar to Dok-1, Dok-2 and Dok-3 were targets of GP63. Moreover, we showed that upon infection with wild-type or  $\Delta gp63$  *L. major* promastigotes, production of nitric oxide and tumor necrosis factor by interferon- $\gamma$ -primed *Dok-1/Dok-2*<sup>-/-</sup> macrophages was reduced compared to WT macrophages. These results suggest that Dok proteins may be important regulators of macrophage responses to *Leishmania* infection.

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**Keywords:** Leishmania; Metalloprotease GP63; Dok proteins; Macrophage; Phagosome