UKE Paper of the Month Dezember 2017

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p38 ^{MAPK}/MK2-dependent phosphorylation controls cytotoxic RIPK1 signaling in inflammation and infection

Manoj B. Menon*, Julia Gropengießer*, Jessica Fischer, Lena Novikova, Anne Deuretzbacher, Juri Lafera, Hanna Schimmeck, Nicole Czymmeck, Natalia Ronkina, Alexey Kotlyarov, Martin Aepfelbacher, Matthias Gaestel, and Klaus Ruckdeschel

** These authors contributed equally to this work.*

ABSTRACT: Receptor-interacting protein kinase-1 (RIPK1), a master regulator of cell fate-decisions, was identified as a direct substrate of MAPKAP kinase-2 (MK2) by phosphoproteomic screens using LPS-treated macrophages and stress-stimulated embryonic fibroblasts. p38^{MAPK}/MK2 interact with RIPK1 in a cytoplasmic complex and MK2 phosphorylates mouse RIPK1 at S321/336 in response to pro-inflammatory stimuli, such as TNF, LPS and infection with the pathogen Yersinia enterocolitica. MK2 phosphorylation inhibits RIPK1 autophosphorylation, RIPK1 integration into cytoplasmic cytotoxic complexes, and suppresses RIPK1-dependent apoptosis and necroptosis. In Yersinia-infected macrophages RIPK1 phosphorylation by MK2 protects against infection-induced apoptosis, a process targeted by Yersinia outer protein P (YopP). YopP suppresses p38^{MAPK}/MK2 activation to increase Yersinia-driven apoptosis. Hence, MK2 phosphorylation of RIPK1 is a crucial checkpoint for cell fate in inflammation and infection that determines the outcome of bacteria-host cell interaction.

STATEMENT: *Bacterial pathogens have developed sophisticated mechanisms to modulate host immune responses in order to establish infection. By exploring the mechanisms of* Yersinia enterocolitica*-induced cell death induction we disclosed a so far unknown feedback signaling circuit that determines the fate of eukaryotic cells. We identified p38^{MAPK}/MK2-dependent phosphorylation of RIPK1 as central signaling checkpoint at the crossroads of infection, inflammation and cell death and deciphered the molecular mechanisms and consequences thereof in collaboration with colleagues of the Institute of Cell Biochemistry at the Medical School Hannover. Our work implies the crosstalk between MK2 and RIPK1 as master control loop of cell vitality in multiple stress conditions, thus impacting a broad spectrum of physiological and pathophysiological biological processes, including infection, development, organ injury and cancer. This gives an outstanding example on how the investigation of the virulence traits of pathogenic bacteria provides fundamental new insights into the regulation of host cell function and physiology.*

BACKGROUND: This work was performed at the Institute for Medical Microbiology, Virology and Hygiene in the group of Prof. Klaus Ruckdeschel in collaboration with the group of Prof. Matthias Gaestel at the Institute of Cell Biochemistry at the Medical School Hannover. It was part of the PhD theses of Julia Gropengießer and Lena Novikova. The research focus of our group lays in the investigation of the crosstalk between the virulence strategies of the enteropathogenic bacterium Yersinia and host innate immune responses to infection. The project was supported by grants from the Deutsche Forschungsgemeinschaft to KR (RU 788/3 and 788/6).