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Dual-specificity phosphatase 3 knockout female mice are resistant to LPS and to polymicrobial induced septic shock in TNF dependent manner. (P1222)

Souad Rahmouni,[1] Pratibha Singh,[1] Lien Dejager,[2] Singh Maneesh,[1] Mathieu Amand,[1] Lucia Musumeci,[1] Michel Moutschen,[1] Tomas Mustelin,[3] and Claude Libert[2]

[1]Immunology and Infectious Diseases, University of Liège, Liege, Belgium [2]Mouse Genetics in Inflammation, University of Ghent, VIB, Ghent, Belgium [3]Infectious and Inflammatory Disease Center, Sanford-Burnham Medical Research Institute, La Jolla, CA

We report the generation of dual-specificity phosphatase 3 (DUSP3) deficient mice. These mice develop normally and do not exhibit any spontaneous phenotype. However, VHR-/- females, but not males, are resistant to LPS- and to polymicrobial infection-induced septic shock. After LPS injection, while VHR-/- males and VHR+/+ mice of both genders, displayed an increased serum levels of TNF-α and IFNγ, the levels of these cytokines remained significantly low in the VHR-/- females. In vitro experiments using peritoneal macrophages showed the same results suggesting that the systemic cytokines profiles observed are macrophages-dependent. Adoptive transfer of VHR-/- females bone marrow to irradiated VHR+/+ female mice, but not to VHR-/- or VHR+/+ males, protected them from death after administration of LPS. Interestingly, VHR-/- females were sensitive to TNF-α- induced lethality. We also report that the decrease of TNF-α production observed in VHR-/- female's macrophages after LPS activation was associated with a decreased ERK1/2, but not MEK1/2, activation. Interestingly, pervanadate (PTP pan inhibitor) treatment prior to LPS activation restored ERK1/2 activation in the VHR-deficient macrophages, suggesting that VHR is targeting one of the ERK1/2 PTPs or DUSPs. These results, together with our observation that DUSP3 is the most highly expressed phosphatase in macrophages, suggest a key non-redundant role of VHR as positive regulator of TNF-α in innate immune response in females.