

Reactive oxygen species derived from mitochondrial *versus* cytoplasmic locations differentially affect the innate antiviral immune response

Regina Gonzalez-Dosal,¹ Stine R. Jensen,¹ Susie S. Mikkelsen,¹ Simon B. Rasmussen,¹ Johanna Rintahaka,² Hidenori Ichijo,³ Zhijian J. Chen,⁴ John J. Mieyal,⁵ Sampsa Matikainen,² Søren R. Paludan¹

¹ Department of Medical Microbiology and Immunology, Aarhus University, Denmark

² Unit of Excellence for Immunotoxicology, Finnish Institute of Occupational Health, Helsinki, Finland

³ Center of Excellence Program, Japan Science and Technology Corporation, The University of Tokyo, Japan

⁴ Department of Molecular Biology, University of Texas Southwestern Medical Center, Dallas, Texas, USA

⁵ Department of Pharmacology, Case Western Reserve University, School of Medicine, Cleveland, USA

The innate immune response constitutes the first line of defense against microbial infections. Pattern recognition receptors (PRR)s recognize non-self and abnormal self structures, but also interact closely with basic cellular activities such as autophagy and production of reactive oxygen species (ROS). Here we demonstrate that ROS profoundly affects the ability of PRRs to signal and to activate antiviral activity in vitro and in vivo. Importantly, the cellular source of ROS was a crucial determinant for the effect of ROS on the innate response, with mitochondria-derived ROS inhibiting innate immunity and general elevation of cellular ROS stimulating this response. Biochemical evidence suggested S-glutanylation of TRAF family proteins to be important for the stimulatory role of ROS on PRR signaling. We propose that the subcellular source of ROS determines the effect of oxygen metabolism by-products on innate immune responses through PRRs.