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Role of the hepcidin-ferroportin axis in controlling the iron content of the cytosol and *Salmonella*-containing vacuoles in infected macrophages

Iron plays a dual-role in bacterial infection: First, it is a critical micronutrient required for the proliferation of infecting bacteria and second, it acts as a cofactor in the generation of bactericidal free radicals. Macrophages provide a major source of serum iron by releasing cytoplasmic iron via the membrane bound iron export protein, Ferroportin (FPN), degradation of which is triggered by hepcidin produced by hepatocytes upon bacterial infection. *Salmonella typhimurium* is an intracellular pathogen capable of invading macrophages and proliferating in the membranous *Salmonella*-Containing Vacuole (SCV). In this study, we first demonstrate that FPN is localized on the SCV and plays a role in iron transport into the SCV. To measure iron content in the SCV, a biosensor was constructed by fusing the iron responsive iroB promoter of *Salmonella* to a mutant GFP with a short half-life (gfpOVA). Using this construct, we estimated the iron levels in macrophages in animals as well as in in vitro cultured macrophages in the presence and absence of hepcidin. In contrast to the generally accepted opinion, the iron level in the SCV in the presence of the iron transporter (FPN) was higher than in its absence (+hepcidin). In general, host defense against pathogens relies on the generation of Reactive Oxygen Species (ROS) in phagocytic cells, especially during the early stage of infection. Thus, we examined for the generation of bactericidal ROS in the SCV using another biosensor composed of the ROS-responsive katG promoter of *Salmonella* fused to gfpOVA. To our surprise, ROS generation in the SCV was higher in the presence of FPN than in its absence. The relatively high level of iron in the SCV increased the generation of bactericidal ROS, which in turn decreased the number of intra-macrophage *Salmonella* and extended infected animal survival. Thus, this study reveals the mechanism via which a block in the hepcidin-FPN circuit controls intra-macrophage *Salmonella* infection.

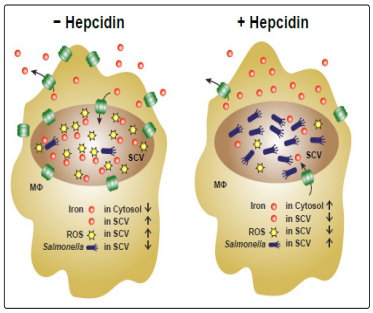

Figure-1: *Graphic summary. Iron level in SCV is determined by presence or absence of ferroportin. The iron level determines ROS generation in the SCV.*

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Biography

Hyon E Choy is a Professor in Microbiology at Chonnam National University Medical School. He has completed his graduation from UC Davis with PhD in Microbiology. Currently, he is engaged two major tracks of research: Bacterial cancer therapy and host response to Salmonella infection.

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