Small Things Make A Big Difference: Small Proteins Regulate *Salmonella* Virulence

**Abstract**

All cells require Mg\(^{2+}\) to replicate and proliferate. The macrophage protein Slc11a1 is proposed to protect mice from invading microbes by causing Mg\(^{2+}\) starvation in host tissues. However, the Mg\(^{2+}\) transporter MgtB enables the facultative intracellular pathogen *Salmonella enterica* serovar Typhimurium to cause disease in mice harboring a functional Slc11a1 protein. Here, we report that, unexpectedly, the *Salmonella* small protein MgtR promotes MgtB degradation by the protease FtsH, which raises the question: how does *Salmonella* preserve MgtB to promote survival inside macrophages? We establish that the novel *Salmonella* small protein MgtU prevents MgtB proteolysis, even when MgtR is absent. Like MgtB, MgtU is necessary for survival in Slc11a1+/+ macrophages, resistance to oxidative stress, and growth under Mg\(^{2+}\) limitation conditions. The *Salmonella* Mg\(^{2+}\) transporter MgtA is not protected by MgtU despite sharing 50% amino acid identity with MgtB and being degraded in an MgtR- and FtsH-dependent manner. Surprisingly, the *mgtB*, *mgtR*, and *mgtU* genes are part of the same transcript, providing a singular example of a transcript specifying proteins that promote and hinder degradation of the same target.

Our findings demonstrate that small proteins can confer pathogen survival inside macrophages by altering the abundance of related transporters, thereby furthering homeostasis.

**Selected Publications**