Public Abstract
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Copper is an essential cofactor of enzymes involved in a variety of important metabolic processes includding ATP producting, iron transport, and antioxidant defense. The maintenance of copper homeostasis requires a balance of copper uptake and export as well as the appropriate partitioning of copper between the cytoplasm, mitochondria and secretory compartments. Although many of the proteins involved in copper homeostasis have been identified, it is unknown whether specific pathophysiological conditions lead to compensatory changes in the intracellular copper distribution. In this study, we identify changes in copper homeostasis in response to pro-inflammatory mediators. We also show a novel role for the copper-transporting ATPase, ATP7A, in the bactericidal activity of RAW264.7 macrophage cell. We also identify striking alterations in copper homeostasis in response to hypoxia in RAW264.7 macrophage cells. In response to hypoxia, we observe a change in the heirarchy of intracellular distribution favoring delivery of copper to ATP7A and to the secretory pathway, as evidenced by enhanced activity of the ferroxidase, ceruloplasmin, and by copper-dependent trafficking of ATP7A in hypoxic macrophages in vitro and in vivo. Our study underscores the potential for pathophysiological condititions to regulate adaptive responses involving altered copper distribution to cuproenzymes.