A lipocalin-2 (NGAL)-iron axis integrates innate immunity, microbiome and cardiometabolic disease.

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Abstract

Lipocalin-2 (Lcn2), a critical component of the innate immune response which binds siderophores and limits bacterial iron acquisition, can elicit spillover adverse proinflammatory effects. We have shown that holo-Lcn2 (Lcn2-siderophore-iron, 1:3:1) increases mitochondrial reactive oxygen species (ROS) generation and attenuates mitochondrial oxidative phosphorylation in adult rat primary cardiomyocytes in a manner blocked by the mitochondria-specific antioxidant SkQ1. We further demonstrate using siderophores 2,3-DHBA (2,3-dihydroxybenzoic acid) and 2,5-DHBA that increased ROS and reduction in oxidative phosphorylation are direct effects of the siderophore component of holo-Lcn2 and not due to iron or apo-Lcn2 alone. At high concentrations such as in iron overload, iron can directly impact mitochondrial function via stimulating ROS production and via inhibiting autophagy flux. The latter is characterized by accumulation of dysfunctional autolysosomes and loss of free lysosomes and leads to decreased insulin stimulated metabolism. This occurs via a mechanism of decreased Akt-mediated repression of tuberous sclerosis complex (TSC2) and Rheb-mediated mTORC1 activation on autolysosomes, thereby inhibiting autophagic lysosomal regeneration. Constitutive activation of mTORC1 or iron withdrawal replenishes lysosomal pools via increased mTORC1-UVRAG signaling, which restores insulin sensitivity. Preliminary data will be presented which indicate that in addition to direct effects on metabolic tissues, iron overload can reshape the microbiome and lead to metabolic dysfunction in the host.

Keywords

Lipocalin-2, iron, autophagy, insulin sensitivity, mitochondria, metabolism