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Novel insights into functional alterations of iron-recycling macrophages

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ABSTRACT

Iron deficiency is a global health burden with profound socio-medical impacts. Little is known about how functions of specialized cells are affected by low systemic iron levels, and how this contributes to the organism. Red pulp macrophages (RPMs) residing in the spleen are responsible for removing aged red blood cells from the bloodstream in the process called erythrophagocytosis. Following red blood cell lysis, RPMs release iron via the exporter ferroportin to replenish the pool of serum iron necessary for sustaining erythropoiesis. Iron efflux from RPMs is negatively controlled by the liver-derived hormone hepcidin according to body iron needs. It was largely unknown if the rates of red blood cell uptake and digestion are regulated by iron availability, and specifically if these processes may be affected by low body iron status. We uncovered that RPMs possess specialized mechanisms that enhance their capacity for red blood cell clearance under iron-deficient conditions, a phenomenon that likely contributes to the adaptation of the whole organism to limited iron supplies. We found that in a mildly anemic mouse model of nutritional iron deficiency, RPMs show enhanced erythrophagocytosis rate and increased potential for red blood cell degradation within lysosomes. Our data suggest that this energy-consuming 'adaptive program' is associated with a switch towards mitochondria-based metabolism, which is unique in comparison to other cell types. Interestingly, these responses were largely absent in peritoneal or liver macrophages, implying their high specificity to RPMs. Our further data suggest that a serum factor associated with systemic iron deficiency modulates RPMs' phagocytic capacity. We hypothesized that one of such signals could be provided by low levels of hepcidin. Confirming this hypothesis, we found that hepcidin mimetic reverts elevated erythrophagocytosis rate and increased mitochondrial activity of RPMs in iron-deficient mice. Taken together, in my talk I will present data from this ongoing project that aims to characterize new physiological responses to iron deficiency.