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Title: Dissecting the relationship between iron accumulation in aging and iron recycling capacity of splenic red pulp macrophages.

Summary

Iron is an essential metal for life due to its ability to exchange electrons with various biomolecules. In mammals, most of the iron is incorporated in heme, the prosthetic group of hemoglobin that binds oxygen in red blood cells. Red pulp macrophages (RPMs) are the main type of cells that ensure the internal iron pool circulation by phagocytosing aging red blood cells in a process called erythrophagocytosis, and then degrading them, releasing iron into the bloodstream for reuse in erythropoiesis. This highlights the importance of RPMs in maintaining blood homeostasis and iron recycling in the body. However, it is not known whether continuous exposure to high levels of iron can impair the ability of these cells to perform erythrophagocytosis and whether red blood cell clearance can be regulated by systemic or cellular levels of iron. Iron accumulation in the spleen occurs physiologically during early aging. Therefore, it has been hypothesized that increased exposure to iron may accelerate RPM aging and in turn affect systemic iron parameters and red blood cell homeostasis. Thus, the purpose of this study was to better understand the relationship between RPMs' iron recycling capabilities and iron accumulation in the spleen during aging.

To investigate the effect of aging on RPMs, we used female mice aged 10-11 months, which show elevated levels of iron in the spleen and liver and lower serum iron bioavailability compared to 2-month-old control mice. It was observed that a very significant accumulation of iron in older mice occurs in the RPMs, which is caused by a reduction in the protein level of the iron exporter ferroportin. Iron overload in RPMs was shown to cause increased oxidative stress, decreased lysosomal and mitochondrial activity, and most importantly, impaired erythrophagocytosis capacity. We also identified loss of RPMs during aging, which was attributed to proteotoxic stress and iron-dependent cell death resembling ferroptosis. These impairments lead to the retention of aging hemolytic erythrocytes in the spleen and the formation of non-degradable extracellular protein aggregates rich in heme and iron, likely derived from ferroptotic RPMs. Furthermore, it was discovered that dietary iron restriction alleviates iron accumulation, reduces oxidative stress, and improves mitochondrial and

lysosomal function, resulting in enhanced old red blood cells removal by RPMs. As a result, this diet improves the condition of red blood cells in the spleen, limiting their hemolysis, and reducing the formation of protein iron-rich aggregates. It further normalizes iron levels in the liver and spleen and increases serum iron bioavailability. Combining in vivo approaches with experiments on a newly established in vitro model of RPMs (induced-RPMs) showed that erythrophagocytosis capacity is chiefly suppressed by iron accumulation and reduced heme oxygenase-1 (HO1) activity, and to a lesser extent, by stress that arises in the endoplasmic reticulum.

In summary, this study identified RPM dysfunction as an early hallmark of aging. It also demonstrated that reducing dietary iron content improves iron turnover efficiency in the body.