General scientific summary

Exploring the role of Ferroportin-mediated Ca^{2+} influx in the functional rewiring of macrophages

Iron is critical for various cellular functions, but its excess can cause oxidative damage. Thus, the maintenance of iron balance is essential for the proper functioning of organisms. In mammals, the daily production of red blood cells in a process called erythropoiesis requires the highest demand for iron. It is required for the synthesis of large amounts of heme and the production of hemoglobin within the red blood cells. Aged red blood cells are removed by splenic red pulp macrophages (RPMs), which are responsible for iron recycling for new rounds of erythropoiesis in the marrow. Iron is released from RPMs through a protein called ferroportin, the only known iron exporter. A recent study found that ferroportin might be involved in allowing calcium (Ca^{2+}) to enter cells. Although Ca^{2+} serves as a widespread signaling molecule in cells, it is unknown whether Ca^{2+} flux through ferroportin may play important biological roles.

Iron deficiency is a prevalent condition worldwide, which has significant social and medical consequences. In our laboratory, we discovered that RPMs of mice fed an iron-deficient diet showed improved capacity to remove and degrade red blood cells and had better metabolic functions. We expect that this well-orchestrated response of RPMs to iron deficiency likely contributes to the ‘adaptation’ of the whole organism to limited iron supplies. In our research, we seek to understand the molecular mechanisms of this adaptation. We noticed that the ‘functional acceleration’ of RPMs in iron deficiency was accompanied by a rise in the expression of surface ferroportin on RPMs and an elevation in cellular Ca^{2+} levels. Hence, this project aims to study whether elevated ferroportin levels and ferroportin-driven Ca^{2+} influx is the signal for the increased capacity of macrophages to recycle iron from red blood cells. To achieve this, we will establish a novel cellular model using primary macrophages that are engineered to express high ferroportin levels and we will investigate how modification of Ca^{2+} flux via ferroportin modifies the potential roles of this transporter in controlling the iron recycling capacity. In sum, this project will provide valuable insights into how macrophages adapt their iron recycling abilities during iron deficiency.