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Does Granulocyte-Macrophage Colony-Stimulating Factor Downregulate Ferroportin Expression in Alveolar Macrophages?

Fach: Kinderheikunde
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Macrophages are located in almost all tissues. Within different microenvironments, macrophages adopt different phenotypes and functions. Alveolar macrophages (AM) are the macrophage subtype that is found in the pulmonary alveolus. There, they play an important role in the immune defense of the lung.

Iron is an important component of numerous cellular enzymes and proteins. Macrophages, localized in spleen and liver play a critical role in iron recycling and iron homeostasis. They export iron from recycled red blood cells via ferroportin (FPN), the only known cellular iron exporter. FPN expression is regulated at the transcriptional, post-transcriptional and post-translational level. Previous data from our group showed that AM express low levels of FPN, both at the mRNA and the protein level.

The aim of my project was to identify mechanisms that explain low FPN expression in AM. I identified CSF2 as a critical regulator of Fpn mRNA. Initially, I analyzed the expression of iron-related genes in AM. I confirmed that AM express low levels of FPN. In addition, I observed that the pro-inflammatory cytokines IL6 and TNFα were highly expressed in AM. Because AM can only be obtained in low numbers under steady-state condition, next I established a cellular model for AM by bone marrow-derived macrophages (BMDM) differentiating with CSF2. I showed that this cell model mimicked an AM-like phenotype and that FPN was downregulated in these cells at the mRNA and the protein level. Furthermore, BMDM differentiated with CSF2 also expressed high levels of IL6 and TNFα. By differentiating BMDM with a low concentration of CSF2, I observed that FPN expression was increased while at the same time the expression of pro-inflammatory cytokines was reduced, revealing a possible link between the expression of pro-inflammatory cytokines and FPN. Importantly, I was also able to show that the downregulation of FPN was independent of hepcidin and the TLR2/TLR6 signaling pathways. Taken together, my work provided insight into the regulation of FPN expression in AM and showed that the FPN downregulation may be a consequence of CSF2-mediated increased expression of pro-inflammatory cytokines.