The Role of Fe-S Cluster Biosynthesis in the Regulation of Fe-S Proteins, Fe-Metabolism, and Downstream Stress Responses in vivo

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Iron-sulfur (Fe-S) clusters are cell-essential cofactors present in roughly 60 proteins, including DNA polymerases, subunits of oxidative phosphorylation complexes, and iron-sensing proteins. Formed by NFS1 and other key assembly enzymes in the mitochondria, Fe-S clusters are directly linked to pathologies like mitochondrial disease, neurodegeneration, cancer, and anemia. Previous studies have found the reduction of Fe-S proteins upon Fe-S cluster inhibition in vitro, but no studies have explored these effects in-vivo or with different age and tissue groups yet—all of which are necessary to develop therapeutic strategies. I investigated the effects of NFS1 knockdown on various Fe-S proteins, iron homeostasis proteins, and downstream stress responses. Using tissues from a mouse model with NFS1 knockdown, I analyzed the abundance of Fe-S proteins and Fe-homeostasis proteins, and found that different proteins (specifically SDHB, CDKAL1, and POLD) were affected to different extents in-vivo compared with previous in vitro studies. Additionally, in tissues (specifically kidney tissues) from older mice, more Fe-S proteins were affected, presenting novel insights on age-related Fe-S metabolism. Furthermore, the iron starvation response and Nrf2 oxidative stress responses were activated, with varied responses depending on age and tissue type. Since Fe-S proteins are necessary for a variety of functions, these results indicate that many crucial cellular processes (eg. DNA repair, cellular respiration, iron regulation) were suppressed upon acute Fe-S cluster inhibition. Together, these findings demonstrate for the first time that Fe-S cluster metabolism varies with age groups and tissue type, providing unprecedented insights into cellular biology and numerous related pathologies.

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