Modulating Ferroptosis for Disease Prevention

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- **Ore 15.00**
- **Aula Magna, complesso Biotecnologie** (Via T. De Amicis 95, 80131 Napoli)

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Ferroptosis is a metabolic form of regulated cell death characterized by an iron-dependent oxidative destruction of cellular membranes and emerges as the underlying cause of several degenerative diseases, including neurodegeneration and tissue ischemia/reperfusion injury. Besides, ferroptosis may present a pharmacologically tractable vulnerability to eradicate difficult-to-treat cancers. Years before the term ferroptosis was coined in 2012, we had shown that the selenoenzyme glutathione peroxidase 4 (GPX4) is the guardian of ferroptosis due to its unique activity to directly scavenge lipid hydroperoxides in cellular membranes. Using genetic suppressor screens, we introduced the second mainstay in ferroptosis control, known as ferroptosis suppressor protein-1 (FSP1). The anti-ferroptotic role of FSP1 is based on the NAD(P)H dependent reduction of extra-mitochondrial coenzyme Q_{10}, thereby halting uncontrolled lipid peroxidation and ferroptosis. We further discovered that FSP1 drives a non-canonical vitamin K cycle that can efficiently protect against ferroptosis. Besides its role in ferroptosis, FSP1 constitutes the long sought-after, warfarin-resistant vitamin K reductase in the canonical vitamin K cycle, thus linking vitamin K biology and ferroptosis. We have further reported the first *in vivo* active FSP1 inhibitor, icFSP1, which induces subcellular relocalisation and phase separation of FSP1 prior to lipid peroxidation and cancer cell death. Ongoing studies in our laboratory are therefore geared towards understanding the *in vivo* relevance of these systems in the control of ferroptosis and their pharmacological tractability as the basis for developing new pharmacotherapies for ferroptosis-related diseases including neurodegeneration and cancer.

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