Genome-wide iron-induced ferroptosis screen uncovers PRDX6 as a novel selenoprotein synthesis factor

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Abstract

Ferroptosis is a form of non-apoptotic cell death induced by iron-dependent accumulation of lipid hydroperoxides. It has been extensively studied due to its involvement in various pathological conditions, such as cancer, neurodegenerative diseases, and ischaemia–reperfusion injury. Selenoprotein glutathione peroxidase 4 (GPX4) is a critical suppressor of ferroptosis that detoxifies toxic lipid hydroperoxides into non-toxic lipid alcohols via a catalytic selenocysteine (Sec) residue. Sec is the genetically encoded 21st amino acid, whose synthesis is essential for life. However, mechanisms underlying selenoprotein synthesis remain elusive.

In this study, we constructed a novel ferroptosis induction system, in which ferroptosis can be induced by the addition of iron alone to the cells to identify new regulators of ferroptosis. By using this system, we performed a genome-wide CRISPR screening and identified peroxiredoxin6 (PRDX6) as a novel selenoprotein synthesis factor. Loss of PRDX6 dec¬reases expression of selenoproteins and induces iron-induced ferroptosis via a reduction in GPX4. Mechanistically, PRDX6 increases the efficiency of intracellular selenium utilization by transferring selenium between selenoprotein synthesis factor as selenium carrier protein. Furthermore, we found that patients harboring cancers with high PRDX6 expression have a poor prognosis from database analysis. Therefore, our findings highlight previously unidentified selenium metabolic systems and provide new insights into iron toxicity, ferroptosis and cancer.