MYCN amplification is tightly associated with the poor prognosis of pediatric neuroblastoma (NB). The regulation of NB cell death by MYCN represents an important aspect, as it directly contributes to tumor progression and therapeutic resistance. However, the relationship between MYCN and cell death remains elusive. Ferroptosis is a newly identified cell death mode featured by lipid peroxide accumulation that can be attenuated by GPX4, yet whether and how MYCN regulates Ferroptosis are not fully understood.

Lu et al. reported MYCN-amplified NB cells are sensitive to GPX4-targeting Ferroptosis inducers. Mechanically, MYCN expression reprograms the cellular iron metabolism by upregulating the expression of TFRC, which encodes transferrin receptor 1 as a key iron transporter on the cell membrane. Further, the increased iron uptake promotes the accumulation of labile iron pool, leading to enhanced lipid peroxide production. Consistently, TFRC overexpression in NB cells also induces selective sensitivity to GPX4 inhibition and Ferroptosis. Moreover, they found that MYCN fails to alter the general lipid metabolism and the amount of cystine imported by System Xc(-) for glutathione synthesis, both of which contribute to Ferroptosis in alternative contexts. In conclusion, NB cells harboring MYCN amplification are prone to undergo Ferroptosis conferred by TFRC upregulation, suggesting that GPX4-targeting Ferroptosis inducers or TFRC agonists can be potential strategies in treating MYCN-amplified NB [1)].

1)
Lu Y, Yang Q, Su Y, Ji Y, Li G, Yang X, Xu L, Lu Z, Dong J, Wu Y, Bei JX, Pan C, Gu X, Li B. MYCN mediates TFRC-dependent Ferroptosis and reveals vulnerabilities in neuroblastoma. Cell Death Dis. 2021 May 19;12(6):511. doi: 10.1038/s41419-021-03790-w. PMID: 34011924.