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CISD3 inhibition drives cystine-deprivation induced ferroptosis

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Ferroptosis, a new form of programmed cell death, not only promotes the pathological process of various human diseases, but also regulates cancer progression. Current perspectives on the underlying mechanisms remain largely unknown. Herein, we report a member of the NEET protein family, CISD3, exerts a regulatory role in cancer progression and ferroptosis both in vivo and in vitro. Pan-cancer analysis from TCGA reveals that expression of CISD3 is generally elevated in various human cancers which are consequently associated with a higher hazard ratio and poorer overall survival. Moreover, knockdown of CISD3 significantly accelerates lipid peroxidation and accentuates free iron accumulation triggered by Xc^- inhibition or cystine-deprivation, thus causing ferroptotic cell death. Conversely, ectopic expression of the shRNA-resistant form of CISD3 (CISD3res) efficiently ameliorates the ferroptotic cell death. Mechanistically, CISD3 depletion presents a metabolic reprogramming toward glutaminolysis, which is required for the fuel of mitochondrial oxidative phosphorylation. Both the inhibitors of glutaminolysis and the ETC process were capable of blocking the lipid peroxidation and ferroptotic cell death in the shCISD3 cells. Besides, genetic and pharmacological activation of mitophagy can rescue the CISD3 knockdown-induced ferroptosis by eliminating the damaged mitochondria. Noteworthily, GPX4 acts downstream of CISD3 mediated ferroptosis, which fails to reverse the homeostasis of mitochondria. Collectively, the present work provides novel insights into the regulatory role of CISD3 in ferroptotic cell death and presents a potential target for advanced antitumor activity through ferroptosis.

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INTRODUCTION

Ferroptosis is a newly described programmed cell death, typically characterized by free iron overload and lethal phospholipid peroxide generation [1, 2]. Currently, studies have screened erastin, RSL3, sorafenib, artemisinin, and other molecules for their ability to induce tumorigenic ferroptosis [3–5], and identified SLC7A11/xCT, glutathione peroxidase 4 (GPX4), nuclear factor erythroid 2-related factor 2 (NRF2), ACSL4 and LPCAT3 enzymes as the ferroptosis regulatory proteins [6]. Although the primary pathway of ferroptosis has been established, the specific molecular mechanism underlying this regulatory network remains largely unknown.

Mitochondria, the core organelle for energy metabolism, plays a pivotal role in the regulation of fatty acid, amino acid, iron, and carbon metabolism [7]. Plenty of evidence demonstrated that diverse cellular metabolic pathways in mitochondrion could trigger ferroptosis [8]. For instance, Minghui Gao et al. illustrated that the TCA cycle and mitochondrial electron transport chain involved in cystine-deprivation induced ferroptosis but not GPX4 inhibition induced ferroptosis [9]. Elsewhere, Daiha Shin et al. demonstrated that dihydrolipoamide dehydrogenase increased α-KG level via glutaminolysis and activated cystine-deprivation ferroptosis [10]. The iron−sulfur cluster is a highly ancient and conservative cofactor that is mainly assembled in mitochondrion [11]. A recent study demonstrated that cancer cells depend on high levels of the ISC biosynthesis, and suppression of NFS1 robustly triggered ferroptosis in conjunction with cystine/glutamate antiporter inhibitor [12]. Our previous work also revealed the dysfunction of Frataxin, the leading cause of Friedreich's ataxia, acted as an essential regulator of ferroptosis through the induction of free iron overload and dysfunction of mitochondrial homeostasis [13]. Altogether, these observations strongly demonstrate that mitochondria play a central regulatory role in ferroptosis.

The highly conserved NEET family proteins are mainly located in mitochondria and play important role in human health and disease [14]. They are unique because the [2Fe−2S] cluster can be redox-activated by binding with the CDGSH motif [15, 16]. In humans, only three different genes are currently known to encode NEET proteins. The least studied is CISD3, also known as Miner2 or MiNT, which differs from the other two family members as it encodes a monomer containing two [2Fe−2S] CDGSH motifs. Current research suggests that CISD3 coordinates a complementary role in mitochondrial iron and ROS regulation within the

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