RESEARCH HIGHLIGHT

cGASing mitochondria to fend off ferroptosis

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Induction of ferroptosis, a form of non-apoptotic cell death caused by phospholipid peroxidation and consequent plasma membrane rupture, has been explored as a potential strategy for cancer therapy. In a recent paper published in *Cell Research*, Qiu et al. report that promoting mitochondria-associated cGAS (cyclic GMP-AMP synthase) signal can block ferroptosis to support cancer progression independently of downstream activation of signaling adapter STING (stimulator of interferon genes).

Ferroptosis is a form of regulated necrosis driven by iron-dependent phospholipid peroxidation that results in plasma membrane damage and eventual cell death.[1,2] The crucial role of mitochondria in promoting ferroptosis has been demonstrated.[3] Perhaps to specifically mitigate such pro-ferroptosis function of mitochondria, a portion of glutathione peroxidase 4 (GPX4) is localized inside of mitochondria,[4] and mitochondrial protein dihydroorotate dehydrogenase (DHODH) converts CoQ to $CoQH_2$, which has free radical trapping activity.[5] Both these enzymes suppress ferroptosis by detoxifying lipid peroxidation.

In a recent paper published in *Cell Research*, Qiu et al.[6] have discovered yet another mitochondrial factor that may function to inhibit ferroptosis. The authors made a surprising finding that mitochondria-localized cGAS promotes cancer progression by suppressing ferroptosis in a manner dependent on mitochondrial fission regulator dynamin-related protein 1 (DRP1) but independent of the canonical cGAS-STING pathway. These findings add a new dimension to our understanding of the mechanistic basis of cGAS function in cancer.

Using hepatocellular carcinoma (HCC) as a model, Qiu et al. first searched previously unrecognized mitochondrial proteins by proteomic analysis. They found that cGAS is one of the top candidates. This was unexpected, as cGAS has so far been characterized as a cytosolic DNA sensor that activates innate immune responses through the production of the second messenger cGAMP and the adaptor protein STING.[7] They further found that cGAS contains a mitochondrial targeting sequence (MTS) and is translocated to the outer mitochondrial membrane (OMM), a process mediated by its MTS and the major preprotein import receptor TOM70.[8]

Importantly, the authors observed that cGAS depletion induced cell death in HCC cells, and the induced cell death could be prevented by ectopic expression of wild-type cGAS or cGAS localized strictly on the OMM (MTS-cGAS), but not of cGAS defective in mitochondrial localization. Death induced by cGAS depletion is ferroptosis, as ferroptosis inhibitors but not inhibitors of apoptosis, necroptosis, or autophagy, restored cell viability upon cGAS depletion. Consistently, MTS-cGAS overexpression restored lipid peroxidation and mitochondrial ROS levels in cGAS-deficient cells. These data revealed an unexpected association between mitochondrial cGAS and ferroptosis in HCC.

The authors next sought to identify the mechanism by which mitochondrial cGAS prevents ferroptosis in HCC. As STING is a downstream target of cGAS for DNA sensing,[7] they first asked whether the cGAS-STING pathway is involved in the regulation of ferroptosis by mitochondrial cGAS. Curiously, STING is not required for the ferroptosis-suppressing activity of mitochondrial cGAS. Instead, they found that the mitochondrial fission protein, DRP1, mediates this novel activity of mitochondrial cGAS. DRP1 oligomerizes on the OMM for mitochondrial fission.[9] They identified DRP1 as an interacting partner of cGAS in mitochondria and found that loss of cGAS suppressed DRP1 oligomerization on the OMM, a defect that can be rescued by overexpression of MTS-cGAS. Therefore, they hypothesize that mitochondrial cGAS facilitates DRP1 oligomerization on the OMM to suppress lipid peroxidation and ferroptosis. Consistent with this hypothesis, inhibition of DRP1 led to a significantly increased mitochondrial ROS, lipid peroxidation, and ferroptosis.

Qiu et al. went on to study the role of mitochondrial cGAS in cancer by using mouse xenograft models for HCC. They found that genetic depletion of cGAS attenuated tumor growth. Such suppressed tumor growth can be rescued by MTS-cGAS overexpression or pharmacological inhibition of ferroptosis. Further, DRP1 inhibition ablated the effect of MTS-cGAS overexpression on tumor growth. These findings suggest the potential of cGAS as a novel cancer therapeutic target whose inhibition may trigger ferroptosis in cancer cells.

Together, the findings by Qiu et al. unveil a novel and unexpected function of mitochondrial cGAS in ferroptosis regulation. This study raises a series of questions for future investigation. Particularly, is there any signaling event regulating the translocation of cGAS to the OMM and more broadly, the distribution of cGAS in distinctive cellular compartments? As mitochondrial DNA stress has been reported previously to trigger autophagy-dependent ferroptosis by the cGAS-STING pathway,[10] how to reconcile that previous report with this current finding, and is the ferroptosis-suppressing activity of mitochondrial cGAS also dependent on cytosolic DNA? In the downstream, how exactly does mitochondrial cGAS regulate DRP1 oligomerization, and how does DRP1 oligomerization/mitochondrial fission prevent ferroptosis? Answering these questions are important for ferroptosis biology and will also provide further insights into the cellular function of cGAS.

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COMPETING INTERESTS

X.J. is an inventor of patents relevant to cell death and autophagy. He is also a consultant and equity holder of Exarta Therapeutics and Lime Therapeutics.

ADDITIONAL INFORMATION

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