Mitoneet mediates TNFα-induced necroptosis promoted by exposure to fructose and ethanol

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Cellometer / Applications: Cellometer Vision... Reactive oxygen species (ROS)

Abstract

Fructose and ethanol are metabolized principally in the liver and are both known to contribute to the development of hepatic steatosis that can progress to hepatic steatohepatitis. The present study identifies a synergistic interaction between fructose and ethanol in promoting hepatocyte sensitivity to TNFα-induced necroptosis. Concurrent exposure to fructose and ethanol induces the overexpression of the CDGSH iron-sulfur domain-containing protein 1 (CISD1 or mitoneet), which is localized to the outer mitochondrial membrane. The increased expression of mitoneet primes the hepatocyte for TNFα-induced cytotoxicity. Treatment with TNFα induces the translocation of a Stat3-Grim-19 complex to the mitochondria, which binds to mitoneet and promotes the rapid release of its 2Fe-2S cluster, causing an accumulation of mitochondrial iron. The dramatic increase of mitochondrial iron provokes a surge in formation of reactive oxygen species, resulting in mitochondrial injury and cell death. Additionally, mitoneet is constitutively expressed at high levels in L929 fibrosarcoma cells and is required for L929 cells to undergo TNFα-induced necroptosis in the presence of caspase inhibition, indicating the importance of mitoneet to the necroptotic form of cell death.