Hepatic TRPC3: An emerging regulator of alcohol-associated liver disease

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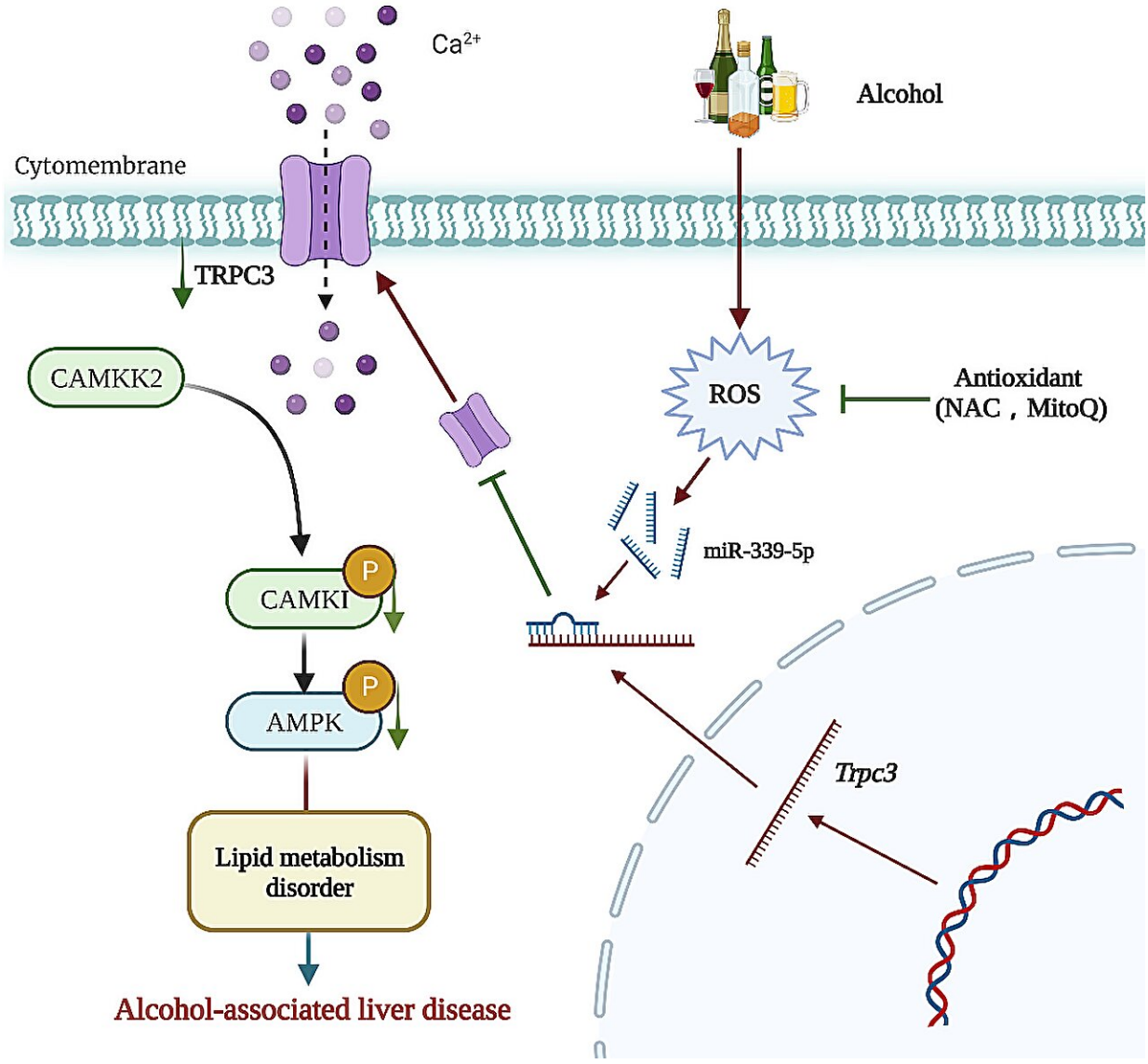

The proposed model of hepatic TRPC3-regulated ALD. Credit: Qinchao Ding,

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Excessive alcohol intake is strongly associated with alcohol-associated liver disease (ALD) which accounts for 25% and 30% of deaths from cirrhosis and hepatocellular carcinoma. Impairment of Ca^{2+} influx and Ca^{2+}-mediated signaling in ALD suggests that Ca^{2+} channels are important in ALD pathological progression.

TRPC (transient receptor potential cation channel protein C) is an evolutionarily conserved non-selective cation channel protein primarily located in the cell membrane with six transmembrane segments. So far, four TRPC subfamilies have been identified, categorized into TRPC1, TRPC2, TRPC4/5, and TRPC3/6/7. Among them, TRPC3 is the most well-studied member of TRPC, and it is commonly expressed in both excitable and nonexcitable cells, including hepatocytes.

TRPC3 maintains cell survival by controlling Ca^{2+} inflow, prevents apoptosis induced by various stimuli, and promotes immune responses. However, the biological role of hepatic TRPC3 in ALD pathology remains unclear.

An article published in *Life Metabolism* titled "Hepatic TRPC3 loss contributes to chronic alcohol consumption-induced hepatic steatosis and liver injury in mice" reports on the role of TRPC3 in ALD by regulating the Ca^{2+}/calmodulin-dependent protein kinase kinase 2 (CAMKK2) signaling pathway.

First, the investigators found that TRPC3 was significantly reduced in the liver tissues of ALD individuals and ALD mice established by

feeding them with a Lieber-De Carli ethanol-containing liquid diet. Liver-specific knockdown of TRPC3 in mice significantly aggravated alcohol-induced hepatic injury, lipid deposition, inflammation, and fibrosis.

On the contrary, liver-specific overexpression of TRPC3 remarkably restored chronic alcohol intake-induced hepatic injury, lipid deposition, inflammation, and fibrotic lesions.

It has been known that chronic alcohol consumption inhibits hepatic AMP-activated protein kinase (AMPK), a core regulator of energy metabolism. However, the link between alcohol exposure and AMPK inhibition in the liver remains unclear.

In the study, the authors found that liver-specific knockdown of TRPC3 enhanced alcohol's inhibitory effect on AMPK through a mechanism of Ca^{2+}-dependent CaMKK2 activation. Bioinformatics analysis and experimental evidence showed that miR-339-5p is an upstream regulator involved in TRPC3 reduction in ALD.

In addition, antioxidant supplementation attenuated alcohol-induced reduction of TRPC3 in mouse liver, suggesting that oxidative stress is a key factor in the regulation of miR-339-5p and TRPC3. Taken together, oxidative stress-induced miR-339-5p/TRPC3/Ca^{2+}/CaMKK2-dependent AMPK inactivation is the key pathological pathway in ALD pathogenesis, providing a potential translational application of TRPC3 as a therapeutic target in ALD.

More information: Qinchao Ding et al, Hepatic TRPC3 loss contributes to chronic alcohol consumption-induced hepatic steatosis and liver injury in mice, *Life Metabolism* (2023). DOI: 10.1093/lifemeta/load050

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