Activation of Novel Autophagy Pathways to Protect Hepatocyte Injury by Chloroquine

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Chloroquine (CQ), a toxic agent, is an anti-malarial drug used to treat rheumatoid arthritis and systemic lupus erythematosus. Recently, the former Trump administration controversially promoted a CQ analog, Hydroxychloroquine (HCQ) to treat COVID-19 infections, despite little medical evidence to suggest its efficacy. Both CQ and HCQ are toxic agents, and high doses of either drug can result in severe side effects, including death. CQ is primarily metabolized by the liver. The damage CQ can cause to hepatocytes and how they respond to CQ injury are poorly researched. In this study, I found that CQ can damage crucial cell organelles including lysosomes and mitochondria. Findings also show that hepatocytes initiate a signal pathway for self-protection. This signaling pathway begins with the ubiquitination and sequestration of CQ-damaged lysosomes through a process called lysophagy, a subtype of autophagy. Next, CQ causes mitochondrial injury. Injured mitochondria generate and shed mitochondrial-derived vesicles (MDVs), which are engulfed by a novel type of autophagy, a process termed MDVphagy. Lastly, CQ-damaged mitochondria are quarantined by autophagy, a process called mitophagy. Further investigation reveals that the mTORC1-ULK1 independent signaling pathway is activated in order to drive the autophagy response against CQ injury. These findings uncover a previously unidentified role of the autophagy machinery in the detoxification of CQ-induced hepatocyte injury.

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