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**Identification of hepatic off-targets of anti-HIV protease inhibitors involved in organelle stress response and liver injury**

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Organelle stress and Liver injuries often occur in HIV infected patients who are under anti-HIV therapies, yet few molecular off-targets of anti-HIV drugs have been identified in the liver. We found through total RNA sequencing that the transcription of a host protease RCE1 was affected in HepG2 cells treated with anti-HIV protease inhibitors, ritonavir and lopinavir. Levels of RCE1 protein were inhibited in HepG2 and primary mouse hepatocytes and in the liver of mice treated with the anti-HIV drugs, which were accompanied with inhibition of two potential substrates of RCE1, small GTP binding protein Rab13 and Rab18 that are with a common CAAX motif and known to regulate the ER-Golgi traffic or lipogenesis. Neither Rce1 transcription nor RCE1 protein level was inhibited by the organelle stress-inducing agent, Brefeldin A that is known to interfere with the ER-Golgi traffic causing Golgi stress. Knocking down Rce1 with RNA interference increased ritonavir and lopinavir-induced cell death as well as expression of Golgi stress response markers, TFE3, HSP47 and GCP60 in both primary mouse hepatocytes and mouse liver, and deteriorated alcohol-induced ALT and fatty liver injury in mice. In addition, overexpressing Rab13 or Rab18 in primary human hepatocytes reduced partially the anti-HIV drugs and alcohol-induced Golgi fragmentation, Golgi stress response and cell death injury. Thus, we identified a novel mechanism linking a hepatic protease and its substrates, small GTP binding proteins, to the anti-HIV protease inhibitors-induced Golgi dysfunction, organelle stress response and fatty liver injury (supported by NIDA/NIH grant No. DA042632).