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New insights in mechanisms involved in drug-induced intra-hepatic cholestasis using HepaRG cells

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Intra-hepatic cholestasis is a frequent manifestation of drug-induced liver injury in humans and its prediction represents a major challenge. We aimed to investigate mechanisms involved in drug-induced cholestasis using human HepaRG cells. We found that bile canaliculi (BC) of untreated HepaRG hepatocytes underwent spontaneous contractions, which are essential for bile acid (BA) efflux and require alternations in myosin light chain phosphorylation/dephosphorylation. Short-term treatment with prototypical cholestatic compounds was found to result in alterations of BC dynamics typified by either constriction or dilation of BC. These morphological alterations were associated with disruption of the ROCK/MLCK/myosin pathway either directly or by targeting different levels of the ROCK/MLCK axis and its associated MAP-kinases. HepaRG cells produced normal conjugated BAs. Cholestatic drugs showed variable potency to cause BAs accumulation: different total BAs content and BAs profiles in either supernatants or cell layers were evidenced. Repeated treatments as well as co-treatments with pro-inflammatory cytokines, IL1 and IL6, aggravate cholestatic features induced by certain cholestatic drugs. Together, these results provide the first demonstration that cholestatic drugs alter BC structures by targeting the ROCK/MLCK pathway and cause BAs accumulation concomitantly to occurrence of various other cholestatic features, in an *in vitro* human liver cell model, thereby mimicking drug-induced in vivo liver cholestasis. These studies highlight new insights into mechanisms underlying bile flow failure and can be used to identify new predictive biomarkers and therapeutics of drug-induced cholestasis

Biography

Ahmad Sharanek has obtained a Master's degree in Cancerology from the Lebanese University in Beirut. He traveled to France to prepare a PhD on mechanisms of drug-induced liver injuries under the supervision of Professor André Guillouzo. He obtained his PhD in June 2015 from Rennes 1 University and is currently pursuing Post-doctoral studies at Rennes 1 University. He has published 6 papers in reputed journals.

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