Putative role for actin organization status in the dynamic localization of canalicular carriers under oxidative stress conditions

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To the Editor: we have read with interest the recent paper by Sekine et al. (8), showing that redox status is a key determinant of dynamic localization of the canalicular transporter Mrp2 in hepatocytes. Although we regard this work as novel and relevant, we believe their results can be reinterpreted when better contextualized within the present body of knowledge on the field.

Oxidative stress in general and particularly the oxidizing agent used by Sekine et al., tert-butylhydroperoxide (t-BHP), induce profound changes in actin spatial organization (1, 4). As acknowledged by Sekine et al. in their article (see their Ref. 27), actin disorganization induces internalization of Mrp2, as shown by Rost et al. (7), using phalloidin as an actin-disorganizing agent. Therefore, a role for the impairment of actin integrity in Mrp2 retrieval induced by t-BHP should have been considered. Indeed, our group showed recently in isolated rat hepatocyte couplets (5) that t-BHP, at the dose used in Sekine’s work (100 μM), triggers endocytic internalization of the bile salt export pump (Bsep), another canalicular transporter that colocalizes with Mrp2 in subcellular vesicles when retrieved under cholestatic conditions (3, 9). In this work, our laboratory also showed that actin disorganization occurs by activation of Ca2+ (“classical”)–dependent PKC (cPKC) and that this phenomenon is causally linked to carrier retrieval. Interestingly, and in total agreement with our previous results (4), Sekine et al. demonstrated activation of cPKC after t-BHP exposure in their experimental settings.

Dynamic changes in actin spatial organization and the activation status of cPKC may explain not only the endocytic internalization process but also the reversal of this phenomenon when redox status is normalized, a phenomenon nicely shown by Sekine et al. in their article. Our laboratory demonstrated recently (4) that administration of cPKC inhibitors after disorganization of actin has been induced by t-BHP exposure leads to both a very rapid actin cytoskeleton remodeling (4) and the recovery of the isolated rat hepatocyte couplet (IRHC) capability to secrete a fluorescent Bsep substrate, indicating reversal of Bsep mislocalization (5). Since Sekine et al. showed a similar switch off of cPKC upon normalization of the redox status to that induced by cPKC inhibitors, a similar reorganization of actin spatial distribution and the further canalicular transporter reinsertion may have occurred when oxidative unbalance was corrected. Furthermore, Sekine’s finding that PKA is involved in the reversal process may be in line with our results that the PKA activator dibutyryl-cAMP accelerates the spontaneous actin reorganization in IRHC when cultured after isolation (6).

Another relevant finding of Sekine et al. is the differential involvement of microtubules in the endocytical internalization of Mrp2 and its reversibility by exocytic reinsertion, the latter phenomenon being the only one that depends on microtubules. A similar differential requirement for microtubule integrity has been described by our group in a paper published in this journal in 2005 under another cholestatic condition (estradiol 17β-d-glucuronide-induced cholestasis) (2), suggesting that this phenomenon can be a general feature of the cholestatic injury. In light of our interpretation of Sekine’s results, a role for microtubules in actin reorganization after recovery of redox balance should be considered. Interestingly, a role for the microtubular network in actin remodeling is just emerging (1) and does deserve experimental confirmation in the reversion of the cholestatic injury induced by oxidative stress.

References