Microcystins in the blood of mothers of biliary atresia patients

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Abstract

Biliary atresia (BA) is a rare but devastating cholangiopathy that affects neonates. It appears to result from an environmental insult (toxic or viral) sustained in utero that spares the mother. Previous work from our group identified biliatresone, a strongly electrophilic plant toxin with an a-methylene ketone moiety, as the etiology of BA in Australian livestock, but it is unlikely to be the cause of BA in humans. We therefore carried out a screen of other strong electrophiles with a-methylene ketone groups, including common toxins of the microcystin family of blue-green algae, which are responsible for toxic algal blooms worldwide. One microcystin, MCRR, but none of the other 8 that we tested, had biliary toxicity. Remarkably, the toxicity was specific for the cells and bile duct explants of neonatal but not adult rodents, making it a plausible cause of BA in humans. We therefore propose a pilot case-control study to determine whether mothers of BA patients have higher serum levels of MCRR than mothers of neonates with other liver diseases. We will use serum/plasma from a well-curated existing repository, with the cases:controls at 4-5:1, and will measure with high sensitivity the levels of MCRR and the most common (but non-biliary toxic) microcystin MCLR using LC-MS through the Translational Biomarker Core. Detectable MCRR in the blood of any of the BA mothers is likely to be significant, although we will formally compare average levels of case vs. control mothers. If there is a difference, it would have public health implications for management of algal blooms and water supply testing and would lead to an R01 application for funding to carry out a larger study.