ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease in the western culture and worldwide. Its morbidity has been raising and it has become a burden on the public health. NAFLD is associated with other metabolic diseases such as Diabetic Mellitus and hypertension. NAFLD is a wide spectrum of symptoms, from an accumulation of fat in the liver (cirrhosis) to production of scar tissue (Fibrosis). The liver along with other distal organs such as the kidney and cardiovascular system can be damaged as ectopic manifestations of NAFLD. Contamination of drinking water with Cyanobacterium toxin (Microcystin) and water disinfection byproduct like trihalomethane (like Bromodichloromethane) play a critical role in progressing NAFLD. Here, I have examined the molecular mechanism of BDCM and microcystin in induce glomerular toxicity and renal inflammation when NAFLD was present. I found that BDCM can induce glomerular inflammation when NAFLD is present. BDCM caused renal immunotoxicity and impacted glomerular function through high mobility group box-1 (HMGB1) and mesangial cell activation. Mesangial cell activation can be caused by increasing leptin level after BDCM exposure. High leptin level upregulated mesangial cell NOX2 and increased miR-21 expression which in turn released TGF-b and caused tubular inflammation. In-vitro, mesangial cells proliferated and increased alpha smooth muscle actin (αSMA) expression after they were treated with leptin. Leptin caused mesangial cell NOX2 subunits Gp91 and P47 phox to colocalize via JAK/ STAT pathway dependence which in turn increased peroxynitrite releasing, miR21 activation,
and TGFb expression. Furthermore, mesangial cells NOX2 activation by leptin exposure attenuated after Apocynin treatment. Comparing with tubular cells kept on cell culture media only, tubular cells incubated with leptin- treated mesangial cell supernatant showed increases in inflammatory marker expressions like IL-1β, TNF-α, and interferon-γ. Microcystin is another example of a toxin that could increase the severity of glomerulonephritis caused by NAFLD. Here I found that microcystin can accelerate NAFLD toxicity in the kidney. High expression of αSMA found in NAFLD mice treated with microcystin compared with NAFLD mice alone and mice treated with microcystin but did not have NAFLD. Renal tissue surrounding the glomeruli had increased NOX2 activation as shown by increased colocalization of NOX2 subunits, GP91 and P47 Phox. Mice lacking miR21 gene and mesangial cell line treated with miR21 inhibitor shown significant decreased in mesangial cell activations and renal immunotoxicity. Thus, microcystin exposure increased the severity of NAFLD caused glomerulonephritis via the NOX2- miR21 axis.