

CROMOLYN SODIUM AMELIORATES MAST CELL(MC)-MEDIATED HEPATIC DAMAGE IN A MURINE MODEL OF NON-ALCOHOLIC STEATOHEPATITIS (NASH)

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BACKGROUND: Hepatic inflammation and mast cell (MC) infiltration are major hallmarks of non-alcoholic steatohepatitis (NASH). We have previously shown that MC infiltration occurs in NASH liver as a response to senescence associated secretory phenotype factors (SASPs) from cholangiocytes. These MCs contribute to i) inflammation ii) senescence and ii) micro-vesicular steatosis in hepatocytes. However, the effect of MC stabilization on NASH phenotypes and senescent cholangiocytes have not been addressed. Moreover, cromolyn sodium, a MC stabilizer treatment in cholangiopathies have been effective in ameliorating the hepatic damages in a murine model of cholestasis. **AIM:** To evaluate the effect of MC stabilization as a therapeutic approach to ameliorate NASH disease phenotypes in mice fed methionine and choline deficient (MCD) diet. **METHODS:** Male C57BL/6J (wild type, WT) mice, 4 weeks of age, were fed MCD diet or control diet (CD) for 5 weeks. To stabilize MCs, a subset of CD and MCD diet fed mice were given cromolyn sodium (crom, 24mg/kg) intraperitoneally, daily for two weeks before sacrifice. Body and liver weight, liver tissue, serum, isolated hepatocytes and cholangiocytes were collected from all groups. Hepatic damage and steatosis were evaluated by H&E and Oil-Red O staining in liver sections respectively. MC activation in total liver was evaluated by qPCR for chymase, tryptase, FcεR1α and histidine decarboxylase. Serum histamine(HA) level in all groups were measured by enzyme-linked immunoassay. Tryptaseβ2 immunohistochemistry was performed in liver to detect MC infiltration and CK-19 immunostaining and semi-quantification was performed to evaluate DR. Biliary senescence was evaluated by co-immunofluorescence of CK-19 with p16 and γH2AX. Serum cytokine levels were analyzed by mouse cytokine array EIA. Fibrosis was evaluated by semi-quantification of Fast Green Sirius Red staining. Inflammation was assessed by F4/80 immunostaining in liver. **RESULTS:** MCD diet induced severe hepatic damage and steatosis in WT mice compared to CD, which was reversed with crom injection. Crom treatment i) stabilized MC activation and infiltration ii) reduced serum HA level in MCD and CD fed mice compared to the respective controls. MCD diet in WT mice increased i) DR ii) biliary senescence iii) inflammation and iii) fibrosis compared to CD. Crom treatment reduced all these parameters in the MCD diet fed mice compared to the control. Pro-inflammatory cytokine levels in serum increased in MCD mice compared to CD fed mice and crom treatment reduced these cytokine levels. **CONCLUSION:** MC infiltration is a critical event in progression of advanced NAFLD/NASH phenotypes that drives biliary senescence, hepatic steatosis, inflammation and fibrosis. Administration of cromolyn sodium may be a therapeutic approach for management of NAFLD/ NASH phenotypes.

