Isothiocyanates inhibit cholesterol crystal-induced steatohepatitis through inhibition of NLRP3 inflammasome activation

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Non-alcoholic fatty liver disease (NAFLD) occurs from the deposition of fat in hepatocytes which leads to the development of hepatic steatohepatitis, fibrosis, cirrhosis, or hepatocellular carcinoma. Evidence indicates that abnormal accumulation of cholesterol and formation of cholesterol crystals play a critical role in the induction of non-alcoholic steatohepatitis (NASH) by activating macrophages. Isothiocyanates are a group of organic sulfides and are rich in cruciferous vegetables. Previous studies have shown that isothiocyanates possess a variety of physiological activities, including anti-cardiovascular diseases, anti-tumor, anti-inflammation and anti-oxidation. In this study, high fat/high cholesterol/high cholic acid diet-fed C57BL/6J mice and primary Kupffer cells were employed to examine the effects of benzyl isothiocyanate (BITC) and phenylethyl isothiocyanate (PEITC) on NLRP3 inflammasome activation and IL-1β release as well as the underlying mechanisms involved. Results showed that BITC and PEITC dose-dependently reduce the release of IL-1β in LPS/cholesterol crystal-induced Kupffer cells. Immuno-precipitation assay revealed that BITC inhibits cholesterol crystals-induced cathepsin B binding to NLRP3, thereby abrogates the activation of caspase 1 (p20) in Kupffer cells. Moreover, BITC and PEITC (0.1% in the diet) effectively reduce the expression of IL-1β, NLRP3 and caspase 1 mRNA and protein as compared with controls. These findings indicate that BITC and PEITC attenuate cholesterol crystal-induced NLRP3-mediated inflammation which suggests BITC and PEITC are potent protective agents against cholesterol crystal-induced NASH.

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