1-Bifidobacterium pseudolongum-generated acetate suppresses non-alcoholic fatty liver disease-associated hepatocellular carcinoma

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Abstract

Background & Aims: Recent studies have highlighted the role of the gut microbiota and their metabolites in non-alcoholic fatty liver disease-associated hepatocellular carcinoma (NAFLD-HCC). We aimed to identify specific beneficial bacterial species that could be used prophylactically to prevent NAFLD-HCC.Methods: The role of Bifidobacterium pseudolongum was assessed in two mouse models of NAFLD-HCC: diethylnitrosamine + a high-fat/high-cholesterol diet or + a choline-deficient/high-fat diet. Germ-free mice were used for the metabolic study of B. pseudolongum. Stool, portal vein and liver tissues were collected from mice for non-targeted and targeted metabolomic profiles. Two human NAFLD-HCC cell lines (HKCI2 and HKCI10) were co-cultured with B. pseudolongum-conditioned media (B.p CM) or candidate metabolites.Results: B. pseudolongum was the top depleted bacterium in mice with NAFLD-HCC. Oral gavage of B. pseudolongum significantly suppressed NAFLD-HCC formation in two mouse models ($p < 0.01$). Incubation of NAFLD-HCC cells with B.p CM significantly suppressed cell proliferation, inhibited the G1/S phase transition and induced apoptosis. Acetate was identified as the critical metabolite generated from B. pseudolongum in B.p CM, an observation that was confirmed in germ-free mice. Acetate inhibited cell proliferation and induced cell apoptosis in NAFLD-HCC cell lines and suppressed NAFLD-HCC tumor formation in vivo. B. pseudolongum restored heathy gut microbiome composition and improved gut barrier function. Mechanistically, B. pseudolongum-generated acetate reached the liver via the portal vein and bound to GPR43 (G coupled-protein receptor 43) on hepatocytes. GPR43 activation suppressed the IL-6/JAK1/STAT3 signaling pathway, thereby preventing NAFLDHCC progression. Conclusions: B. pseudolongum protected against NAFLD-HCC by secreting the anti-tumor metabolite acetate, which reached the liver via the portal vein. B. pseudolongum holds potential as a probiotic for the prevention of NAFLD-HCC.(c) 2023 The Author(s). Published by Elsevier B.V. on behalf of European Association for the Study of the Liver. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords

Author Keywords

B. pseudolongumNAFLD-HCCProbioticsAcetateMicrobiota

Keywords Plus

GUT MICROBIOTARECEPTORSTRAINSACIDSAXIS

2-Clinical profiles and mortality rates are similar for metabolic dysfunction-associated steatotic liver disease and non-alcoholic fatty liver disease

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Abstract

Background & Aims: Recently, the term metabolic dysfunction -associated steatotic liver disease (MASLD) has replaced nonalcoholic fatty liver disease (NAFLD). Concern remains regarding whether the evidence generated under the NAFLD definition can be used for MASLD. We compared the clinical profile and outcomes of NAFLD to MASLD using tertiary care- and populationbased data. Methods: Comparison data were obtained from our NAFLD database and the National Health and Nutrition Examination Survey (NHANES III). Clinical profiles and non-invasive tests (enhanced liver fibrosis [ELF] score, fibrosis -4 index [FIB -4] and vibrationcontrolled transient elastography) were compared. Mortality data were obtained from NHANES-National Death Index. All -cause mortality was assessed by Cox proportional hazards regression models and cause -specific mortality by competing risk analysis. Results: There were 6,429 patients in the NAFLD database (age: 54 +/- 12 years, 42% male, BMI 35.4 +/- 8.3, waist circumference 112 +/- 17 cm, 52% type 2 diabetes). Average scores for ELF, FIB -4 and liver stiffness were 9.6 +/- 1.2, 1.69 +/- 1.24,14.0 +/- 11.8 kPa, respectively; 99% met MASLD criteria; 95% met MASLD on BMI only. Predictive accuracy of ELF and FIB -4 were identical between MASLD and NAFLD. We included 12,519 eligible participants from NHANES (age 43.00 years, 47.38% male, 22.70% obese, 7.28% type 2 diabetes, 82.51% >= 1 cardiometabolic criteria). Among the NHANES study population, there was excellent concordance between MASLD and NAFLD diagnoses: Cohen's kappa coefficient: 0.968 (95% CI 0.962-0.973) with 5.29% of NAFLD cases not meeting MASLD criteria. After a median follow-up of 22.83 years, there were no mortality differences between MASLD and NAFLD diagnoses (p values >= 0.05). Conclusions: NAFLD and MASLD are similar except individuals with MASLD seem to be older with slightly higher mortality risk, likely owing to cardiometabolic risk factors. Clinical profiles and non-invasive test thresholds were also identical. These data provide evidence that NAFLD and MASLD terminologies can be used interchangeably. For the small proportion of patients with NAFLD who do not meet MASLD criteria, further consideration is needed.

Keywords
Author Keywords
NITsNHANESalcoholcardiometabolic criteriaconcordance
Keywords Plus
AWARENESSBURDEN