

Administration of Gut Bacteria Expressing N-acyl Phosphatidylethanolamine Reduces Steatohepatitis in LDLR^{-/-} Mice Fed a Western Diet

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Background: The rise in obesity in the United States has led to a concomitant rise in prevalence of non-alcoholic fatty liver disease (NAFLD). The four stages of NAFLD include accumulation of triglyceride (hepatosteatosis), development of chronic inflammation (non-alcoholic steatohepatitis, NASH), fibrosis, and finally cirrhosis. Unlike wildtype C57BL6 mice, low density lipoprotein receptor (LDLR)^{-/-} mouse fed a diet enriched in fat and cholesterol (Western Diet) progress to NASH and fibrotic stages of NAFLD. We showed that incorporating engineered bacteria expressing N-acyl phosphatidylethanolamine (NAPE) into the gut microbiota can inhibit development of obesity. NAPE is a precursor of N-acylethanolamines, which are bioactive lipids with anti-inflammatory functions. Here, we test the hypothesis that administering these NAPE-expressing bacteria inhibits development of NASH and fibrosis.

Methods: NAPE-expressing *E. coli* Nissle 1917 (pNAPE-EcN, n=10), control Nissle 1917 (pEcN, n=10), or vehicle (veh, n=10) were given via drinking water to LDLR^{-/-} mice fed a Western diet for 12 weeks. LDLR^{-/-} mice fed a low fat diet (LFD) (n=10) were included for comparison. **Results:** pNAPE-EcN reduced adiposity by 26% compared with pEcN and veh (P<0.05). pNAPE-EcN also dramatically reduced hepatic triglyceride levels by 45% (p<0.05) and lipid droplet size, as well as the hepatic expressions of tissue necrosis factor α (TNF α , p<0.05), chemokine receptor 2 (CCR2, p<0.01), and tissue inhibitor of matrix metalloproteinase (TIMP1, p<0.05), consistent with reduced NASH and fibrosis. Sirius Red staining of liver sections further demonstrated reduced fibrosis. Because fatty liver is associated with atherosclerosis, we checked to see if pNAPE-EcN was able to reduce the development of atherosclerotic lesions. While serum cholesterol was reduced by 23% with pNAPE-EcN treatment (p<0.05), atherosclerotic lesion size in proximal or en face aortas only tended to be reduced (20%, 18.6%) but was not statistically significant. **Conclusions:** Our results demonstrate that incorporating therapeutically modified bacteria into the gut microbiota has potential to inhibit the development of NAFLD.

Disclosure Block:

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