Microbiome

Gut bacteria degrade nicotine

Tobacco smoking is one of the leading causes of death in the world. Nicotine can accumulate in the upper digestive tract and this could have pathological implications, as it has been correlated with tobacco-smoking-related liver diseases such as non-alcoholic fatty liver disease (NAFLD). NAFLD could progress to non-alcoholic steatohepatitis (NASH) and then potentially to cirrhosis and hepatocellular carcinoma. The mechanistic bases for the association of nicotine with liver diseases are not clear. Chen et al. report that nicotine accumulates in the gut during smoking and promotes the progression of NAFLD, and show that the gut bacterium *Bacteroides xylanisolvens* can degrade nicotine.

The authors first analysed ileum mucosa biopsy, serum and stool samples from non-smokers and smokers and confirm that nicotine accumulates in the intestine. The authors validated these findings using specific-pathogen-free (SPF) and germ-free (GF) mice administered with nicotine, and further determined that endogenous gut bacteria can degrade nicotine. Next, the authors screened public metagenome databases and performed metagenomics analyses of stool samples from the smokers, and identified the commensal gut bacterium *B. xylanisolvens* as the degrading microorganism. *B. xylanisolvens* degraded nicotine in vitro and in vivo, with a subsequent increase of the nicotine metabolite 4-hydroxy-1-(3-pyridyl)-1-butanone (HPB). The authors performed whole genome sequencing of *B. xylanisolvens*, together with knockout and heterologous complementation assays, and identified NicX as the bacterial enzyme responsible for nicotine catabolism.

Next, the authors used a set of in vivo assays where SPF mice were administered nicotine and a high-fructose and high-cholesterol diet, and were inoculated with wild-type and *nicX*-knockout *B. xylanisolvens* strains. The authors observed that nicotine supplementation accelerated NAFLD progression, hepatic inflammation and fibrosis, and that these effects were ameliorated by colonization of nicotine-degrading *B. xylanisolvens* expressing *nicX*.

Mechanistically, the authors show that nicotine induces the phosphorylation and activation of AMP-activated protein kinase AMPKα1, which stabilizes sphingomyelin phosphodiesterase 3 (SMPD3), increasing intestinal ceramide production, and potentiating NAFLD progression to NASH. However, *nicX*-expressing bacteria suppressed nicotine-induced activation of the AMPKα–SMPD3 axis, potentially relieving hepatic disease.

Finally, the authors sampled 83 patients with NAFLD, both smokers and non-smokers. The authors found that *B. xylanisolvens* levels were negatively correlated with faecal nicotine and ceramide levels in serum and severity, and were positively correlated with HPB levels in smokers. No correlation was found in non-smokers.

> "the gut bacterium *Bacteroides xylanisolvens* can degrade nicotine"

Overall, these findings provide mechanistic insight into the role of intestinal nicotine accumulation in the progression of NAFLD, and highlight the potential of the gut bacterium *B. xylanisolvens* for treatment of nicotine-associated NASH. Future studies will be needed to better understand the ability of gut bacteria to degrade nicotine.

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Public health

Ending the COVID-19 pandemic

COVID-19 remains a public health threat, despite widespread control measures aimed at ending the pandemic. Much scientific and medical progress has been made regarding our understanding of COVID-19 pathophysiology and regarding the development of vaccines, treatments and care, yet the actions of individual countries have often been insufficient and heterogeneous. To gain a global consensus on COVID-19 responses, Lazarus et al. conducted a multidisciplinary and multinational study of a diverse panel of 386 experts, including academic, health, non-governmental organization, government and other experts in COVID-19 response. The study yielded a set of 41 consensus statements and 57 recommendations that could be subsumed into six categories of action: improve communication; strengthen health systems; promote vaccination combined with additional prevention measures; encourage preventive behaviours; expand treatment and care; and end inequities. These findings can serve as a basis for decision making by governments in an attempt to finally put an end to COVID-19 as a persistent and global health threat.

Michael Attwaters

Original article: Lazarus, J. V. et al. A multinational Delphi consensus to end the COVID-19 public health threat. *Nature* **611**, 332–345 (2022)