齐齐哈尔医学院附属第三医院
The Third Affiliated Hospital Of Qiqihar Medical University
齐齐哈尔市肿瘤医院
Qiqihar Cancer Hospital

吸烟与非酒精性脂肪肝(二)

中心实验室
池涛

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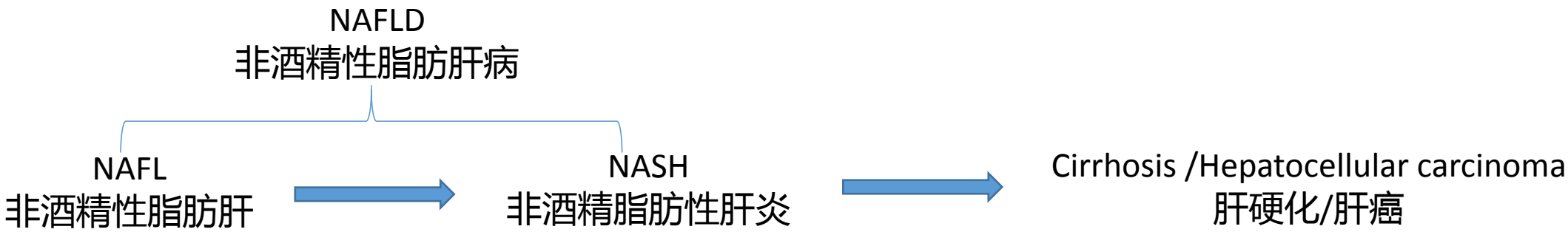
Gut bacteria alleviate smoking-related NASH by degrading gut nicotine

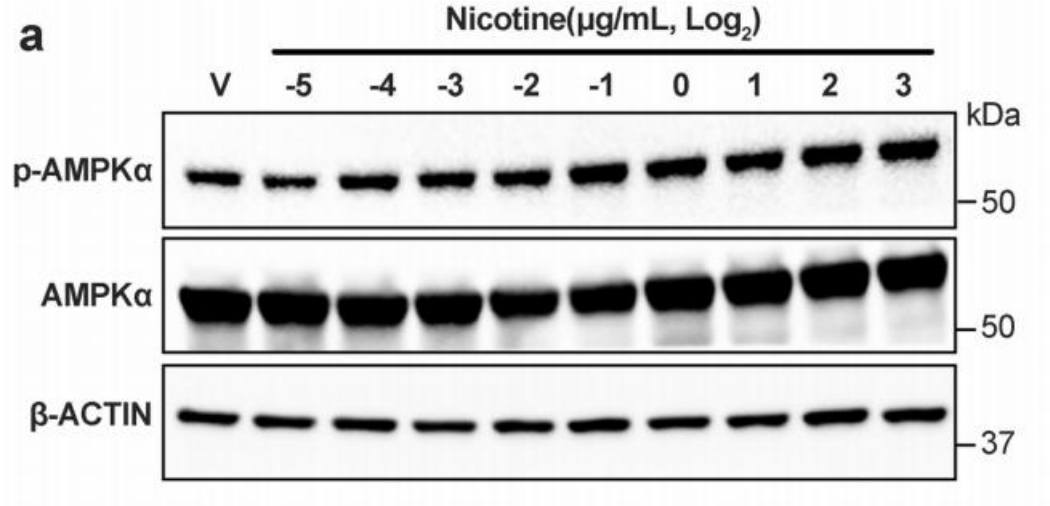
Bo Chen, Lulu Sun, Guangyi Zeng, Zhe Shen, Kai Wang, Limin Yin, Feng Xu, Pengcheng Wang, Yong Ding, Qixing Nie, Qing Wu, Zhiwei Zhang, Jialin Xia, Jun Lin, Yuhong Luo, Jie Cai, Kristopher W. Krausz, Ruimao Zheng, Yanxue Xue, Ming-Hua Zheng ✉, Yang Li ✉, Chaohui Yu ✉, Frank J. Gonzalez ✉ & Changtao Jiang

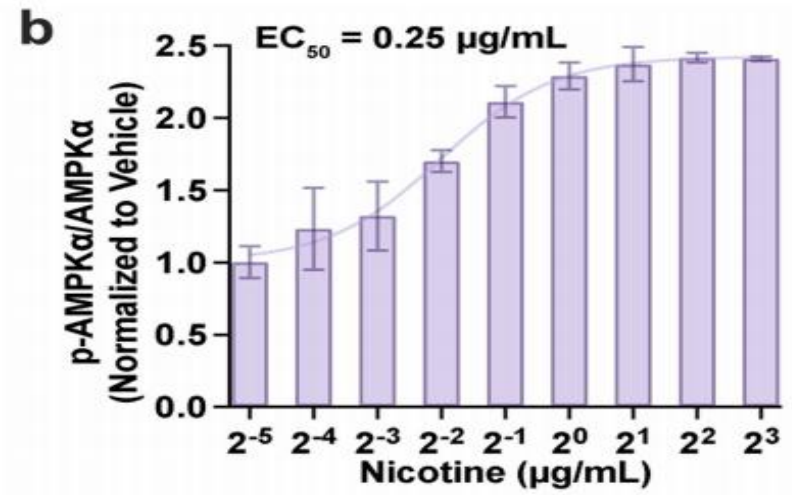
2022年10月19日，北京大学基础医学院姜长涛团队联合美国国立卫生研究院的Frank J. Gonzalez发表



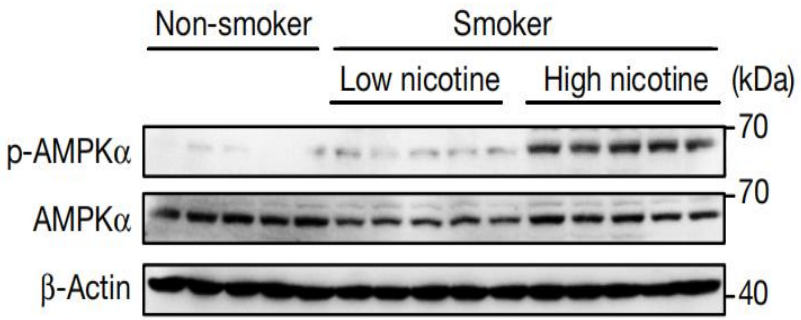
3.Nicotine activates intestinal AMPKα1

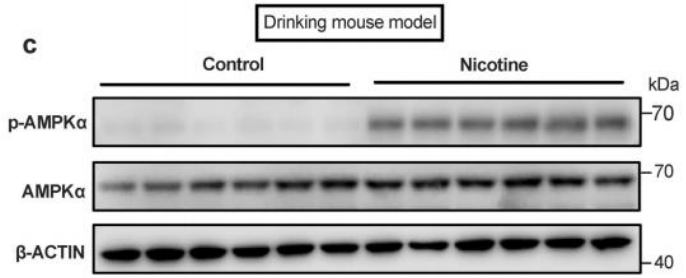
(1)Nicotine treatment induced the phosphorylation of AMPKα at Thr172 in ileal organoids in a dose-dependent manner

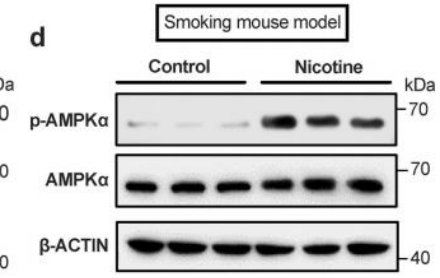


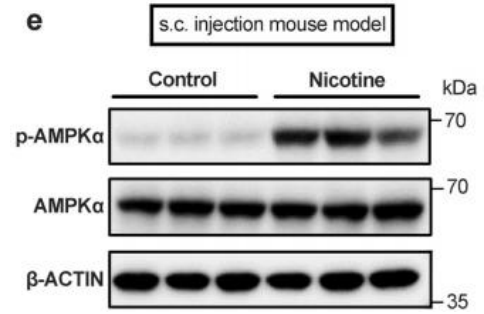


(2)Ileal AMPKα was activated by tobacco smoking in the terminal ileum, and the strength of the effect was positively related to the level of nicotine in the tissue of smokers

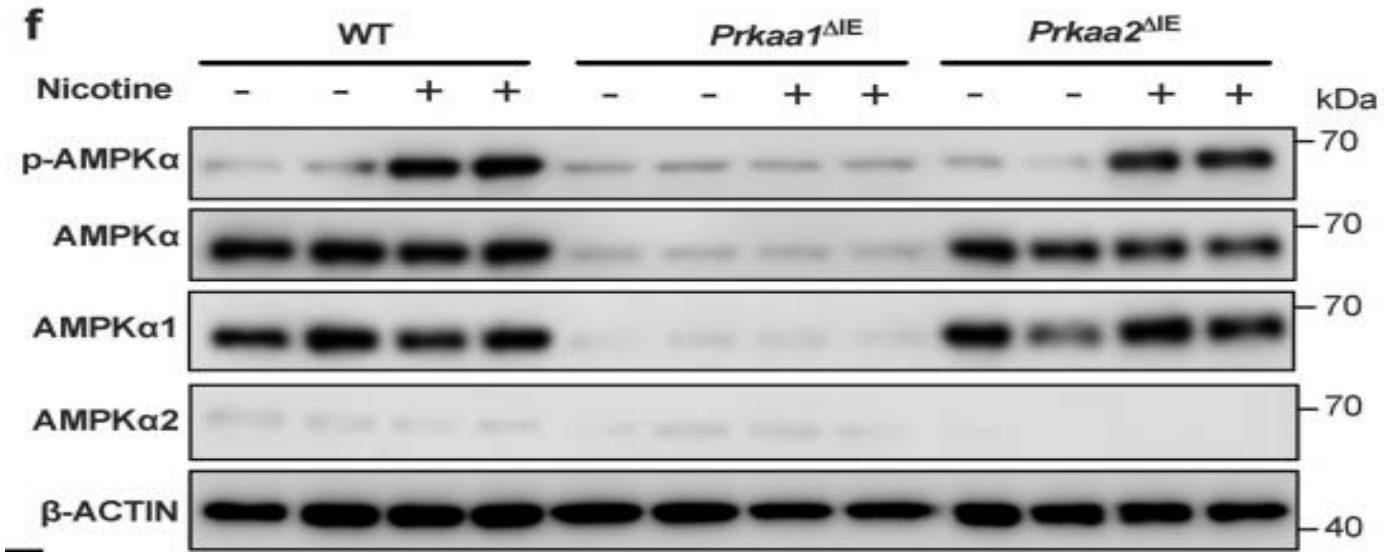




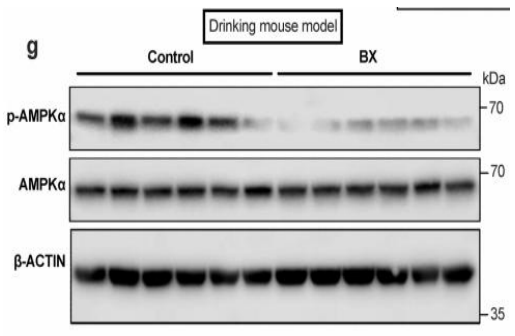


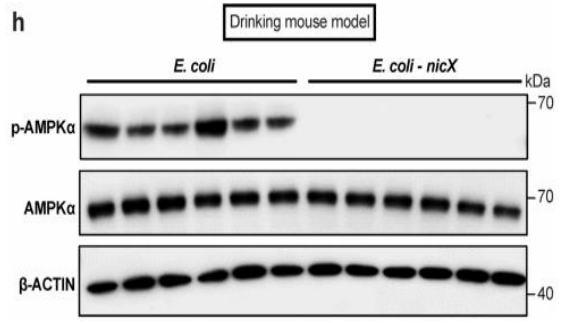


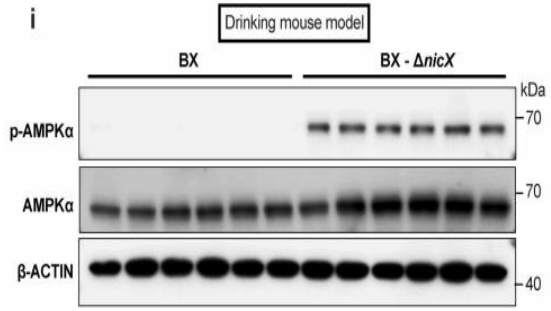
（3）AMPKα1 is the main target of nicotine in the intestine



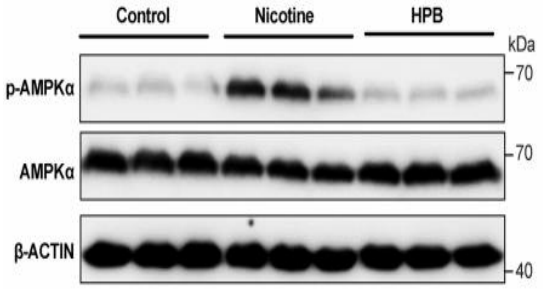
（4）B. xylanisolvens colonization inhibited nicotine-induced AMPKα phosphorylation in the ileum



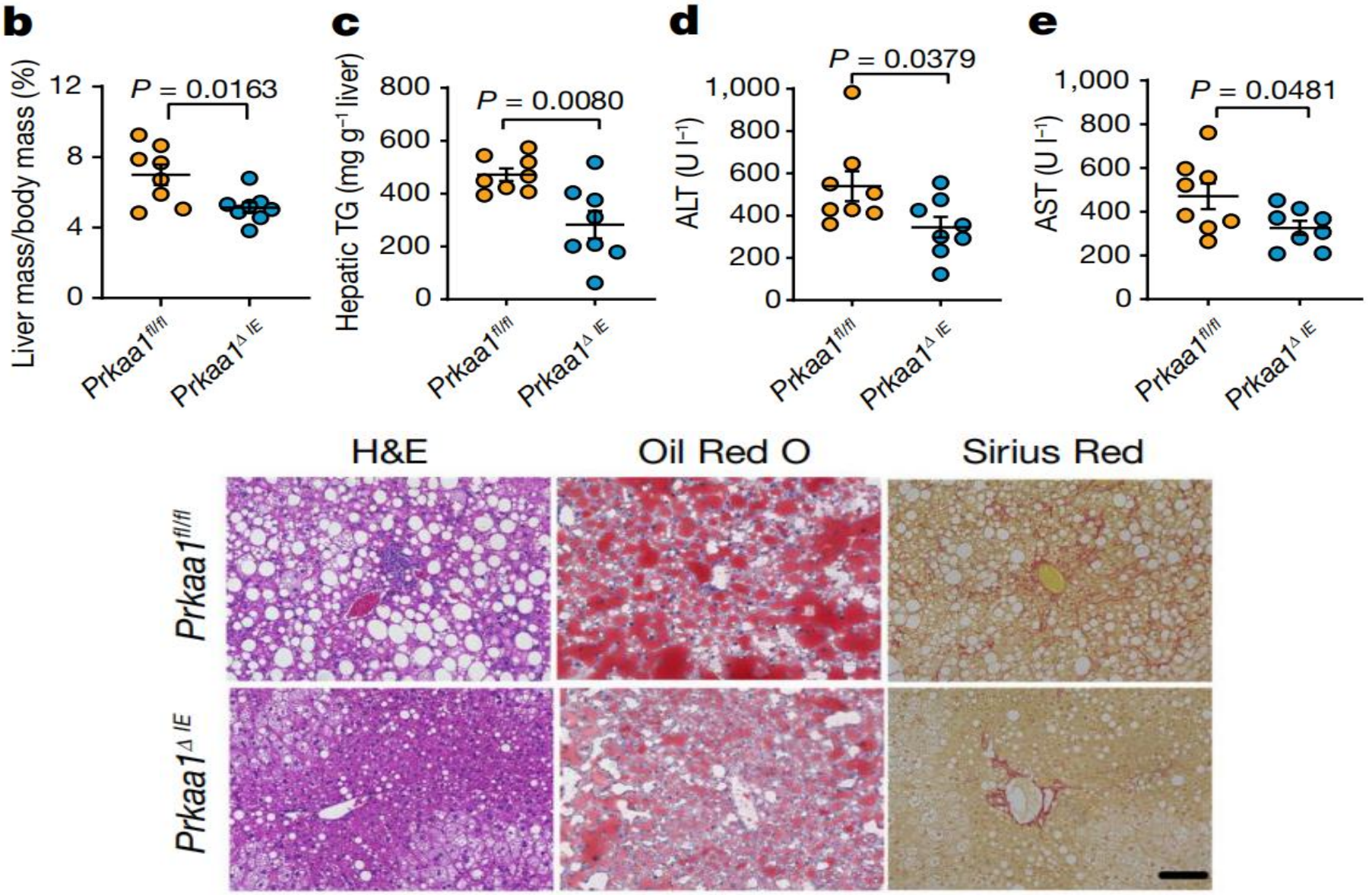




sw480 cell



（5）The loss of intestinal epithelial AMPKα1 contributes to improvements in hepatic steatosis, inflammation and fibrosis in the nicotine-accelerated NASH mouse model

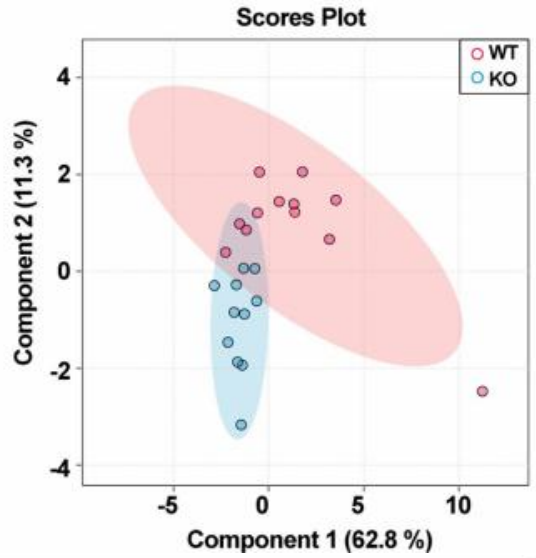


4.p-AMPKα phosphorylates SMPD3 at Ser208/209

(1)Identified ceramides as the primary metabolites leading to clustering-based differentiation

n

lipidomic analysis



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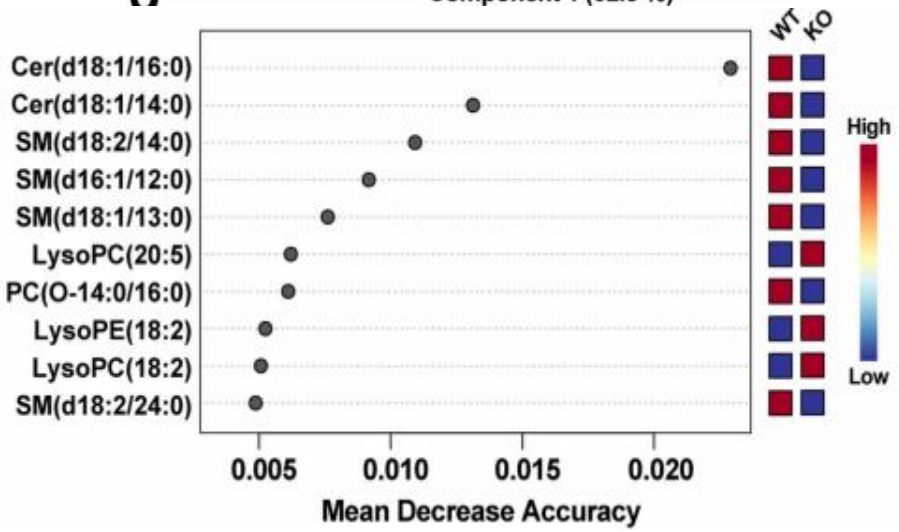

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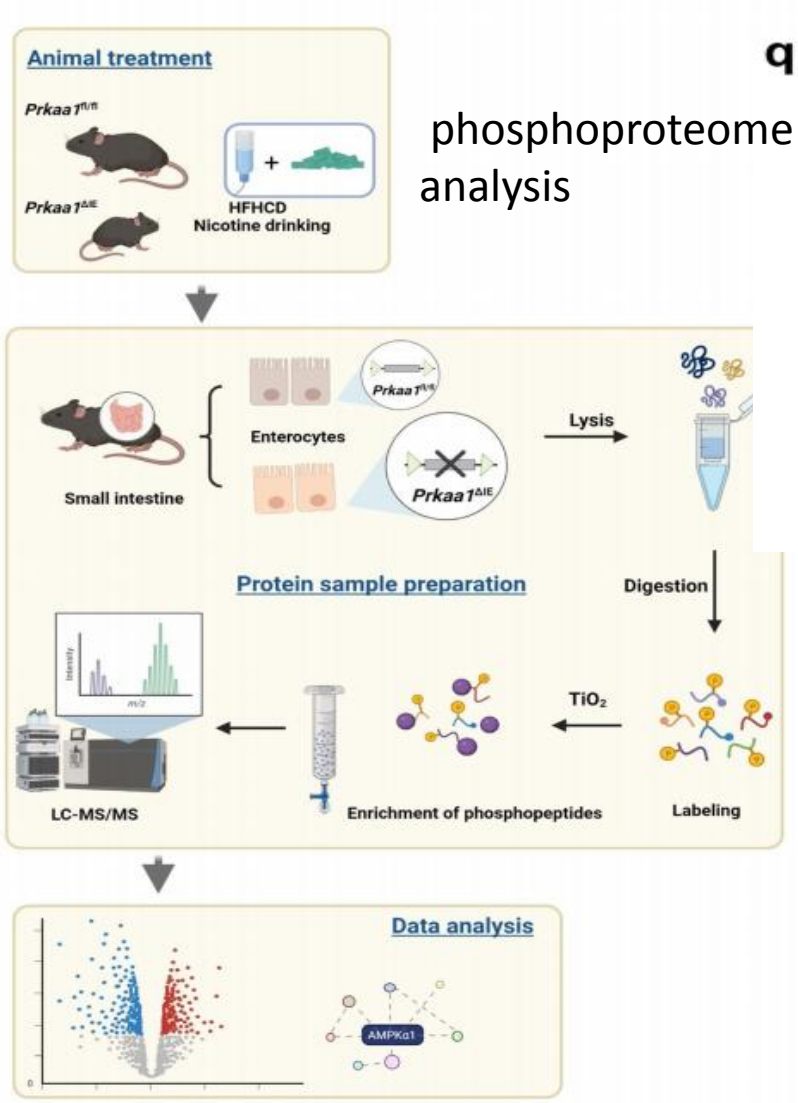
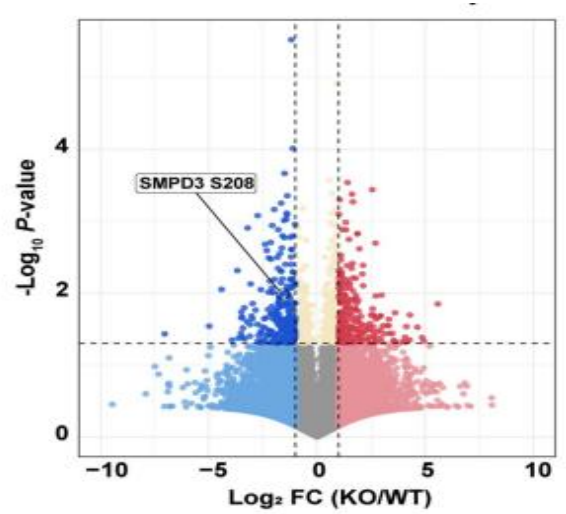


q

phosphoproteome analysis



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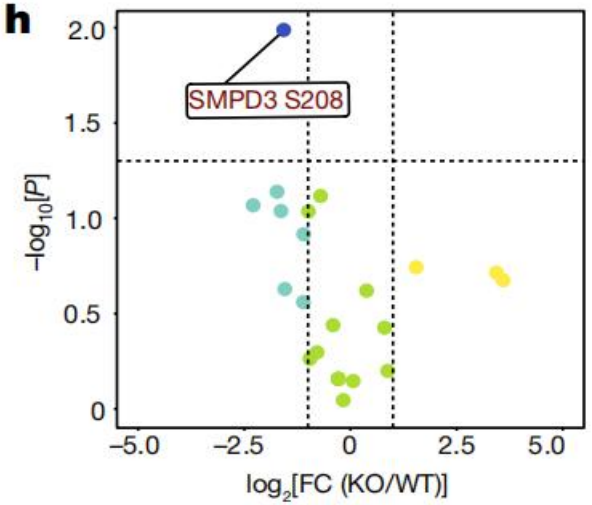
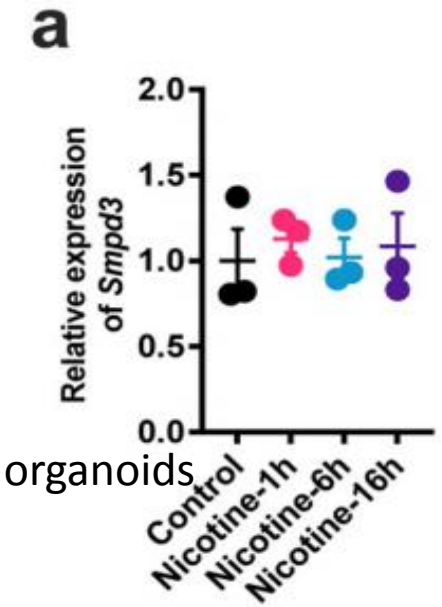
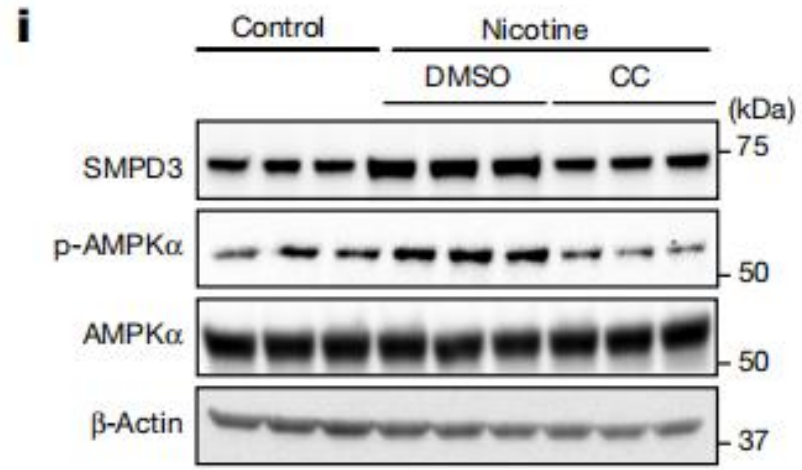


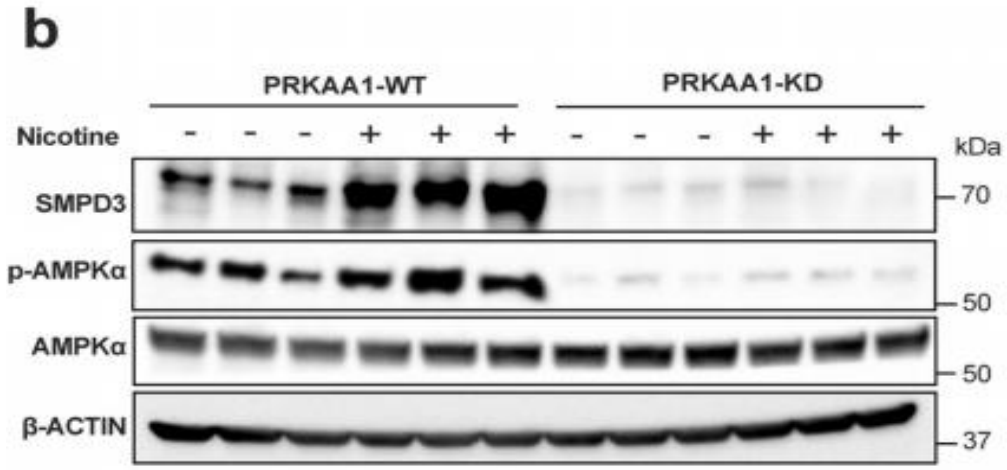
(2)The effect of nicotine on SMPD3 is post-translational



ileal organoids

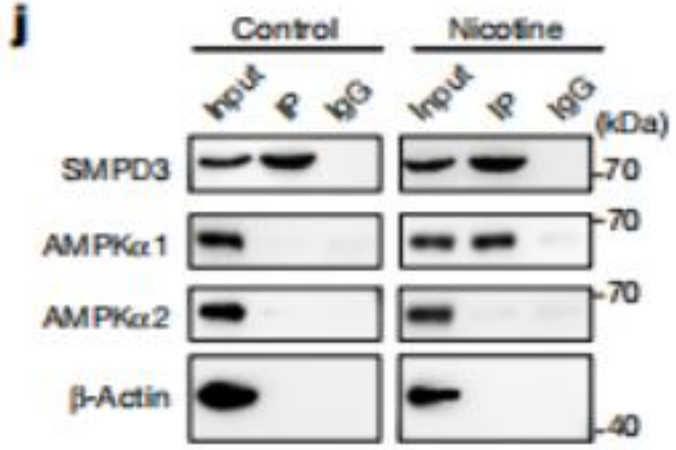


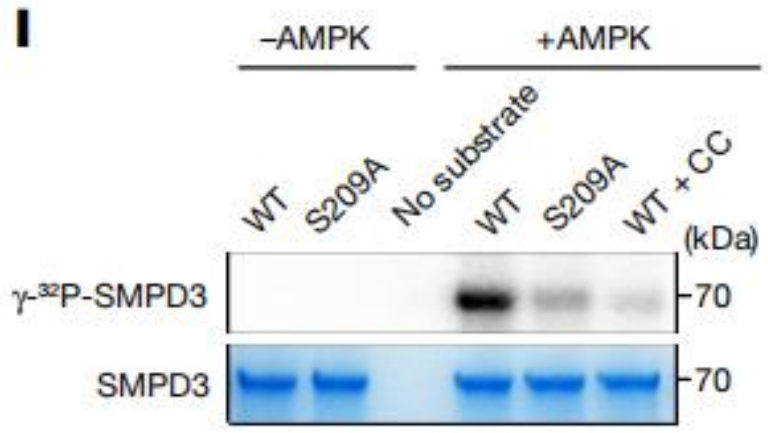
CC, AMPK inhibitor

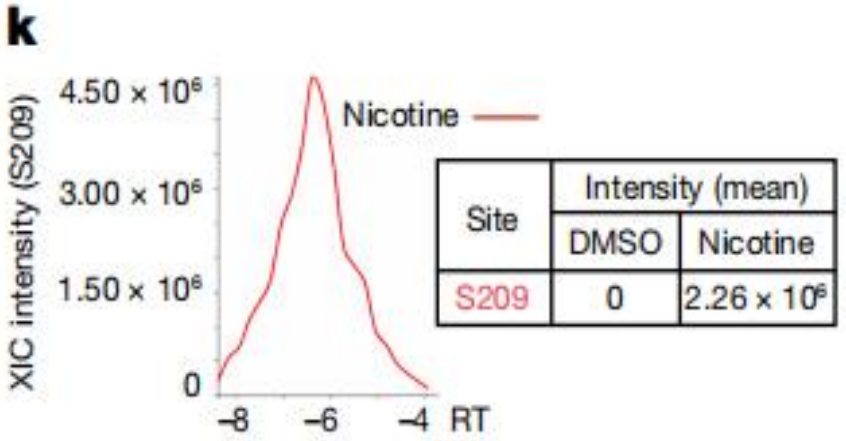


SW480 cells

(3)Under nicotine treatment, SMPD3 bound to AMPKα1



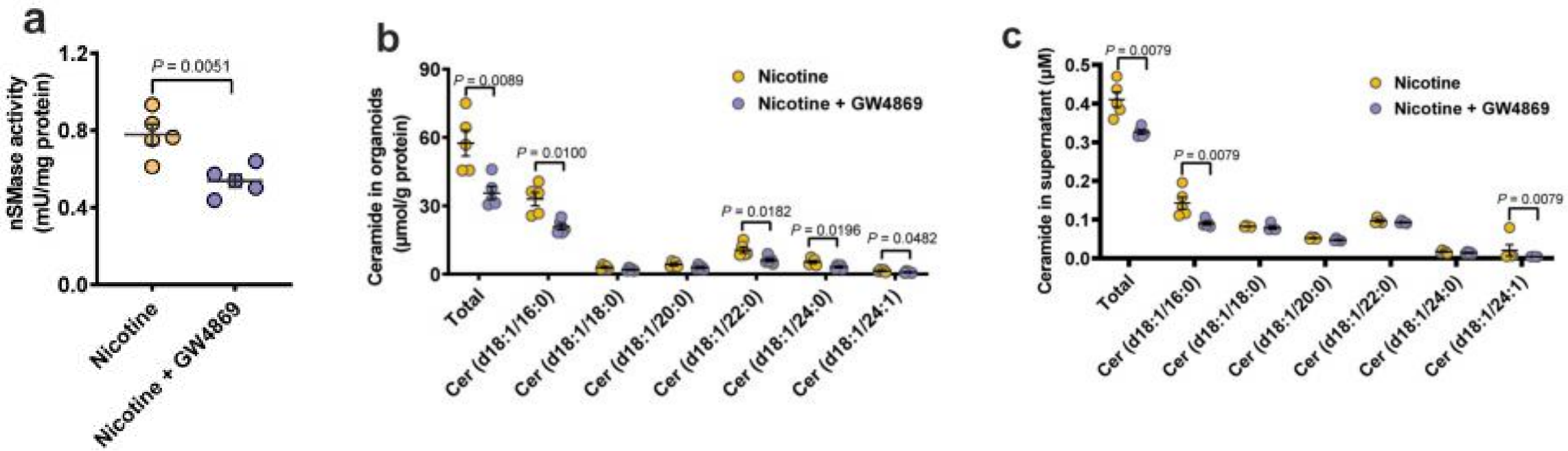




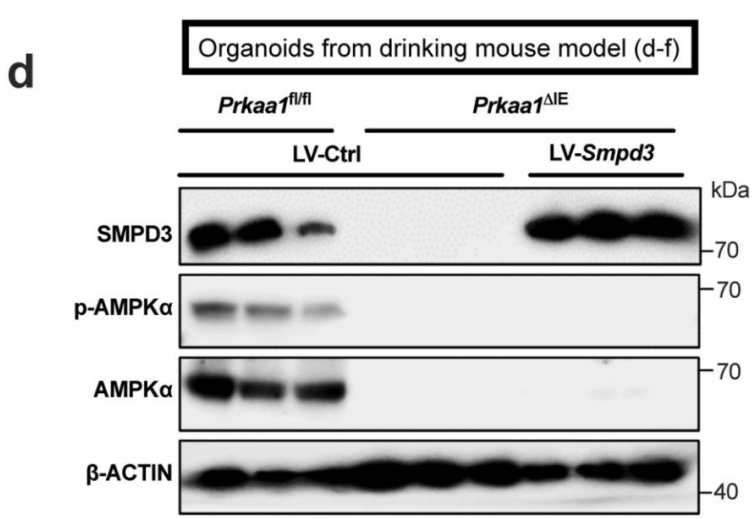
Site	Intensity (mean)	
	DMSO	Nicotine
S209	0	2.26 × 10⁶

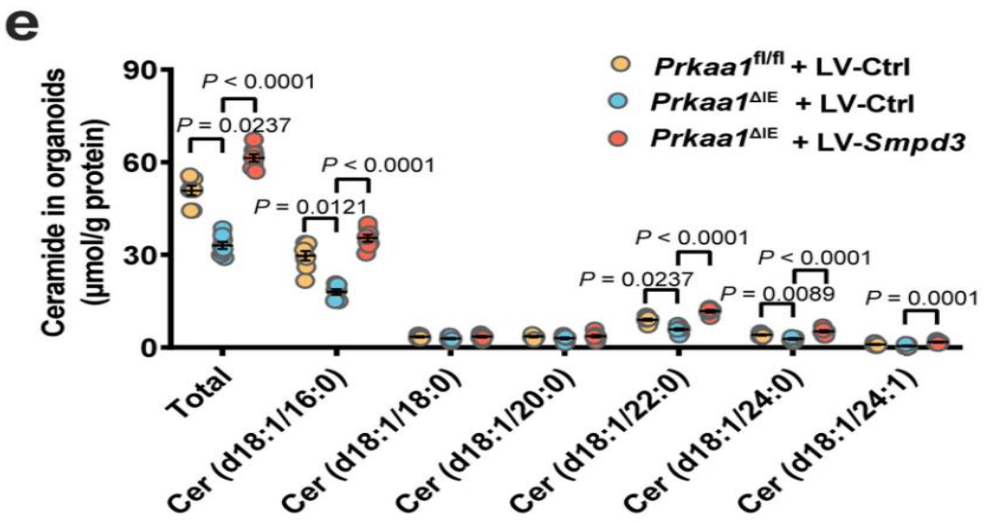
5.The p-AMPKα–SMPD3–ceramide axis and NASH

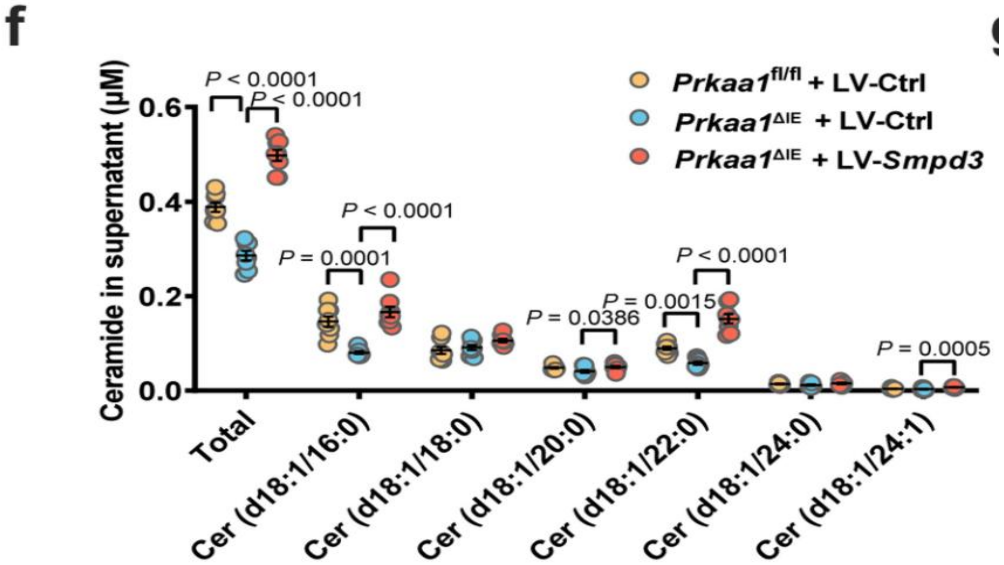
（1）The ceramide levels in organoids and their supernatants under nicotine treatment were decreased by GW4869

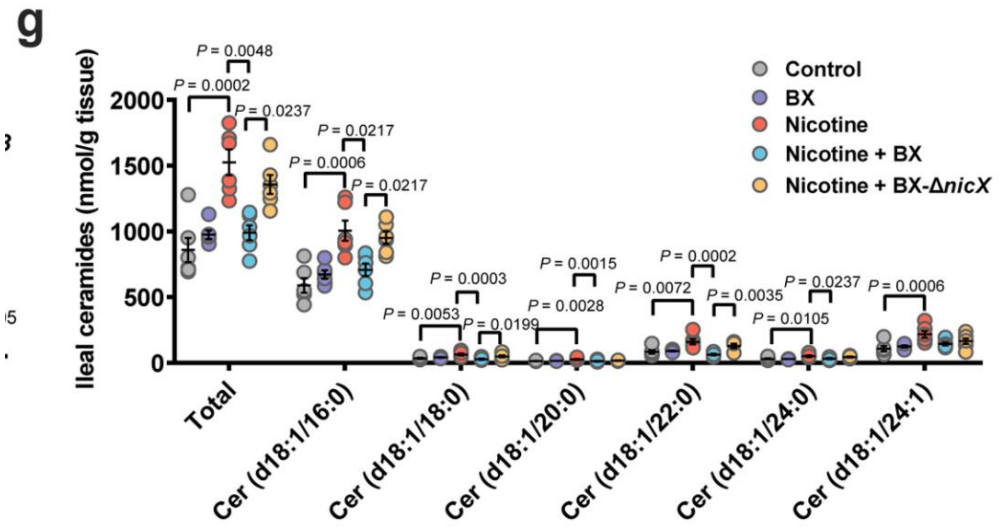


（2）SMPD3 overexpression reversed the reduction in ceramide levels resulting from AMPKα1 deficiency in ileal organoids

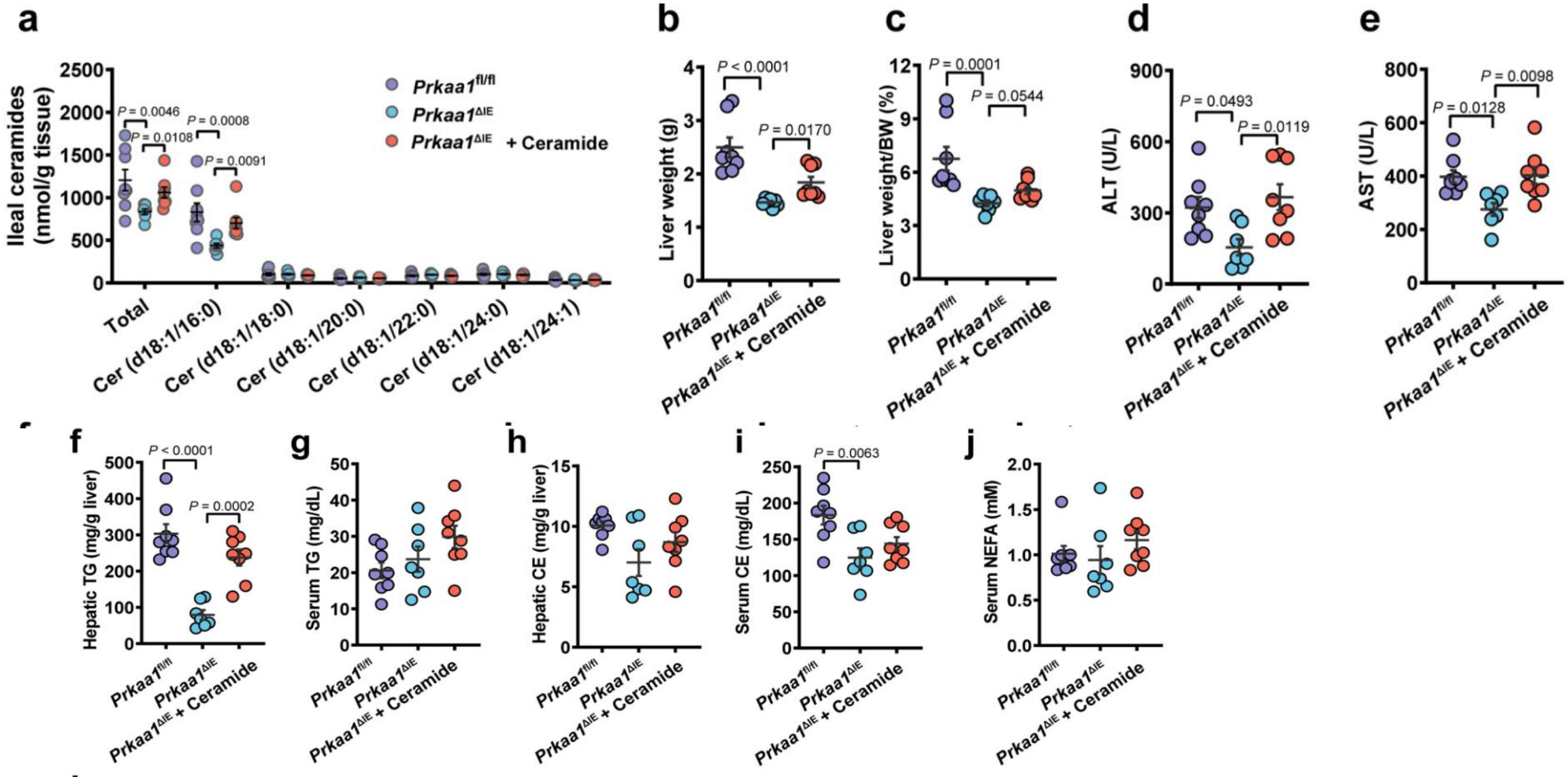








（3）The protective effects on hepatic steatosis, inflammation and fibrosis resulting from the genetic disruption of intestinal epithe lium AMPKα1 were reversed by ceramide (d18:1/16:0) administration



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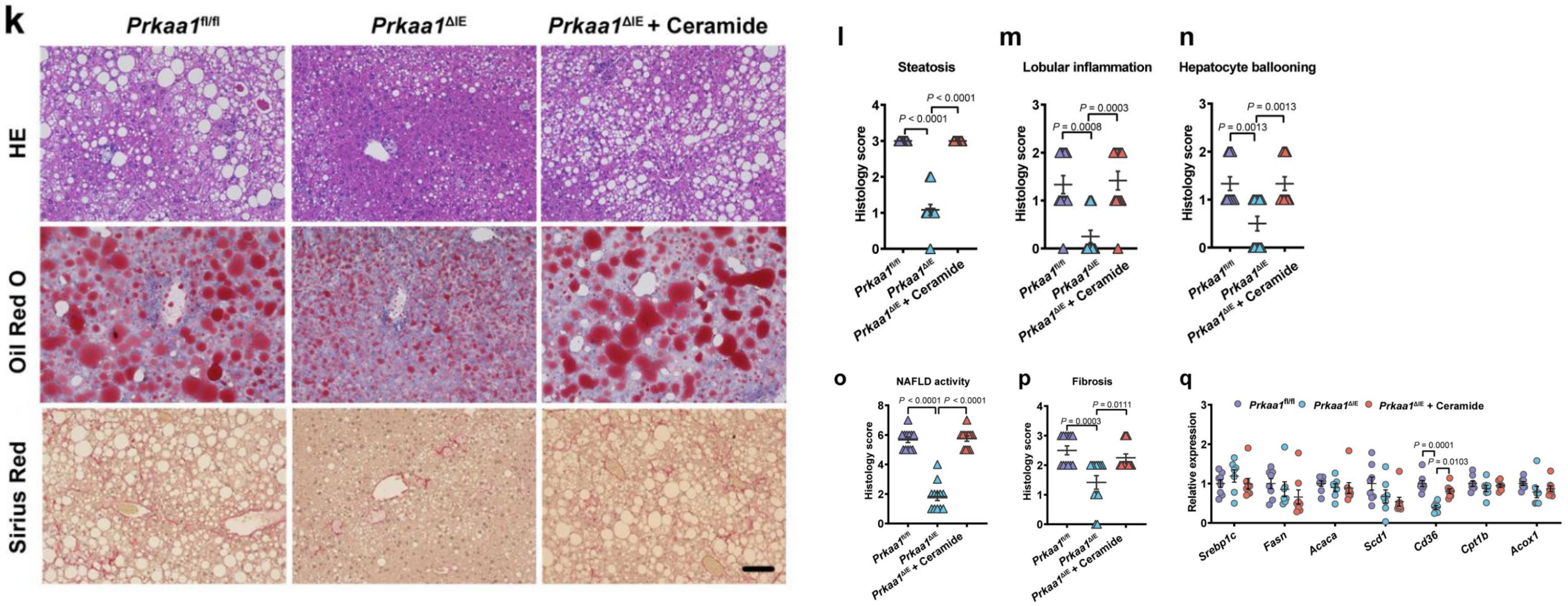
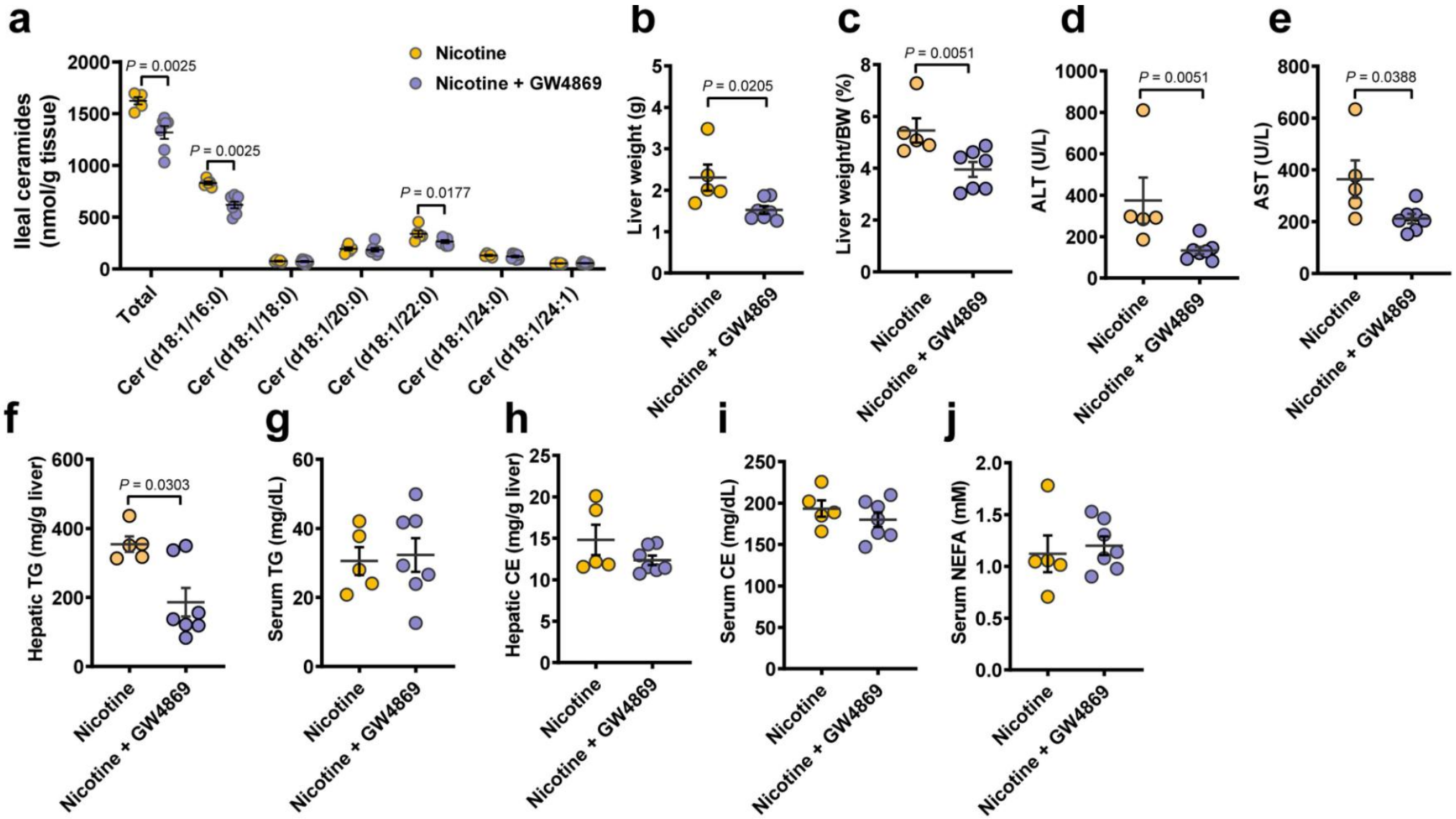


（4）oral GW4869 delivery decreased the ileal levels of ceramides, and the decrease was accompanied by lower NAFLD severity in the nicotine-drinking model



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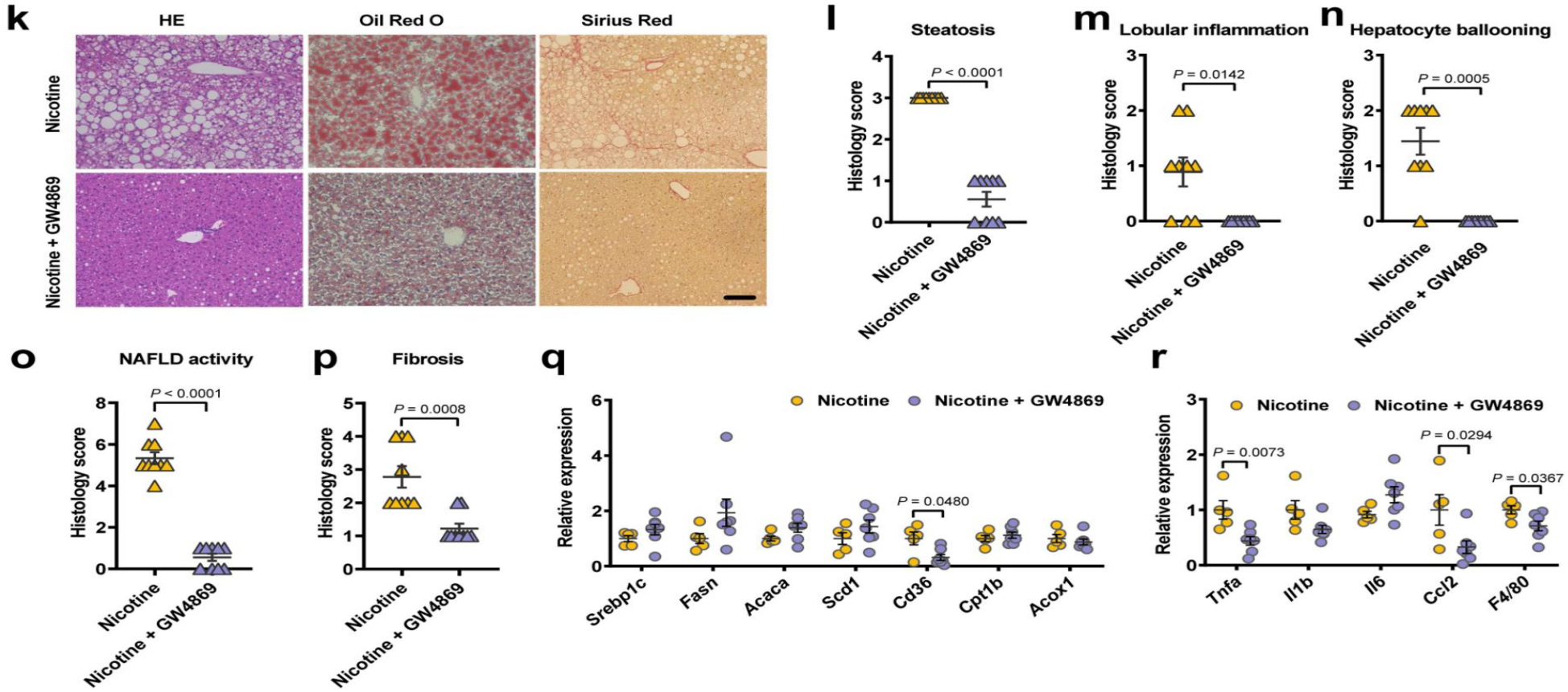
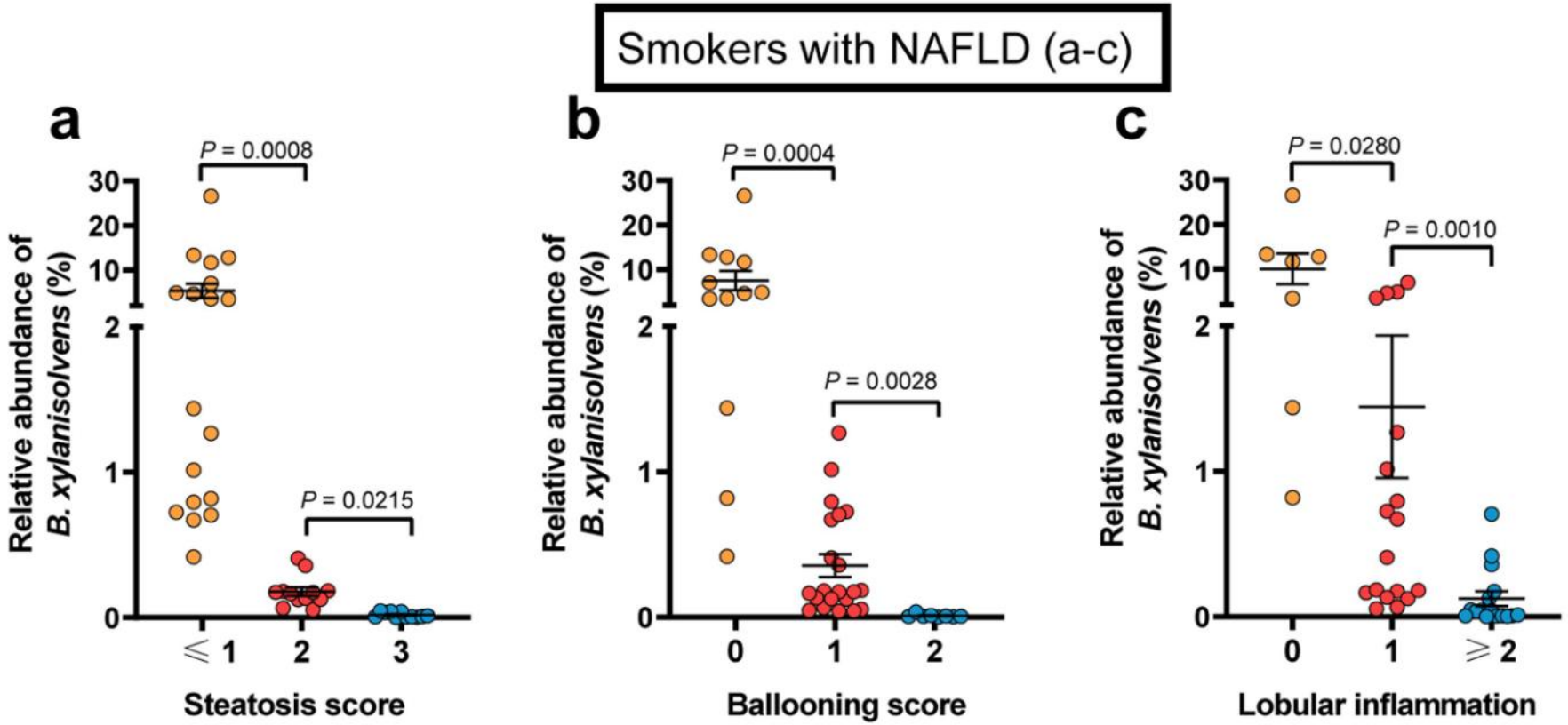


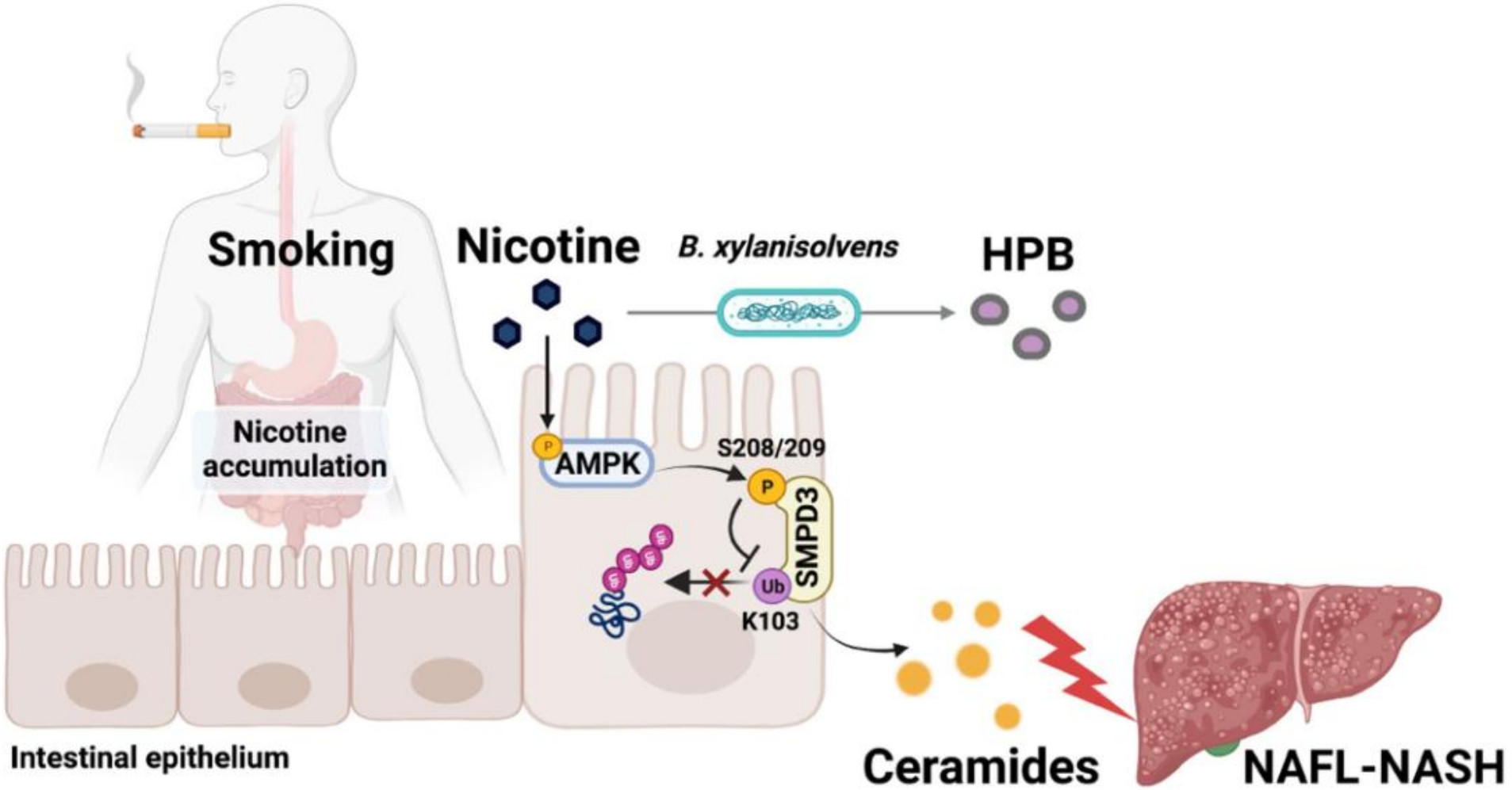
In conclusion, nicotine-induced activation of the intestinal AMPKα–SMPD3 axis potentiates NAFLD progression by increasing intestinal ceramide production, and thus SMPD3 suppression is a potential strategy for relieving hepatic steatosis, inflammation and fibrosis.

6.B. xylanisolvens and clinical NAFLD

（1）B. xylanisolvens levels were negatively correlated with NAFLD severity



Discussion


Smoking
Nicotine
B. xylanisolvens
HPB
Nicotine accumulation
P
AMPK
S208/209
P
SMPD3
Ub
K103
Intestinal epithelium
Ceramides
NAFL-NASH

谢 谢 ！