嗜黏蛋白阿克曼菌来源的低酰基化粗糙型脂多糖通过激活TLR4-IL-23-IL-22免疫轴缓解饮食诱导的肥胖

孙莉[1,2]，张玉婷[1,2]，董望[1,2]，孙敬祖[1]，王涛[1]，邵菲[3]，代焕琴[1,2]，韩俊杰[1,2]，王文昭[1]，王硕[3]，赵彤[4]，王亮亮[5]，刘畅[6]，刘双江[6]，刘宏伟[1,2,5]

[1]中国科学院微生物研究所微生物多样性与资源创新利用全国重点实验室

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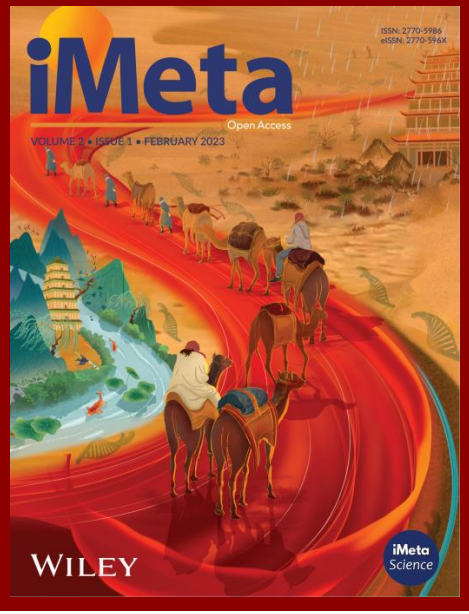
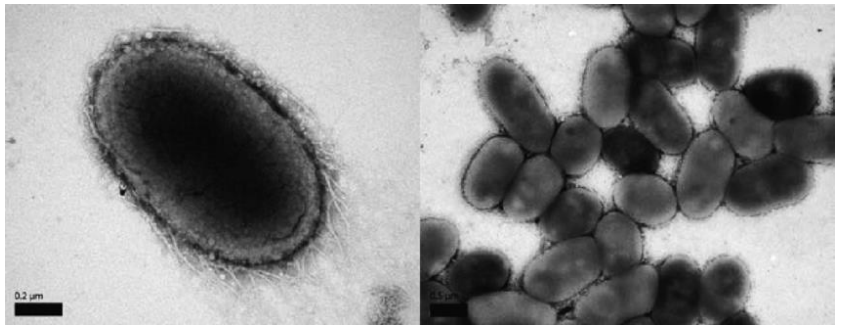


Li Sun, Yuting Zhang, Wang Dong, Jingzu Sun, Tao Wang, Fei Shao, Huanqin Dai, et al. 2025. *Akkermansia muciniphila*-derived hypoacylated rough-type lipopolysaccharides alleviate diet-induced obesity via activation of TLR4−IL-23−IL-22 immune axis. ***iMeta*** 4: e70066.
https://doi.org/10.1002/imt2.70066

背景



Akkermansia muciniphila

Efficacy

1. Prevention and treatment of obesity
预防和治疗肥胖
2.Promote intestinal barrier
促进肠道屏障
3.Manage diabetes
调节糖尿病
4.Delaying senescence
延缓衰老
5.Inhibit inflammation and improve metabolism
抑制炎症，改善代谢
6.Prevention of non-alcoholic fatty liver disease
预防非酒精性脂肪肝

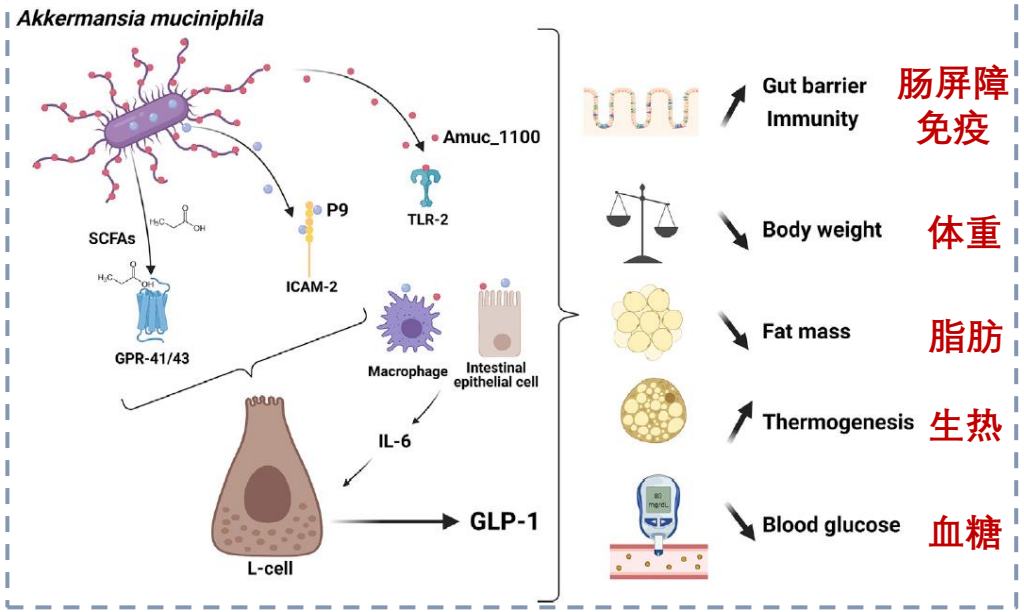
LETTERS
https://doi.org/10.1038/s41591-019-0495-2
nature medicine

临床试验：补充*A. muciniphila*可改善胖人代谢，死菌效果好

Supplementation with *Akkermansia muciniphila* in overweight and obese human volunteers: a proof-of-concept exploratory study

A. muciniphila改善小鼠动脉粥样硬化症状

***Akkermansia Muciniphila* Protects Against Atherosclerosis by Preventing Metabolic Endotoxemia-Induced Inflammation in *Apoe*$^{-/-}$ Mice**



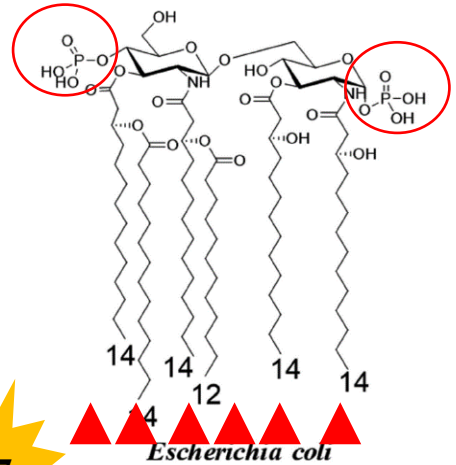
Cell Metab. 2021;33(6):1073-1075.

◆ ***A. muciniphila* 相关产品的成功上市**

Human Gut Microbiome Atlas available from https://www.microbiomeatlas.org

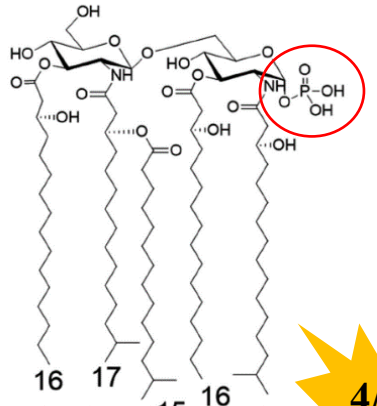
背景

2



Escherichia coli

6/7

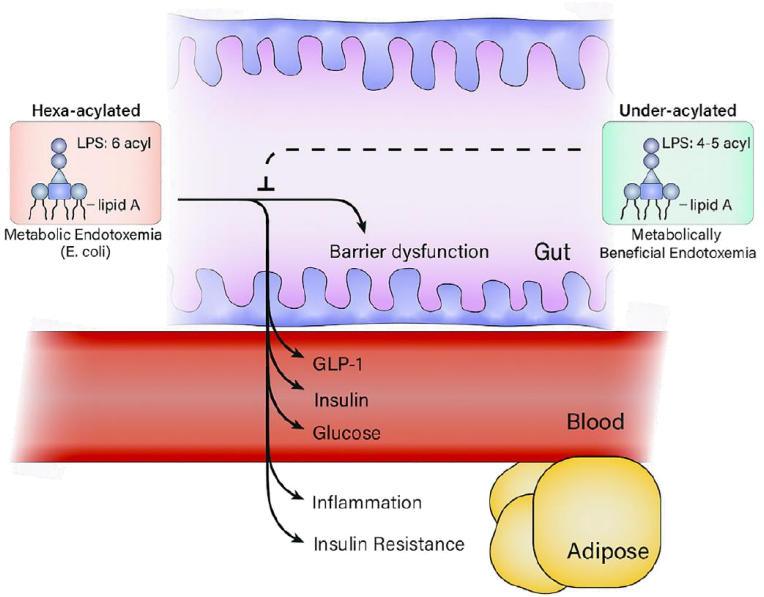


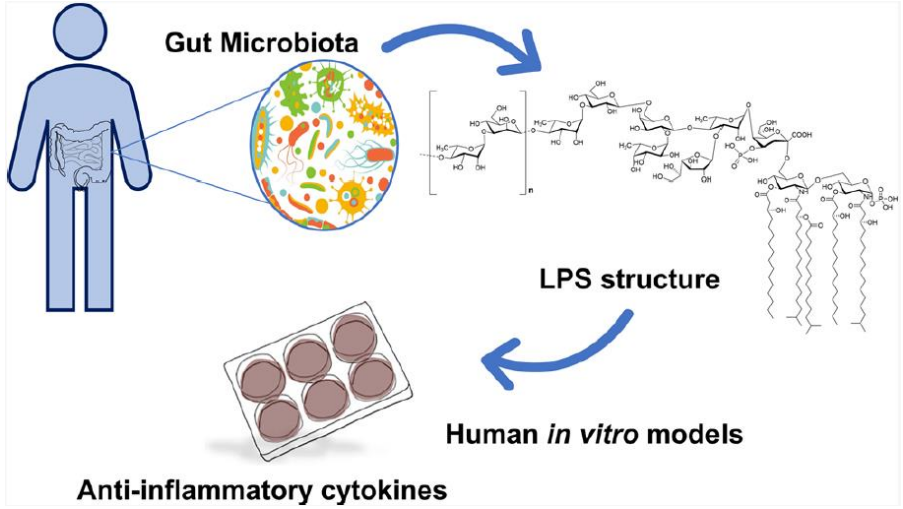
Bacteroides dorei

1

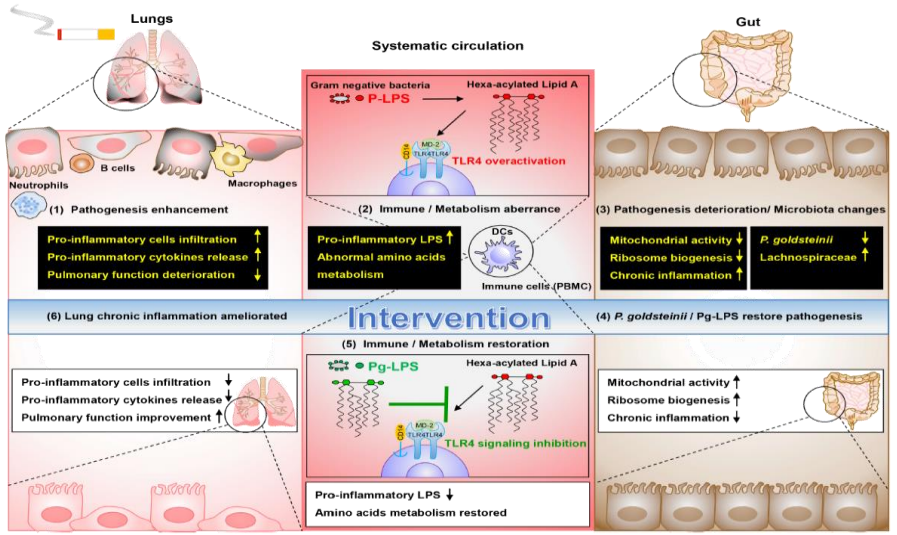
4/5

代谢性内毒素血症取决于脂多糖的类型





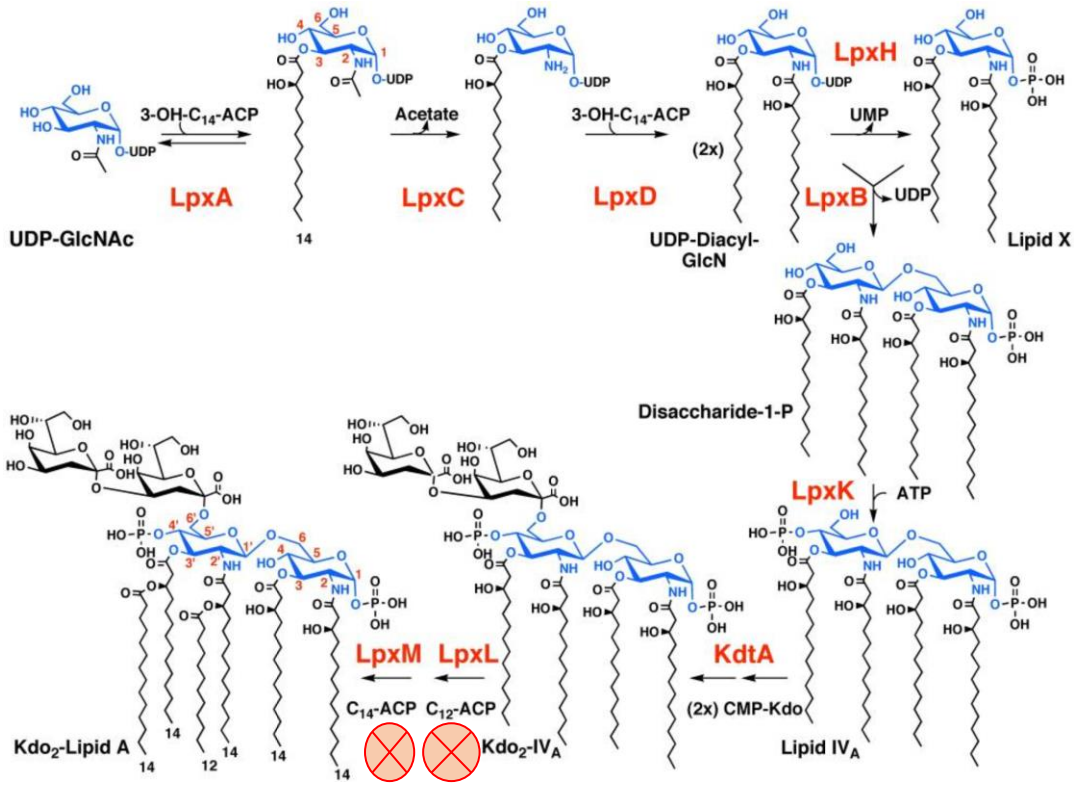
◆ 普通拟杆菌的五酰基化、单磷酸化LPS通过MD-2/TLR4信号通路发挥抗炎作用



◆ 戈氏副拟杆菌的五酰基化LPS可改善慢性阻塞性肺病

背景

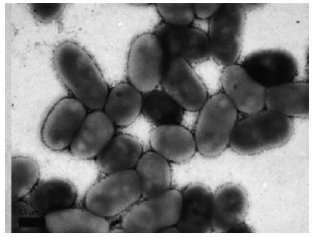
LPS的生物合成途径

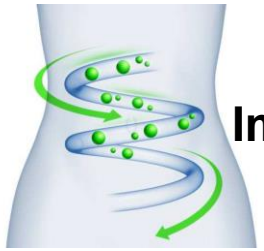


BLAST分析

Gene	Function	*E. coli* MG1655	*A. muciniphila* HW07	Identity (%)	Query cover (%)	E-value	*A. muciniphila* ATCC BAA-835	Identity (%)	Query cover (%)	E-value
lpxA	acyl-ACP-UDP-N-acetylglucosamine O-acyltransferase	B1XD50	JFJHEM_00188	48.3	87.02	4.5E-74	B2ULY0	48.3	87.02	4.5E-74
lpxB	lipid-A-disaccharide synthase	B1XD51	JFJHEM_02115	29.7	96.33	3E-48	Q5LH14	29.7	96.33	3E-48
lpxC	UDP-3- O-acyl- N - acetylglucosamine deacetylase	B1XC73	JFJHEM_01977	38.7	89.83	3.9E+54	B2UNL5	38.7	89.83	3.9E+54
lpxD	UDP-3-O-(3-hydroxymyristoyl) glucosamine N-acyltransferase	P21645	JFJHEM_00425	33.9	95.01	6.1E-51	B2UND2	33.9	95.01	6.1E-51
lpxF	lipid A 4'-phosphatase	P10441	—	—	—	—	—	—	—	—
lpxH	UDP-2,3-diacylglucosamine diphosphatase	P43341	—	—	—	—	—	—	—	—
lpxK	tetraacyldisaccharide 4'-kinase	B1X855	JFJHEM_00598	30.1	96.64	9.3E-28	B2UPD5	30.1	96.64	9.3E-28
lpxL	lauroyl/palmitoleoyl acyltransferase	P0ACV0	JFJHEM_01585	23.7		0.00000012	B2ULH5	23.7		0.00000012
lpxM	Lipid A biosynthesis myristoyltransferase	P24205	—				—			
lpxP	palmitoleoyl acyltransferase	P0ACV2	JFJHEM_01585	21.9	86.93	0.00000012	B2ULH5	21.9	86.93	0.00000012

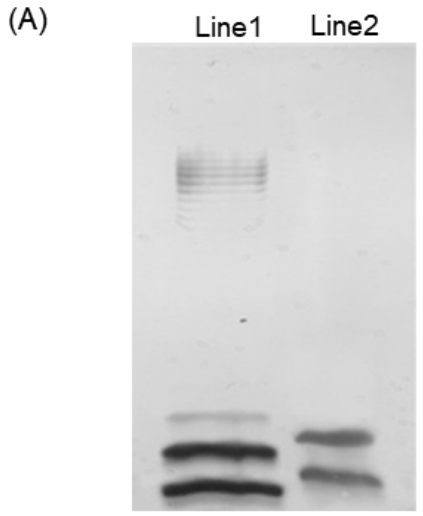
- 基因组预测嗜黏蛋白阿克曼氏菌脂多糖生物合成途径中缺失次级脂肪酸链合成基因

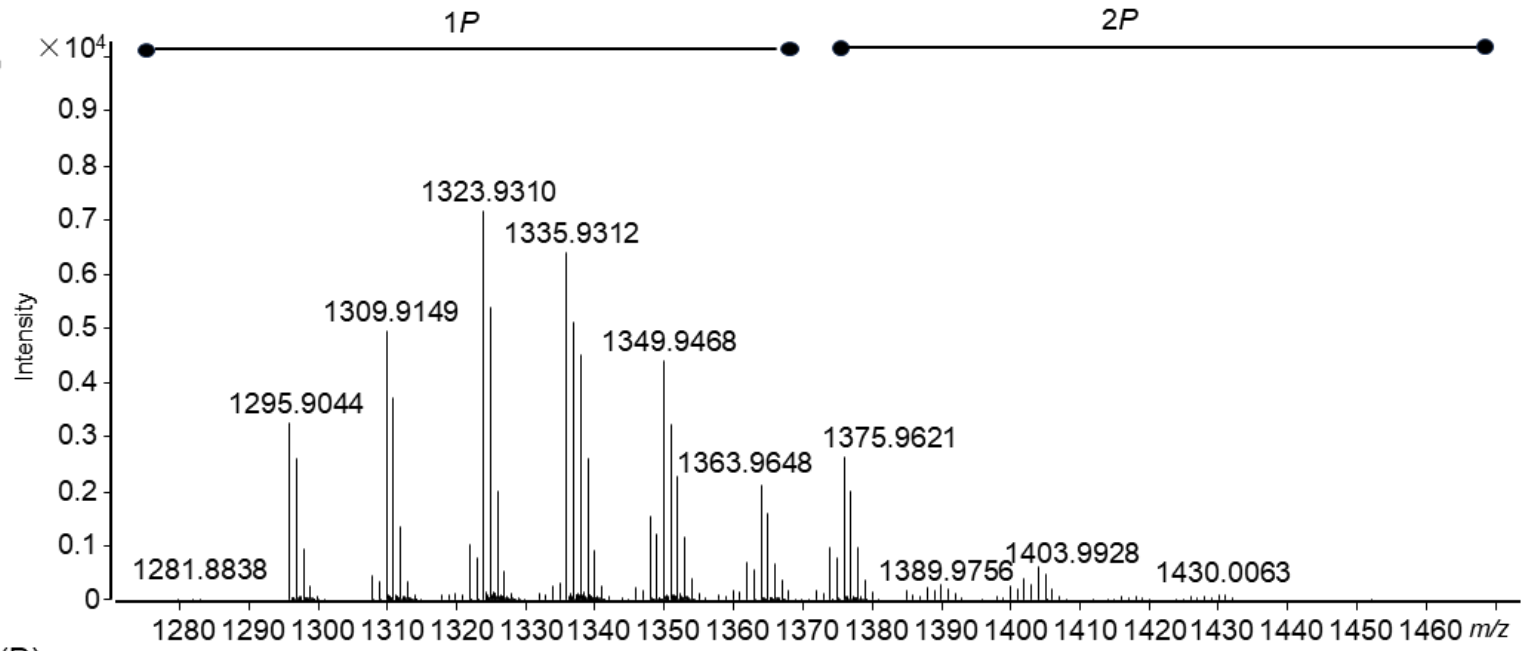


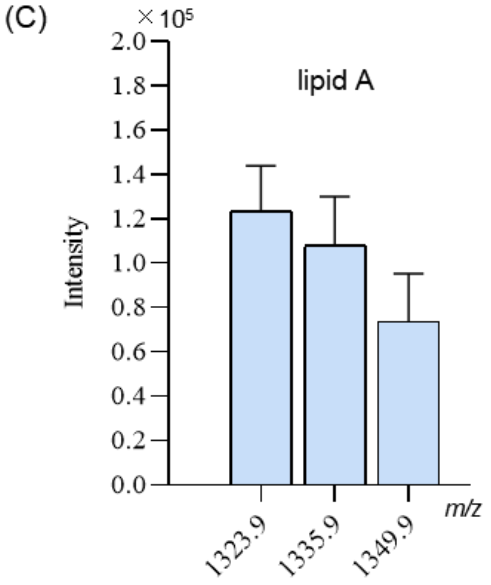
→ *A.muciniphila* LPS → ?  Improve metabolism

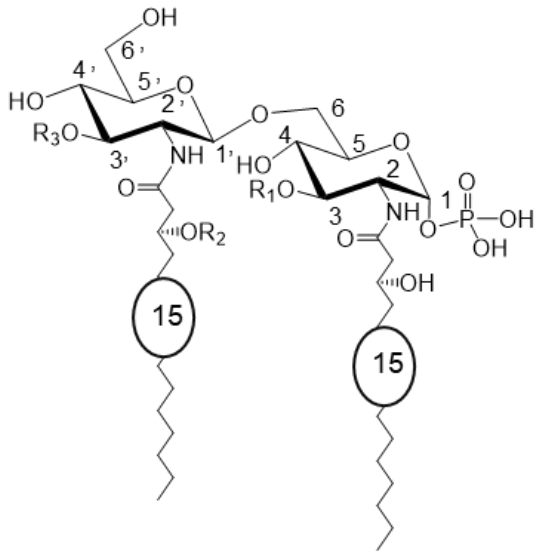
J Lipid Res. 2009;50 :S103-S108.

脂多糖的SDS-PAGE银染及代表性脂质A化学结构表征



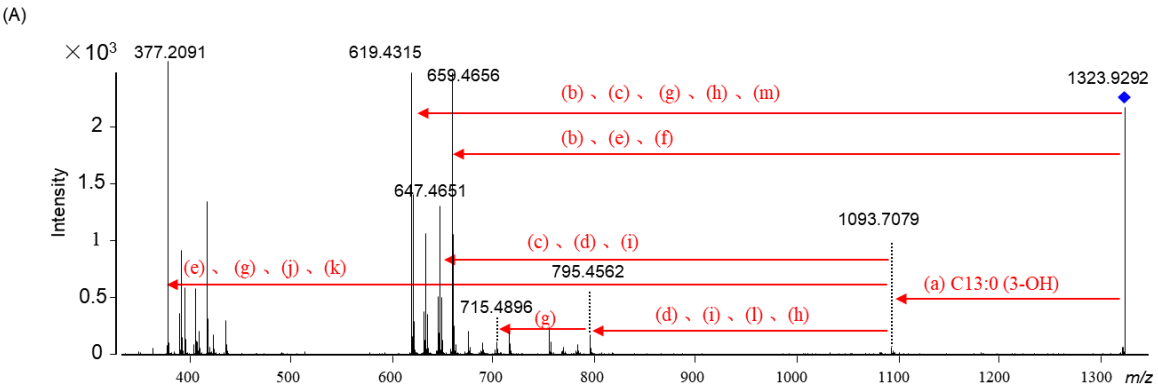


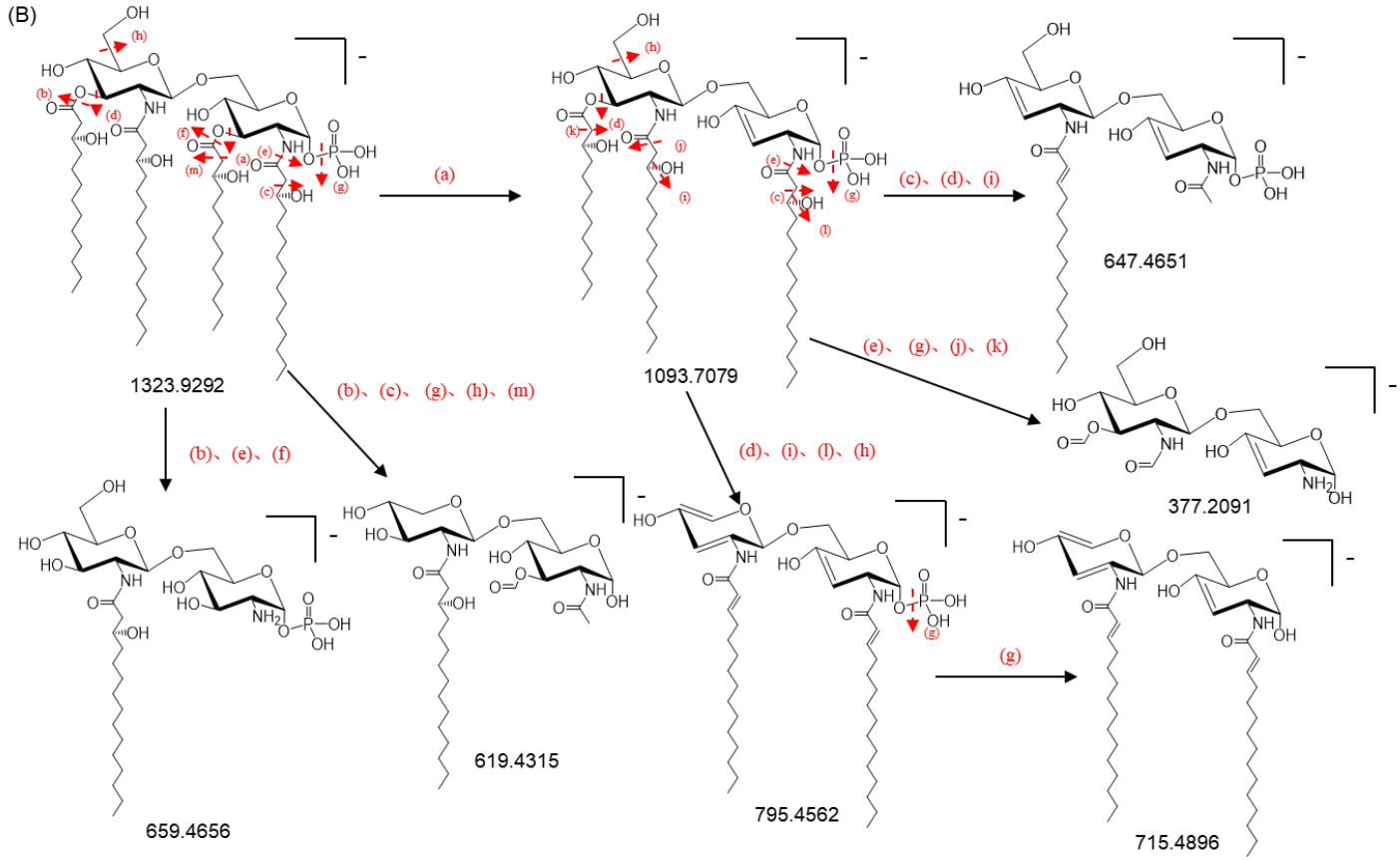




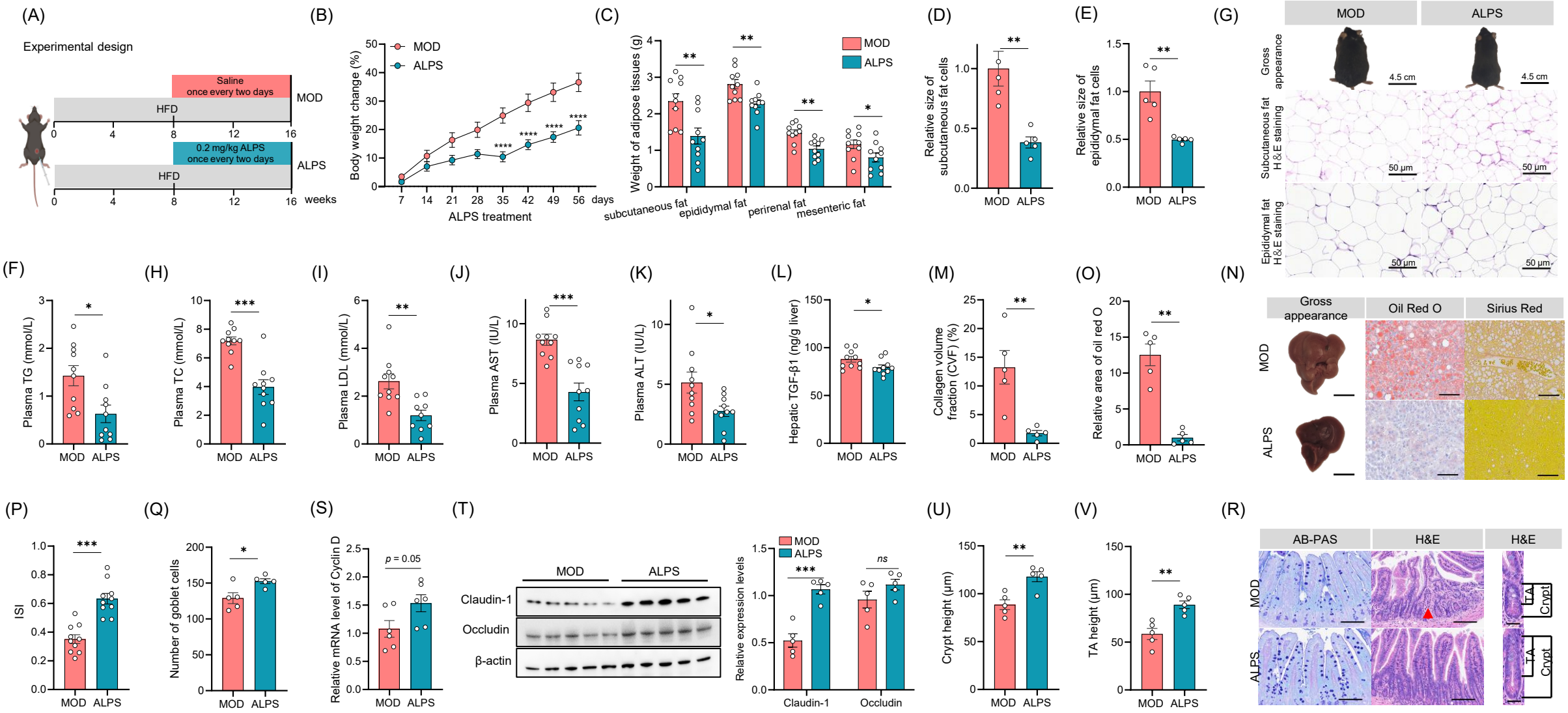
m/z	R_1	R_2	R_3
1323.9310	C13:0 (3-OH)	H	C13:0 (3-OH)
1335.9312	C13:0 (3-OH)	C15:0	H
1349.9468	C14:0 (3-OH)	C15:0	H

ALPS中脂质A的HPLC-ESI-MS2二级质谱分析





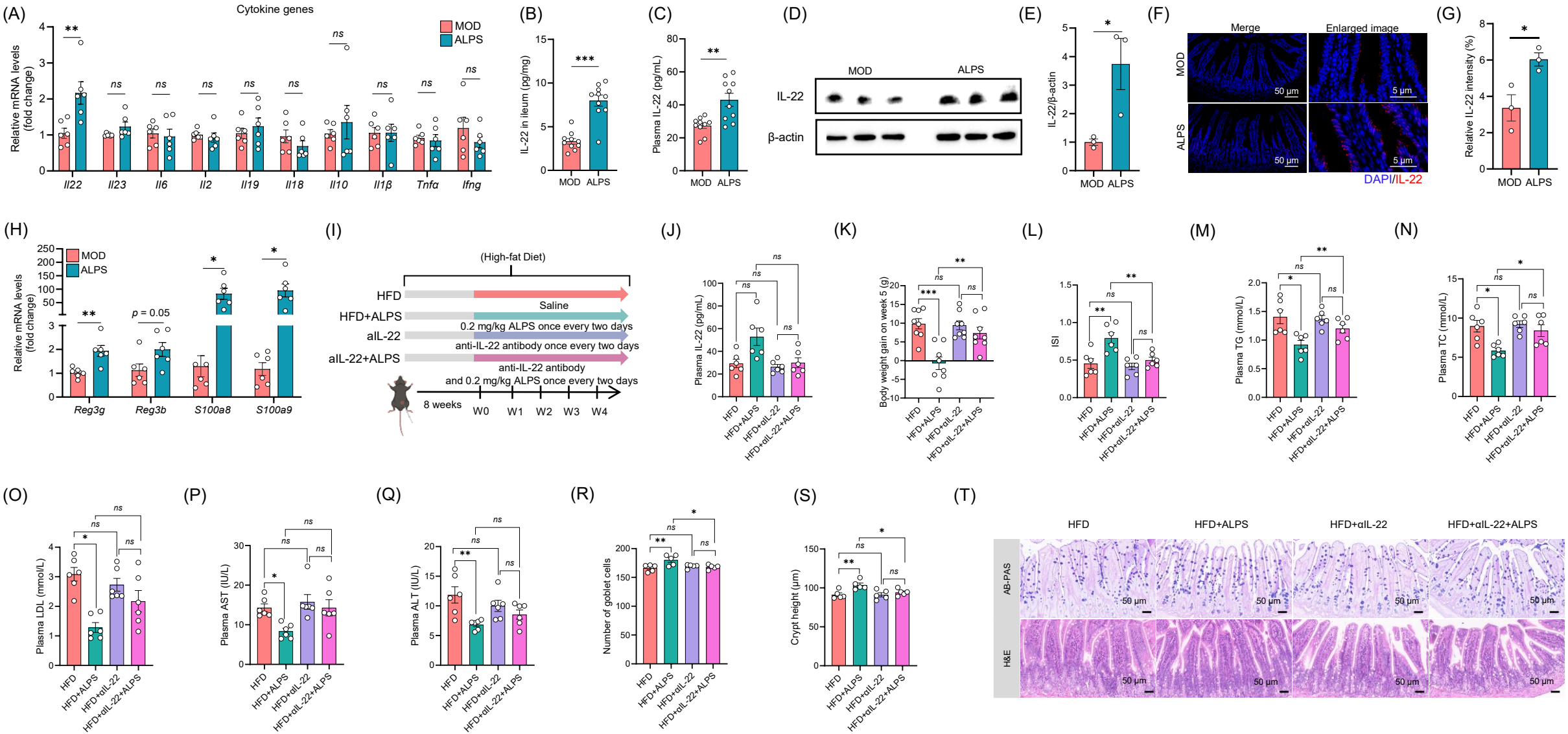
ALPS缓解了饮食诱导肥胖（DIO）小鼠的代谢紊乱



改善代谢紊乱，肠道屏障功能

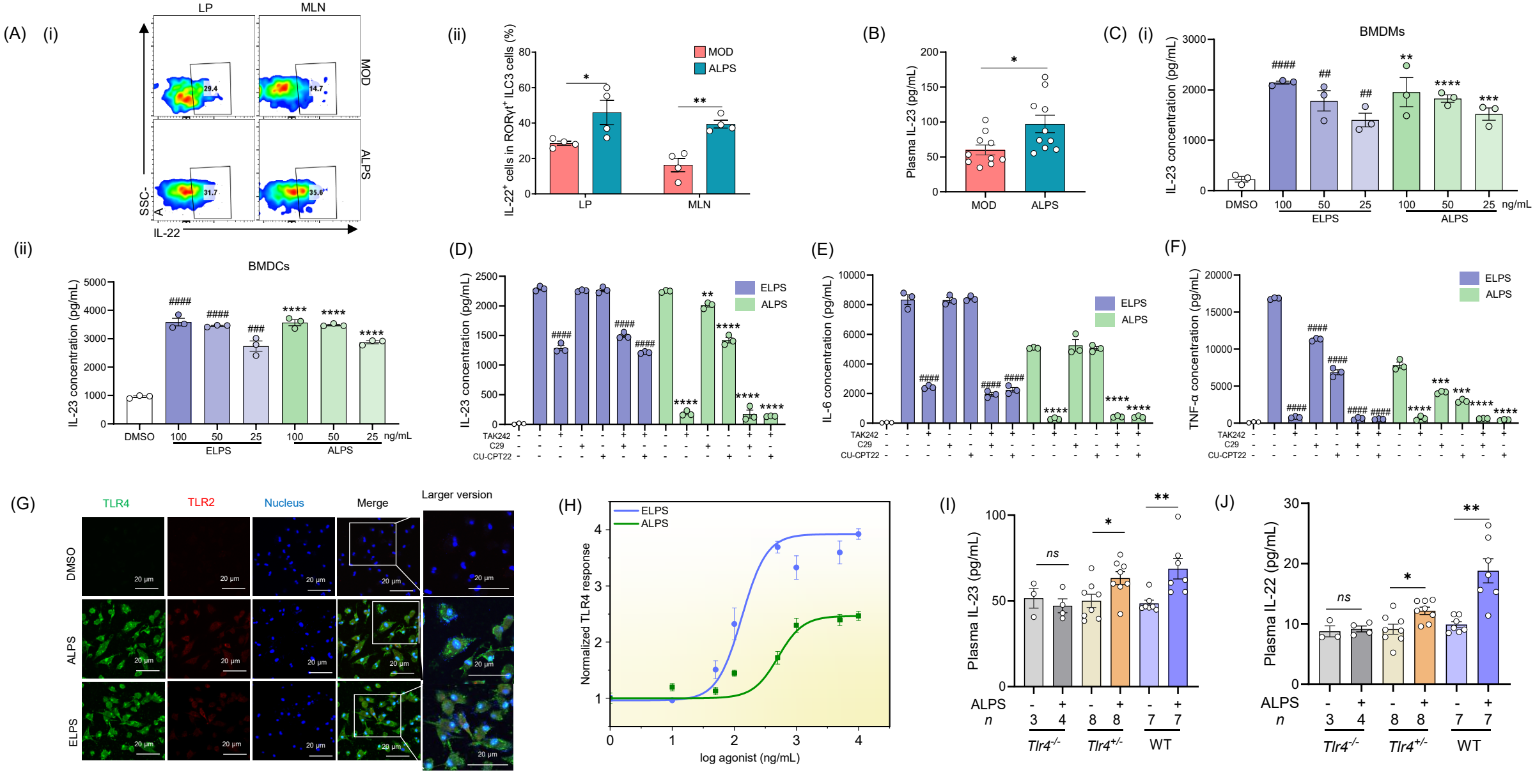
ALPS促进DIO小鼠中IL-22的产生

检测IL-22的产生



抗体中和IL-22

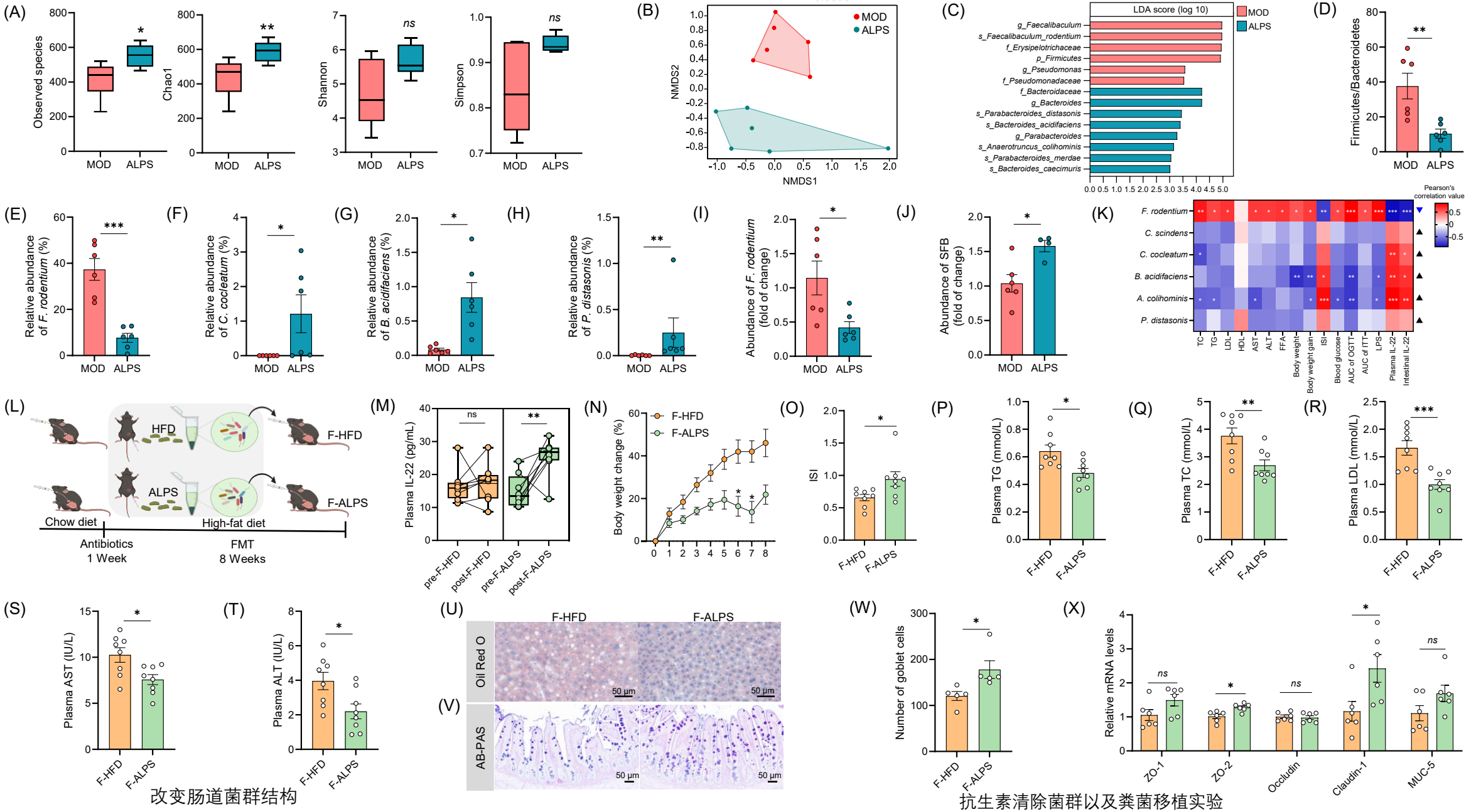
ALPS激活TLR4–IL-23–IL-22信号通路



TLR4受体的筛选

IL-22及其上游IL-23的产生

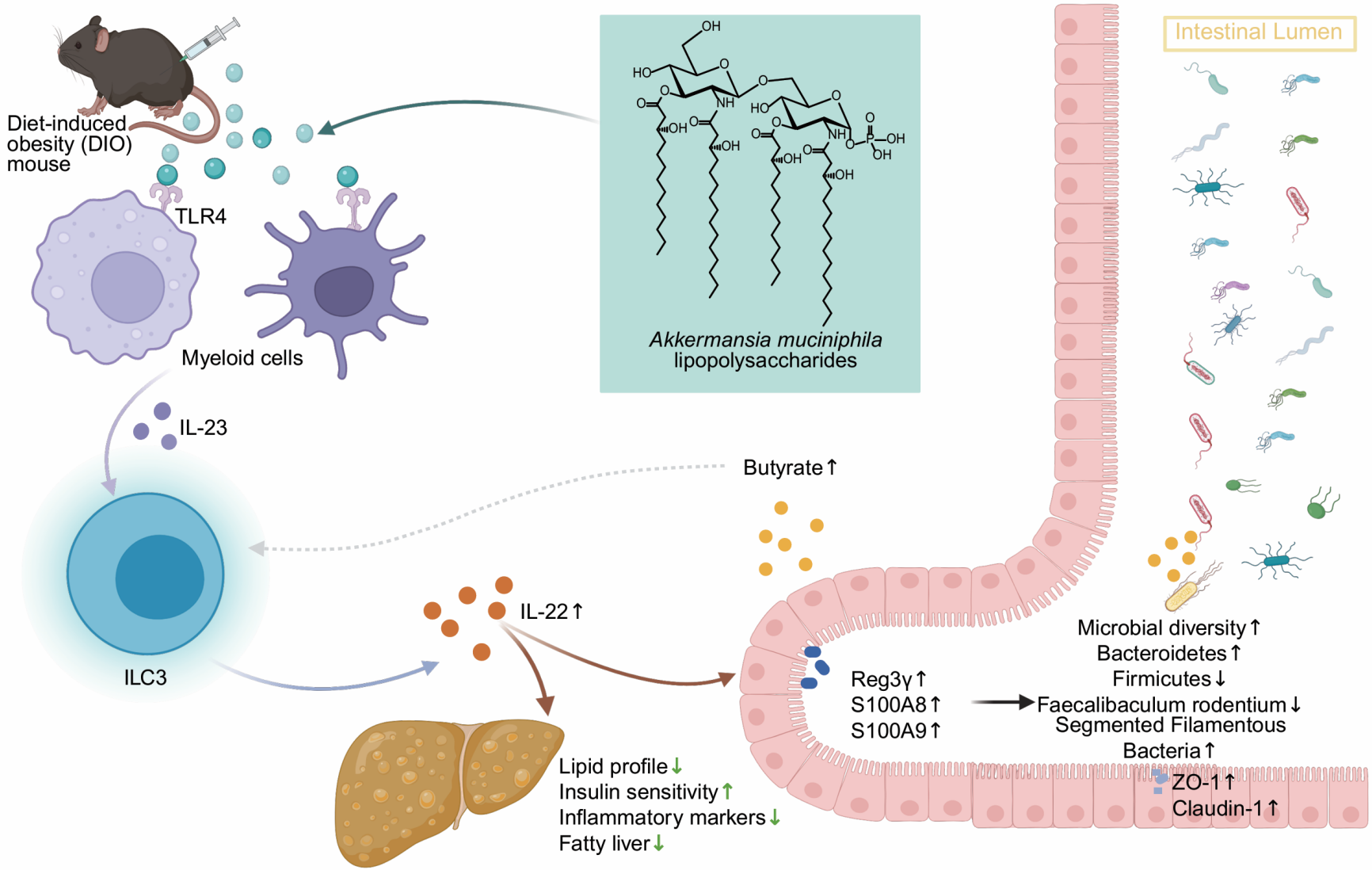
ALPS改变肠道菌群结构及ALPS诱导的肠道菌群在DIO小鼠中的保护作用



改变肠道菌群结构

抗生素清除菌群以及粪菌移植实验

总结



Li Sun, Yuting Zhang, Wang Dong, Jingzu Sun, Tao Wang, Fei Shao, Huanqin Dai, et al. 2025. Akkermansia muciniphila-derived hypoacylated rough-type lipopolysaccharides alleviate diet-induced obesity via activation of TLR4−IL-23−IL-22 immune axis. ***iMeta*** 4: e70066.
https://doi.org/10.1002/imt2.70066

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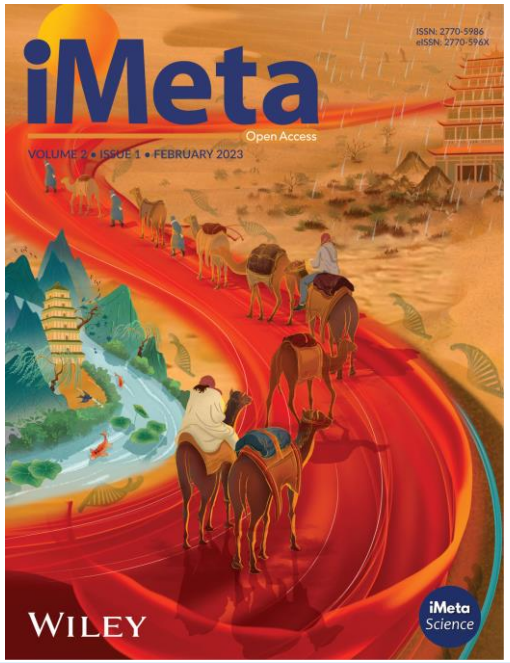

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