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Renoprotective Effects of Empagliflozin in Obesity-Related Glomerulopathy Mice through Regulation the Gut-Kidney Axis

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Objectives : The rising incidence of obesity-related glomerulopathy (ORG) poses a significant threat to public health. Sodium-glucose co-transporter-2 (SGLT2) inhibitors effectively reduce body weight and total fat mass in obese individuals, as well as to halt the progression of ORG. However, the underlying mechanism of the renoprotective effects of SGLT2 inhibitors in ORG remains unclear.
Methods : A high-fat diet-induced ORG model was established using C57BLJ mice. The mice were divided into three groups: normal chow diet (NCD group), high-fat diet (HFD) mice treated with placebo (ORG group), and HFD mice treated with Empagliflozin (EMPA) (EMPA group). 16S ribosomal RNA gene sequencing of feces, and metabolites of kidney, feces, liver and serum were analyzed.
Results : We found that the levels of the urinary albumin creatinine ration, cholesterol, triglyceride and diameter of glomerulus increased in ORG mice compared to NCD mice (all $p < 0.0001$); EMPA treatment alleviated these parameters (all $p < 0.05$). Multi-tissues metabolomics analysis revealed lipid metabolic reprogramming in ORG mice, and EMPA treatment altered the metabolic profiles. Furthermore, MetOrigin analysis unveiled a close association between EMPA-related lipid metabolic pathways and gut microbiota alterations, characterized by reduced abundances of Firmicutes and Desulfovibrio, and increased abundance of Akkermansia (all $p < 0.05$).
Conclusions : The metabolomic homeostasis of ORG mice was disrupted, especially in lipid metabolism. This disruption is closely associated with gut microbiota and is related to the progression of ORG. EMPA treatment improved kidney function and morphology by regulating lipid metabolic through the gut-kidney axis.

Figure 2.png

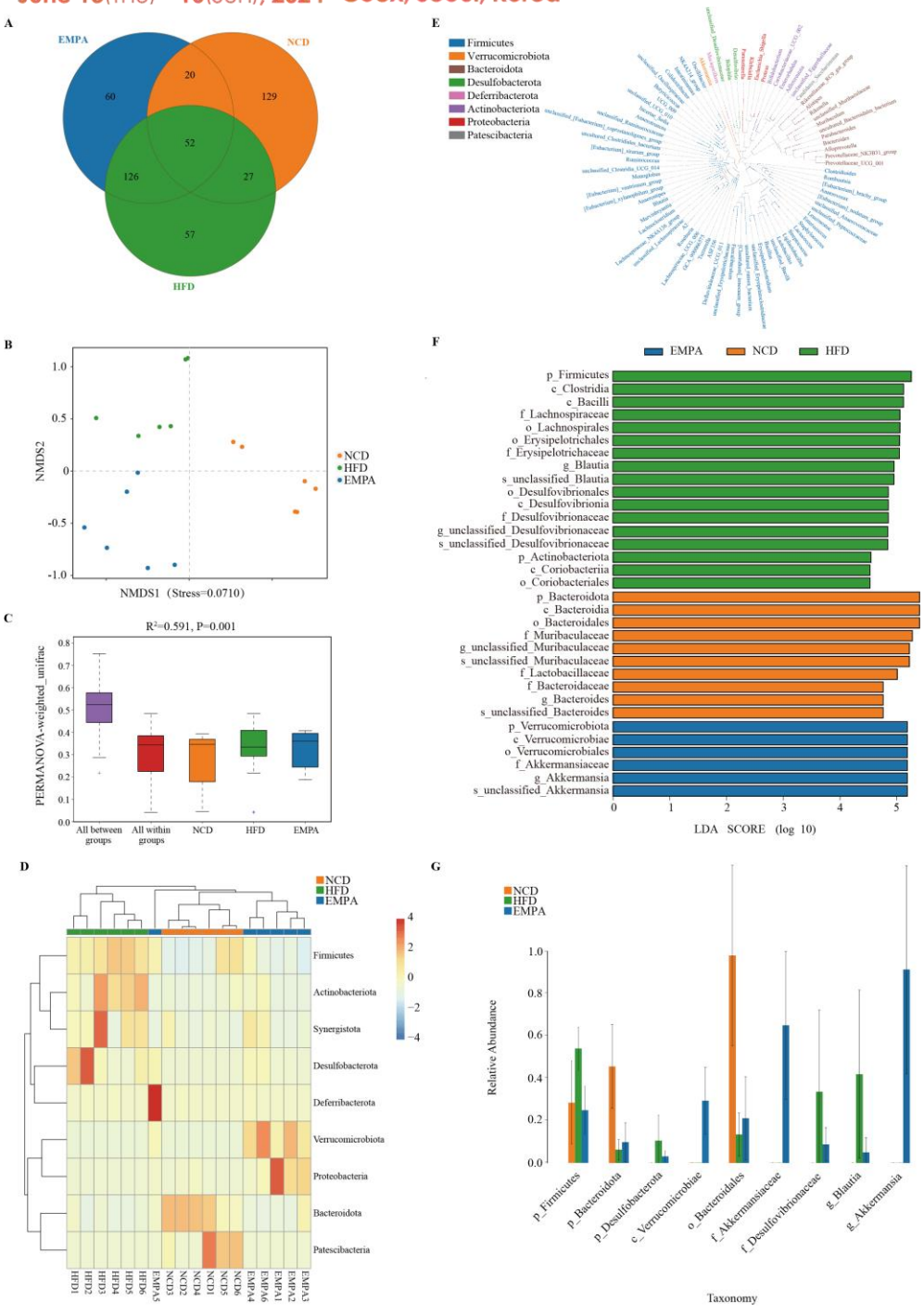
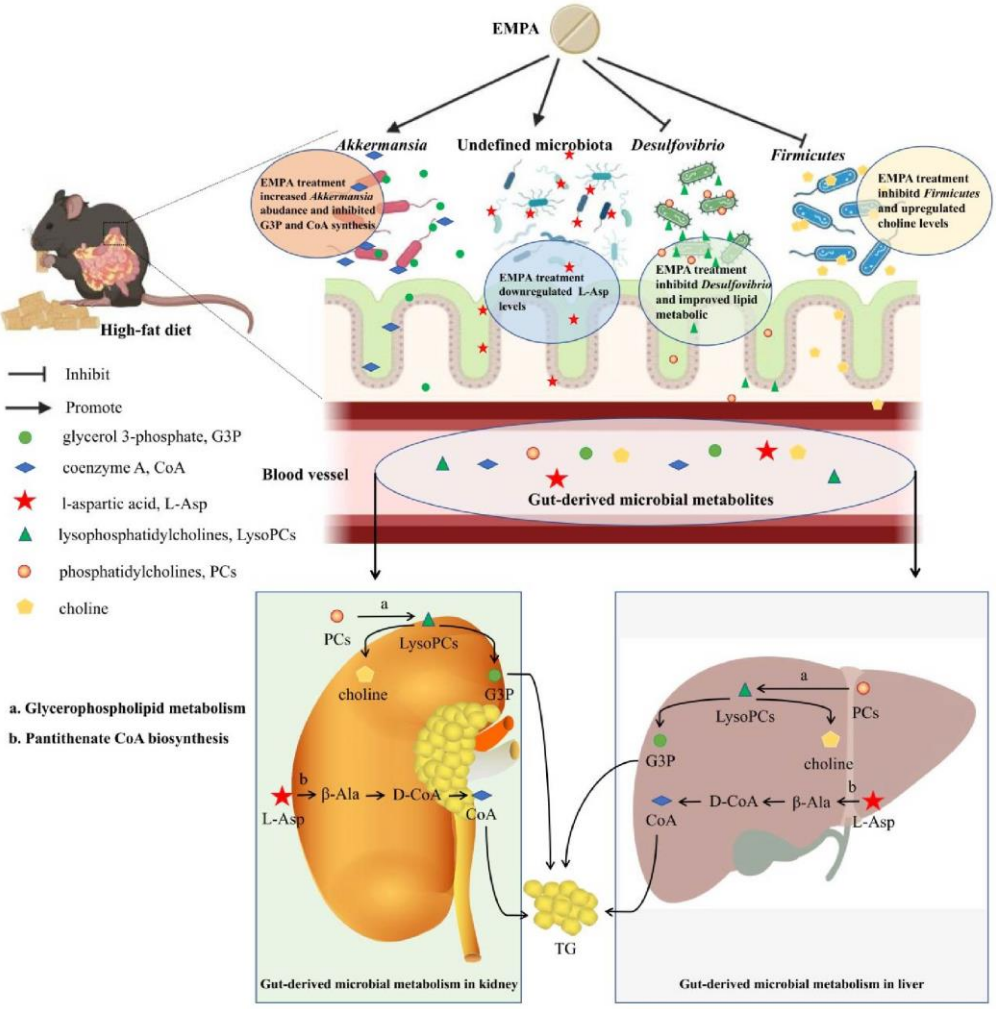

A
EMPA
NCD
HFD
60
20
129
52
126
27
57
B
NMDS2
NMDS1 (Stress=0.0710)
NCD
HFD
EMPA
C
R²=0.591, P=0.001
PERMANOVA-weighted_unifrac
All between groups
All within groups
NCD
HFD
EMPA
D
NCD
HFD
EMPA
Firmicutes
Actinobacteriota
Synergistota
Desulfobacterota
Deferribacterota
Verrucomicrobiota
Proteobacteria
Bacteroidota
Patescibacteria
E
Firmicutes
Verrucomicrobiota
Bacteroidota
Desulfobacterota
Deferribacterota
Actinobacteriota
Proteobacteria
Patescibacteria
F
EMPA
NCD
HFD
p_Firmicutes
c_Clostridia
o_Lachnospirales
o_Erysipelotrichales
f_Erysipelotrichaceae
g_Blautia
s_unclassified_Blautia
o_Desulfovibrionales
c_Desulfovibrionia
f_Desulfovibrionaceae
g_unclassified_Desulfovibrionaceae
s_unclassified_Desulfovibrionaceae
p_Actinobacteriota
c_Coriobacteriia
o_Coriobacteriales
p_Bacteroidota
c_Bacteroidia
o_Bacteroidales
f_Muribaculaceae
g_unclassified_Muribaculaceae
s_unclassified_Muribaculaceae
f_Lactobacillaceae
f_Bacteroidaceae
g_Bacteroides
s_unclassified_Bacteroides
p_Verrucomicrobiota
c_Verrucomicrobiae
o_Verrucomicrobiales
f_Akkermansiaceae
g_Akkermansia
s_unclassified_Akkermansia
LDA SCORE (log 10)
G
NCD
HFD
EMPA
Relative Abundance
p_Firmicutes
p_Bacteroidota
p_Desulfobacterota
c_Verrucomicrobiae
o_Bacteroidales
f_Akkermansiaceae
f_Desulfovibrionaceae
g_Blautia
g_Akkermansia
Taxonomy

Figure 2.png


EMPA
Akkermansia
Undefined microbiota
Desulfovibrio
Firmicutes
EMPA treatment increased Akkermansia abudance and inhibited G3P and CoA synthesis
EMPA treatment downregulated L-Asp levels
EMPA treatment inhibitd Desulfovibrio and improved lipid metabolic
EMPA treatment inhibitd Firmicutes and upregulated choline levels
High-fat diet
Inhibit
Promote
glycerol 3-phosphate, G3P
coenzyme A, CoA
l-aspartic acid, L-Asp
lysophosphatidylcholines, LysoPCs
phosphatidylcholines, PCs
choline
Blood vessel
Gut-derived microbial metabolites
a. Glycerophospholipid metabolism
b. Pantithenate CoA biosynthesis
PCs
LysoPCs
choline
G3P
L-Asp
β-Ala
D-CoA
CoA
TG
Gut-derived microbial metabolism in kidney
Gut-derived microbial metabolism in liver