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# Ceramide Mediates the Mitochondrial Dysfunction in Diabetic Kidney Disease

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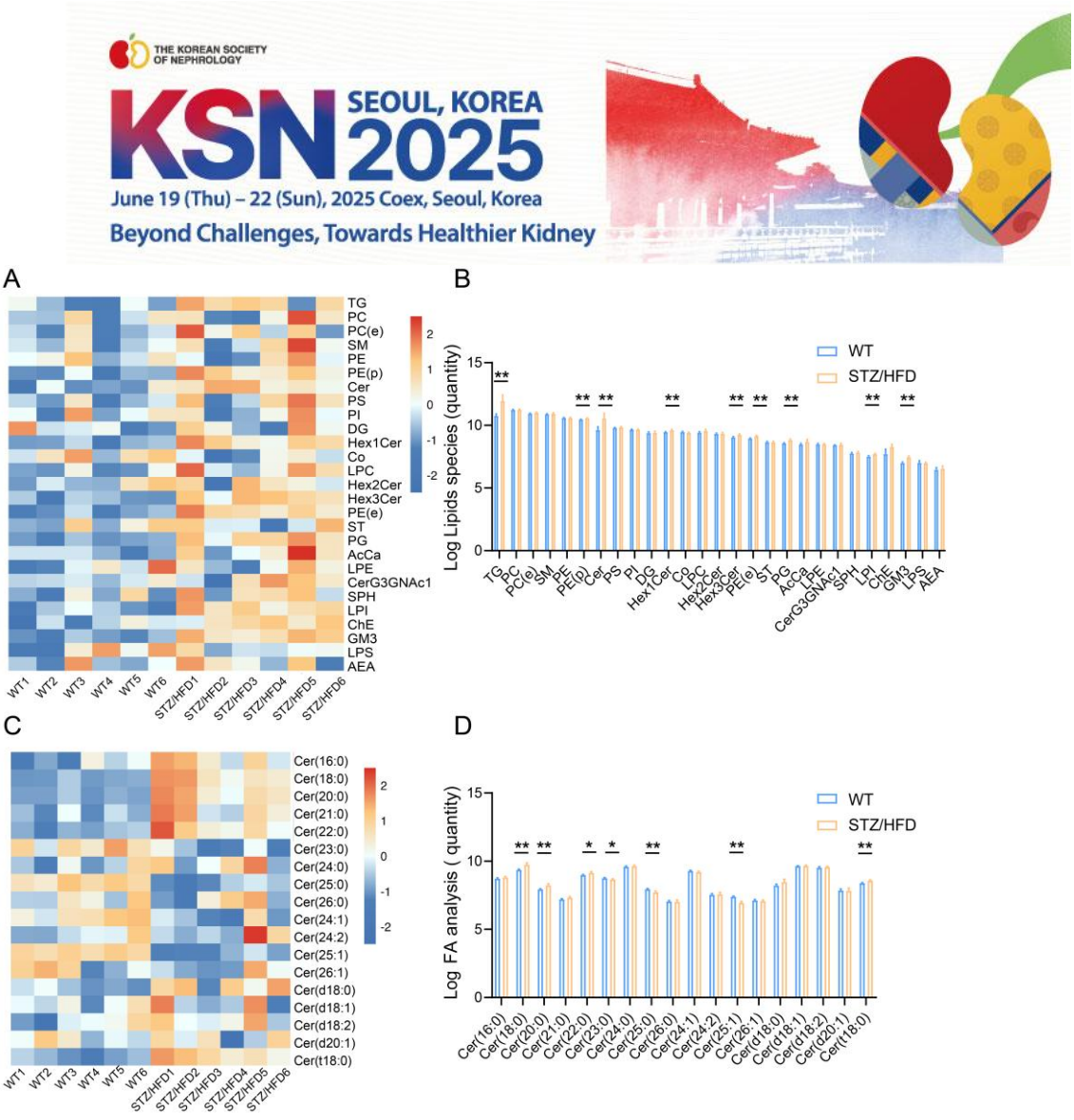
**Objectives :** Cumulating evidences suggested the pathogenic role of phospholipid metabolism in diabetic kidney disease (DKD). The current study aimed to investigate the effect of ceramide (Cer) on lipid metabolism in the development of DKD.
**Methods :** Streptozotocin combined with high-fat diet induced diabetes mice were divided into diabetes mice and control mice, and the changes of proteinuria and kidney injury were detected. Lipidomes and transcriptomic analysis was conducted on the kidney cortex of diabetes model mice and their litters of wild-type mice. Further, the differences in mitochondrial damage and apoptosis were compared between the two groups of mice.
**Results :** Compared with wild-type mice, urinary protein, renal tubulointerstitial injury, foot process fusion of podocyte, and renal inflammatory infiltration were aggravated in diabetic mice. Furthermore, the results showed that many lipid components, including triglycerides, sphingolipids, and phospholipids, were different between the two groups. According to the classification of ceramide with different fatty acid chain lengths, the contents of Cer (18:0), Cer (20:0), Cer (22:0) and Cer (t18:0) in the kidney tissues of diabetic mice were significantly increased compared with those of wild-type mice. Ultra-long chain ceramides such as Cer (23:0), Cer (25:0), and Cer (25:1) were significantly reduced. There were significant differences in ceramide synthase in proximal tubular epithelial cells between the two groups. Compared with wild-type mice, the renal cortical cleaved caspase-3/caspase-3 ratio of diabetic mice was significantly increased. Transcriptomic analysis showed that genes related to apoptosis and division/fusion of mitochondrial pathway cells. Compared with wild-type mice, Bax and MFF were significantly increased, while Bcl-2, MFN1 and MFN2 were significantly decreased in diabetic mice, and mitochondria became swollen and mitochondrial ridge was disorganized or partially disappeared.
**Conclusions :** These results indicated that the renal ceramide profile of diabetic mice was changed and was closely related to mitochondrial dysfunction.

1.jpg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Beyond Challenges, Towards Healthier Kidney
A
TG
PC
PC(e)
SM
PE
PE(p)
Cer
PS
PI
DG
Hex1Cer
Co
LPC
Hex2Cer
Hex3Cer
PE(e)
ST
PG
AcCa
LPE
CerG3GNAc1
SPH
LPI
ChE
GM3
LPS
AEA
WT1 WT2 WT3 WT4 WT5 WT6 STZ/HFD1 STZ/HFD2 STZ/HFD3 STZ/HFD4 STZ/HFD5 STZ/HFD6
B
Log Lipids species (quantity)
WT
STZ/HFD
C
Cer(16:0)
Cer(18:0)
Cer(20:0)
Cer(21:0)
Cer(22:0)
Cer(23:0)
Cer(24:0)
Cer(25:0)
Cer(26:0)
Cer(24:1)
Cer(24:2)
Cer(25:1)
Cer(26:1)
Cer(d18:0)
Cer(d18:1)
Cer(d18:2)
Cer(d20:1)
Cer(t18:0)
D
Log FA analysis ( quantity)
WT
STZ/HFD

1.jpg


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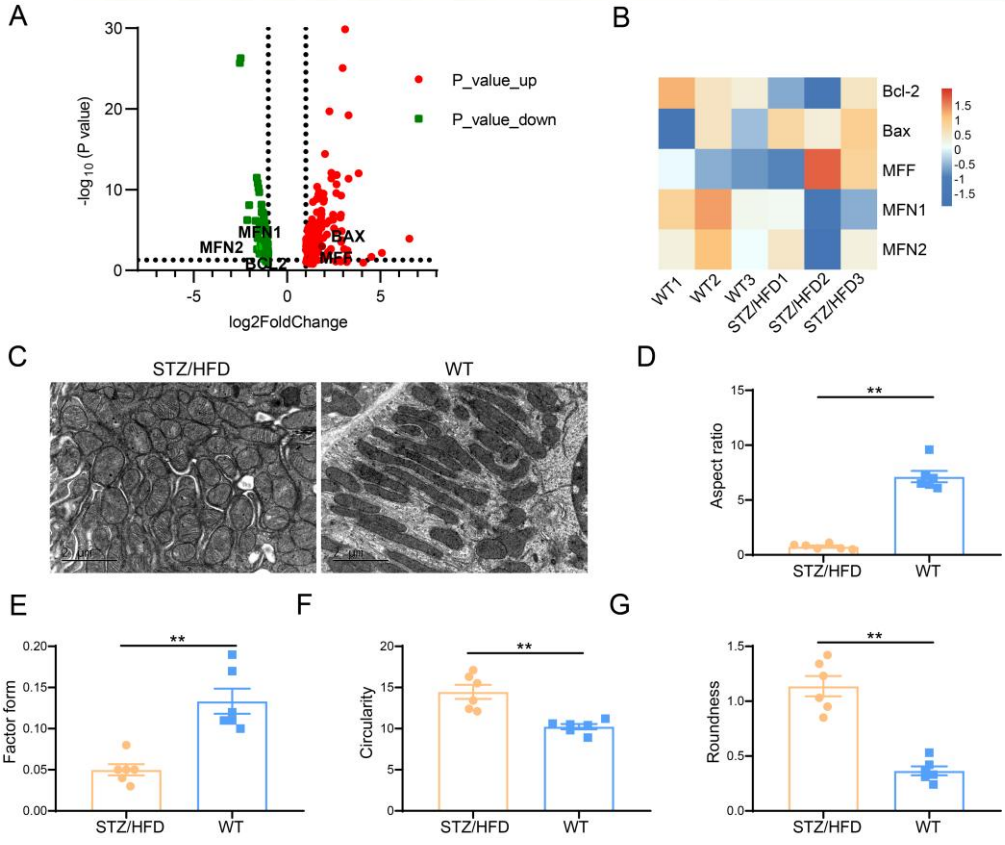
A
B
C
D
E
F
G
P_value_up
P_value_down
-log10 (P value)
log2FoldChange
MFN1
MFN2
BAX
BCL2
MFF
Bcl-2
Bax
MFF
MFN1
MFN2
WT1
WT2
WT3
STZ/HFD1
STZ/HFD2
STZ/HFD3
STZ/HFD
WT
Aspect ratio
Factor form
Circularity
Roundness
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