Supplementary Figures

Figure S1: Related to figure 1

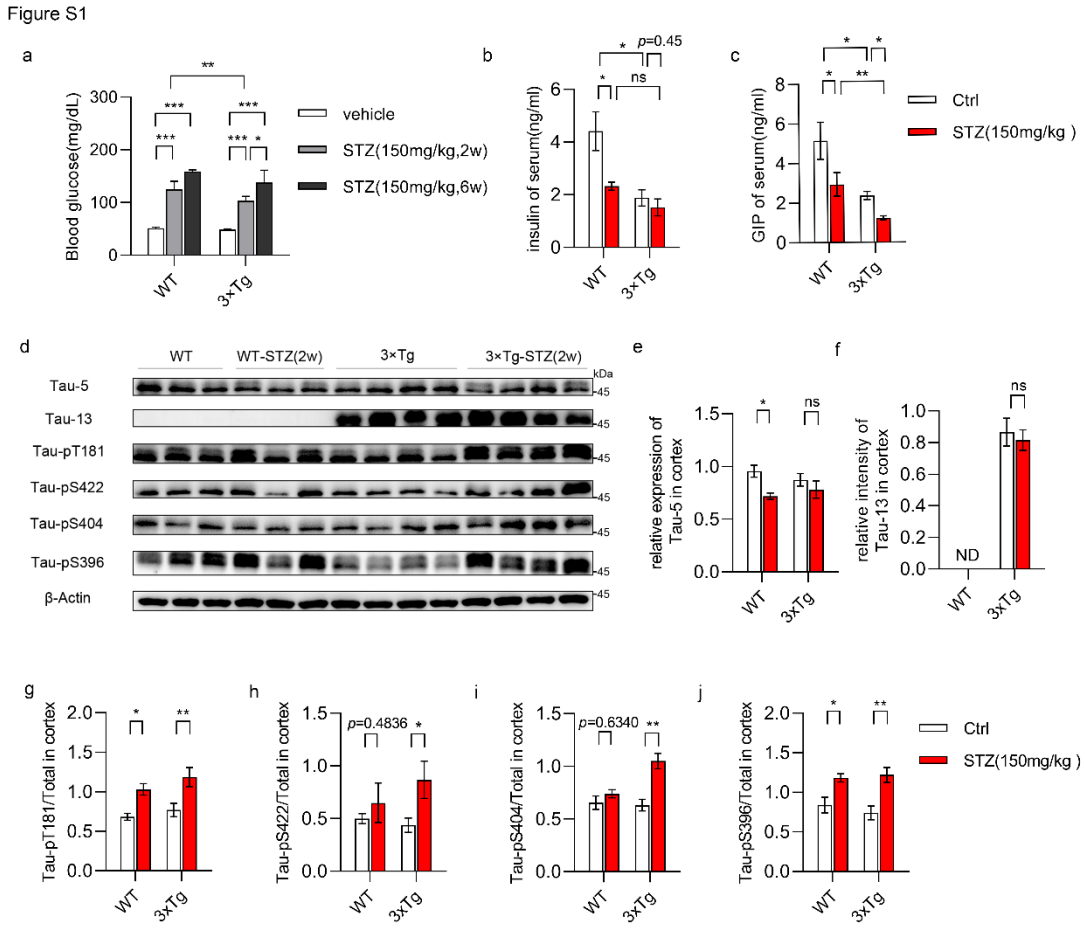


Figure S1 STZ injection induced tau phosphorylation in 3xTg AD mice

a, The fasting blood glucose levels of WT and 3xTg AD model mice at 4 months of age were measured (WT, n=14. 3x Tg AD, n=18), and then these mice were subjected to STZ treatment, thereafter, the fasting blood glucose were measured at 2 w (WT, n=8. 3x Tg AD, n=11) as well as at 6 w (WT, n=6. 3x Tg AD, n=7) after STZ injection, respectively. The results are shown as the mean±s.e.m., **P*<0.05, ***P*<0.01, ****P*<0.001 by two-way ANOVA with Tukey's test.

b-c, The levels of insulin (**b**) and GIP (**c**) in non-fasting serum of WT mice (n=3) and 3xTg AD model mice (n=6) that were injected with STZ (150 mg/kg) for 2 w, compared with that of WT mice (n=4) and 3xTg AD model mice (n=7) which were injected with PBS. The results are shown as the mean±s.e.m., **P*<0.05, ***P*<0.01, by two-way ANOVA with Tukey's test.

d, Immunoblot and quantifications of the protein levels of total tau and the phosphorylation levels of tau.

e-j, total tau (tau-5) (**e**), human tau (tau-13) (**f**), phosphorylated tau-pT181 (**g**), tau-pS422 (**h**), tau-pS404 (**i**), tau-pS396 (**j**) in the lysates of cortex from WT mice injected with PBS (n=3), or STZ (n=3) for 2 w, as well as 3xTg AD model mice injected with PBS (n=4), or STZ (n=4) for 2 w. The results are shown as the mean±s.e.m., **P*<0.05, ***P*<0.01, by two-tailed unpaired student's *t*-test (**e-j**).

Figure S2: Related to figure 2

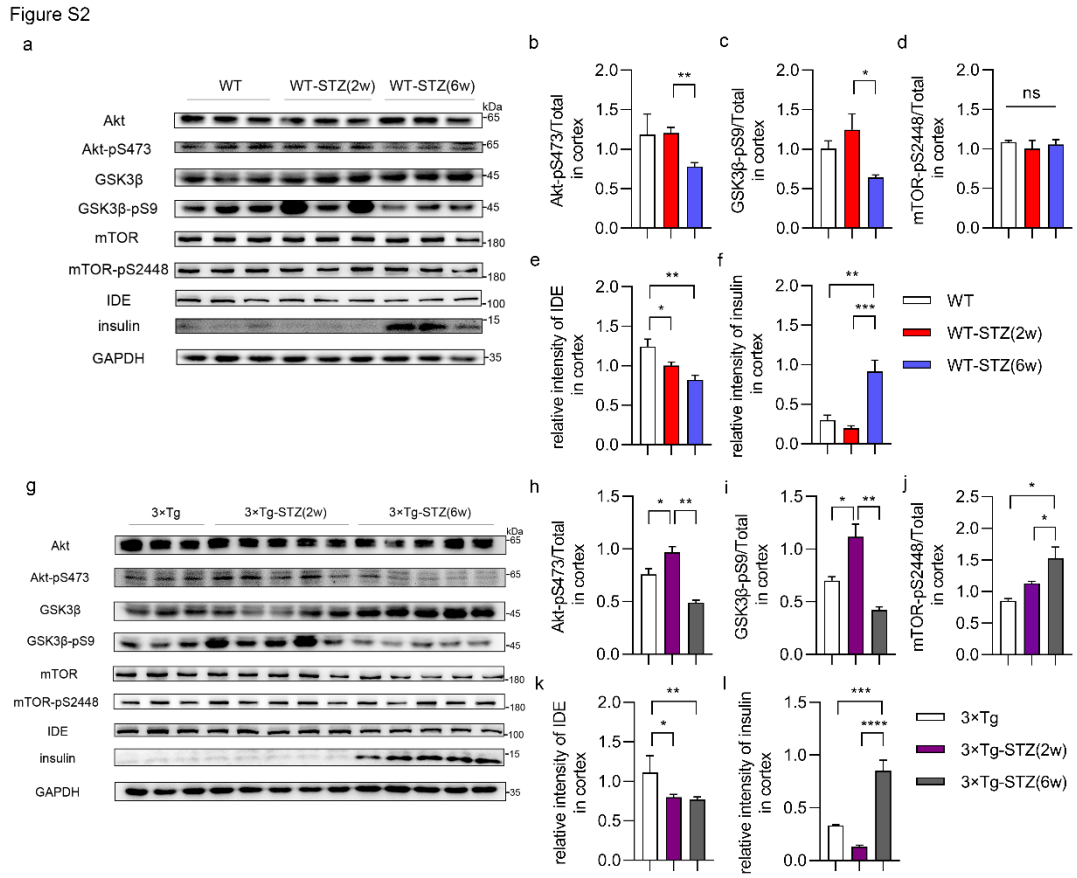


Figure S2 Prolonged hyperglycemia induced insulin resistance in brain

a, WT mice injected with STZ for 2 w (n=3), and 6 w (n=3), respectively, the lysates of cortex were isolated and subjected for immunoblot analysis compared with that of WT mice (n=3) injected with PBS for 2 w.

b-f, Quantifications of the blot were shown as the mean ± s.e.m. of the ratios of Akt-pS473/Akt (**b**), GSK3β-pS9/GSK3β (**c**), mTOR-pS2448/mTOR (**d**), IDE/GAPDH (**e**), and insulin/GAPDH (**f**). The results are shown as the mean ± s.e.m., **P*<0.05, ***P*<0.01, ****P*<0.001, by one-way ANOVA with Tukey's test.

g, 3x Tg AD mice were injected with STZ for 2 w (n=5), and 6 w (n=5), respectively, the lysates of cortex were isolated and subjected for **i**mmunoblot analysis compared with that of 3x Tg AD mice (n=3) injected with PBS for 2 w (n=3).

h-l, Quantifications the blot were shown as the mean±s.e.m. of the ratios of Akt-pS473/Akt (**h**), GSK3β-pS9/GSK3β (**i**), and mTOR-pS2448/mTOR (**j**), IDE/GAPDH (**k**), and insulin/GAPDH (**l**), The results are shown as the mean ± s.e.m., **P*<0.05, ***P*<0.01, ****P*<0.001, *****P*<0.0001 by one-way ANOVA with Tukey's test.

Figure S3: Related to figure 2

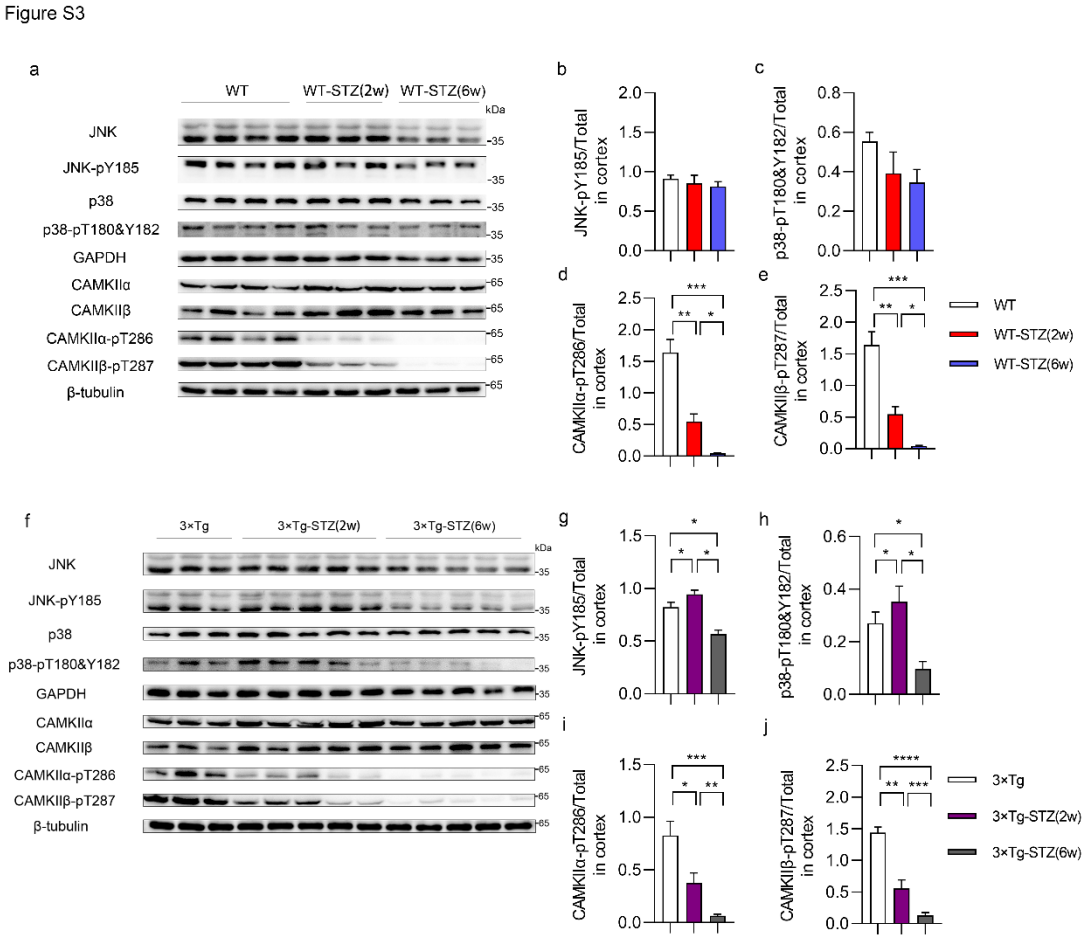


Figure S3 Prolonged hyperglycemia inhibited the phosphorylation of MAPKs and CaMKII

a, WT mice injected with STZ for 2 w (n=3), or 6 w (n=3), respectively, the lysates of cortex were isolated and subjected for **i**mmunoblot analysis compared with that of WT mice (n=4) injected with PBS for 2 w.

b-e, Quantifications of the blot were shown as the mean±s.e.m. of the ratios of JNK-pY185/JNK (**b**), p38-pT180&182/p38 (**c**), CAMKIIα-pT286/CAMKIIα (**d**), and CAMKIIβ-pT287/CAMKIIβ (**e**). The results are shown as the mean±s.e.m., **P*<0.05, ***P*<0.01, ****P*<0.001, by one-way ANOVA with Tukey's test.

f, 3x Tg AD mice were injected with STZ for 2 w (n=5), or 6 w (n=5), respectively, the lysates of cortex were isolated and subjected for **i**mmunoblot analysis compared with that of 3x Tg AD mice (n=3) injected with PBS for 2 w (n=5).

g-j, Quantifications the blot were shown as the mean±s.e.m. of the ratios of JNK-pY185/JNK (**g**), p38-pT180&182/p38 (**h**), CAMKIIα-pT286/CAMKIIα (**i**), and CAMKIIβ-pT287/CAMKIIβ (**j**). The results are shown as the mean±s.e.m., **P*<0.05, ***P*<0.01, ****P*<0.001, *****P*<0.0001 by one-way ANOVA with Tukey's test.

Figure S4: Related to figure 6

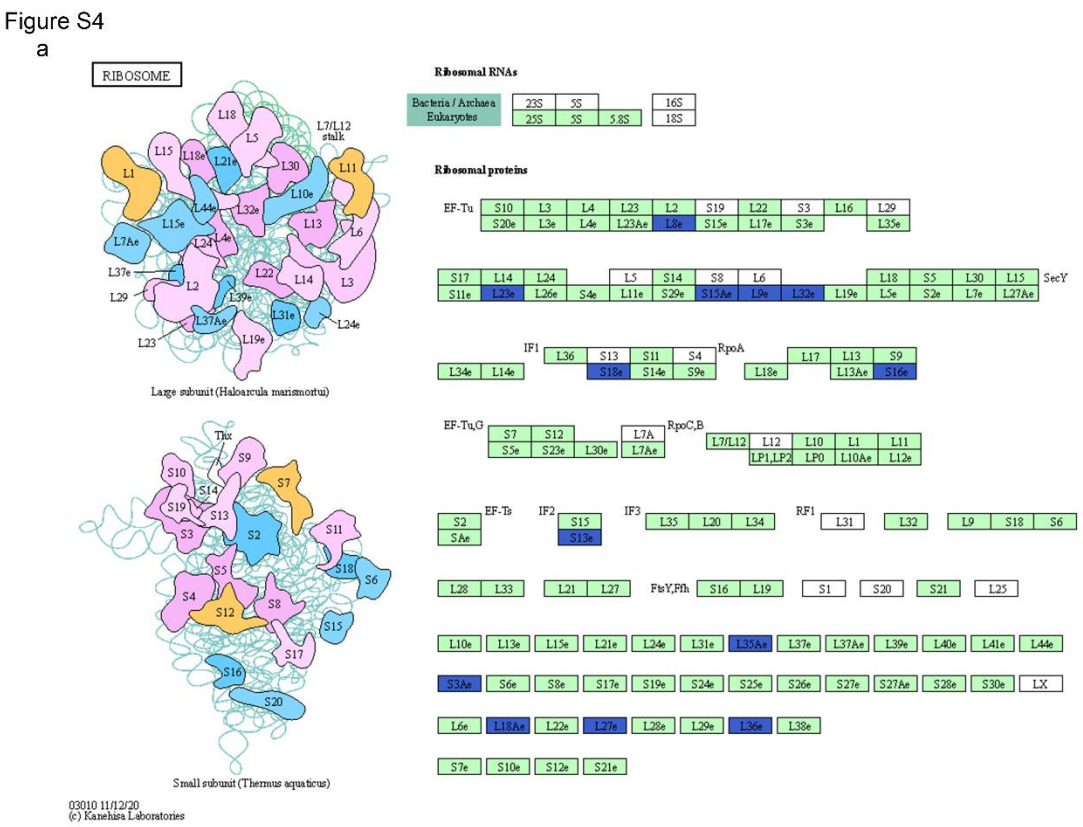


Figure S4 human tau arrested the association of the of 26s proteasome and ribosome related proteins with membrane

a-b, KEGG analysis of membrane-associated proteome indicated that the components of ribosome (**a**) and proteasome (**b**) were less abundant in association with membrane in the hippocampus from hTau mice than that from Tau KO mice. The cells with green background indicated the proteins that did not show significant difference in the membrane extract of hippocampus between hTau mice and Tau KO mice. The cells with blue background indicated the proteins that were significant less abundant in association with membrane in the hippocampus between hTau mice and Tau KO mice.

Figure S5: Related to figure 7 (next page)

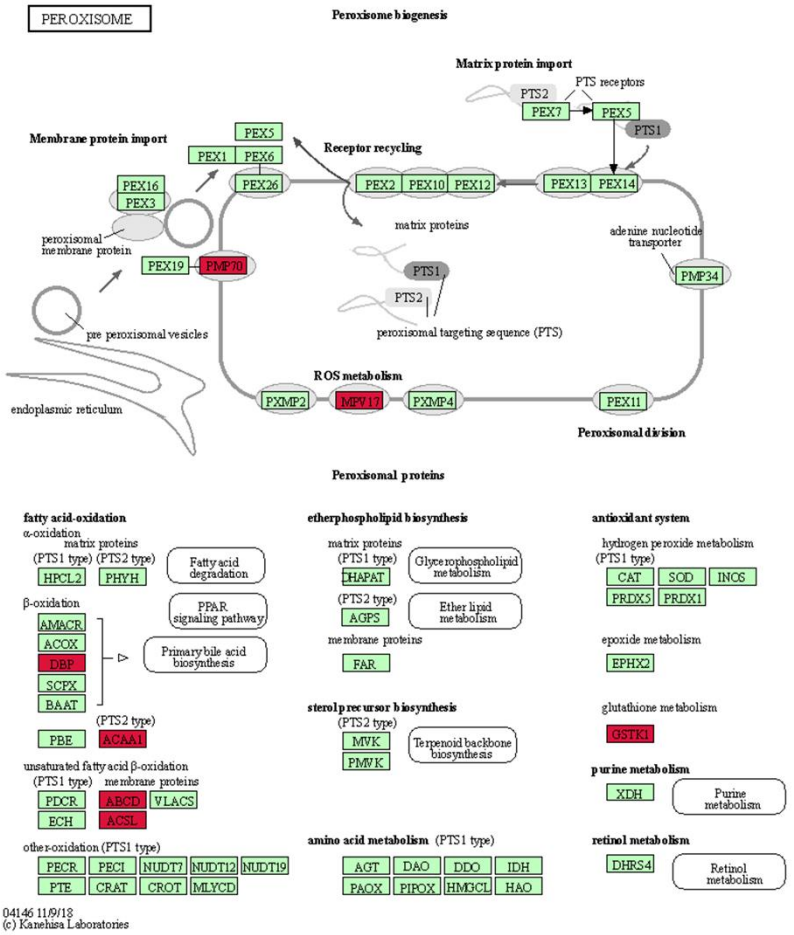
Figure S5 human tau augment the membrane-association of the peroxisome components and fatty acid degradation enzyme

a-b, KEGG analysis membrane-associated proteome indicated that the components of peroxisome (**a**) and the enzymes that are involved in fatty acid degrading (**b**) were more abundant in association with membrane in the hippocampus from hTau mice than that from Tau KO mice. Significantly different proteins were indicated with red. The cells with green background indicated the proteins that did not show significant difference in the membrane extract of hippocampus between hTau mice and Tau KO mice. The cells with red background indicated the proteins that were significant more abundant in association with membrane in the hippocampus between hTau mice and Tau KO mice.

6.2.1.3: acyl-CoA synthetase long-chain family member 1,
1.3.8.7: acyl-Coenzyme A dehydrogenase,
1.3.8.8: acyl-Coenzyme A dehydrogenase,
2.3.1.16: acetyl-Coenzyme A acyltransferase 1A,
1.2.1.3: aldehyde dehydrogenase family 7, member A1.

Figure S5

a



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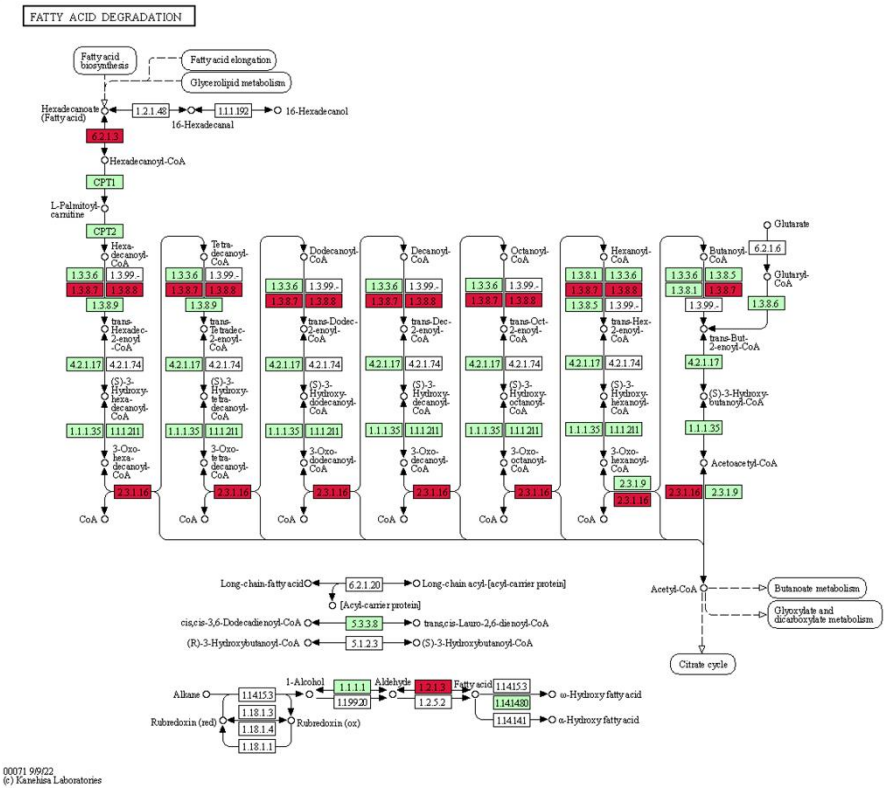
(c) Kanehisa Laboratories

b



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(c) Kanehisa Laboratories

Figure S6: Related to figure 7

Figure S6

a

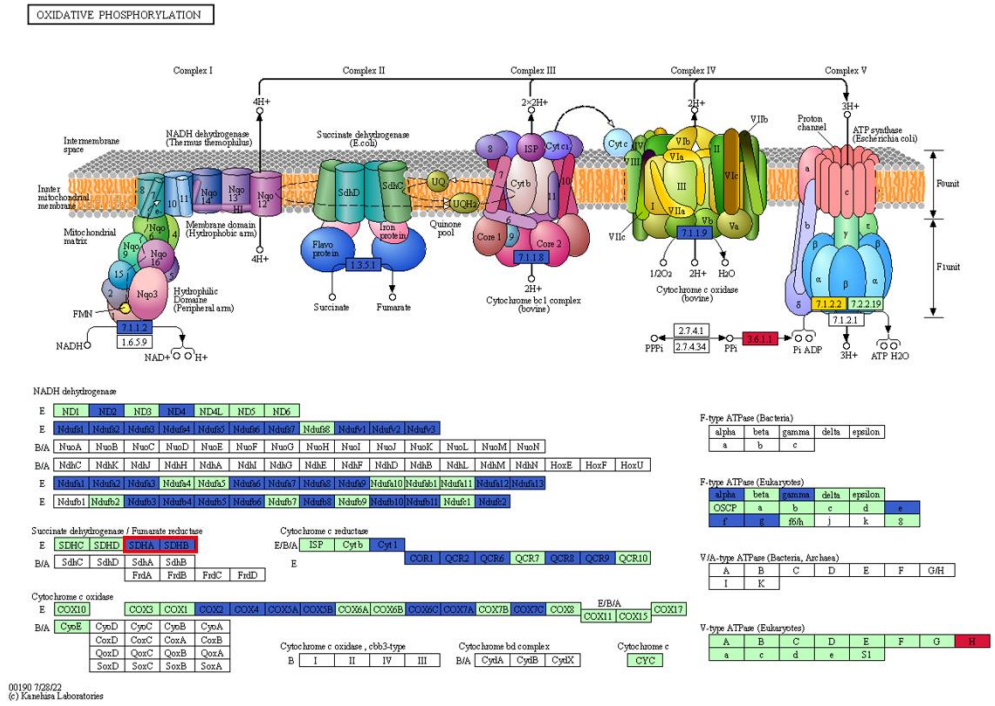

Figure S6 tau knockout resulted in dysregulation of the oxidative phosphorylation related protein locating on membrane under acute hyperglycemia conditions

KEGG analysis of membrane-associated proteome indicated that upon STZ treatment, more oxidative related proteins, including SDHA and SDHB were less abundant in association with membrane the hippocampus from hTau mice than that from Tau KO mice. The cells with white background indicated the proteins that were not detected by TMT-MS. The cells with green background indicated the proteins that did not show significant difference in the membrane extract of hippocampus between hTau mice and Tau KO mice. The cells with blue background indicated the proteins that were significant less abundant in association with membrane in the hippocampus between hTau mice and Tau KO mice. The cells with red background indicated the proteins that were significant more abundant in association with membrane in the hippocampus of hTau mice compared with Tau KO mice.