读书报告

张文雅

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Adipocyte-Derived Exosomal MiR-27a Induces Insulin Resistance in Skeletal Muscle Through Repression of PPARγ

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01 研究背景

肥胖诱导的胰岛素抵抗导致胰岛素靶组织中的胰岛素信号传导受损，并且骨骼肌中的胰岛素抵抗是2型糖尿病（T2DM）发展的前兆。脂肪组织与骨骼肌肥胖相关胰岛素抵抗的发病机制有关。许多研究都将脂肪来源的脂肪因子或脂肪细胞诱导的巨噬细胞作为调节脂肪和骨骼肌之间串扰的潜在因子。然而，这些促进胰岛素抵抗的已知因素仅部分解释了脂肪和骨骼肌间复杂信号网络。

01 研究背景

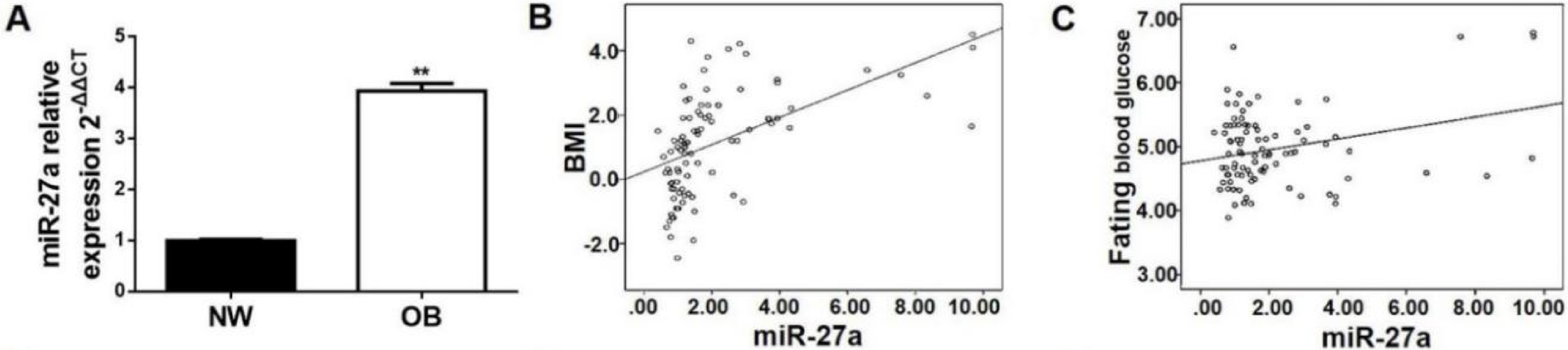
MiR-27a在脂肪组织中高度表达，最初被认为是脂肪形成和脂肪形成途径的负调控因子。 MiR-27a在前驱糖尿病和T2DM肥胖个体的血清中高表达。MiR-27a是过氧化物酶体增殖物激活受体γ（PPARγ）的负调节因子。 PPARγ是脂质代谢和胰岛素敏感性的有效调节剂。 激活的PPARγ与RXR异源二聚化，通过直接调节携带PPAR反应元件（PPREs）的基因（包括葡萄糖转运蛋白GLUT4和胰岛素受体底物IRS-1）来维持葡萄糖稳态。 骨骼肌PPARγ丢失会导致严重的胰岛素抵抗。 然而，PPARγ是否是miR-27a在骨骼肌胰岛素抵抗作用中的靶点尚不清楚。

Part 02
实验结果

02 血清miR-27a水平与肥胖诱导的胰岛素抵抗有关

Table 2. Serum level of adipocytokines in non-obese and obese

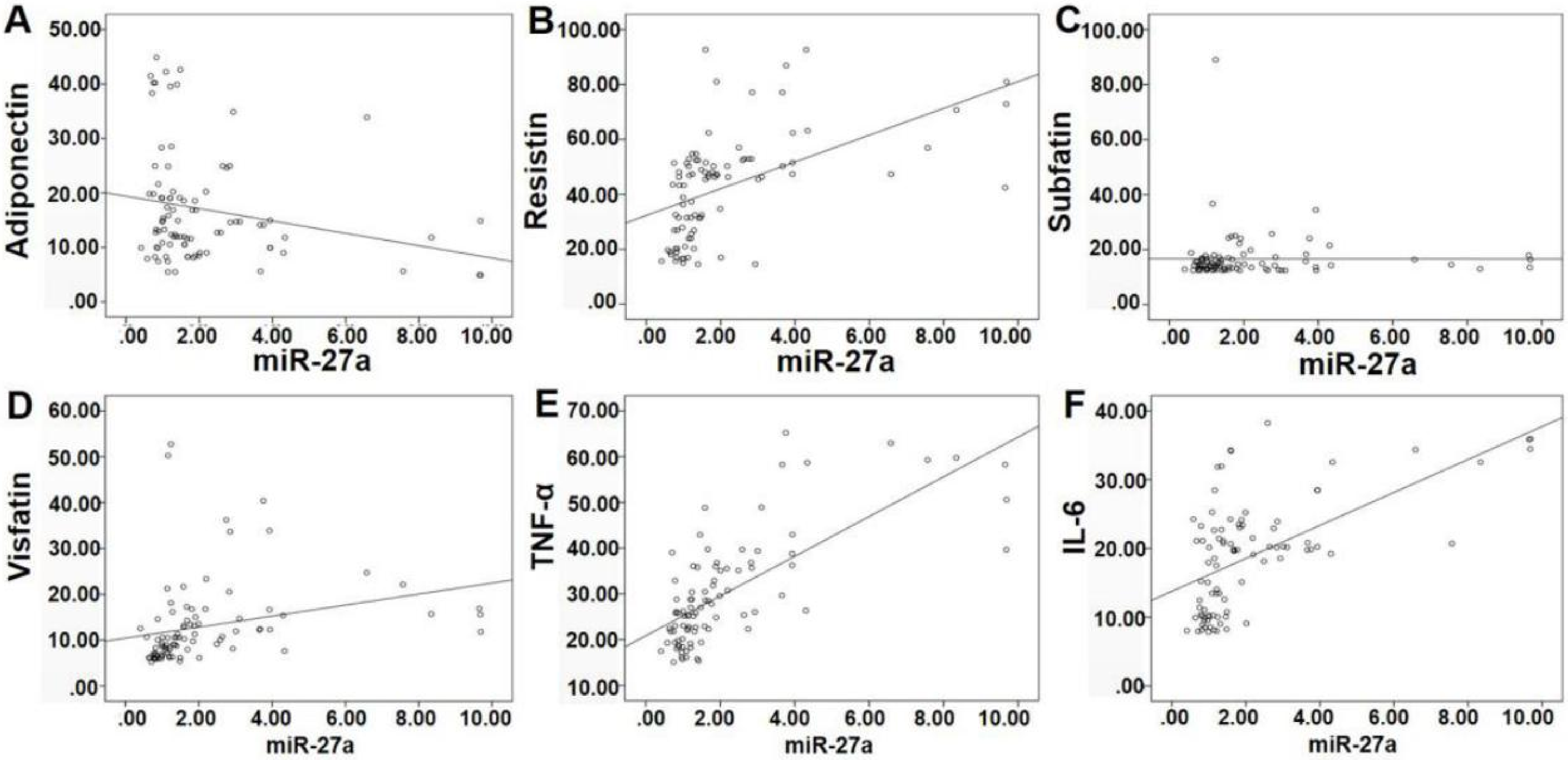
Table S1 Height Weight waist circumference body mass index in non-obese and



p<0.01 compared to the non-obese subject group.

the variances. Values are presented as mean ± SEM, n=45, *p<0.05 compared to Non obesity subject group.

02 血清miR-27a水平与肥胖诱导的胰岛素抵抗有关



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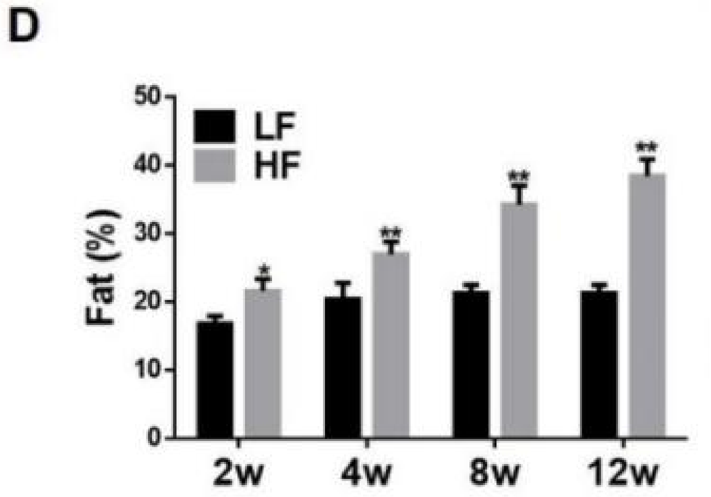
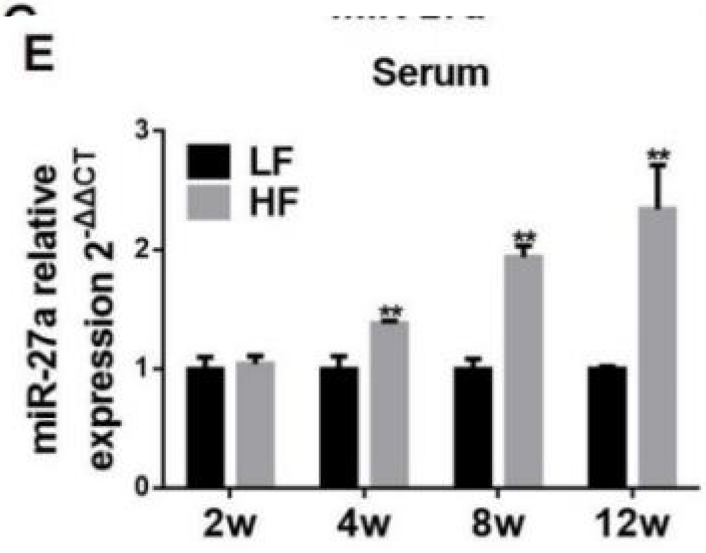
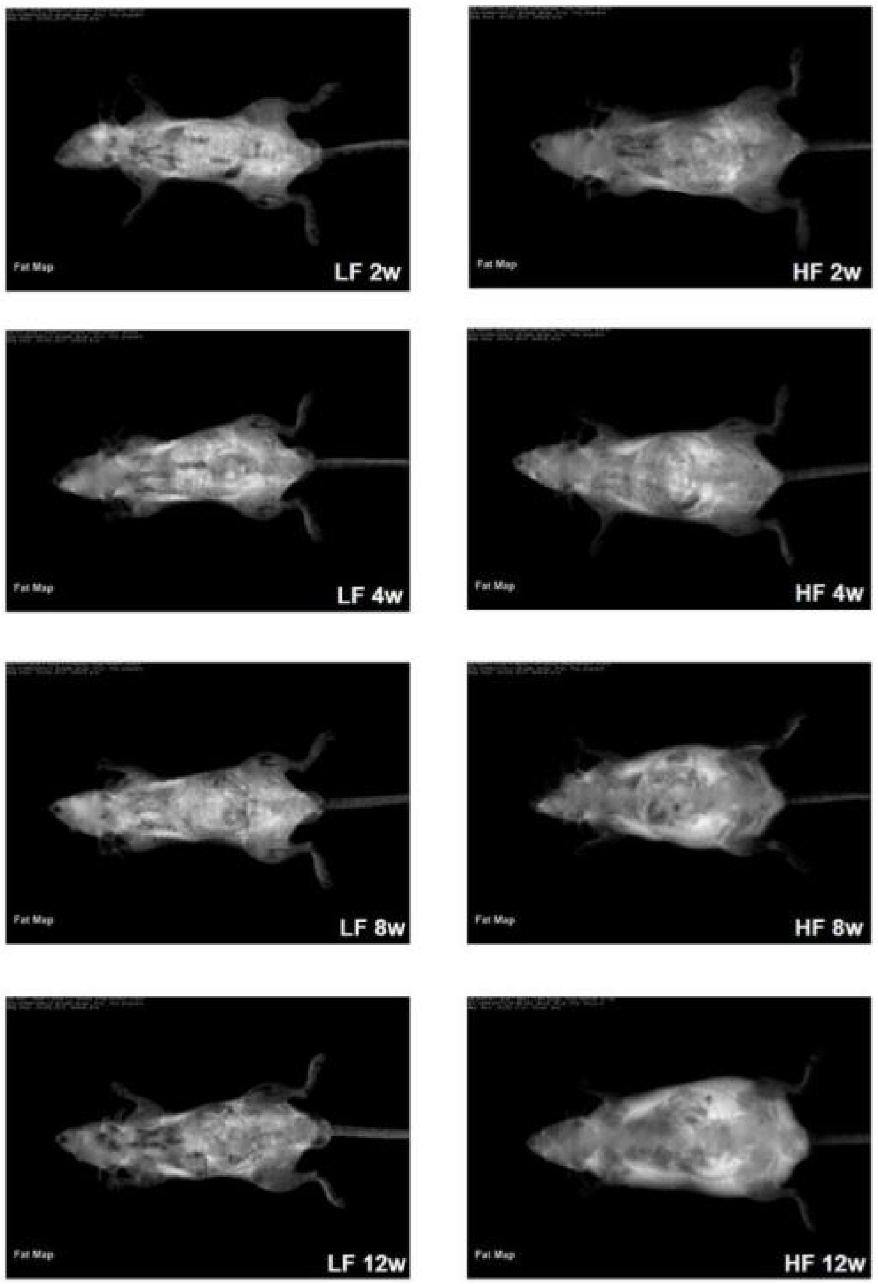




C57BL/6J



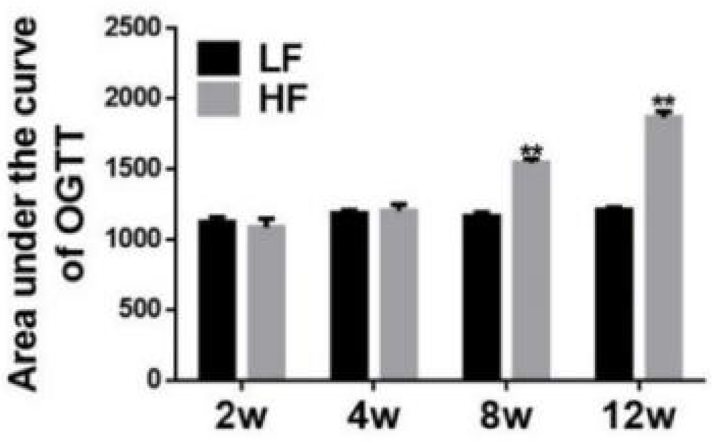
02 血清miR-27a水平与肥胖诱导的胰岛素抵抗有关

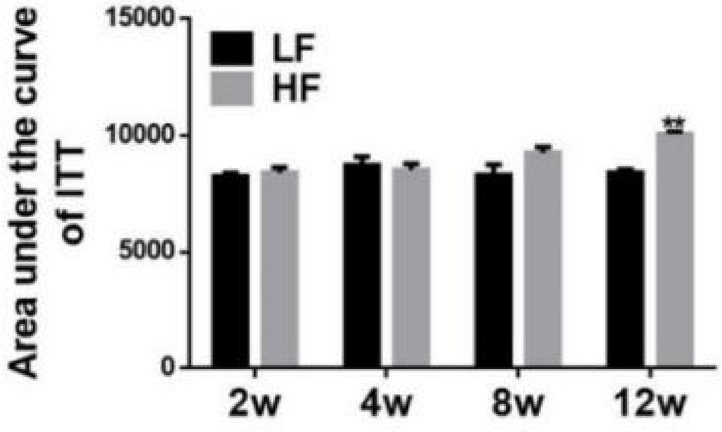
Table 3. Serum biochemical parameters of LF and HF diet-fed C57BL/6J mice

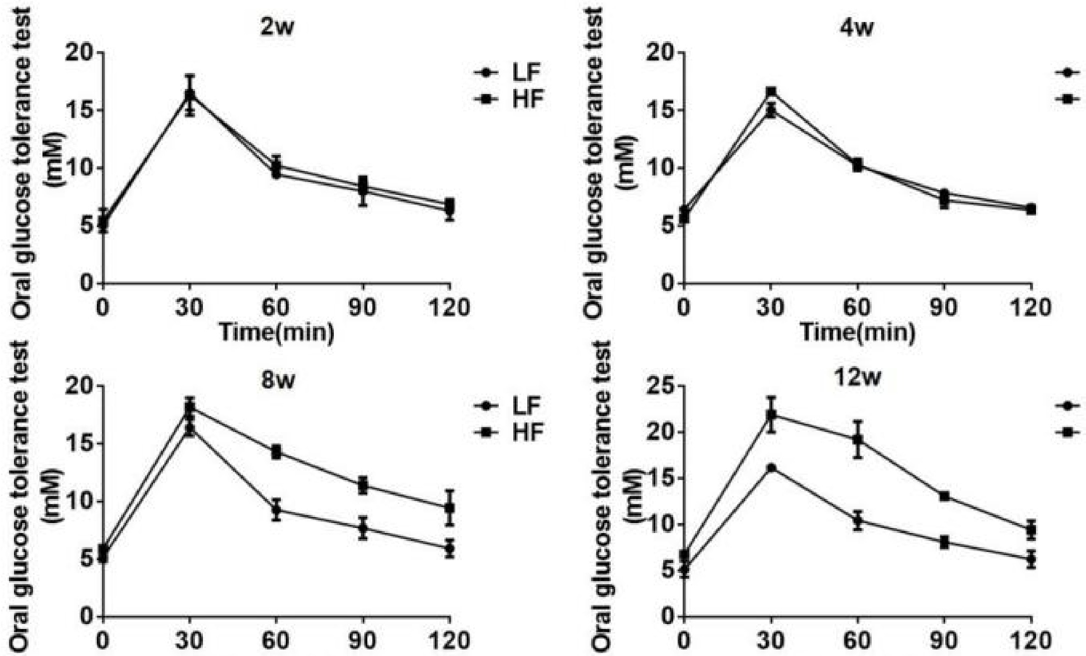
Parameter	LF (2w)	HF (2w)	LF (4w)	HF (4w)	LF (8w)	HF (8w)	LF (12w)	HF (12w)
CHOL (mM)	3.57±0.33	4.22±0.23**	4.08±0.16	5.91±0.17**	3.96±0.26	6.16±0.19**	3.83±0.29	7.17±0.35**
FBG (mM)	4.52±0.32	4.58±0.43	4.33±0.33	4.92±0.29	4.65±0.54	5.42±0.39	4.81±0.16	5.69±0.28*
HOMA-IR	1.39±0.11	1.51±0.16	1.48±0.11	2.28±0.20**	2.24±0.33	4.43±0.44**	2.42±0.07	6.91±0.29**
INS (mIU/L)	6.93±0.22	7.44±0.82	7.74±0.14	10.46±0.80**	10.62±0.58	18.31±1.11**	11.34±0.25	27.52±0.52**
K_{ITT} (%/min)	3.27±0.27	3.23±0.36	3.14±0.31	3.09±0.25	3.34±0.35	3.17±0.10	3.13±0.25	1.79±0.43**
TAG (mM)	0.95±0.09	1.03±0.10	1.13±0.07	1.35±0.09*	1.14±0.07	1.42±0.06*	1.28±0.07	1.87±0.07**

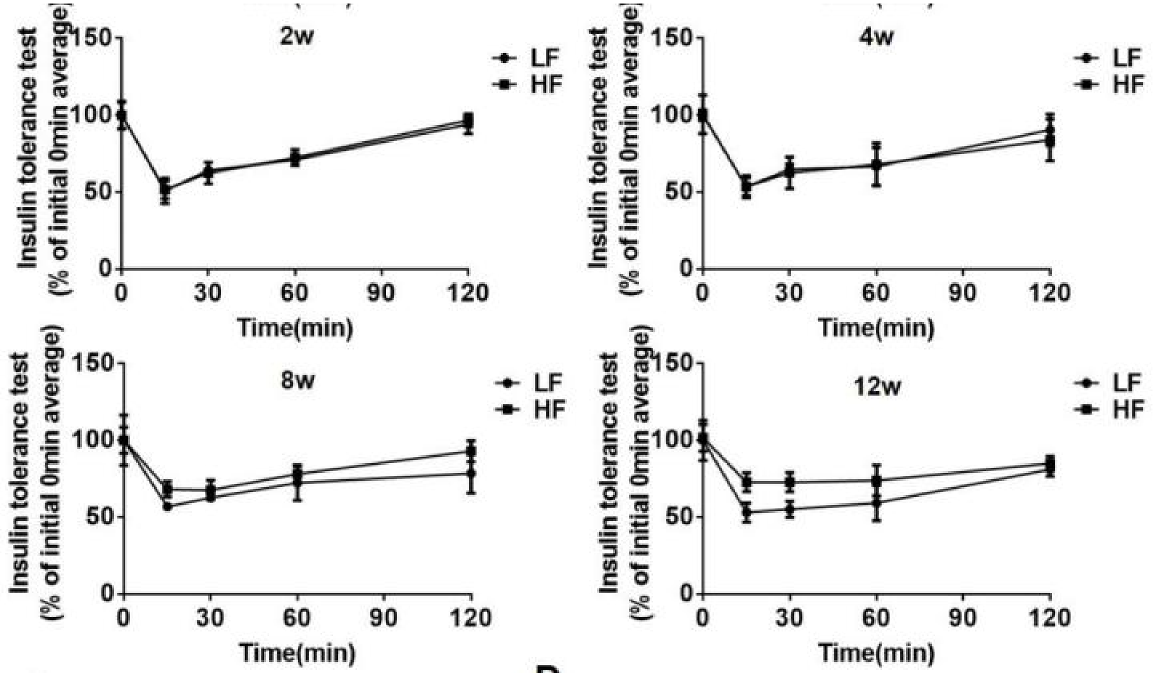
Mice were treated with LF or HF diet for 2, 4, 8 and 12 weeks, and FBG, TAG, CHOL, INS, HOMA-IR and K_{ITT} were determined. HF: high-fat diet group; LF: low-fat diet group. The interactions between week and group were cholesterol (CHOL; F=5.485, $p<0.05$), fasting blood glucose (FBG; F=0.088, $p>0.05$), homeostasis model assessment of insulin resistance (HOMA-IR; F=28.025, $p<0.01$), insulin (INS; F=46.773, $p<0.01$), the slope of insulin tolerance test (K_{ITT}; 0-15 min; F=3.157, $p<0.05$) and triglyceride (TAG; F=4.579, $p<0.05$). Analyses were performed by two-way ANOVA, followed by a post-hoc Bonferroni test to determine individual differences among groups. Values are presented as mean ± SEM, n=10, *$p<0.05$ and **$p<0.01$ compared to the corresponding LF group.

02 血清miR-27a水平与肥胖诱导的胰岛素抵抗有关









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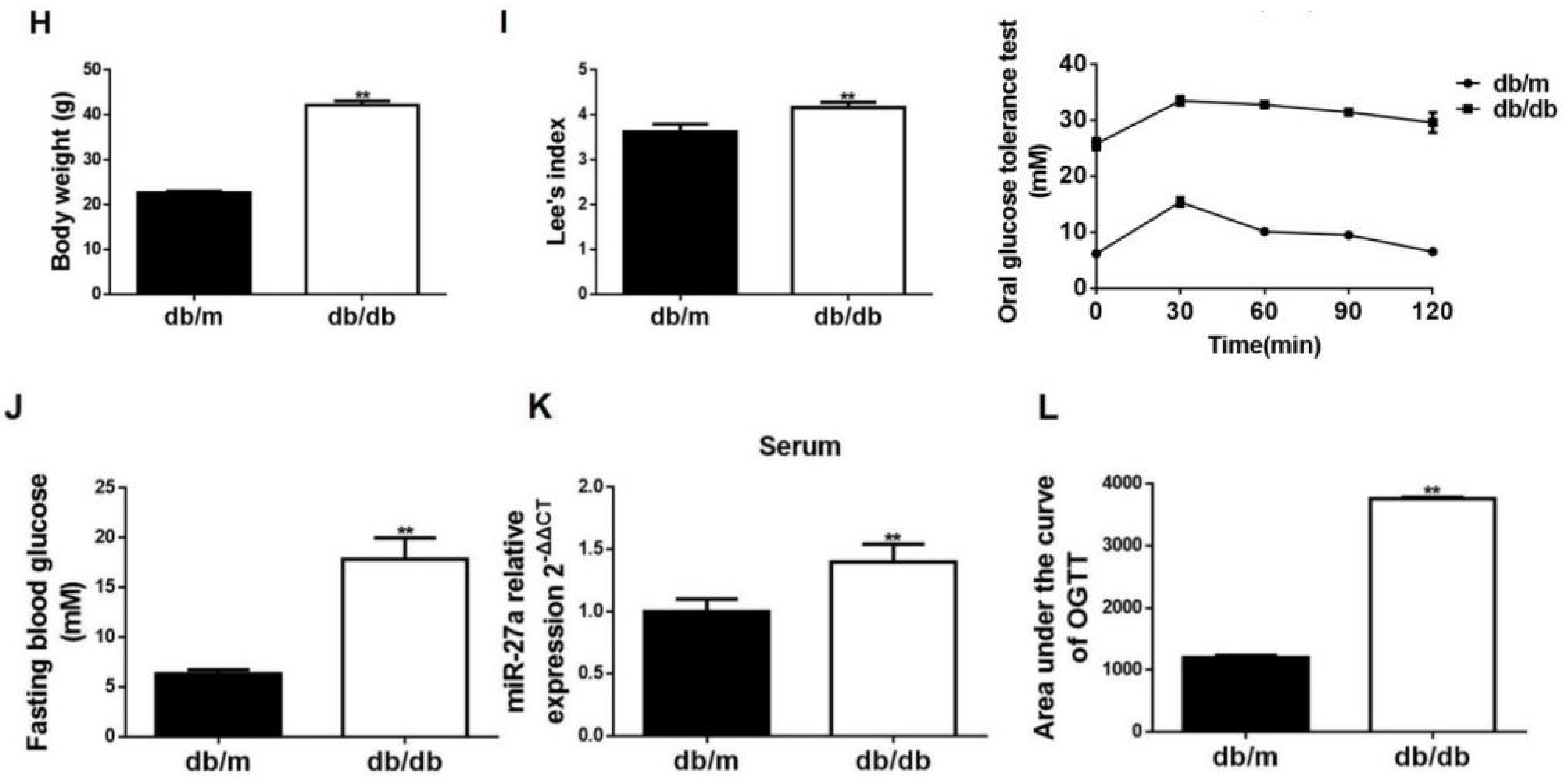

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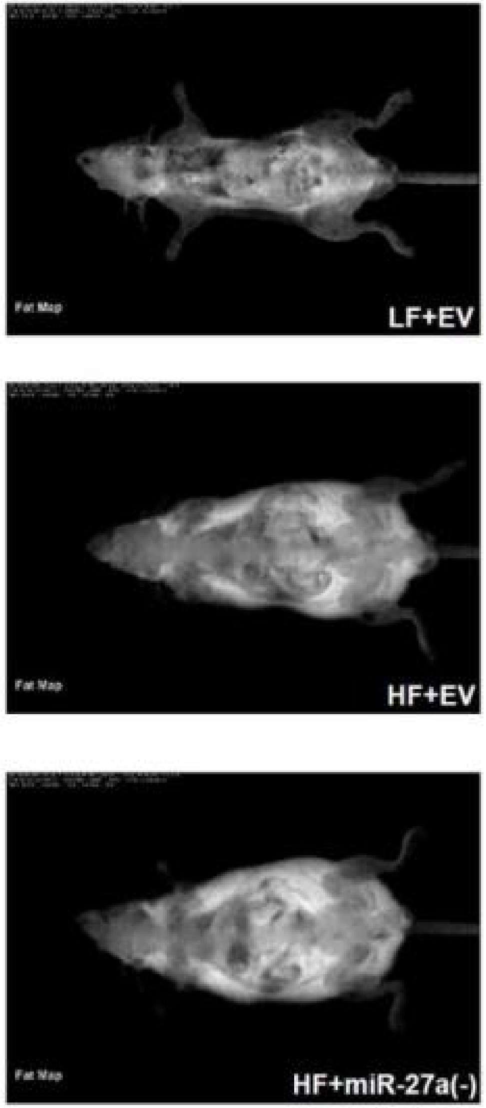

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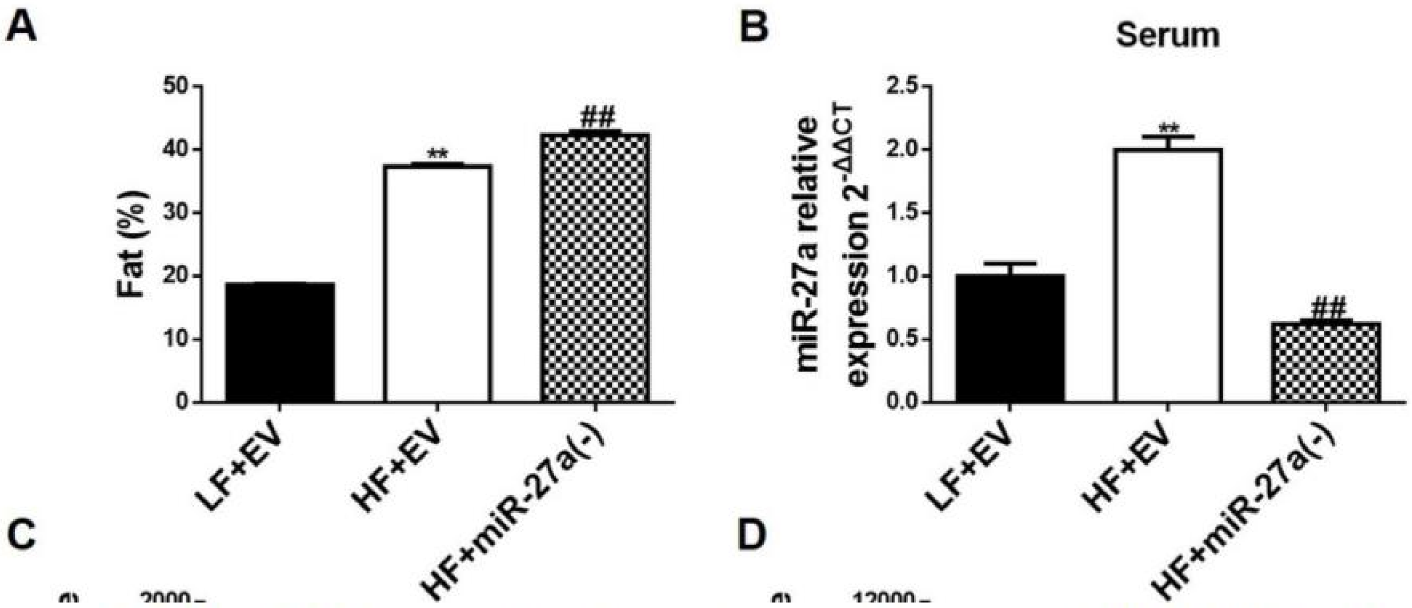
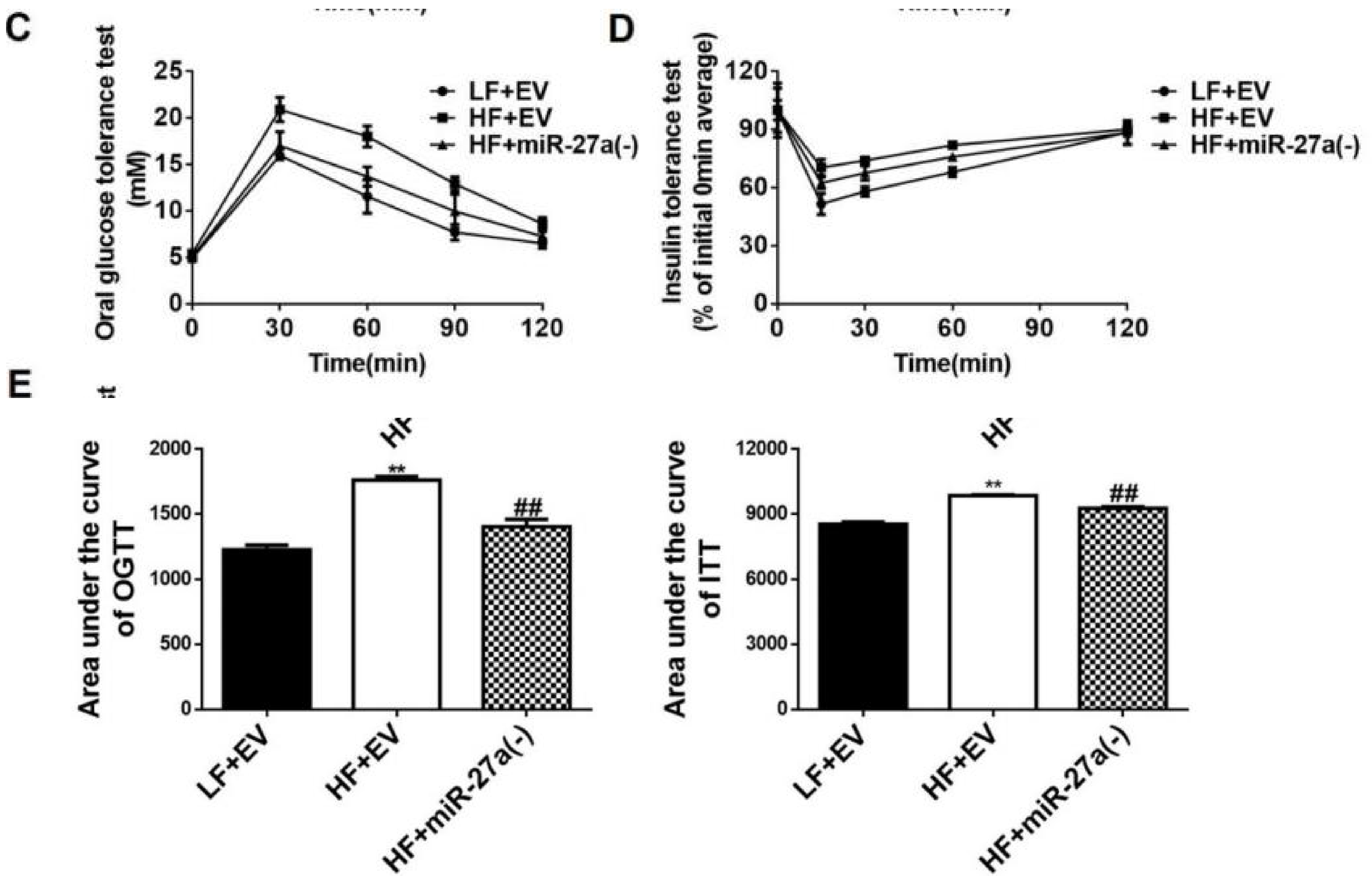


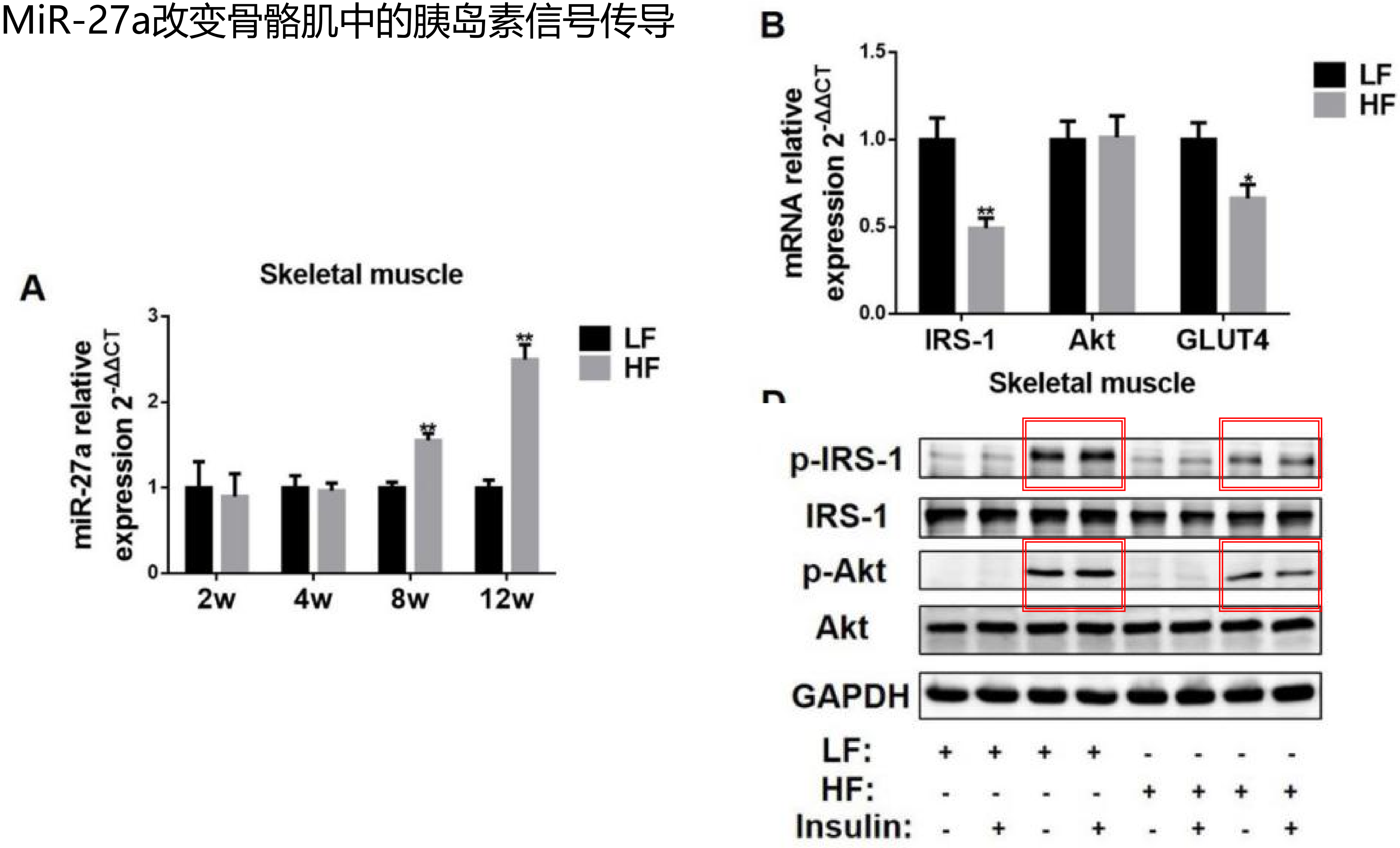
Table 4. Serum biochemical parameters of LF, HF and HF+miR-27a(-) mice

Parameter	LF+EV	HF+ EV	HF+miR-27a(-)
CHOL (mM)	3.54±0.19	7.21±0.17**	5.98±0.15**,#
FBG (mM)	4.78±0.11	5.3±0.21	4.82±0.06
HOMA-IR	2.12±0.11	6.21±0.36**	3.71±0.06**,##
INS (mIU/L)	9.97±0.36	26.29±0.59**	17.34±0.18**,##
K_{ITT} (%/min)	3.23±0.52	1.96±0.20**	2.50±0.11#
TAG (mM)	1.10±0.05	1.79±0.04**	1.13±0.03**,##

02 血清miR-27a水平与肥胖诱导的胰岛素抵抗有关



02 MiR-27a改变骨骼肌中的胰岛素信号传导



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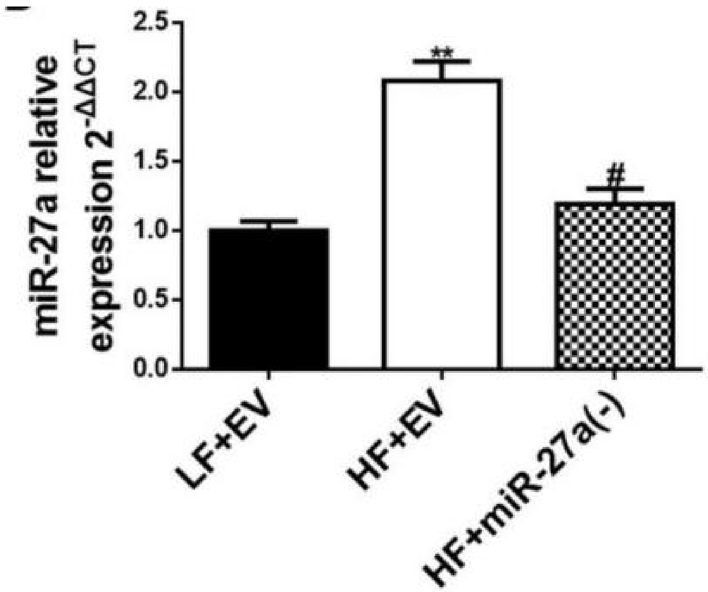

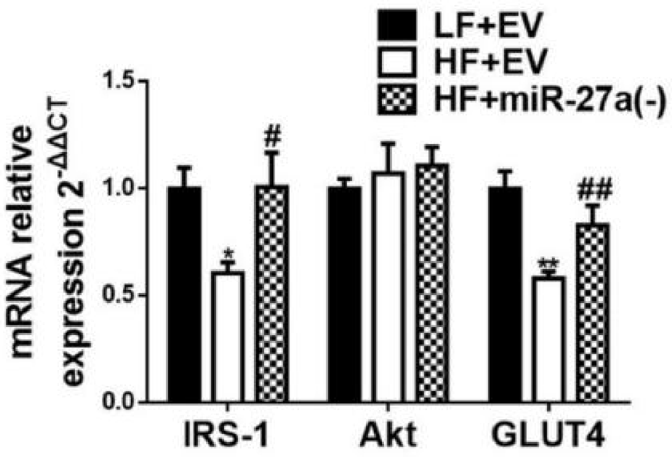

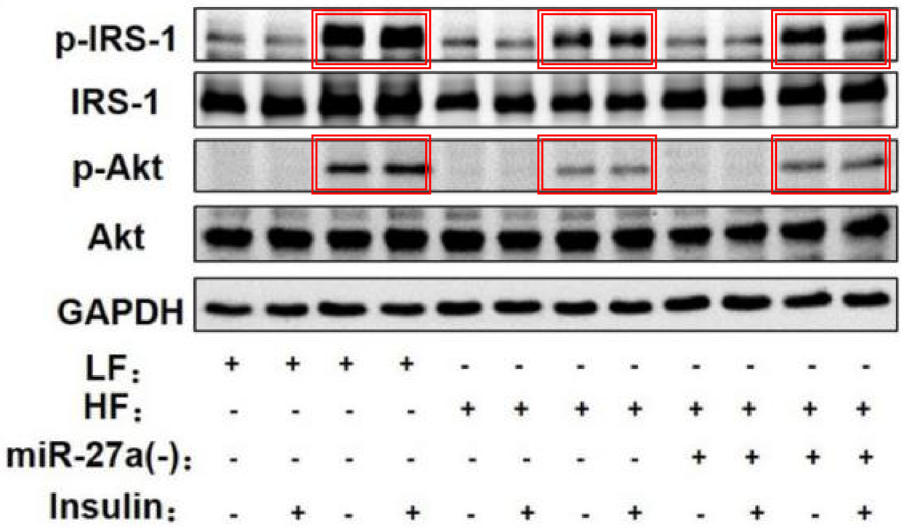

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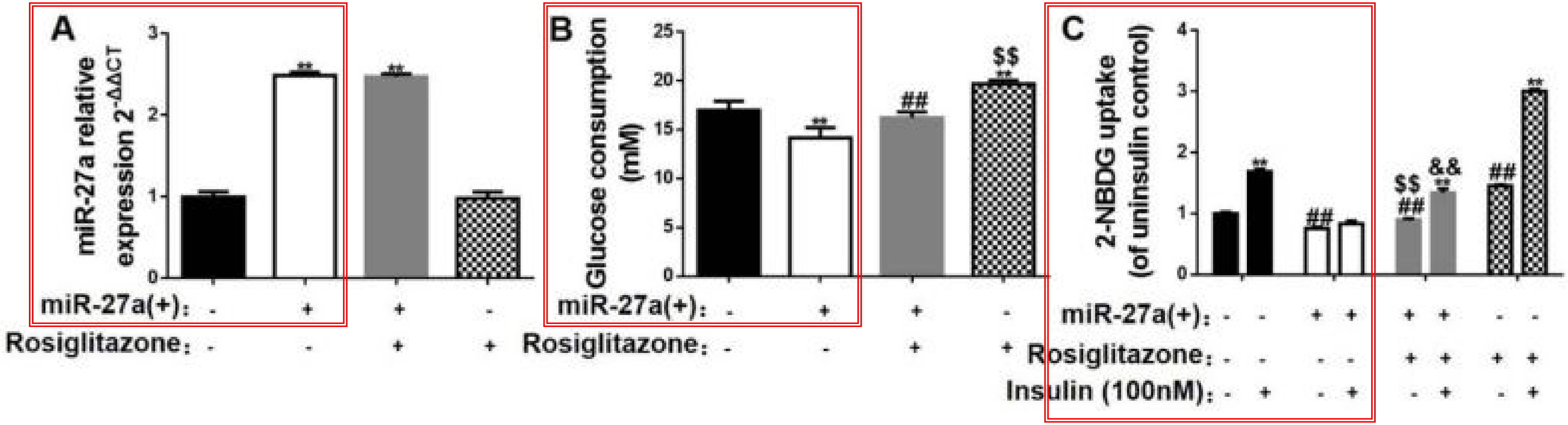

C2C12细胞（成肌细胞）

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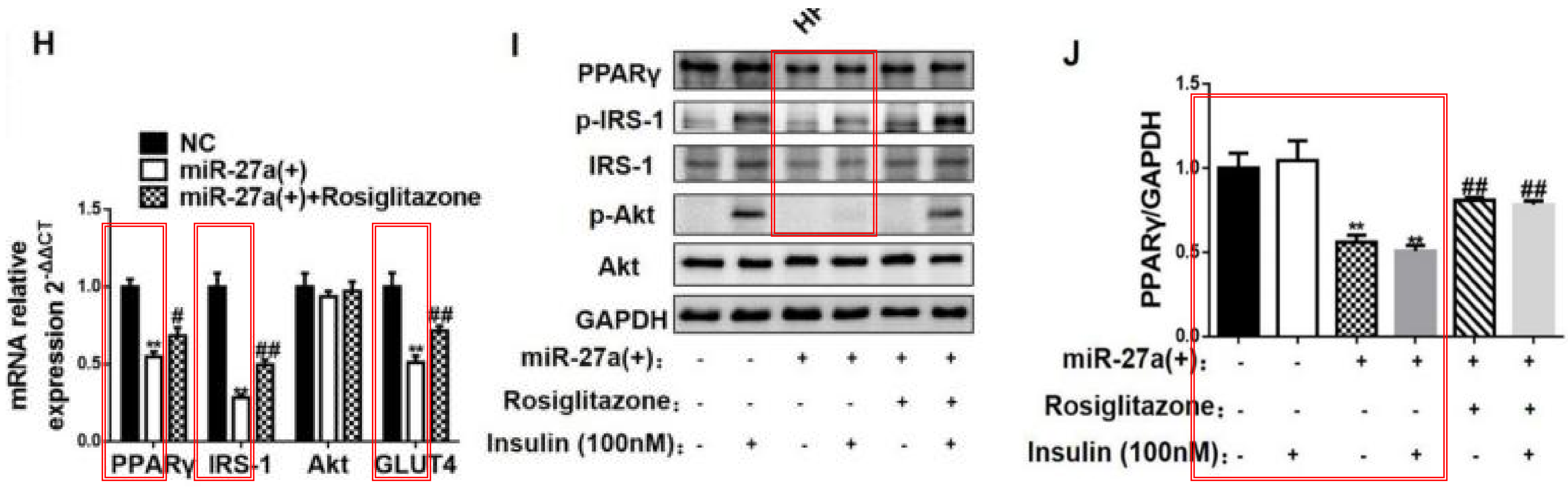
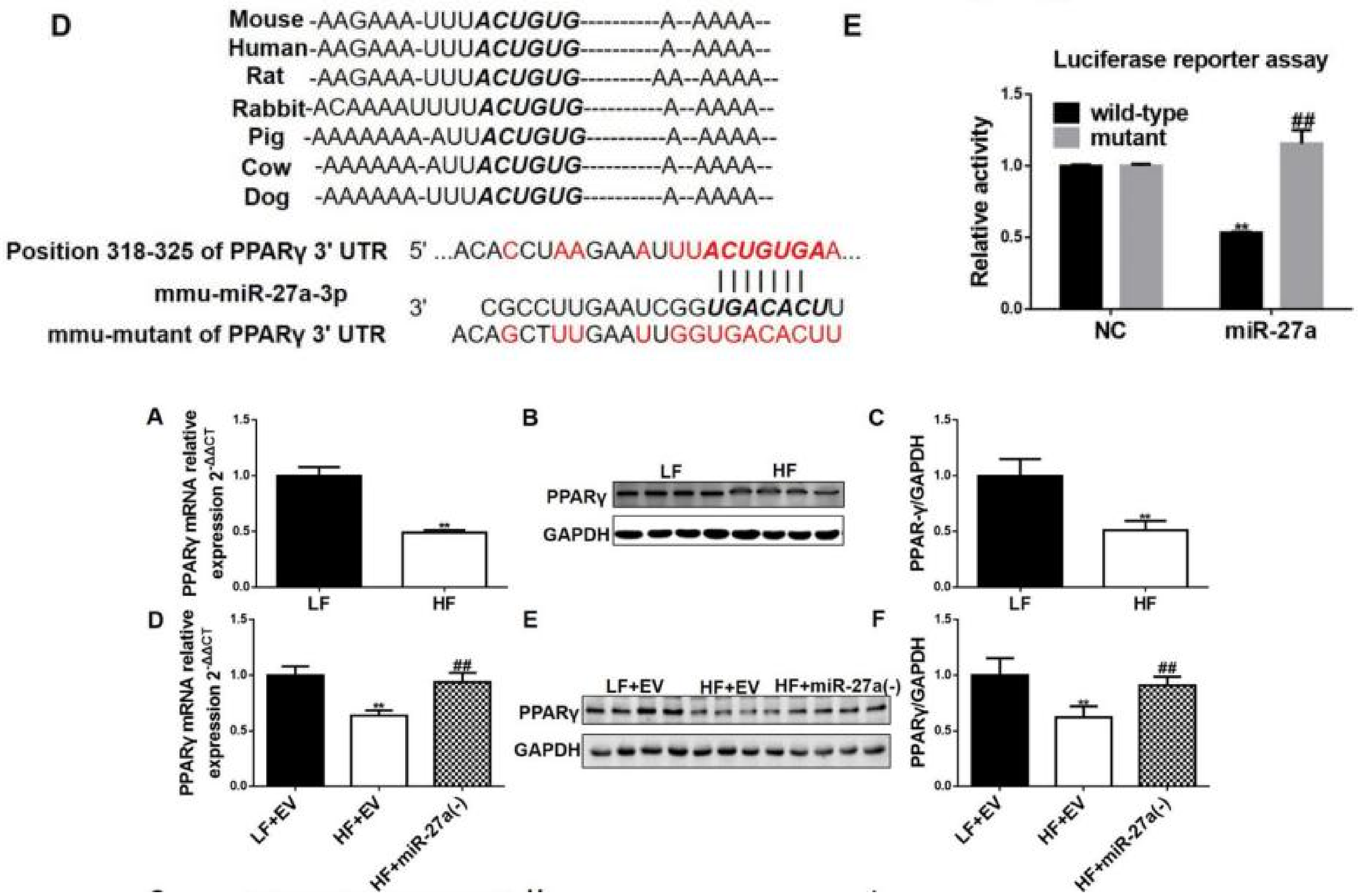


02 MiR-27a通过PPARγ抑制作用损害骨骼肌中的胰岛素信号传导



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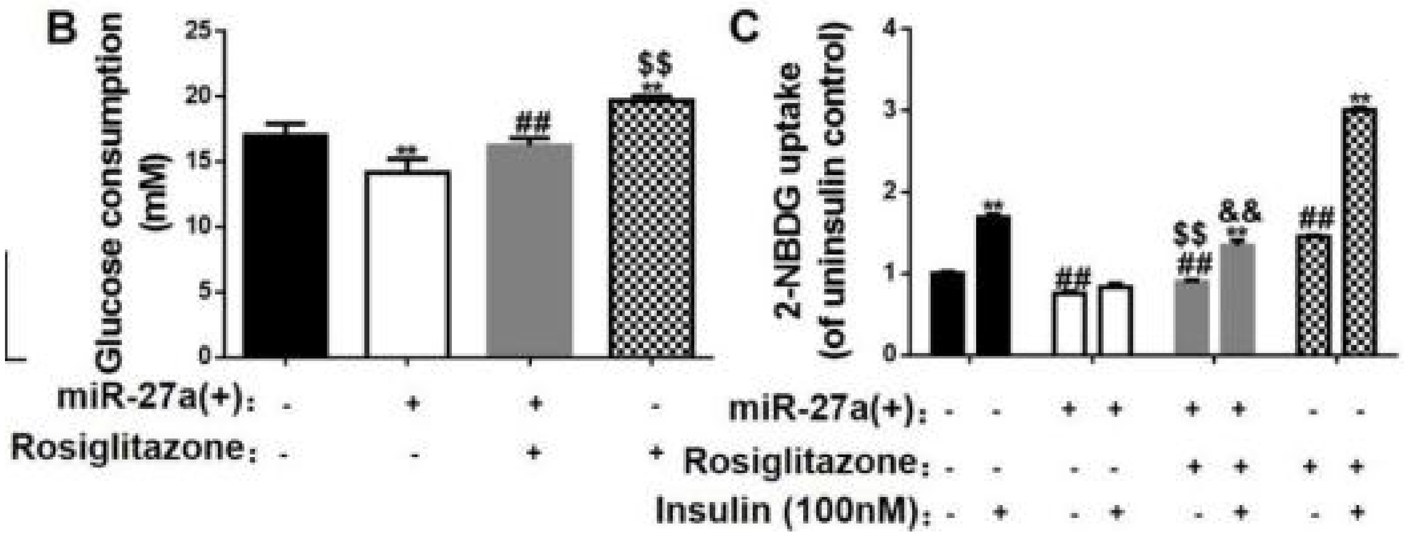

rosiglitazone罗格列酮：PPARγ激活剂

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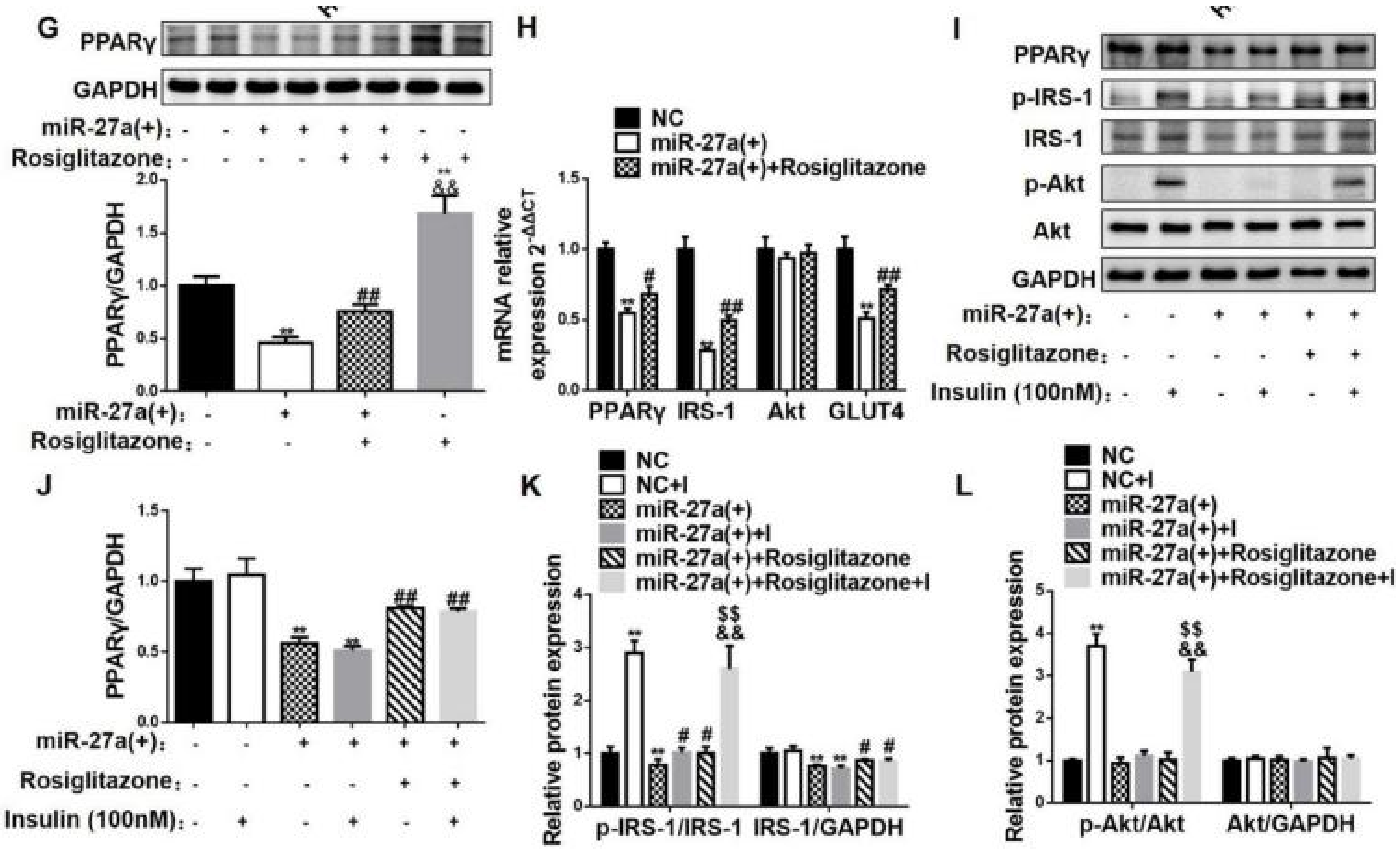
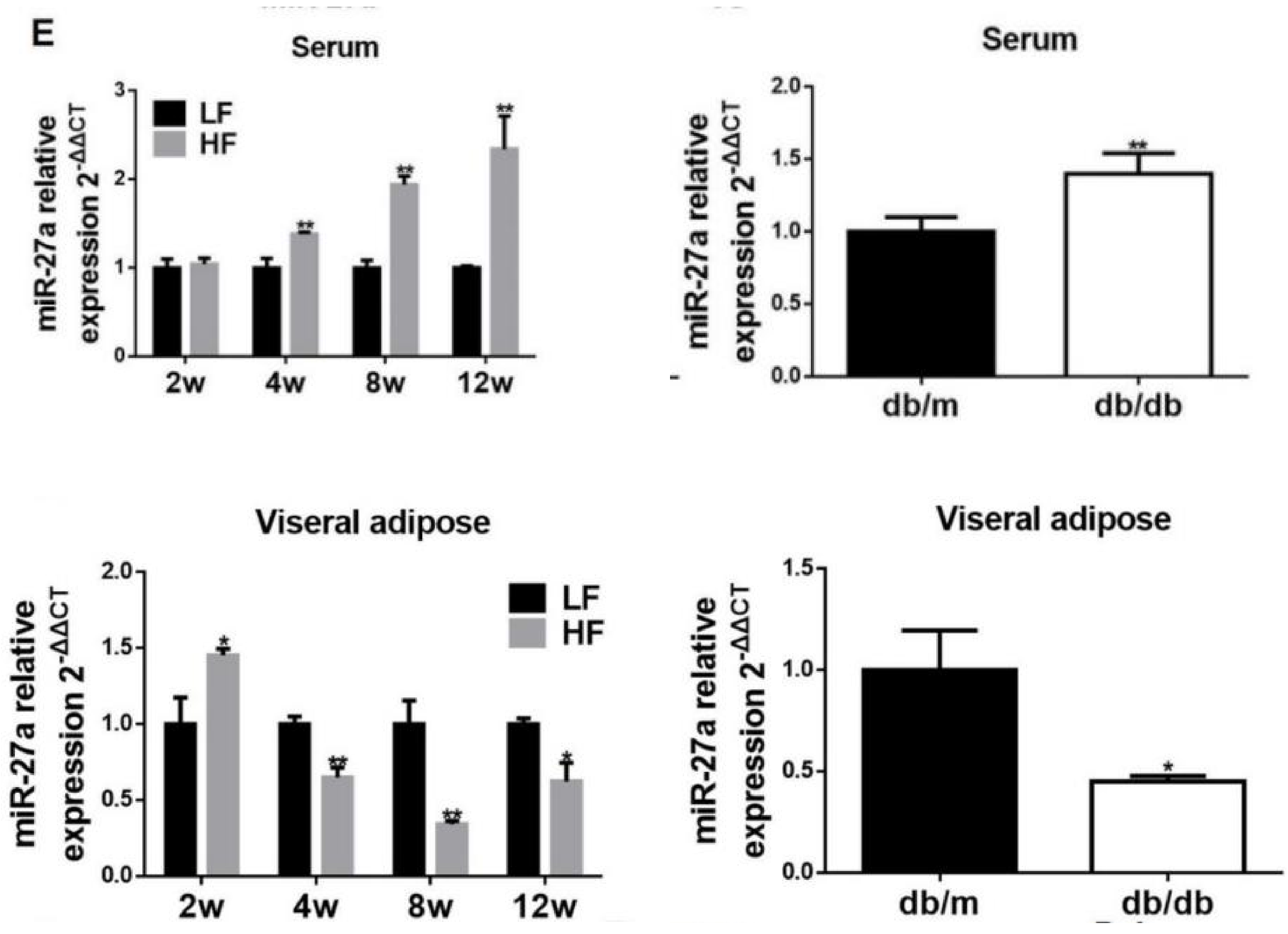
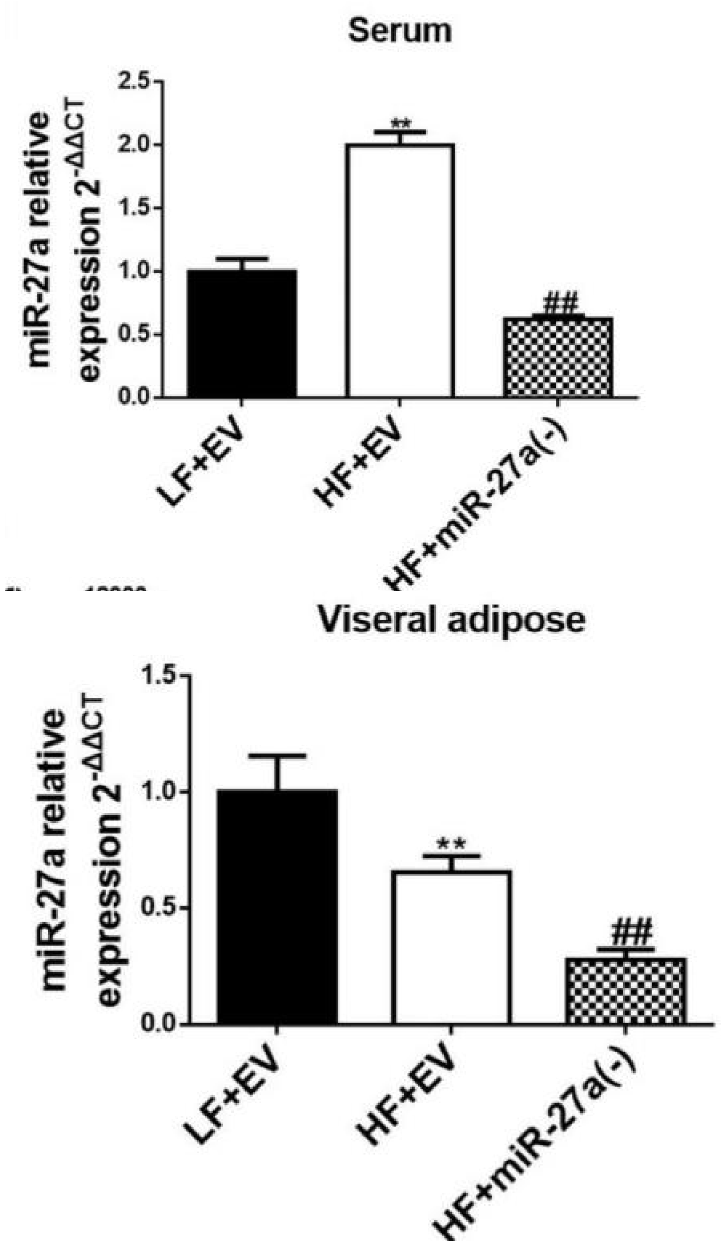


02 负载脂质的脂肪细胞会将miR-27a分泌到外泌体中





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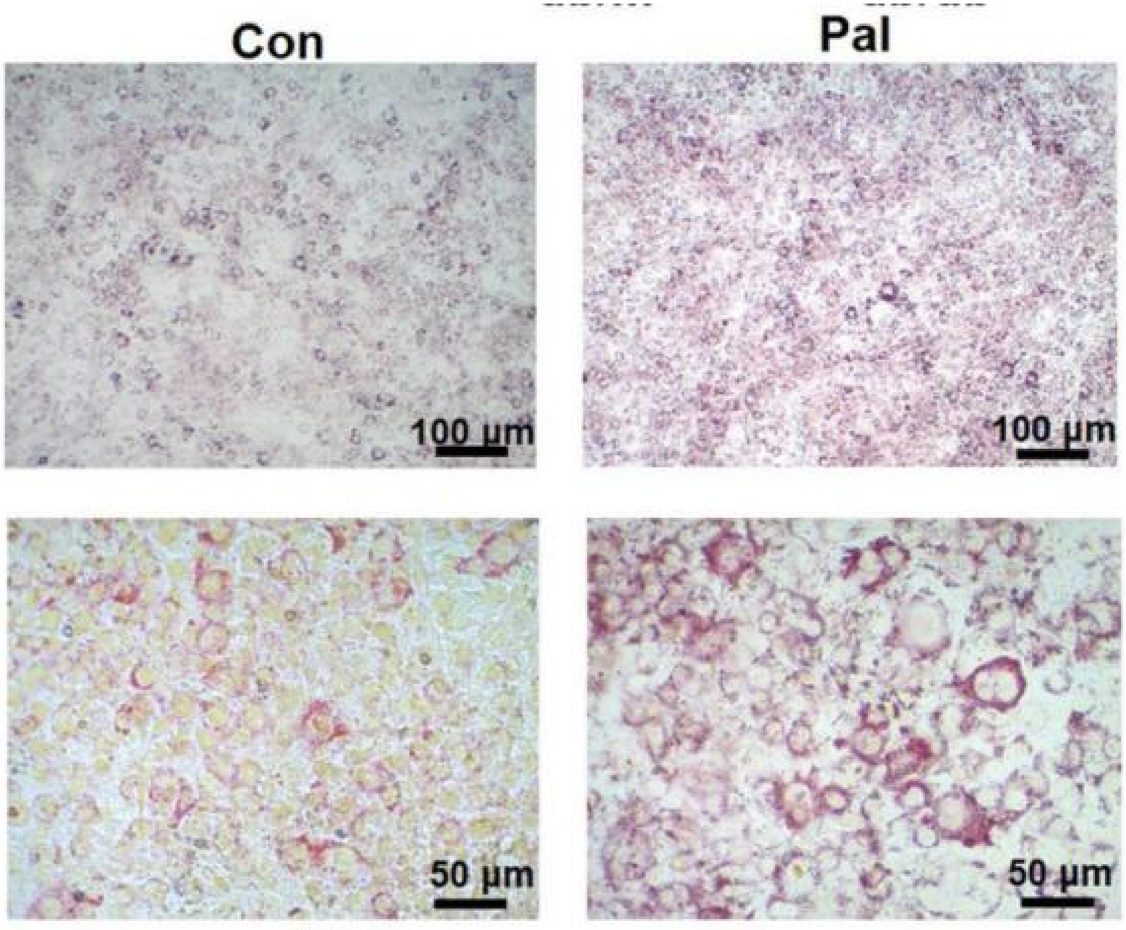

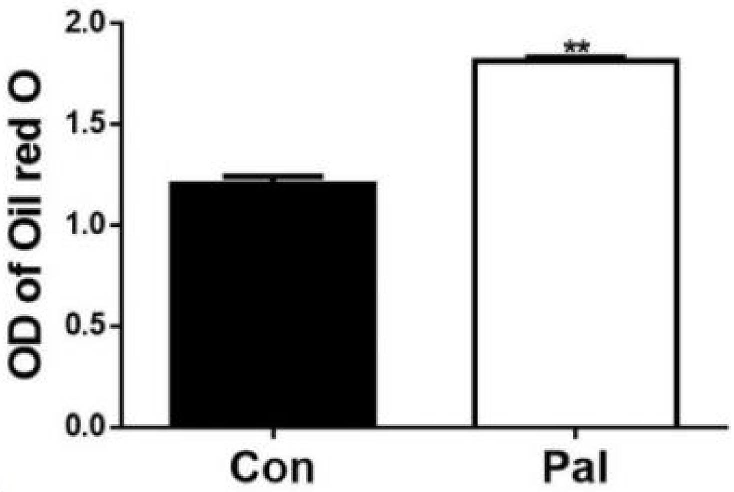

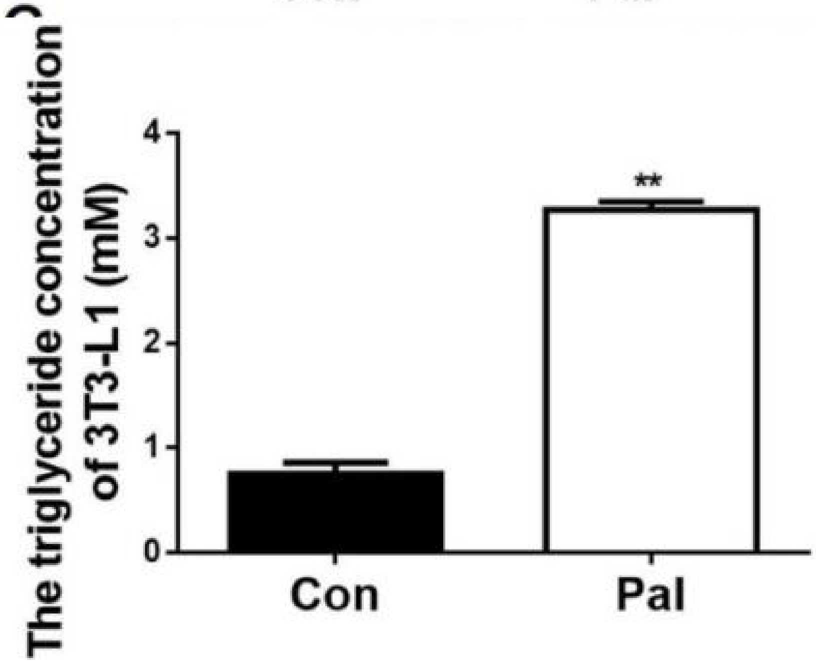

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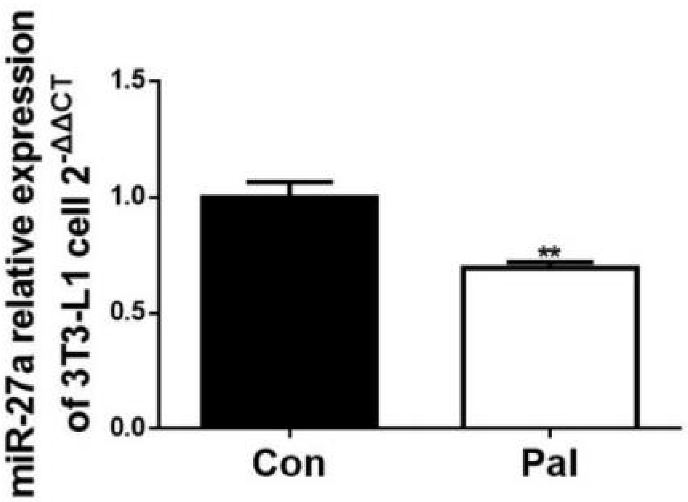

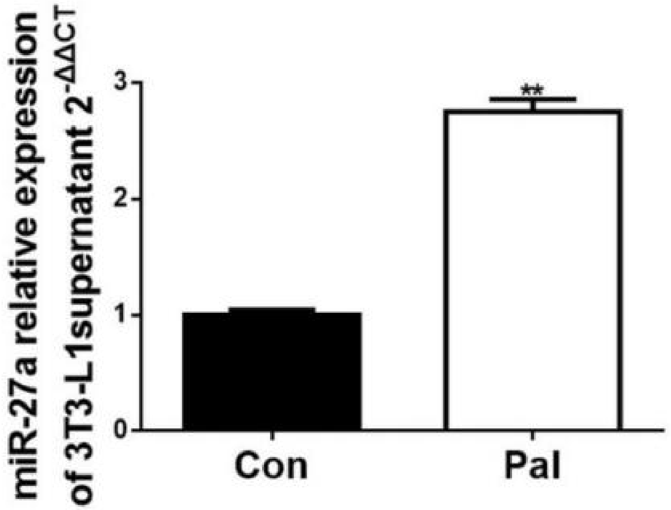

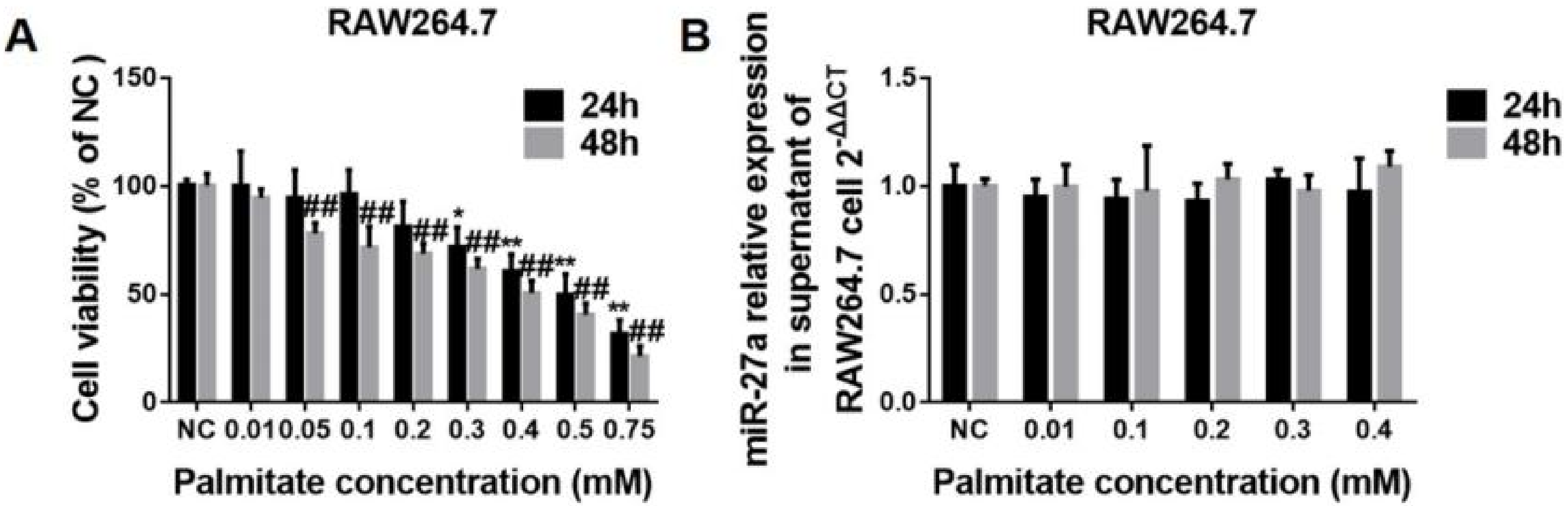

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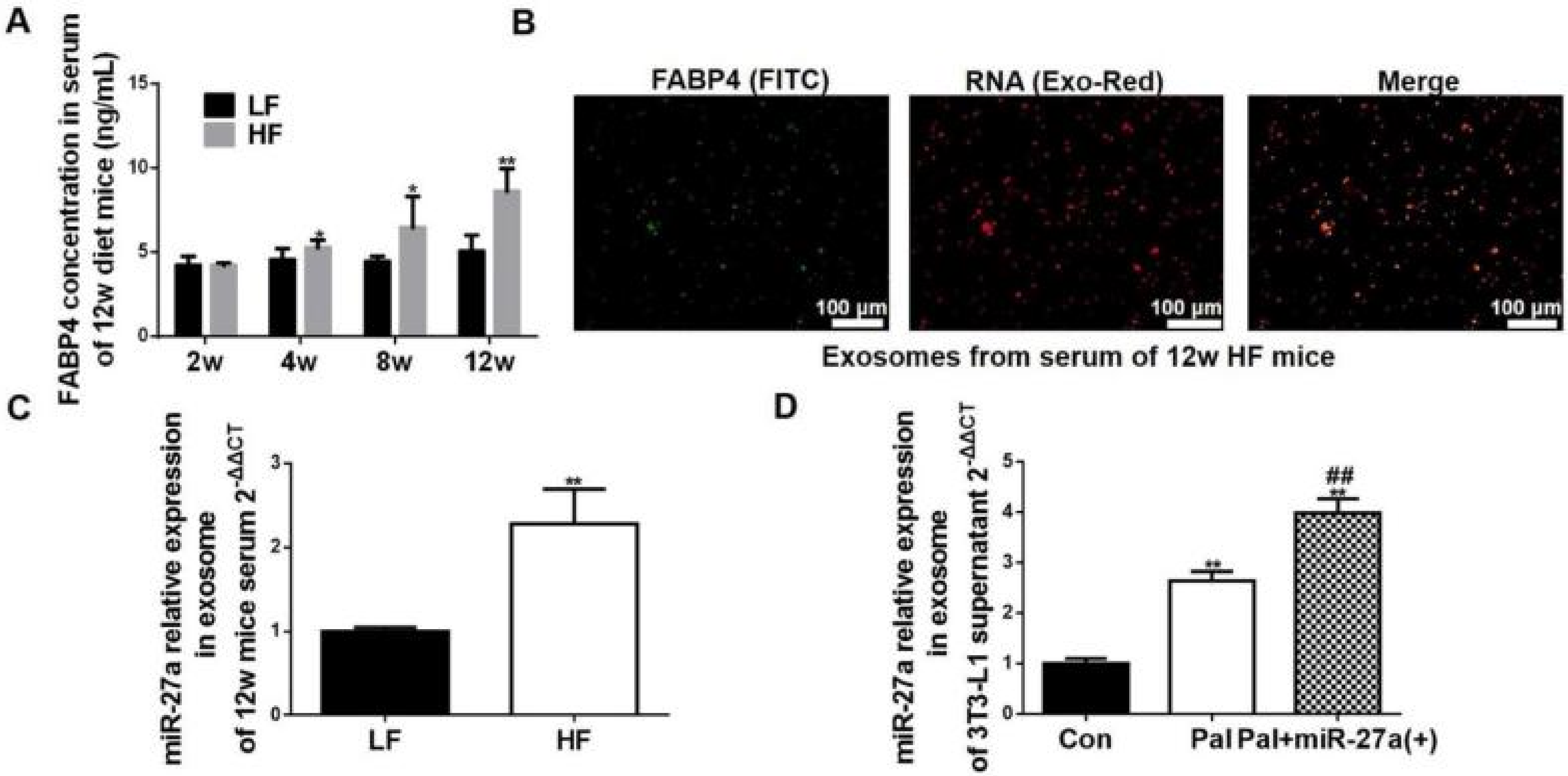
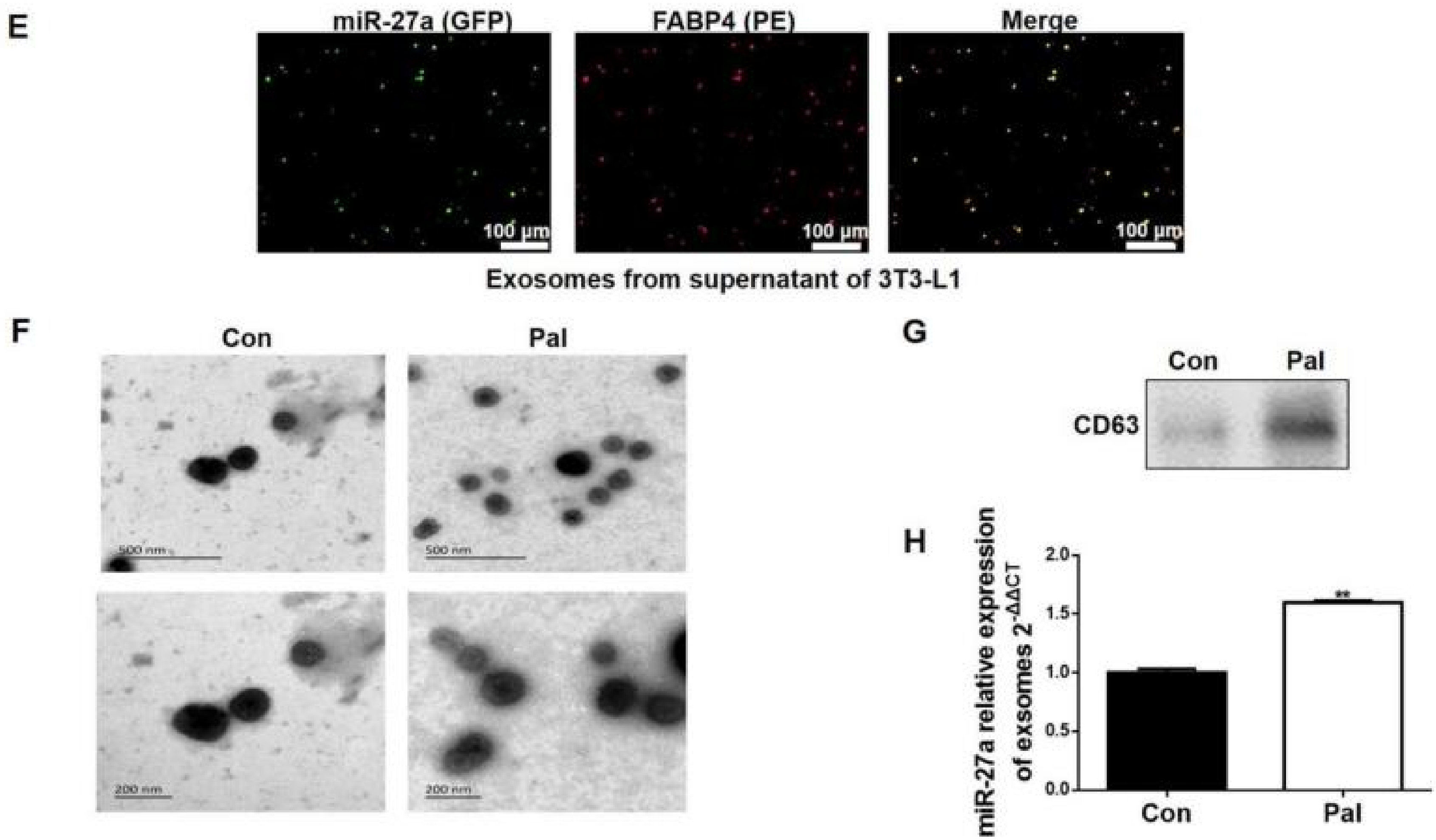
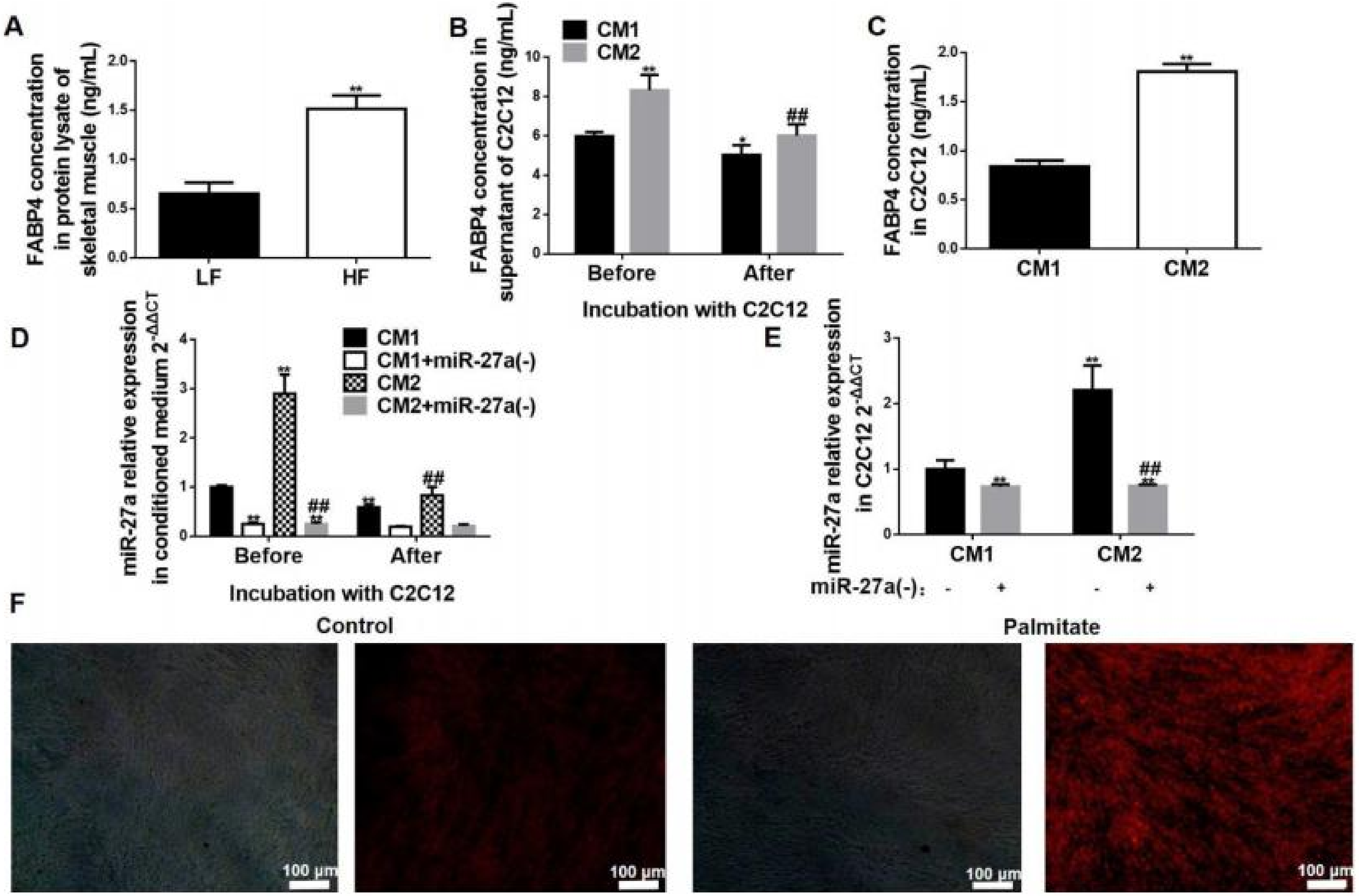


02 负载脂质的脂肪细胞（但不是巨噬细胞）会将miR-27a分泌到外泌体中



02 脂肪细胞衍生的外泌体miR-27a被C2C12骨骼肌细胞摄取



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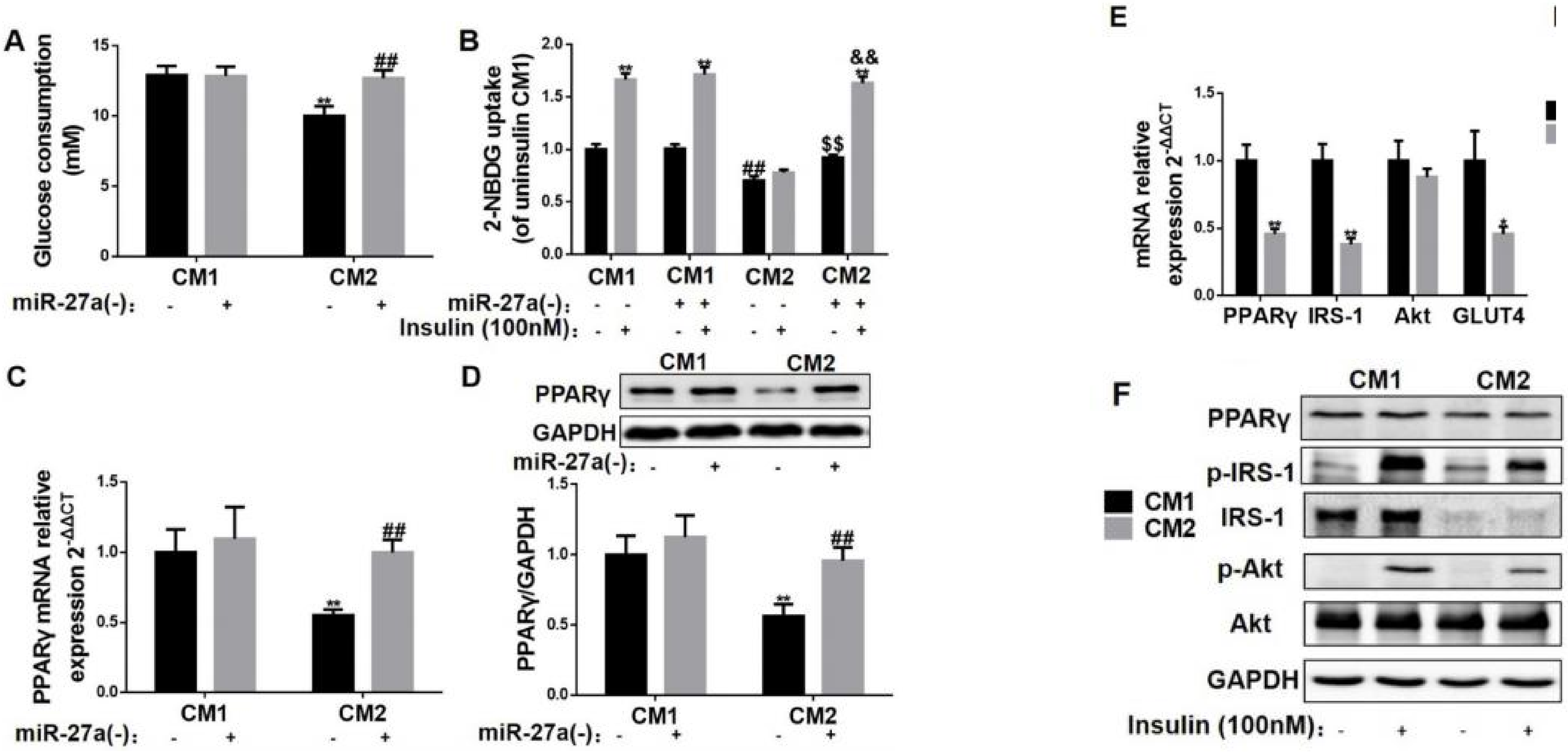
脂肪细胞衍生的miR-27a在骨骼肌细胞中积累，并且通过阻抑PPARγ而损害胰岛素信号传导



Part 03
总结讨论

03 总结讨论

1. MiR-27a在肥胖诱导的骨骼肌胰岛素抵抗中起关键作用；

2.miR-27a由脂肪细胞分泌，以外泌体为载体，被骨骼肌细胞摄取；

3.脂肪细胞衍生的外泌体MiR-27a通过抑制PPARγ诱导骨骼肌胰岛素抵抗。

脂肪细胞衍生的内分泌因子促进骨骼肌胰岛素抵抗的分子机制还不完全清楚。

谢谢观看