Adipose tissue FGF21 resistance contributes to hypoadiponectinemia and insulin resistance in obesity: Role of miR-34a

Karen Siu Ling LAM, Yuk Cheung CHAN, Alexia STILLITANO, Chi Ming WONG, Yong PAN, Aimin XU
State Key Laboratory of Pharmaceutical Biotechnology and Department of Medicine, University of Hong Kong, Hong Kong

Abstract 1866-P

American Diabetes Association. 75th ANNIVERSARY scientificsessions
JUNE 5-9, 2015 · BOSTON, MA

Financial Disclosures

This work was supported by Collaborative Research Fund (HKU2/CRF/12R) from the Hong Kong Research Grant Council.

Introduction

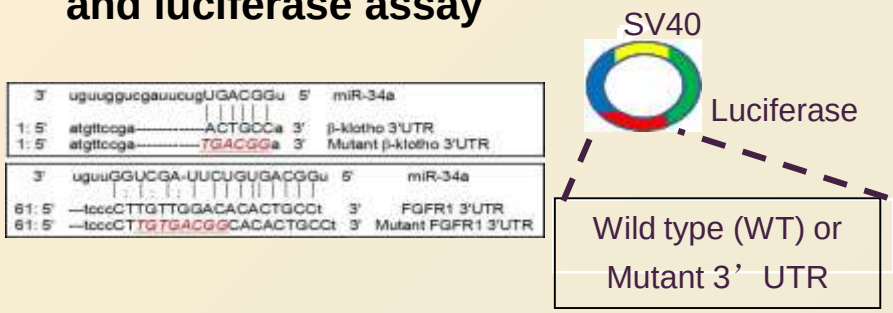
1. Fibroblast growth factor 21 (FGF21) has beneficial effects on glucose and lipid homeostasis.
2. FGF21 exerts its metabolic actions via binding to FGF receptor (FGFR) 1 and its co-receptor β-klotho.
3. FGF21 has stimulatory effect on adiponectin secretion.
4. The possible existence of FGF21 resistance in the development of obesity-related type 2 diabetes.
5. MicroRNAs (miRs) are important regulators of gene expression at both transcriptional and post-transcriptional levels.
6. MiR dysfunction contributes to metabolic dysfunction and insulin resistance in obese state.

Objectives

1. To confirm the presence of FGF21 resistance in the adipose tissues of obese/overweight humans.
2. To investigate whether adipose tissue miR-34a is involved in FGF21 actions.

Materials & Methods

1. The expression levels of FGFR1, β-klotho and miR-34a were measured in visceral adipose tissues (VAT) collected during surgery from 24 overweight/obese (BMI > 23) Chinese women and 29 age- and sex-matched lean controls.
2. Expression levels of FGFR1, β-klotho and adiponectin were analyzed in 3T3-L1 adipocytes infected with lentiviral vector expressing miR-34a.
3. Luciferase reporter gene constructs and luciferase assay



4. Correlations between different parameters were examined by Pearson correlation. Comparison between groups was performed using ANOVA or Student's t-test as appropriate.

Results

1. Adipose tissue miR-34a mediates FGF21 resistance in overweight/obese human subjects.

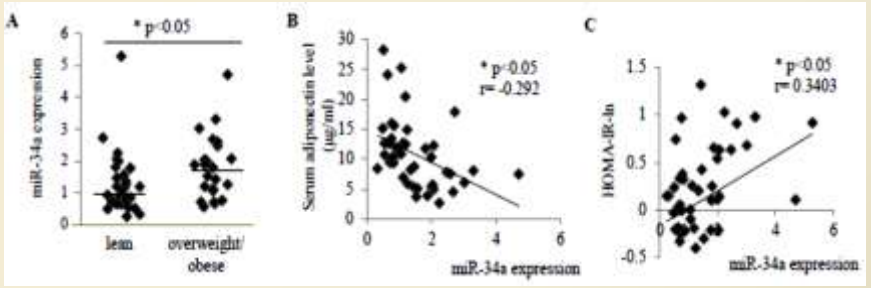


Figure1. Increased adipose tissue miR-34a is associated with hypoadiponectinemia and insulin resistance. A. miR-34a expression levels in visceral fat from lean (BMI<23) and overweight/ obese (BMI>23) human subjects. B-C. Correlation between miR-34a expression and the level of plasma adiponectin (B) or the insulin resistance index HOMA-IR (C) in human subjects (lean n=29 and overweight/obese n=24; p<0.05). Data were expressed as mean ± SEM.

2. The abnormal expression of β-klotho and FGFR1 in visceral fat.

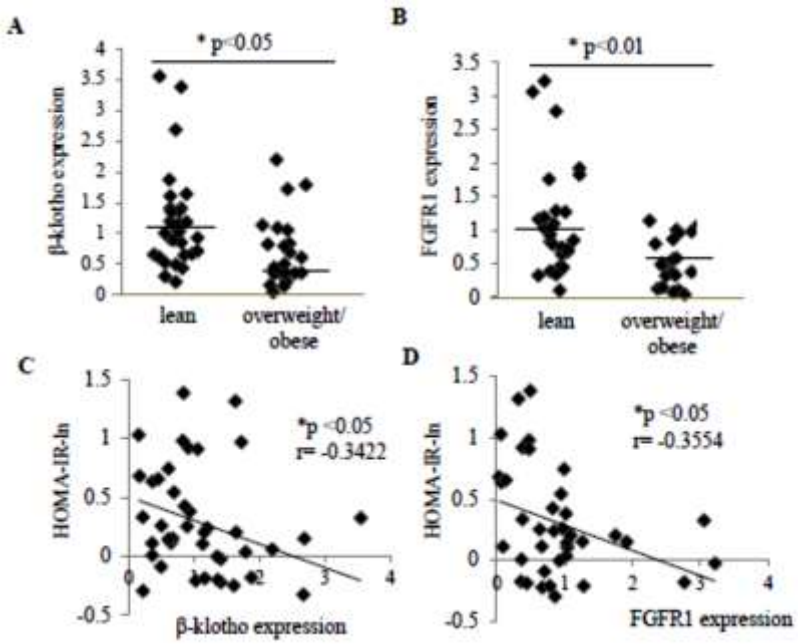


Figure 2. The decreased expression of β-klotho and FGFR1 in visceral fat is closely related to HOMA-IR. A-B. The expression levels of β-klotho (A) and FGFR1 (B) in visceral fat from lean (BMI<23) and 24 overweight/ obese (BMI>23) individuals analyzed with real-time PCR. C-D. Correlation between the insulin resistance index (HOMA-IR) and the expression level of β-klotho or FGFR1 in human visceral fat. (lean n=29 and overweight/obese n=24; *p<0.05 and **p<0.01). Data were expressed as mean ± SEM.

3. Elevated miR-34a in adipose tissues is inversely related to β-klotho and FGFR1 in visceral fat.

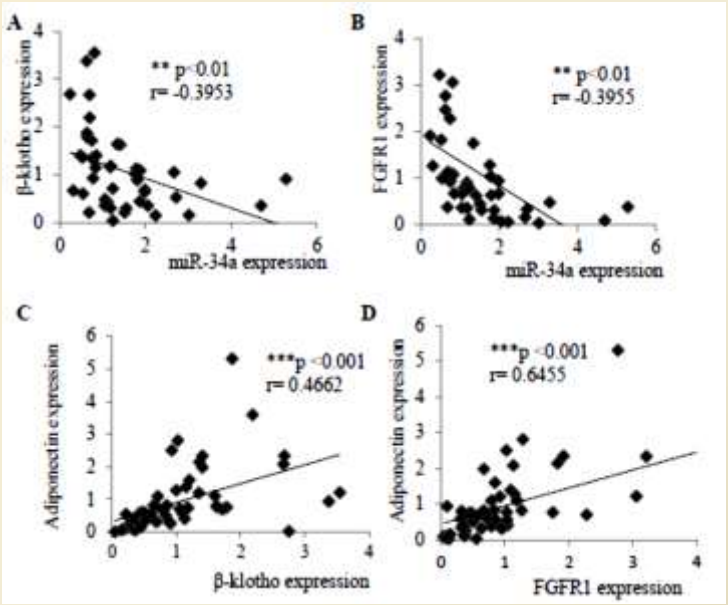


Figure 3. The expression of β-klotho and FGFR1 are inversely related to adipose tissue miR-34a level, but positively correlated to plasma adiponectin . A-B. Correlation between miR-34a expression and the level of β-klotho (A) and FGFR1 (B) in visceral fat. C-D. Correlation between plasma adiponectin level and β-klotho (C) and FGFR1 (D) expression in visceral fat. (lean n=29 and overweight/obese n=24; **p<0.01 and ***p<0.001). Data were expressed as mean ± SEM.

4. MiR-34a directly targets β-klotho and FGFR1 in 3T3-L1 pre-adipocytes

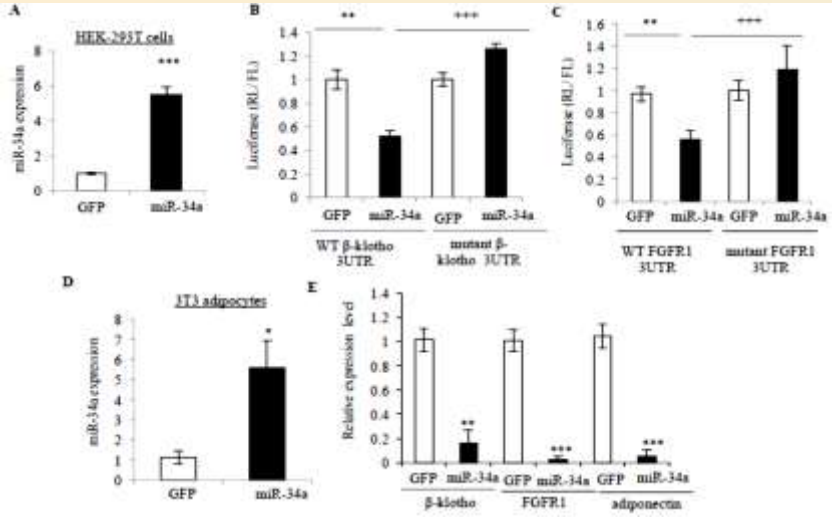


Figure 4. Overexpression of miR-34a suppresses β-klotho and FGFR1 expression in vitro. HEK293 cells were co-transfected with a plasmid encoding miR-34a or GFP control together with a construct carrying wild type (WT) or mutant 3' UTR of the β-klotho or FGFR1 gene. A. The expression levels of miR-34a as determined by real-time PCR. B-C. Luciferase reporter activity expressed as fold over GFP control. D. Expression of miR-34a after infection of lentivirus expressing GFP or miR-34a in 3T3 adipocytes. E. Expression of β-klotho, FGFR1 and adiponectin after over-expression of miR-34a in differentiated 3T3 adipocytes. (n=5-6, *p<0.05, and **p<0.01, and ***p<0.001). Data were expressed as mean ± SEM.

Conclusion

MiR-34a mediated FGF21 resistance is present in the adipose tissues of obese/overweight subjects and may contribute to obesity-related insulin resistance, in part via inducing hypoadiponectinaemia

References

1. Zhang X, et al. *Diabetes* 2008;57:1246-53
2. Lin Z, et al. *Cell metabolism* 2013;17:779-789