The Role of GATA3 in Adipogenesis & Insulin Resistance

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ABSTRACT

Background:

Impaired adipogenesis plays an important role in the development of obesity-associated insulin resistance and type 2 diabetes. Adipose tissue inflammation is a crucial mediator of this process. In hyperglycemia, immune system is activated partially through upregulation of GATA3, causing exacerbation of the inflammatory state associated with obesity. GATA3 also plays a role as a gatekeeper of terminal adipocyte differentiation. Here we are examining the impact of GATA3 inhibition in adipose tissue on restoring adipogenesis, reversing insulin resistance and potentially lowering the risk of type 2 diabetes.

Results:

GATA-3 expression was higher in insulin resistant obese individuals compared to their insulin sensitive counterparts. Targeting GATA-3 with GATA-3 specific inhibitors reversed impaired adipogenesis and induced changes in the expression of a number insulin signaling-related genes, including up-regulation of insulin sensitivity-related gene and down-regulation of insulin resistance-related genes.

Conclusion:

GATA3 expression is higher in differentiating adipocytes from obese insulin resistant. Inhibiting GATA3 improves adipocytes differentiation and rescues insulin sensitivity in insulin resistant cells.

INTRODUCTION

Obesity is a well-known risk factor for T2D that induces insulin resistance in peripheral insulin target tissues [1, 2]. Shulman [3], hypothesized that alteration in fat distribution between adipose tissue and muscle or liver can be a major cause of insulin resistance [4]. Adipose tissue is a complex organ that contains many cell types. Experiments revealed that the proinflammatory condition of adipose tissue in obesity is responsible for the hypertrophied adipocytes and the increase of circulating levels of proinflammatory cytokines such as TNF-α and IL-6. On the other hand, lean individuals favorably secrete anti-inflammatory cytokines such as IL-4, IL-10 and TGFβ [5]. Inflammation is postulated to be important for enhancing insulin resistance and hence increasing the risk of T2D [6]. Several mechanisms have been shown to mediate the crosstalk between obesity and insulin resistance. GATA3 is a transcription factor found to suppress adipocyte differentiation trapping the cells at the preadipocyte stage [7]. GATA-3 also plays a critical role in inflammatory status of adipose tissue. In this work, we investigate the effect of GATA-3 inhibition on adipogenesis and insulin signaling. Our previous data has indicated that GATA3 expression is higher in adipocytes from obese insulin resistant individuals compared with their insulin sensitive counterparts [8].

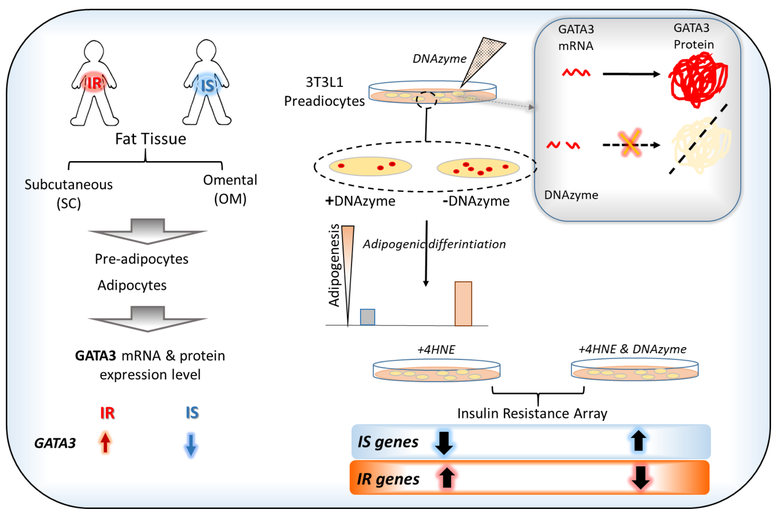


Fig 1. A schematic diagram summarizing the general methods and results that were followed to examine the effect of GATA3 inhibition on preadipocyte differentiation and insulin resistance. ***IR***: Insulin resistance, ***IS***: Insulin sensitive.

RESULTS

○ High GATA3 expression in adipose tissue from Insulin resistance individual:

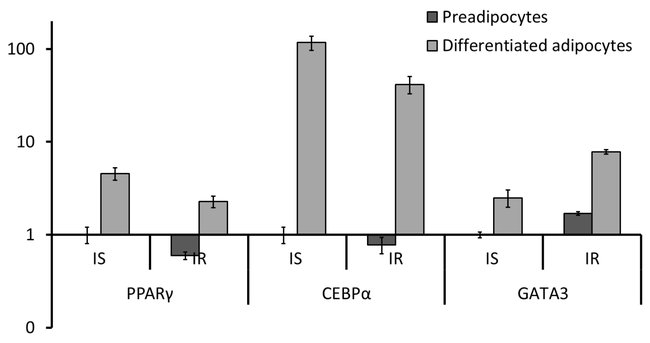


Fig 2. Relative expression of adipogenic factors mRNA levels in adipocytes and pre-adipocytes from human adipose tissues obtained from insulin sensitive (IS) and insulin resistant (IR) obese individuals. *PPARγ*: peroxisome proliferator-activated receptor gama, *CEBPα*: CCAAT/Enhancer Binding Protein, *GATA3*: a transcription factor that bind G-A-T-A nucleotide sequences.

RESULTS *"Cont."*

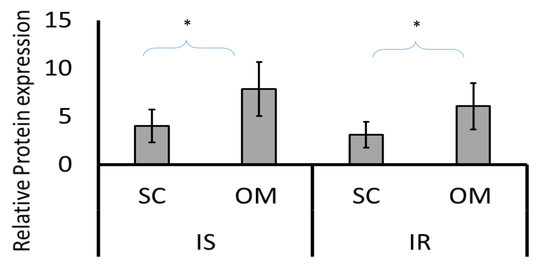
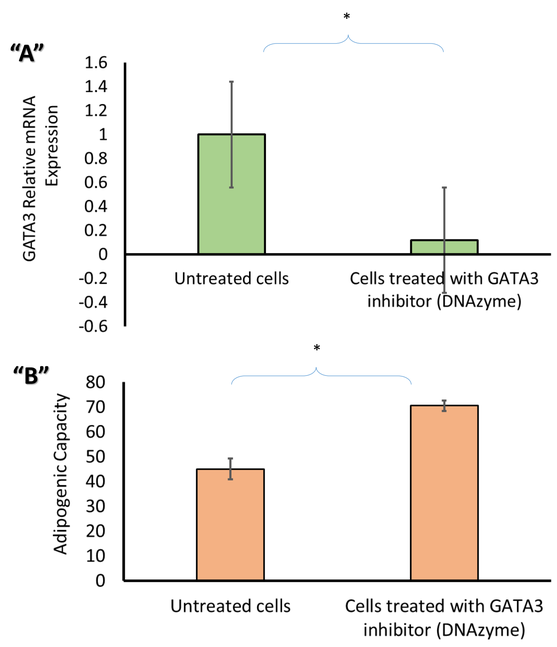


Fig. 3 Relative expression of GATA3 protein in human adipose tissue. Fat tissues from IS and IR individuals were obtained from two body compartments (OM and SC) and GATA3 protein level was measured. The graph shows relative GATA3 protein level. *SC*: subcutaneous, *OM*: omental, *IR*: insulin resistance, *IS*: insulin sensitive.

○ GATA3 inhibition enhanced preadipocyte adipogenic differintiation:



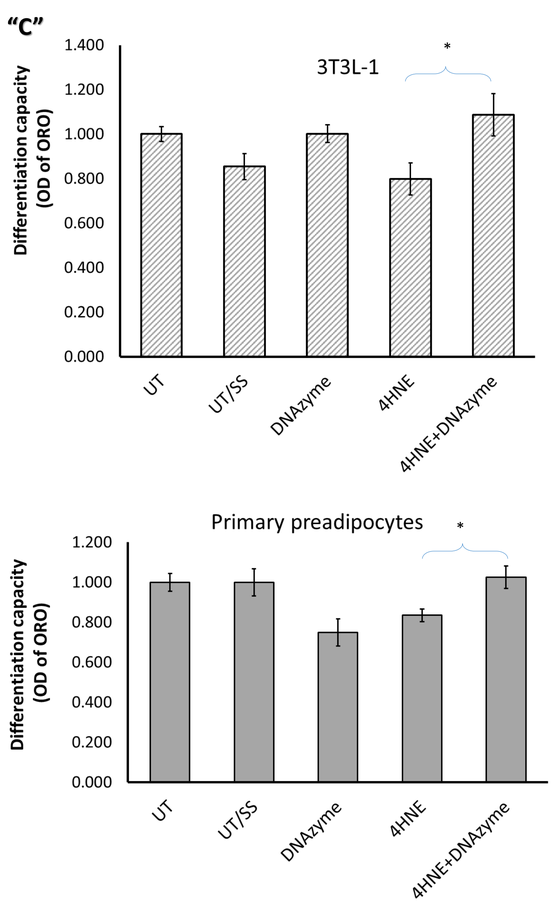
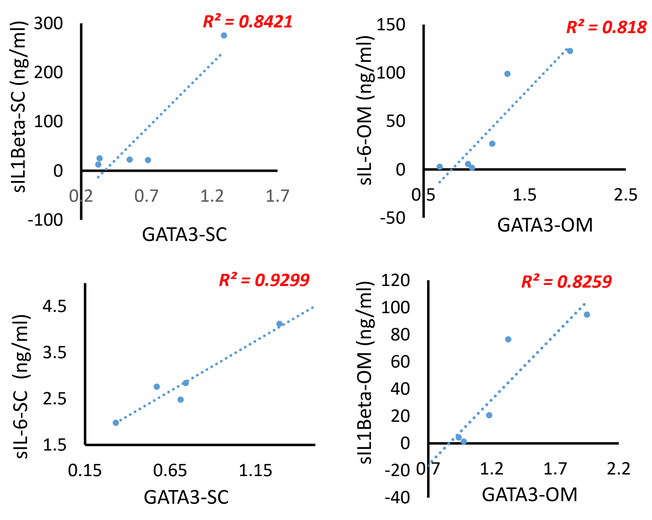


Fig. 4 GATA3 inhibition improved adipogenesis of 3T3L1 and primary pre-adipocytes. ***A-*** A lower GATA3 mRNA level following treatment with GATA3 inhibitor (DNAzyme) compared with the untreated cells. ***B-*** Reversal of 4-HNE-induced impairment of adipogenesis in 3T3L1 cells and ***C-*** primary mouse preadipocytes treated with GATA3 inhibitor. *UT*: untreated, *UT/SS*: untreated scrambled sequence, *4HNE:* 4-Hydroxynonena, *ORO*: oil red O.



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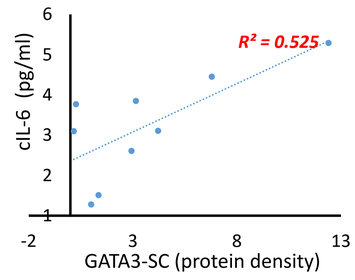

Fig. 4 Correlation between GATA3 mRNA "or protein" expression and some inflammatory cytokines (IL1Beta, IL6). *(s)*: secreated by adipocytes. *(c)*: circulating.

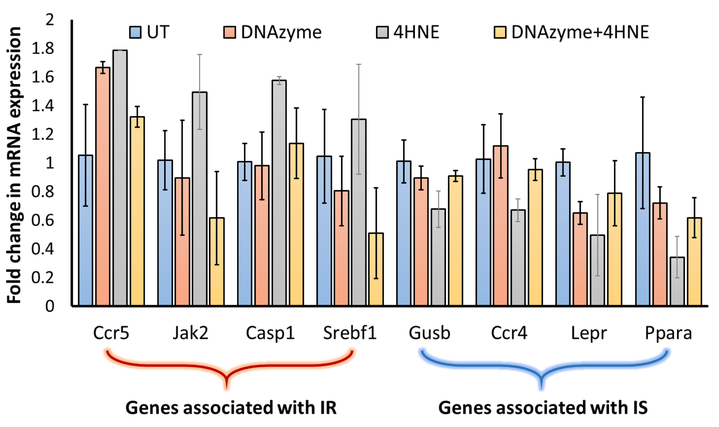

Fig. 5 GATA3 inhibition enhanced insulin sensitivity of differentiated preadipocytes. The graph shows relative mRNA expression of selected insulin signaling genes in mouse 3T3L1 cells. The expression level of genes associated with insulin resistance was significantly reduced following GATA3 inhibition in 4HNE treated cells, whereas a notable induction in the expression of insulin sensitivity genes was found after GATA3 inhibition. *Ccr5*: C-C chemokine receptor type 5, *Jak2*: Janus Kinase 2, *Casp1*: caspase 1, *Srebf1*: Sterol regulatory element-binding transcription factor 1, *Gusb*: glucuronidase beta, *Ccr4*: C-C chemokine receptor type 4, *Lepr*: leptin receptor. *Ppara*: peroxisome proliferator-activated receptor alpha.

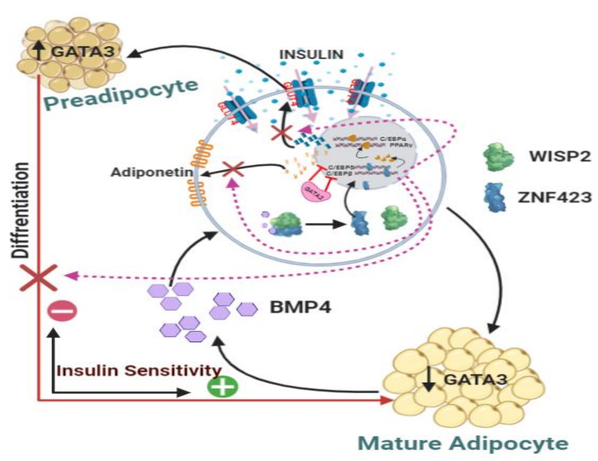

Fig. 5 Role of GATA3 in preadipocyte differentiation to adipocytes and insulin sensitivity.

CONCLUSION

- Our previous results have indicated that GATA3 expression was higher in differentiating preadipocytes from obese insulin resistant compared to their insulin sensitive counterparts.
- Our novel data has shown that there is a positive correlation between GATA3 expression in differentiating preadipocytes and secreted IL-6 and IL-beta as well circulating IL-6.
- The data also showed that GATA3 inhibition leads to recovery of impaired differentiation and rescue of insulin signaling in cells insulin resistant-cells treated with 4-HNE.

REFERENCES

1. Meissburger, B., et al., Adipogenesis and insulin sensitivity in obesity are regulated by retinoid-related orphan receptor gamma. EMBO Mol Med, 2011. 3(11): p. 637-51.
2. Smith, U. and B.B. Kahn, Adipose tissue regulates insulin sensitivity: role of adipogenesis, de novo lipogenesis and novel lipids. J Intern Med, 2016. 280(5): p. 465-475.
3. Shulman, G.I., Cellular mechanisms of insulin resistance. J Clin Invest, 2000. 106(2): p. 171-6.
4. Dubois, S.G., et al., Decreased expression of adipogenic genes in obese subjects with type 2 diabetes. Obesity (Silver Spring), 2006. 14(9): p. 1543-52.
5. Makki, K., P. Froguel, and I. Wolowczuk, Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines. ISRN Inflamm, 2013. 2013: p. 139239.
6. King, G.L., The role of inflammatory cytokines in diabetes and its complications. J Periodontol, 2008. 79(8 Suppl): p. 1527-34.
7. Tong, Q., et al., Function of GATA transcription factors in preadipocyte-adipocyte transition. Science, 2000. 290(5489): p. 134-8.
8. Almuraikhy, S., Kafienah, W., Bashah, M., Diboun, I., ..and Elrayess, M. Interleukin-6 induces impairment in human subcutaneous adipogenesis in obesity-associated insulin resistance. Diabetologia. 2016. doi:10.1007/s00125-016-4031-3.