

Tissue factor mediates coagulation and insulin resistance crosstalk in type II diabetes and obesity

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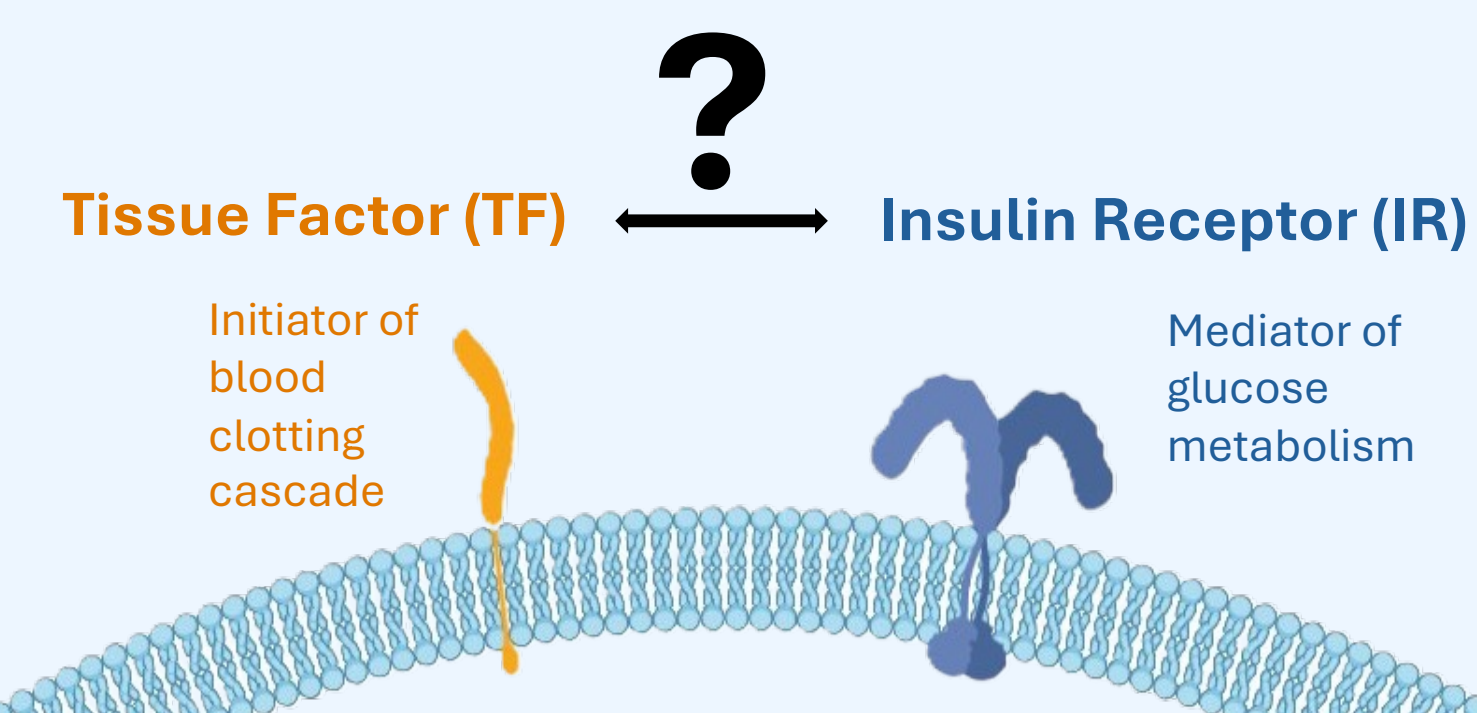
Background

Obesity

- 30% of Canadians are obese¹
- High comorbidity with **type II diabetes** and **cardiovascular disease**²
 - Link between insulin resistance and blood clotting is unknown

Tissue factor

- Initiator of the **blood clotting cascade**
- May interact with **insulin receptor**



Methods

Binding Assays

Proximity Ligation Assay

- Incubation of two proximity probes with the sample to visualize colocalization

Enzyme-Linked Immunosorbent Assay

- Protein immobilization and incubation with second protein and antibody to detect binding

Microscale Thermophoresis (MST)

- Proteins exposed to thermostatic gradient to quantify binding interaction

Functional Assays

Factor Xa Generation

- Activation of FX by FVIIa and TF is quantified for generation of coagulation FXa

2-NBDG Glucose uptake

- Incubation of adipocytes with fluorescent analog of glucose to measure uptake

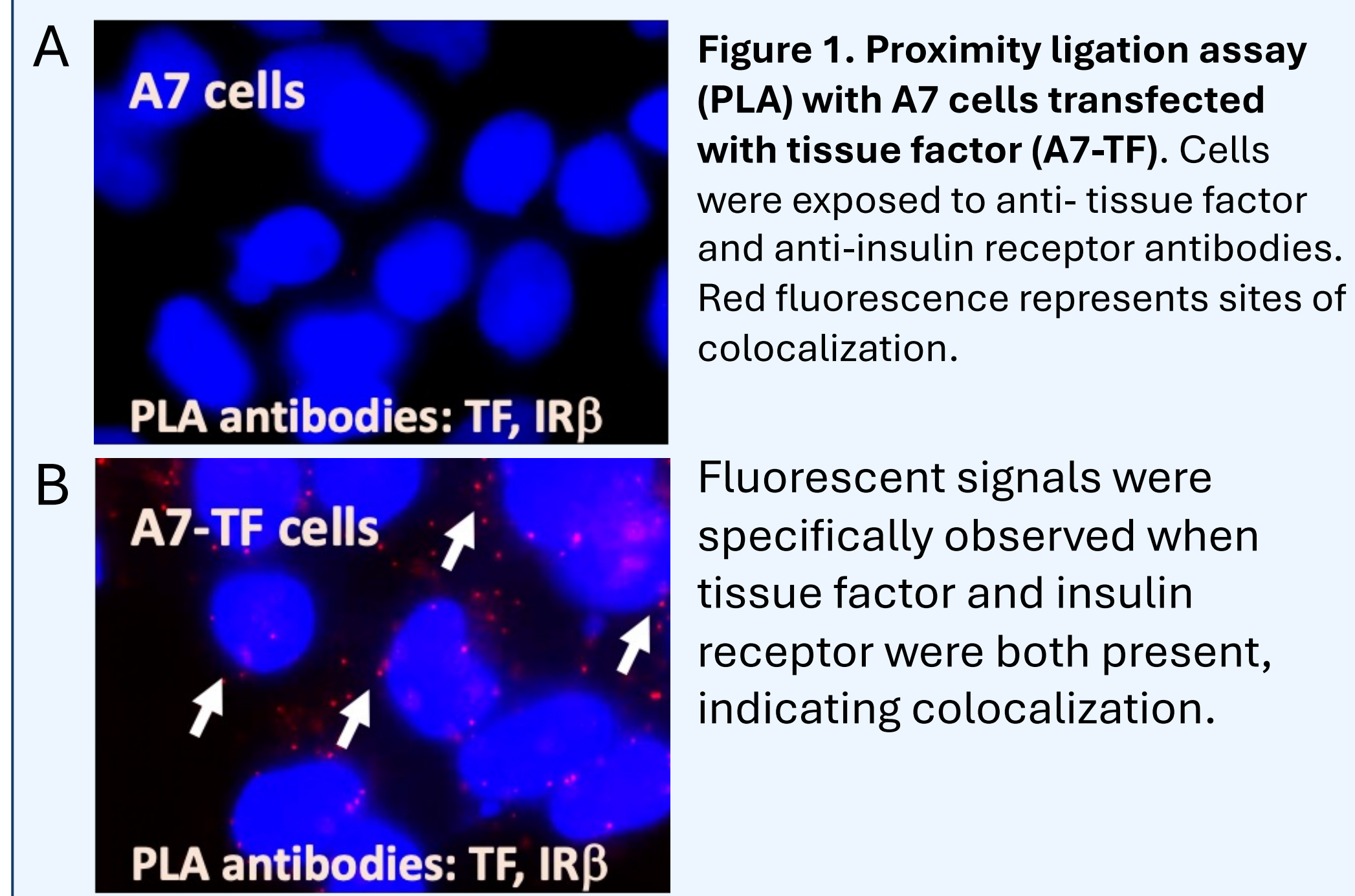
Glucose tolerance test

- Following a dose of glucose, blood glucose levels are measured to evaluate insulin-triggered uptake

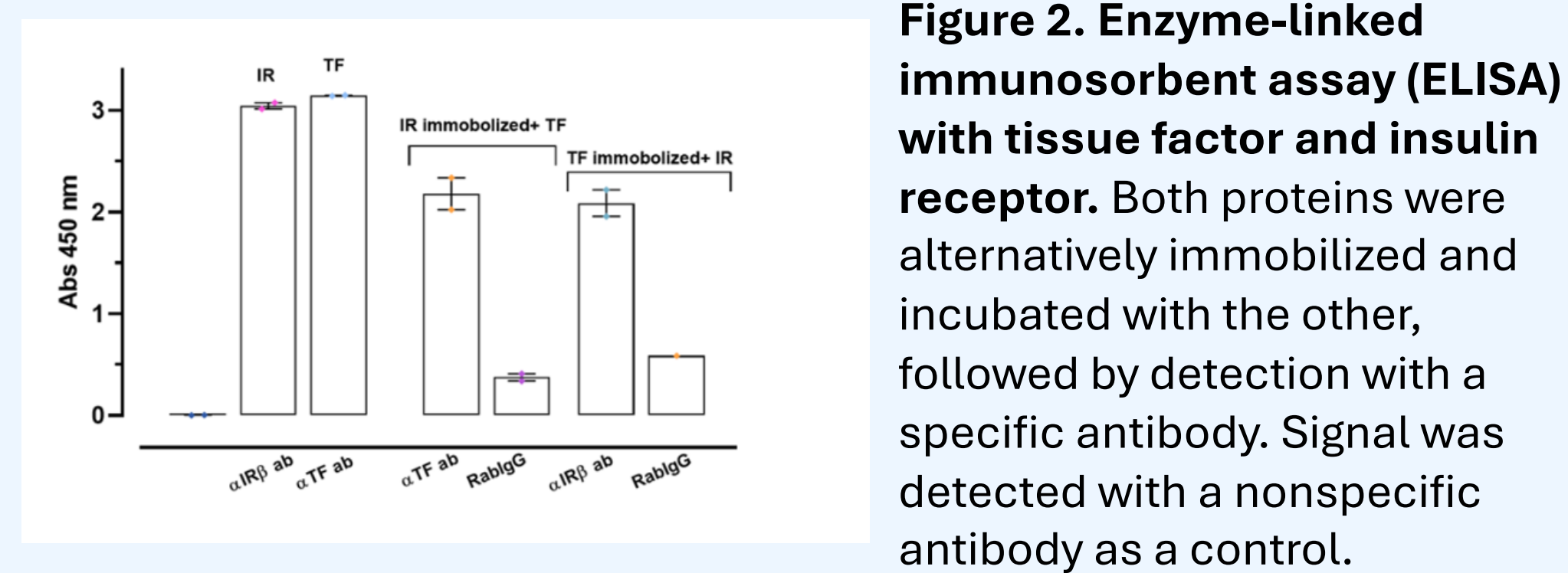
Results

1. Binding

Tissue factor and insulin receptor colocalize



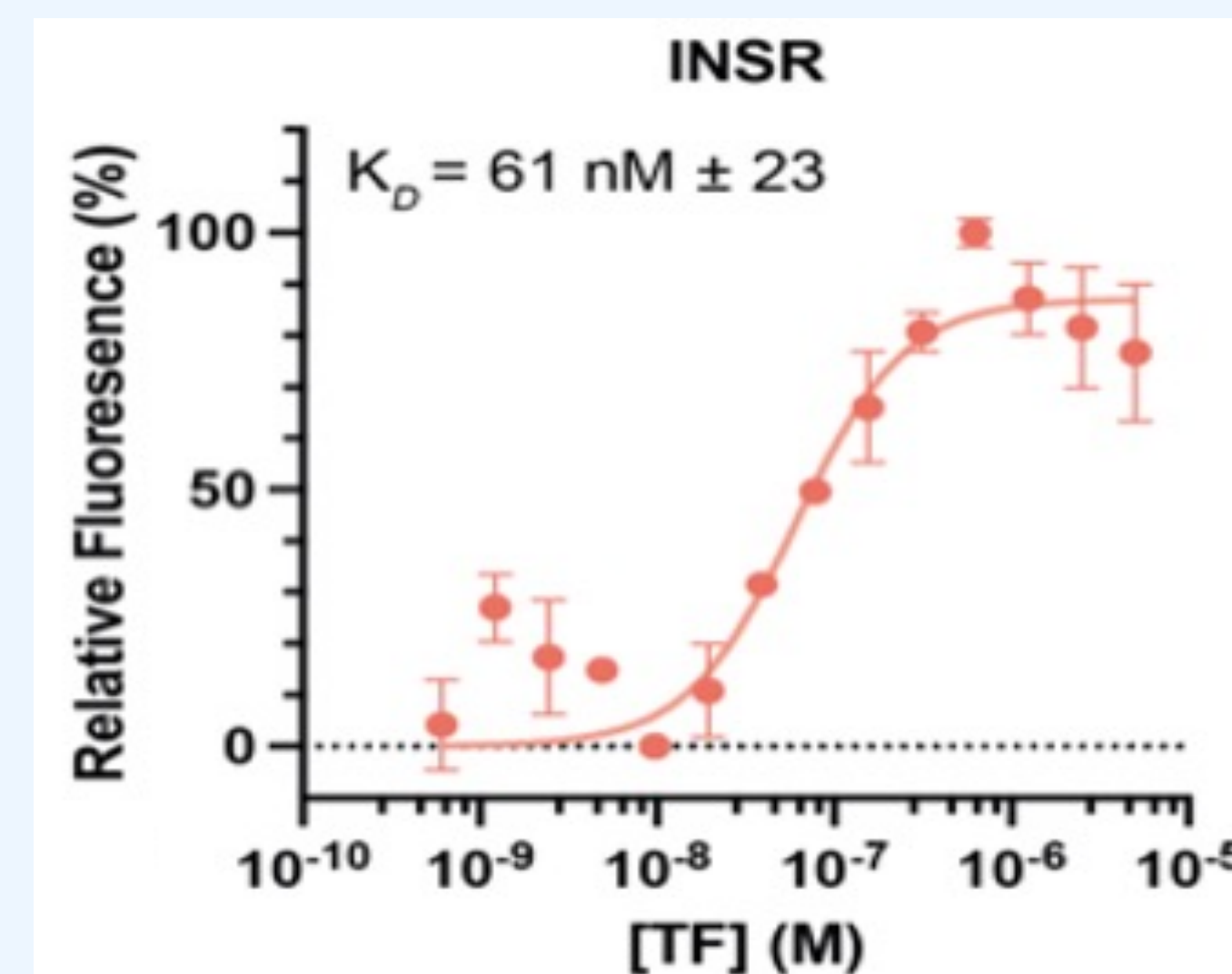
Tissue factor and insulin receptor bind



Elevated levels of signal compared to the control were observed.

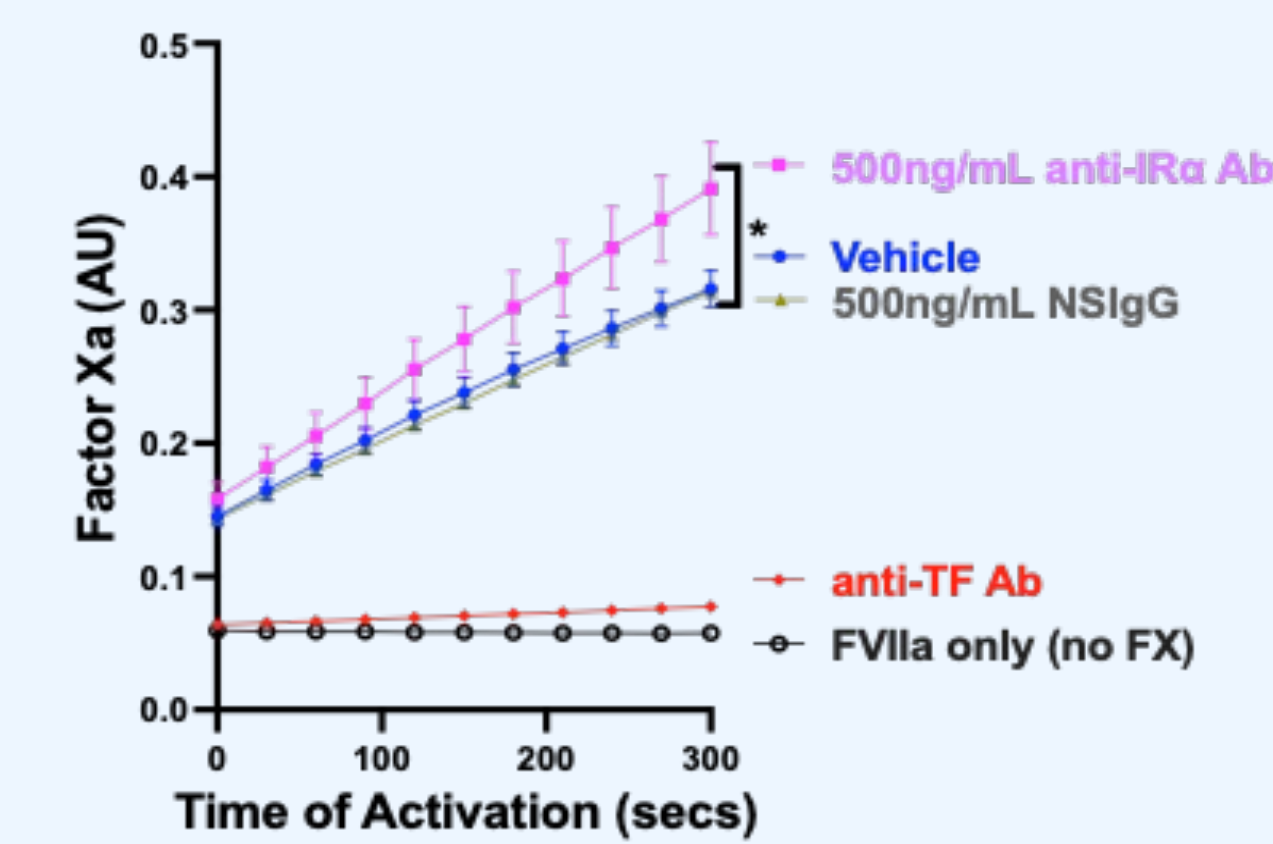
Figure 3. Microscale thermophoresis (MST) using insulin receptor and tissue factor.

MST results revealed a K_d of 61 nM \pm 23 nM for binding affinity of the insulin receptor and tissue receptor.



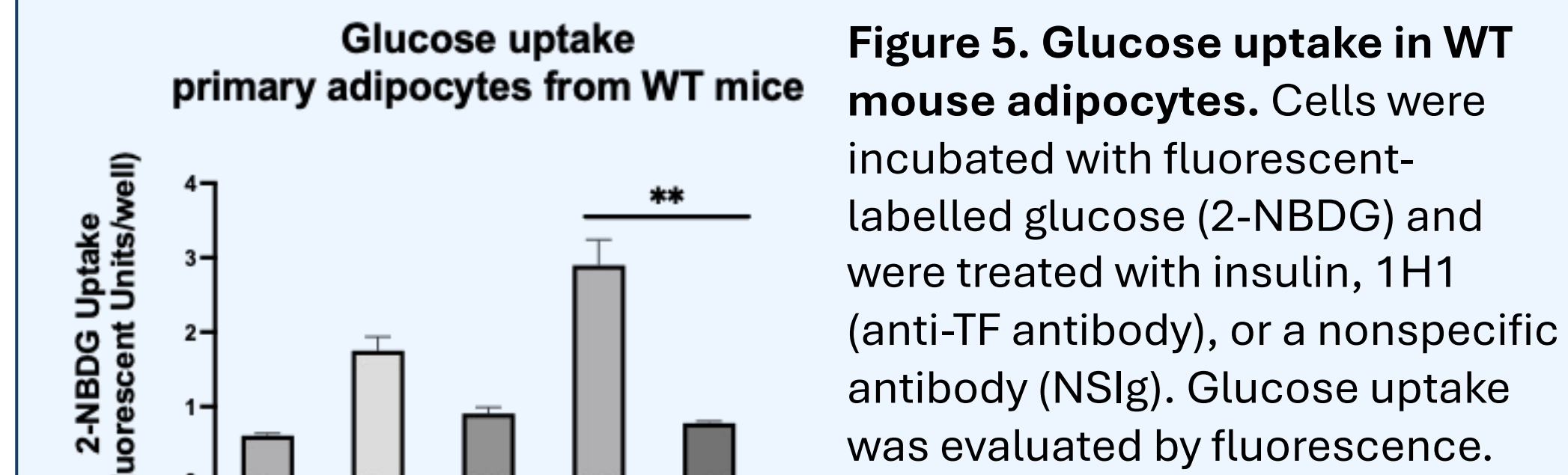
2. Activity

Insulin receptor reduces coagulative activity

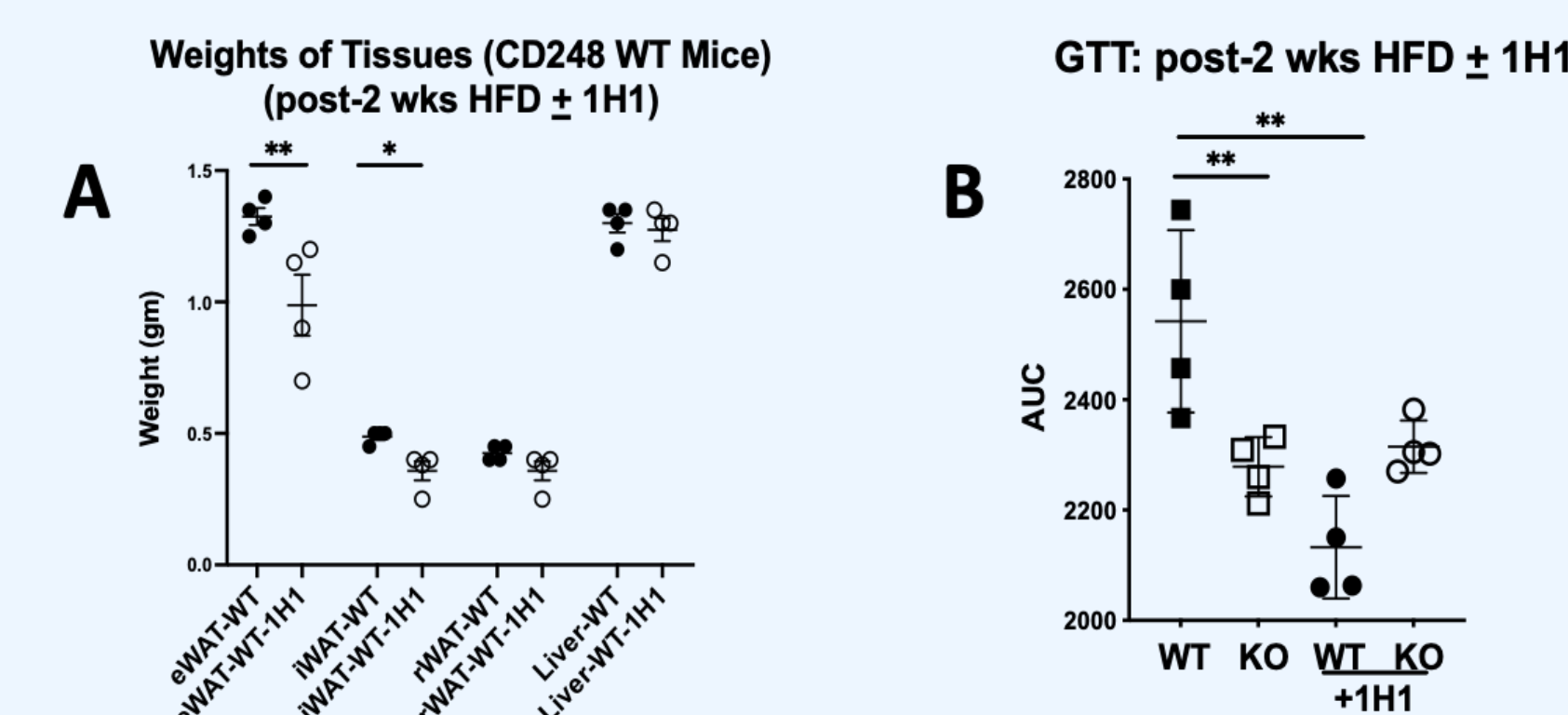


Presence of anti-IR antibodies increased Factor X activation into Factor Xa.

Tissue factor reduces glucose metabolism



Presence of anti-TF antibodies increased insulin-induced glucose uptake.



Presence of anti-TF antibodies significantly lowered adipose tissue weight and improved glucose tolerance.

Conclusion

Tissue factor interacts with insulin receptor to reduce insulin sensitivity and promote coagulation.

- Both receptors are transmembrane proteins expressed by several tissues throughout the body^{3,4}
- Our results indicate that tissue factor and insulin receptor bind on the cell surface and co-operatively regulate coagulation and glucose metabolism.

Future Directions

Generation of mouse lines with tissue factor knocked out in:

- Vascular smooth muscle cells
- Adipose tissue

In vivo experiments to observe tissue specific effects of tissue factor or insulin receptor loss on:

- Coagulation
- Insulin-induced glucose metabolism

References

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3. Duse, L. M., das Graças Carvalho, M., Cooper, A. J., & Lwaleed, B. A. (2006). Tissue factor and tissue factor pathway inhibitor: A potential role in pregnancy and obstetric vascular complications? *Clinica Chimica Acta*, 372(1–2), 43–46. <https://doi.org/10.1016/j.cca.2006.03.025>
4. Evans, M. (2012). Diabetes mellitus, insulin, oral antidiabetic agents, obesity. In *Clinical Pharmacology* (11th ed., pp. 572–586). essay, Churchill Livingstone. Retrieved November 4, 2024, from <https://www.sciencedirect.com/science/article/abs/pii/B9780702040849.000756>.

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