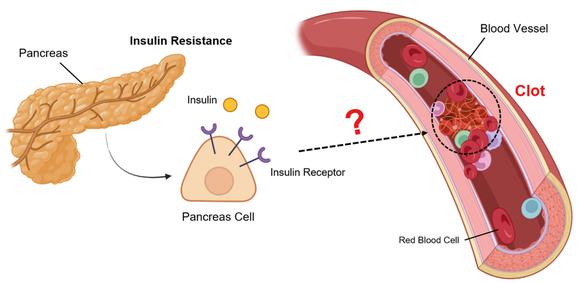
Exploring Molecular Mechanisms of Increased Thrombotic Risk in Type 2 Diabetes

Paniz Ghavimi, Kevin Gonzalez, Nooshin Safikhan, Patricia Benedet, Nathanael Caveney, Natalie Strynadka, Edward Conway
Centre for Blood Research, University of British Columbia, Vancouver, BC

BACKGROUND

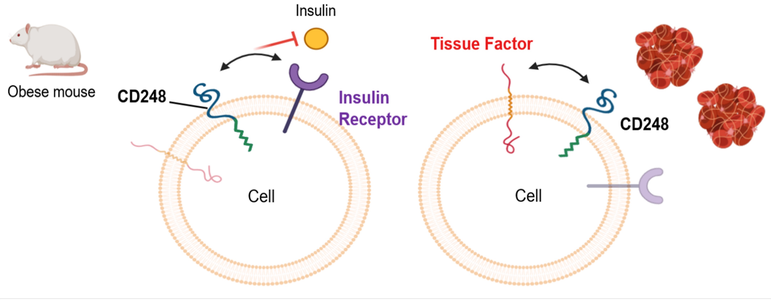
Patients with type 2 diabetes experience an **increased risk** of blood clots, the cause of which remains unclear.



The transmembrane proteins: **tissue factor, CD248, and insulin receptor** are expressed on pre/adipocytes.

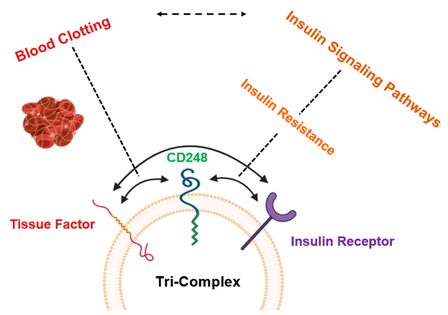
Previous research in Conway Lab showed:

- High levels of adipocyte CD248 correlates with obesity and type 2 diabetes
  - **CD248 interacts with insulin receptor** causing insulin resistance
- High levels of vascular smooth muscle cell CD248 is associated with increased blood clot formation
  - **CD248 interacts with tissue factor** to increase procoagulant activity



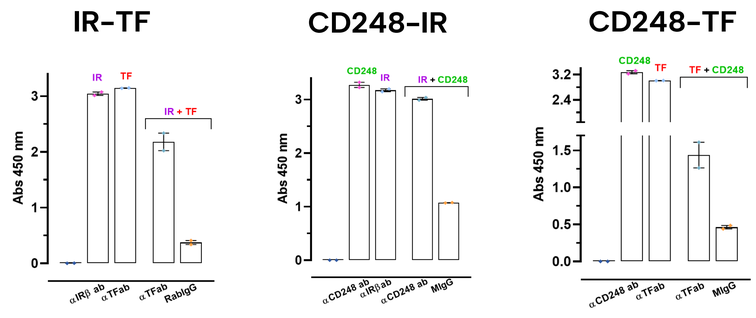
HYPOTHESIS

CD248 **directly** interacts with insulin receptor & tissue factor, and l**inks insulin signaling and coagulation.**

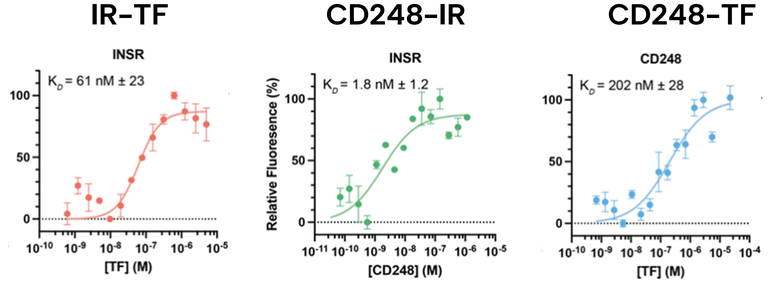


RESULTS

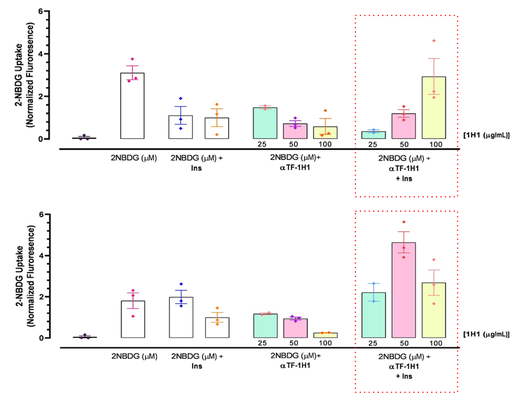
1. The ectodomains of CD248, tissue factor & insulin receptor **directly bind** to each other determined by ELISA.



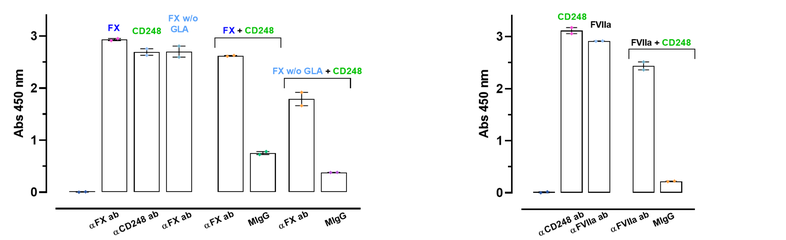
2. The **direct interaction of CD248, tissue factor, and insulin receptor** further verified by microscale thermophoresis (MST).



3. The glucose uptake into mouse smooth muscle cells **increases in the absence** of CD248 and tissue factor.



4. The ectodomains of CD248, FX & FVIIa have a direct interaction.

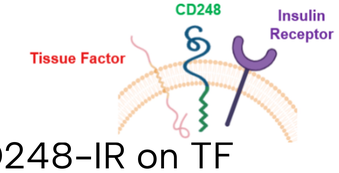


CONCLUSION

- There is a direct interaction between CD248–TF–IR
  - Tri-complex may be a therapeutic target

Next:

- Steps underway to identify which domains bind to each other
- Functional studies to evaluate the effects of CD248–TF on IR and CD248–IR on TF



Kapopara, P. R., Safikhan, N. S., Huang, J. L., Meixner, S. C., Gonzalez, K., Loghmani, H., Ruf, W., Mast, A. E., Lei, V., Pryzdial, E. L. G., & Conway, E. M. (2021). CD248 enhances tissue factor procoagulant function, promoting arterial and venous thrombosis in mouse models. *Journal of Thrombosis and Haemostasis*, *19*(8), 1932–1947. https://doi.org/10.1111/jth.15338

Norledge, B. V., Petrovan, R. J., Ruf, W., & Olson, A. J. (2003). *Theoretical Model of the Tissue Factor/Factor VIIA/Factor Xa Complex*. https://doi.org/10.2210/pdb1nl8/pdb