A new potential therapeutic target for type 2 diabetes: Delineating the mechanisms of its actions

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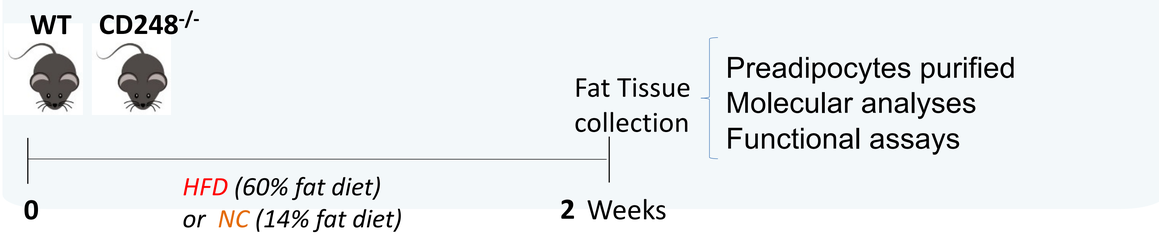
BACKGROUND

- CD248 is a type I transmembrane glycoprotein belonging to the C-type lectin-like domain superfamily[1]
- Normally expressed at low levels by cells of mesenchymal origin, CD248 is highly expressed in pre/adipocytes of white adipose tissue (WAT)[1,2]
- We previously reported that in mice and humans, WAT expression levels of CD248 are inversely correlated with WAT function, insulin sensitivity, and glucose and lipid homeostasis [2]
- Global or adipocyte-specific *CD248* gene inactivation in mice protects against high fat diet (HFD)-induced obesity and insulin resistance[2]
- Our data suggested that CD248 acts as a molecular switch that induces the transition of WAT from a healthy to an unhealthy, insulin resistant state

OBJECTIVE

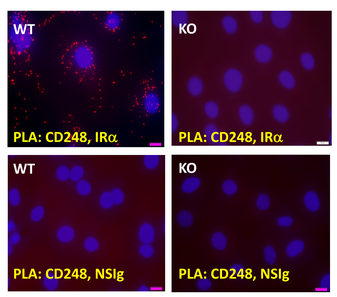
To delineate the mechanisms by which CD248 modulates canonical insulin signaling pathways that impact on key metabolic activities

METHODS

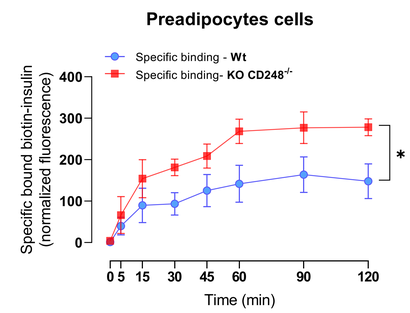


RESULTS

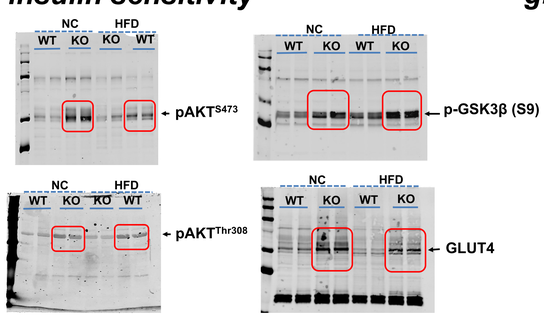
1- Proximity ligation assay (PLA): CD248 is close to the insulin receptor (IRα)



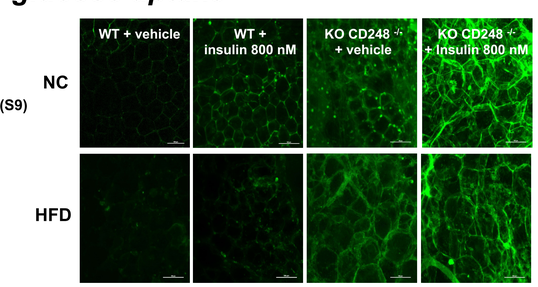
2- CD248 reduces insulin binding to the insulin receptor



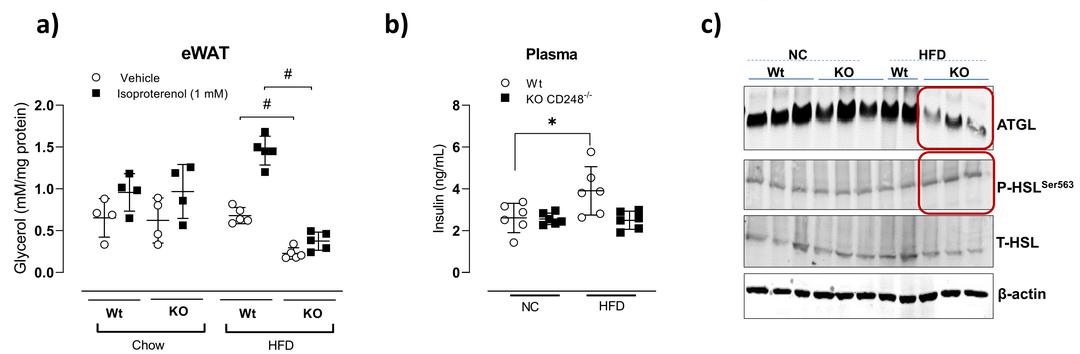
3- CD248 KO eWAT has increased insulin sensitivity



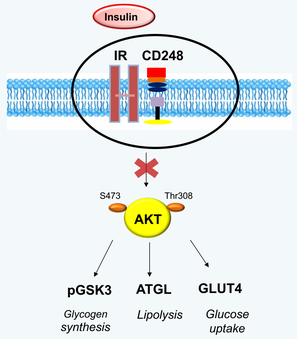
4- CD248-KO WAT exhibits increased glucose uptake



5- CD248-KO adipose reduces lipolysis and protects against insulin resistance



CONCLUSION



1. CD248 binds to Insulin receptor and dampens insulin signaling
2. Lack of CD248 improves glucometabolism
   - Increases glucose uptake
   - Dampens hyperinsulinemia and lipolysis

FUTURE DIRECTIONS

1. Validate findings in humans
2. Screen compounds/antibodies to block CD248-dependent signaling *in vitro* and *in vivo*

Potential impact

1. Novel therapeutic target for type 2 diabetes

References

1- Rupp C, Dolznig H, Puri C, Sommergruber W, Kerjaschki D, Rettig WJ, et al. Mouse endosialin, a C-type lectin-like cell surface receptor: Expression during embryonic development and induction in experimental cancer neoangiogenesis. Cancer Immunity. 2006;6:10

2. Petrus P, Fernandez TL, Kwon MM, Huang JL, Lei V, Safikhan NS, Karunakaran S, O'Shannessy DJ, Zheng X, Catrina SB, Albone E, Laine J, Virtanen K, Clee SM, Kieffer TJ, Noll C, Carpentier AC, Johnson JD, Rydén M, Conway EM. Specific loss of adipocyte CD248 improves metabolic health via reduced white adipose tissue hypoxia, fibrosis and inflammation. EBioMedicine. 2019;44:489-50.

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