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
- 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

<table>
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<tr>
<th>NO</th>
<th>WT</th>
<th>CD248-/</th>
<th>HFD (60% fat diet) or NC (14% fat diet)</th>
<th>2 Weeks</th>
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Preadipocytes purified
Molecular analyses
Functional assays

RESULTS

1. Proximity ligation assay (PLA): CD248 is close to the insulin receptor (IRa)

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

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