

Role of Gremlin1 and Bone Morphogenic Protein 4 (BMP4) in metabolic diseases

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligen försvaras i M106 K Isaksson, Medg 16, den 2024.10.18, klockan 13:00.

Av Roxana Khatib Shahidi

Fakultetsopponent:

Professor Maria Gomez

Department of Clinical Science, Diabetes Centre, Lund University, Malmö-Sweden

Avhandlingen baseras på följande delarbeten

I. Shahram Hedjazifar, Roxana Khatib Shahidi, Ann Hammarstedt, Laurianne Bonnet, Christopher Church, Jeremie Boucher, Mathias Bluher and Ulf Smith. **The novel adipokine Gremlin1 antagonizes insulin action and is increased in type-2 diabetes and NAFLD/NASH.** *Diabetes* 2020, 69(3); 331–41.

II. Roxana Khatib Shahidi, Jenny M. Hoffman, Shahram Hedjazifar, Laurianne Bonnet, Ritesh K. Baboota, Stephanie Heasman, Christopher Church, Ivet Elias, Fatima Bosch, Jeremie Boucher, Ann Hammarstedt, Ulf Smith. **Adult mice are unresponsive to AAV8-Gremlin1 gene therapy targeting the liver.** *PLoS One* 2021, 16(2); e0247300.

III. Roxana Khatib Shahidi and Jeremie Boucher. **BMP4 gene therapy delays diabetes progression in the diabetic *db/db* mice.** [Manuscript].

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Role of Gremlin1 and Bone Morphogenic Protein 4 (BMP4) in metabolic diseases

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Gremlin1, a protein highly expressed in human adipocytes, plays a key role in the differentiation of precursor cells into white adipose tissue and is linked to insulin resistance in hypertrophic obesity. This study investigated Gremlin1 expression in patients with obesity, type 2 diabetes (T2D), and related metabolic disorders, as well as its effects on obesity and insulin sensitivity in a diet-induced obese mouse model. We further investigated BMP4 for its potential therapeutic effects in a diabetic mouse model.

We found elevated Gremlin1 mRNA levels in adipose tissue of first-degree relatives of T2D patients, correlated with body fat percentage and insulin resistance markers. Increased expression was also observed in the subcutaneous and visceral fat, and liver of T2D patients, particularly those with metabolic dysfunction-associated steatohepatitis (MASH). Additionally, Gremlin1 levels were higher in obese T2D patients compared to lean individuals.

In vitro, Gremlin1 was shown to disrupt insulin signaling in human hepatocytes, adipocytes, and muscle cells by inhibiting Akt phosphorylation. However, in vivo studies in mice revealed that neither increasing Gremlin1 expression nor administering Gremlin1 protein significantly affected metabolism.

BMP4 gene therapy in diabetic mice showed limited benefits, such as short-term weight gain and delayed insulin decline, but did not reverse diabetes or have lasting metabolic effects.

CONCLUSIONS: Gremlin1 is a secreted protein that antagonizes insulin signaling, particularly in adipose tissue and liver, and is associated with insulin resistance and metabolic dysfunction in humans. While it presents a potential therapeutic target for obesity-related conditions, its metabolic impact appears to be species-specific. BMP4 therapy showed initial promise in diabetic mice but requires further research for long-term effectiveness.

Keywords: Gremlin1, obesity, type 2 diabetes, metabolic dysfunction-associated fatty liver disease, MASLD, metabolic dysfunction-associated steatohepatitis, MASH, BMP4.

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