C3aR1 on beta cells preserves beta cell function and glucose homeostasis in diabetic mice by decreasing metabolic stress and dedifferentiation

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INTRODUCTION

Obesity and type 2 diabetes (T2D) are multifactorial metabolic diseases with the latter characterized by insulin resistance and insufficiency of the pancreatic islets. Adipose tissue is an important endocrine organ responsible for regulating processes such as energy homeostasis, insulin sensitivity, and inflammation, due to the secretion of a variety of cytokines, including adipsin/complement factor D. We previously showed that adipsin plays an important role in the preservation of β-cells by controlling the complement pathway and generating complement component C3a in diabetic mice. Furthermore, elevated adipsin levels are linked to protection against T2D in humans, while insulin secretion appears to be influenced, at least partially, by C3aR1.

AIM

We aimed to define how attenuating the function C3aR1 on β-cells effects insulin secretion and beta cell health.

CONCLUSION

This study suggests that the interactions between C3a/C3aR1 have a significant impact on β-cell health and function in a long-term metabolic stress model.

METHODS

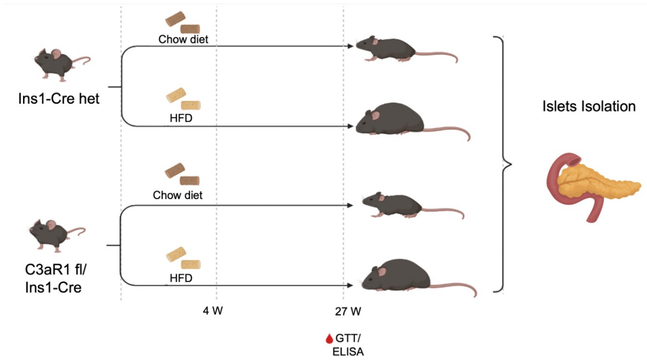

Fig 1. Schematic representation of a long-term metabolic stress model.

RESULTS

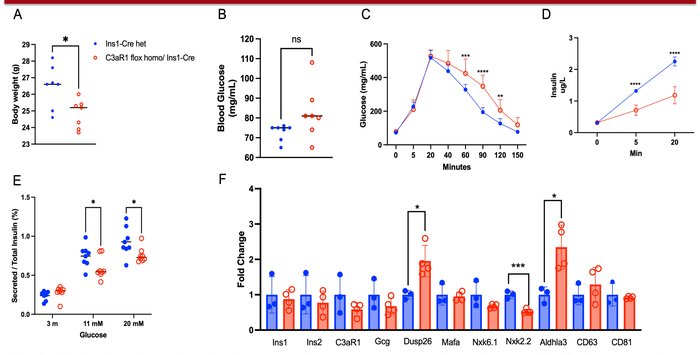

Fig 2. C3aR1 Regulates Insulin Secretion in vivo and in vitro. Ins1-Cre and C3aR1 flox homo/Ins1-Cre male mice were fed a chow diet for 27 weeks and challenged with i.p. glucose injections, and plasma insulin levels were assayed. A: Fasting body weight; B: Fasting blood glucose; C: GTT; D: Glucose-stimulated insulin secretion assay (GSIS) in vivo; E: GSIS on islets and F: gene expression in islets.

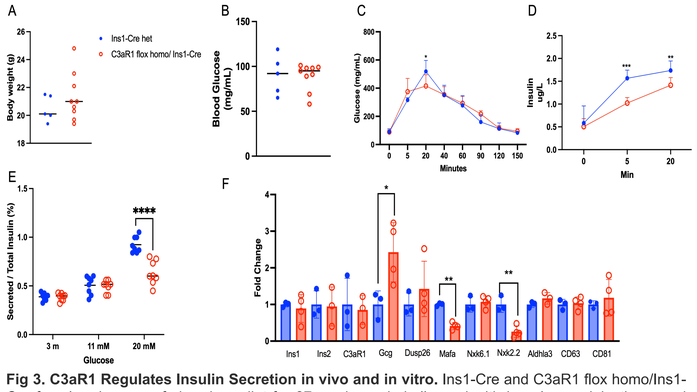

Fig 3. C3aR1 Regulates Insulin Secretion in vivo and in vitro. Ins1-Cre and C3aR1 flox homo/Ins1-Cre female mice were fed a chow diet for 27 weeks and challenged with i.p. glucose injections, and plasma insulin levels were assayed. A: Fasting body weight; B: Fasting blood glucose; C: GTT; D: GSIS in vivo; E: GSIS on islets and F: gene expression in islets.

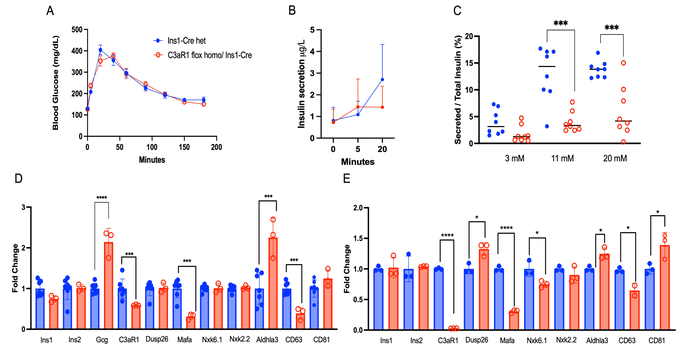

Fig 4. C3aR1 Regulates Insulin Secretion in vivo and in vitro. Ins1-Cre and C3aR1 flox homo/Ins1-Cre male mice were fed a HFD diet for 27 weeks starting at 1 month of age and challenged with i.p. glucose injections, and plasma insulin levels were assayed. A: GTT; B: GSIS in vivo; C: GSIS on islets; D: gene expression in islets and E: gene expression in sorted β-cells

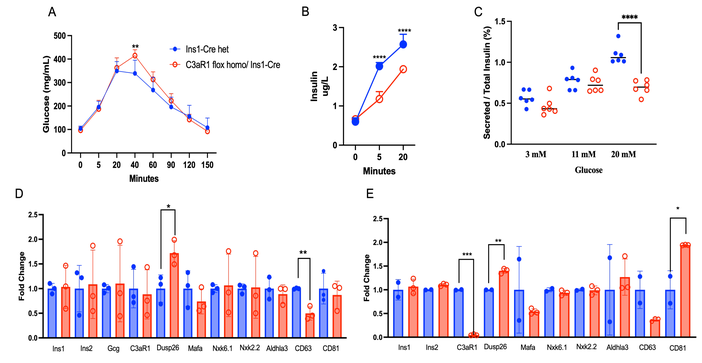

Fig 5. C3aR1 Regulates Insulin Secretion in vivo and in vitro. Ins1-Cre and C3aR1 flox homo/Ins1-Cre female mice were fed a HFD diet for 27 weeks starting at 1 month of age and challenged with i.p. glucose injections, and plasma insulin levels were assayed. A: GTT; B: GSIS in vivo; C: GSIS in islets; D: gene expression on islets and E: gene expression in sorted β-cells.

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