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

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Abstract

Background: Obesity and type 2 diabetes (T2D) are multifactorial diseases with the latter characterized by insulin resistance and insufficiency of the pancreatic islets, and their incidence has increased at alarming rates in recent years, becoming a global health problem. Furthermore, elevated adipsin levels are linked to protection against T2D in humans, while insulin secretion appears to be influenced, at least partially, by C3aR1. We here aimed to define how attenuating the functions of C3a and C3aR1 on beta cells effect insulin secretion. **Methods:** Mice with beta cell specific knockout of C3aR1 (C3aR1-Ins1 Cre) were fed regular diet (RD) or high-far-diet (HFD; 60% kcal) for 27 weeks. We performed a glucose tolerance test, blood chemistry, and serum insulin analysis. After 27 weeks, pancreatic islets were isolated by perfusion of the pancreases, followed by in vitro glucose-stimulated insulin secretion, FAC-sorted β-cells islet, and real-time qPCR analysis.

Results: For male and female mice fed with RD or HFD for 27 weeks, there were impairments in glucose tolerance and insulin secretion in the KO group, in vivo and in vitro. Pancreatic islets and β cells in the KO group showed increased expression of genes related to metabolic stress and immature/stressed β cells, and a decrease in genes related to β cell identity, metabolic activity, and insulin secretion. **Conclusion:** This study suggests that C3aR1 signaling on beta cells are critical to maintain insulin secretion and protect the health of beta cells in a long-term metabolic stress model.