京都大学大学院医学研究科　循環器内科学　博士課程　西清人

学位論文要約

Nardilysin Is Required for Maintaining Pancreatic β-Cell Function

Abstract

Type 2 diabetes (T2D) is associated with pancreatic β-cell dysfunction, manifested by reduced glucose-stimulated insulin secretion (GSIS)(1). Several transcription factors enriched in β-cells, such as MafA, control β-cell function by organizing genes involved in GSIS(2). Here we demonstrate that nardilysin (N-arginine dibasic convertase; Nrd1 and NRDc) critically regulates β-cell function through MafA. Nrd1(-/-) mice showed glucose intolerance and severely decreased GSIS. Islets isolated from Nrd1(-/-) mice exhibited reduced insulin content and impaired GSIS in vitro. Moreover, β-cell-specific NRDc-deficient (Nrd1(delβ)) mice showed a diabetic phenotype with markedly reduced GSIS. MafA was specifically downregulated in islets from Nrd1(delβ) mice, whereas overexpression of NRDc upregulated MafA and insulin expression in INS832/13 cells. Chromatin immunoprecipitation assay revealed that NRDc is associated with Islet-1 in the enhancer region of MafA, where NRDc controls the recruitment of Islet-1 and MafA transcription. Our findings demonstrate that NRDc controls β-cell function via regulation of the Islet-1-MafA pathway.

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References

1. Muoio DM, Newgard CB: Mechanisms of disease:Molecular and metabolic mechanisms of insulin resistance and beta-cell failure in type 2 diabetes. Nat Rev Mol Cell Biol 2008;9:193-205
2. Guo S, Dai C, Guo M, Taylor B, Harmon JS, Sander M, Robertson RP, Powers AC, Stein R: Inactivation of specific beta cell transcription factors in type 2 diabetes. J Clin Invest 2013;123:3305-3316