

Joint Research Programs Annual Report

Principal Investigator	Sigurd Lenzen, MD, PhD
Affiliation	Institute of Experimental Diabetes Research, Hannover Medical School
IAMS Host Researcher	Professor: Seiichi Oyadomari
Project Title	Role of the integrated stress response transcription factor ATF4 in the progression of lipotoxicity in pancreatic β -cells.
Project Purpose	The underlying molecular mechanisms linking lipotoxicity to β -cell failure remain incompletely understood. In this study, we investigated the role of ATF4 as a key transcriptional regulator of endoplasmic reticulum- and integrated stress response in palmitate-mediated lipotoxicity using ATF4 knockout MIN6 cells.
Research Results	We have completed the analysis for the six research items proposed in the application as planned. However, we would like to withhold the detailed results from public release until the paper is accepted for publication, as it is currently under submission. The research items are: 1. Investigation of the PERK signaling pathway and ATF4 expression 2. Assessment of ATF4-KO on downstream targets 3. Evaluation of the role of ATF4 in palmitate-mediated β-cell apoptosis 4. Investigation of the role of ATF4 in palmitate-induced mitochondrial stress response 5. Assessment of ATF4 knockout on palmitate-mediated depolarization of the mitochondrial membrane potential 6. Examination of the role of ATF4 in palmitate-mediated H₂O₂ generation
Publications	1. Mechanisms of lipotoxicity-induced dysfunction and death of human pancreatic beta cells under obesity and type 2 diabetes conditions. Plötz T, <u>Lenzen S</u>. <i>Obes Rev</i>. 2024 Feb 7:e13703. 2. Potentiation of Lipotoxicity in Human EndoC-βH1 β-Cells by Glucose is Dependent on the Structure of Free Fatty Acids. von Hanstein AS, Tsikas D, <u>Lenzen S</u>, Jörns A, Plötz T. <i>Mol Nutr Food</i>. 2023 Mar;67(5):e2200582.
Future Plan	Due to comments from peer reviewers, we need to conduct additional investigations on four items, so we wish to continue our collaborative research into 2024. These are: 1. Confirmatory Experiments in Alternative Cell Models 2. siRNA-mediated ATF4 Suppression 3. Additional Stressor Experiments 4. Insulin Secretion and Content Analysis