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TITLE

# Impaired Cleavage of Preproinsulin Signal Peptide Linked to Autosomal

**Ming Liu[1], Roberto Lara-Lemus[1], Shu-ou Shan[2], Fabrizio Barbetti[3], Leena Haataja[1] and Peter Arvan[1]**

[1]The Division of Metabolism, Endocrinology & Diabetes, University of Michigan Medical Center, Ann Arbor Michigan, 48105.

[2]Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena CA 91125.

[3]Laboratory of Molecular Endocrinology and Metabolism, Bambino Gesù Children's Hospital, Scientific Institute (IRCCS), Rome, Italy and Department of Internal Medicine, University of Tor Vergata, Rome, Italy

In pancreatic beta cells, insulin synthesis begins with the precursor, preproinsulin, which must undergo co-translational translocation into the endoplasmic reticulum (ER), signal peptide (SP) cleavage, and downstream proinsulin folding. These earliest events are critical to insulin biosynthesis, but they are relatively understudied. Recently, two missense mutations immediately upstream of the signal peptide (SP) cleavage site of preproinsulin were reported as potential causes of *Mutant INS-gene-induced Diabetes* of *Youth* (MIDY). While it is known that insulin haploinsufficiency does not cause diabetes, patients with MIDY are heterozygous for insulin gene mutations, suggesting that mutants act in a dominant-negative fashion. The molecular mechanisms of beta cell failure caused by these mutants remain unknown. We establish that preproinsulin-A(SP23)S is cleaved normally, with no diminution in human insulin production or increased endoplasmic reticulum (ER) stress, and is unlikely to cause autosomal dominant diabetes. By contrast, preproinsulin-A(SP24)D is inefficiently cleaved at an improper location, resulting in a small subpopulation of aberrant proinsulin as well as a large subpopulation of uncleaved preproinsulin — both of which remain entrapped in the ER, causing ER stress. More importantly, A(SP24)D blocks ER exit of co-expressed wild-type proinsulin, accounting for its dominant-negative behavior. Interestingly, these dominant-negative effects are ameliorated upon augmented expression of ER-oxidoreducin-1 (Ero1). This maneuver does not rescue A(SP24)D, but for co-expressed wild-type proinsulin it enhances oxidative folding to the native state, decreases ER-associated degradation (ERAD) and increases ER export — suggesting new molecular therapeutic options to rescue insulin production in patients with MIDY.

## Biography

Ming Liu M.D., Ph.D. was originally trained as a physician and endocrinologist with extensive knowledge of diabetes pathogenesis and treatment. His research has mostly focused on the early events of insulin biosynthesis and how defects of those events lead to pancreatic β-cell failure and diabetes. He was one of the first to describe proinsulin misfolding in normal pancreatic β- cells, and to propose a novel molecular mechanism of β-cell failure caused by misfolded proinsulin. He is currently a Principal Investigator (PI) of four ongoing research grants, including a Research Grant (RO1) from NIH, and a grant from March of Dimes Foundation.