Peptide amidation in physiology and disease

by Elisa Araldi

Abstract:
Peptidylglycine alpha-amidating monooxygenase (PAM) is a bifunctional enzyme that catalyses the C-terminal amidation of certain peptide hormones. Among post-translational enzymatic modifications, C-terminal alpha-amidation is essential for the specific recognition of peptides by their cognate receptors, and for the stability of biologically active peptides. Recent genome-wide association studies (GWAS) have highlighted the importance of PAM in diabetes predisposition, and studies have shown that loss of PAM in pancreatic islets in vitro impairs insulin secretion. With this study, we aim at understanding the broader impact of PAM on human physiology.

The UK Biobank is one of the largest biobanks available to researchers collecting genotypes, phenotypic traits, clinical and behavioral data from >450,000 patients, and allowing to carry on explorative genomic research with the statistical power of big data. Combining genomic and phenotypic data from the UK Biobank with genotype-tissue expression data from the GTEX project, we could identify several endocrine traits associated with loss or gain of function of PAM. Patients carrying SNPs that affect PAM expression or function are more predisposed to imbalances in fluid homeostasis, thyroid function, growth, sleep and adrenal function. Interestingly, PAM knockout mouse models mirror most of the phenotypes seen in the human cohort, and we could demonstrate that hormone amidation is essential to drive the endocrine dysfunctions. Of note, patients with PAM mutations have an increased all-cause mortality rate and this data reflects the decrease in survival of PAM knockout mice. Taken together this work shows the importance of peptide amidation in human physiology.

BRIEF BIOGRAPHY:
After a Masters degree in Cellular and Molecular Biology from the Scuola Normale Superiore and the University of Pisa, I obtained a PhD in Pathobiology and Translational Medicine from the New York University, working on macrophage function and cholesterol metabolism with professors Carlos Fernandez-Hernando and Yajaira Suarez at Yale University. Since October 2016, I am working on peptide amidation a postdoctoral fellow at ETH Zurich in the lab of professor Markus Stoffel.