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My name is Alina Walth-Hummel and I am a PhD student at the Institute for Diabetes and Cancer at the Helmholtz Munich. I studied Nutrition and Biomedicine at the Technical University Munich and started my PhD in the group of Maria Rohm in 2019. Just recently, in January 2023 I submitted my Thesis.

My project aims to understand the underlying mechanisms of transcriptional processes in beta cells in physiological and pathological states. The loss of functional beta cell mass, which is observed upon type 2 diabetes is in part attributed to the loss of beta cell identity. Exact mechanisms are currently elusive but previous studies identified the dysregulation of transcriptional events as major contributor to the loss of beta cell identity. Here, I focused on the transcription co-factors TBL1 (transducin β -like 1) and TBLR1 (TBL-related 1) as they were originally identified as ligand and signal dependent exchange factors for regulatory complexes such as the NCOR/SMRT (nuclear receptor corepressor/silencing mediator for retinoid and thyroid receptors) repressor complex. Through their ability to exchange activator and repressor complexes, TBL1 and TBLR1 act as a switch for transcriptional repression and activation.

To address the beta cell specific role of TBL1 and TBLR1, mice with an Ins1-cre-driven double deletion of TBL1 and TBLR1 (TBL/R β KO) were generated. TBL/R β KO mice developed hyperglycemia starting at the age of 6 weeks which was accompanied by impaired insulin gene expression. Alterations in islet architecture and reduced numbers of insulin positive cells preceded the hyperglycemia. Using multi-omics approaches we showed that β -cells deficient for TBL1 and TBLR1 downregulated identity genes and started to express disallowed genes instead, indicative for a loss of beta cell identity. An interactome analysis but also endogenous immunoprecipitation experiments revealed that both TBL1 and TBLR1 directly interacted with PAX6, a master regulator of beta cell identity. Also components of the NCOR/SMRT repressor complex directly bound to PAX6. Ultimately this indicates that beta cell identity under the control of PAX6 is mediated by TBL1 and TBLR1 through their ability to recruit regulatory complexes such as NCOR/SMRT.