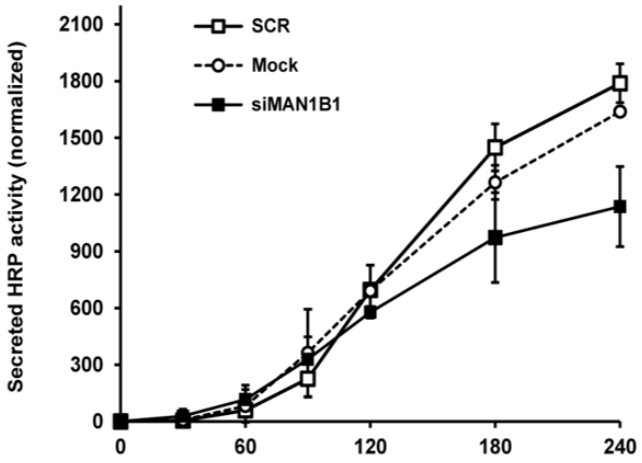
Introduction: Congenital Disorders of Glycosylation (CDG) are a group of genetic diseases, due to deficient protein and lipid glycosylation. Our group recently identified MAN1B1-deficiency as a frequent type of CDG associated with impaired Golgi glycosylation, intellectual disability and obesity. The mannosidase MAN1Bl was for long assumed to contribute to ER-associated protein degradation by initiating the formation of degradation signals on misfolded N-linked glycoproteins. However, it was recently demonstrated that MAN1B1 is Golgi-localized, and may have a gatekeeping role to retrieve escaped misfolded glycoproteins back to the ER for degradation. While perturbations in homeostasis of the endoplasmic reticulum (ER) are known to create a condition termed ER stress and leading to activation of a complex signaling cascade, the mechanisms regulating Golgi capacity still remain unclear. We hypothesized that MAN1B1-deficiency would lead to an accumulation of escaped misfolded proteins in the Golgi, overwhelming its capacity.

Results: we were able to evidence a delay in the anterograde trafficking of MAN1B1-deficient cells (panel A) as well as an accumulation of (misfolded) glycoproteins in the Golgi apparatus. We could also demonstrate that MAN1B1-deficient fibroblasts generate a targeted mild to moderate transcriptional response, which appears to be specific to MAN1B1-CDG. In addition, RNA-seq analysis highlighted a handful of highly upregulated transcripts in MAN1B1-CDG fibroblasts, including *GSAG1* (panel B). GSAG1 is already associated in literature to a disorder of connective tissues, which might allow to explain part of the pathophysiology of MAN1B1 deficiency.

A.



B.