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Engineering patterned human brain cells on silicon chip

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N-glycanase 1 is a deglycosylase that plays a role in proteasome mediated degradation of misfolded proteins translocated to the cytosol from the endoplasmic reticulum. While the molecular function of *NGLY1* is known, we are only beginning to understand how its loss alters basic cellular processes and can lead to various patient phenotypes? Due to the role of *NGLY1* in protein degradation, it was assumed that cells lacking *NGLY1* would accumulate misfolded proteins; however, this has not been observed in human cells. Using proteomic and transcriptomic profiling, as well as screening for genes that in influence *NGLY1* related phenotypes, we determined phenotypically causative genes and pathways. Furthermore, we profiled *NGLY1* patient/parent trio's cells and model cell lines from multiple tissues and under different growth conditions using methods developed in our lab to determine the genes that are consistently misregulated across environments and cell types. We generated an analysis pipeline and used profiling data from these independent systems to observe a consistent down-regulation of proteasome related genes across all cell types analyzed. Based on our data and newly published results from multiple organisms, we hypothesize that this down-regulation is mediated by an evolutionarily conserved interaction of *NGLY1* with a family of transcription factors. Data suggests that, in addition to its canonical role in proteostasis, *NGLY1* is important for functional processing of at least one protein. Orthogonal analyses of cellular proteins suggest that there is a secondary effect on mitochondria. In this seminar, I will discuss the method we developed to understand the wide-reaching effects of the deglycosylase *NGLY1* and we determined downstream effects and how the relate back to *NGLY1* deficiency.

Biography

William F Mueller brings his expertise in gene regulation to rare disease. He has earned his PhD in Biomedical Sciences at UC-Irvine studying the regulation of alternative splicing and devoted the last two years to understanding rare diseases, specifically N-glycanase 1 (*NGLY1*) deficiency. In his current position of Team Leader for the rare disease/*NGLY1* section of Lars Steinmetz's lab at EMBL, he is applying the multiomic analysis principles developed in the Steinmetz lab to rare disease. This approach has already lead to the discovery of novel results for the *NGLY1* community.

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