YEAST AS A MODEL FOR BATTEN DISEASE: ROLES FOR BTN1 AND BTN2 IN ENDOSOME-GOLGI PROTEIN RETRIEVAL

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We use yeast as a model system to understand the role of conserved proteins involved in Batten disease and related lysosomal storage disorders in humans. Neuronal ceroid lipofucinoses (NCLs), including the juvenile onset form known as Batten disease, are characterized by abnormal accumulation of autofluorescent material in lysosomes. Thus, the study of NCLs requires an in-depth understanding of the intracellular trafficking pathways that deliver proteins and lipids from Golgi to lysosomes and back via the endosomal compartments. Defects in protein delivery to the lysosome via endosomes may result in organelle expansion, cellular degeneration, and onset of the disease state. We previously demonstrated that Btn2 - a yeast ortholog of Hook1 and a potential Batten disease-related protein - mediates protein retrieval from late endosomes (LEs) to the Golgi (Kama *et al*, 2007, *Mol. Cell. Biol.* 27:605-621). Btn2 resides on a late endosomal compartment and interacts with known proteins involved in LE-Golgi protein retrieval in yeast. These include SNAREs of the endosomal SNARE complex, a sorting nexin – Snx4, and components of the retromer complex which mediates LE-Golgi protein sorting. Importantly, the deletion of *BTN2* in yeast leads to specific defects in the trafficking of cargo proteins destined to reach the LE. We found that the retrieval of an essential Golgi protein, Yif1, from late endosome to the Golgi is perturbed in the absence of Btn2, as seen earlier (Chattopadhyay *et al*, 2003, *BBRC* 302:534-538). In addition, recycling of a subtilisin-like protease is also defective in the absence of *BTN2*. Importantly all defects in protein trafficking in *btn2D* cells are phenocopied by mutations in retromer and other genes known to be involved in LE-Golgi sorting. We now show that a deletion in *BTN1*, which encodes the ortholog of a known Batten Disease associated gene - *CLN3*, also leads to defects in LE-Golgi sorting. Moreover, Btn1 localizes to the ER and, thus, acts in a distal fashion to regulate LE-Golgi protein retrieval. Our results demonstrate that Batten disease (and, perhaps, other NCLs) are likely to result from defects in endosomal protein sorting.