

Ultrastructural and dynamic studies of the endosomal compartment in Down syndrome

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SUMMARY

Abnormal early endosomal enlargement was widely characterized in the brain of individuals with Down syndrome and Alzheimer's disease patients. In both diseases, it precedes amyloid deposition and clinical symptoms, thus constituting one of the earliest neuropathological alterations. However, this early phenotype was characterized with conventional light microscopy at a resolution above the actual size of early endosomes.

Here, for the first time, we used ultrastructural imaging and super-resolution light microscopy to revisit the endosomal compartment in Down syndrome. Importantly we combine this morphological characterization with dynamic and molecular studies to unravel mechanisms.

Major results are the following:

Ultrastructural studies on unfixed material unequivocally show that early endosomes are normal-sized and more numerous.

Dynamic studies reveal that endocytosis is unchanged in Down syndrome while endosomal recycling is increased and late endosome-dependent degradation is delayed.

RNA sequencing revealed a subgroup of differentially-expressed genes related to cargo sorting in the endosomal compartment.

Finally, we show that the level of the key endosomal regulator phosphatidylinositol-3-phosphate is decreased in Down syndrome, in accordance with published data in Alzheimer's disease.

Altogether, we show new morphological, dynamic and molecular deregulations implicated in endo-lysosomal dysfunctions and protein trafficking in Down syndrome and Alzheimer's disease. These results provide new hypotheses to explain endosomal abnormalities in DS and AD and bring insights into the comprehension of the role the endo-lysosomal pathway in both pathologies.