

P020 Altered cellular zinc homeostasis contributes to pathology in Niemann-Pick type C disease, a neurodegenerative lysosomal storage disorder.

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Niemann-Pick C (NPC) is an inherited neurodegenerative lysosomal storage disease characterised by loss of cerebellar Purkinje neurons. NPC cells present with defects in endocytosis and lysosomal accumulation of a variety of lipids including sphingolipids and cholesterol. The disease is caused by mutation in one of two unrelated genes, NPC1 or NPC2, which encode putative lipid transporters. The NPC1 protein (which accounts for 95% of NPC cases) is a lysosomal transmembrane protein with homology to bacterial RND permeases (transporters of heavy metals, cationic drugs and detergents) and a zinc-binding domain. We have studied the role of zinc in NPC cellular pathology using a variety of different NPC cell types (fibroblasts, neuroblastomas, glia) and drug-induced NPC models (U18666A). Using fluorescent intracellular zinc indicators we have discovered a dramatic change in cellular zinc localisation from the cytosol in normal cells to lysosomes in all NPC cells. This change in localisation occurs early in the disease process (4h after inhibition of NPC1 function) and precedes lipid storage. Further depletion of intracellular zinc with TPEN induced NPC cell death.

Further studies are underway to determine whether zinc efflux from lysosomes is dependent on the function of the NPC1 protein using NPC1 overexpressing CHO cells. The role of altered zinc homeostasis in NPC neurodegeneration is being studied in the NPC1-null mouse model.