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A new role for glycolipids in Niemann-Pick C

Niemann-Pick type C disease (NPCD) is a devastating neurodegenerative condition most commonly due to mutations in endolysosomal NPC1. Mutations in NPC1 are associated with impaired endocytic transport via decreased endolysosomal calcium release. Endocytosis and luminal calcium are dependent on correct endolysosomal acidification and have been found to be controlled by glycolipids in neurons, melanocytes, Gaucher disease, plant vacuoles and *C. elegans*. NB-DNJ (miglustat) has approval for the treatment of NPCD as a GlcCer synthase inhibitor to lower lysosomal GlcCer. However, increased brain GlcCer when administered to animal models has led to wide speculation of off-target inhibition of non-lysosomal GlcCer (GBA2) breakdown. Off target inhibition of GBA2 was recently strengthened by the utility of a more specific GBA2 inhibitor AMP-DNM as well as GBA2 knockout in NPCD mice. Several studies have shown increased pH in NPC cell culture models. We show here that disrupted endocytic trafficking in NPCD cell culture models is associated with increased endolysosomal pH using lysosensor yellow blue to label all acidic compartments. To study these phenomena we examined the effects of U18666A on endolysosomal pH and glycolipid transport. NPCD cell culture models were found to have increased endolysosomal pH and inhibition of non-vesicular glucosylceramide (GlcCer) but not GalCer transport. In contrast, inhibiting non-lysosomal glucocerebrosidase (GBA2) decreased endolysosomal pH in normal cells, reversed increased endolysosomal pH and restored disrupted BODIPY-LacCer trafficking in NPCD fibroblasts.

Biography

Dan J Sillence is a cell Biologist with a particular interest in the molecular role of Glucosylceramide. He has worked in the laboratories of Prof Fran Platt, Prof Gerrit van Meer and Prof Richard Pagano after completing his PhD with Prof Peter Downes, University of Dundee. Glucosylceramide knockouts are embryonically lethal and recent research has pointed to regulation of basic cellular processes such as the regulation of lysosomal pH. He has over 30 publications in high impact journals including J Clin Invest., Nature Medicine, J Lipid Research and Trends Cell Biology

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