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SPOTLIGHT

A calcium message for Niemann-Pick type C

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Calcium is a ubiquitous secondary messenger that is critical for cellular function. In the highlighted article, Tiscione et al. (2019. *J. Cell. Biol.* https://doi.org/10.1083/jcb.201903018) describe a link between lysosomal cholesterol storage, calcium distribution alterations, and neuronal morphology in the neurodegenerative disorder Niemann-Pick type C.

Calcium ions (Ca^{2+}) are responsible for numerous cellular processes, and the role of Ca^{2+} as a secondary messenger is broad. Accordingly, defects in Ca^{2+} signaling have been implicated in several neurodegenerative disorders (1). Intracellular Ca^{2+} levels are regulated by activation of a variety of ion channels in the plasma membrane and the ER, which stores a substantial amount of Ca^{2+} (2, 3). In Tiscione et al., altered Ca^{2+} dynamics are shown in the fatal, lysosomal storage disease, Niemann-Pick type C (NPC; 4).

NPC is a fatal, genetic, lysosomal storage disorder that is biochemically characterized by lysosomal accumulation of unesterified cholesterol and glycosphingolipids (5). Mutations of the *NPC1* or *NPC2* genes, and therefore their respective proteins, result in impaired endo-lysosomal cholesterol trafficking, leading to cholesterol and glycosphingolipid accumulation in these compartments. As a result of this storage, a number of downstream alterations occur, including progressive cerebellar degeneration, and NPC has been referred to as childhood Alzheimer's disease. The mechanistic link between cholesterol storage and neurodegeneration, however, remains elusive and there is no FDA-approved therapy.

A Ca^{2+} defect in NPC was first proposed by Lloyd-Evans et al., with a specific focus on lysosomal Ca^{2+} alterations (6). Additional studies that implicated Ca^{2+} alterations were then expanded to include induced pluripotent stem cell–derived neurons (7) in regard to Ca^{2+} signaling and the WNT pathway, as well as connections to decreased Ca^{2+} flux and increased AMPA receptor expression (8). A proteomics study in brain tissue from a NPC mouse model revealed differential expression of Ca^{2+} binding proteins as well as Ca^{2+}-regulated signaling pathways (9). Additionally, a linkage between Ca^{2+} and autophagy alterations in NPC was recently published (10), pointing to the timely nature of the current article.

In the study by Tiscione et al. (4), several key conclusions can be made. First, the loss of function of the NPC1 cholesterol transporter results in increased flux of Ca^{2+} at the plasma membrane, yet decreased ER Ca^{2+} levels and overall increased resting cytosolic Ca^{2+} in NPC patient fibroblasts with different disease-causing mutations in the *NPC1* gene as well as in *NPC1* null cells and a pharmacologically induced NPC cell model. Second, defects at the plasma membrane contribute to Ca^{2+} alterations, namely, increased flux of Ca^{2+} across the plasma membrane, which is related to a channel-sensor system. Third, the authors then considered the Ca^{2+} ER stores as contributing factors, and, in fact, decreased ER luminal Ca^{2+} was observed in NPC, suggesting a "leaky" Ca^{2+} ER system. Additional contributions to Ca^{2+} defects in NPC were associated with the Presilin 1 protein.

Going back to the cholesterol defect in NPC, the study explores the role of the classical cholesterol biosynthesis and regulation pathways, namely, the membrane-bound sterol regulatory element binding protein (SREBP) pathway. From their data, the authors conclude that activation of SREBP contributes to the Ca^{2+} imbalance and signaling protein defects observed in NPC (4).

Ultimately, one may argue that understanding the mechanisms of defects to the central nervous system in NPC are the most critical aspects for making progress in the development of new therapies. Appropriately, Tiscione et al. (4) evaluate these observed deficits from their fibroblasts studies to cultured hippocampal neurons using the pharmacological NPC model and also in a point mutant mouse model of NPC. The authors find that neuronal Ca^{2+} is also decreased at the ER, whereas an increase in cytoplasmic Ca^{2+} is noted. Finally, the morphological changes observed in specific neuronal populations under cholesterol storage and, therefore, Ca^{2+} defects provide a glimpse into disease progression.

From the work by Tiscione et al., it is reasonable to consider how balancing Ca^{2+} levels may be an appropriate stance to consider in therapy development for NPC. While the primary defect in NPC certainly is lipid transport, the immediate link to altered Ca^{2+} levels and the crucial role of Ca^{2+} as a secondary messenger highlights the importance of these findings. It is also interesting to consider how changes in Ca^{2+} pools and signaling may occur during disease progression and if modulating these aspects could reduce the disease phenotype. This important study now provides additional insight into the molecular mechanisms leading to neurodegeneration in NPC (summarized in Fig. 1). As continued research efforts and clinical trials move forward, researchers should consider how modulating cholesterol storage may address deficits in Ca^{2+} pools and signaling or vice versa. This multifaceted approach will be

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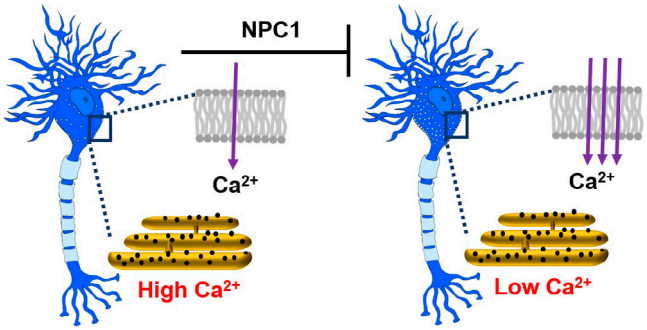

Figure 1. **Representative comparison of a control and a neuron with impaired or loss of NPC1 protein leading to NPC disease.** As a result, lysosomal cholesterol accumulates and Ca^{2+} flux across the plasma membrane and depleted Ca^{2+} stores in the ER increase. In neurons, this also shows decreased dendritic spines, relating the function to altered neuronal plasticity.

important, particularly in light of combination therapy methodologies.

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