Nuclear sphingomyelin in neurodegenerative diseases

Elisabetta Albi*, Alice V. Alessenko

Introduction: Recently, sphingolipids (SphLs) have become increasingly appreciated as a family of molecules involved in the growth, differentiation, and death of the central nervous system cells. The disequilibrium among the different SphLs leads to changes in the neuronal cell physiology and induces the development of neurodegenerative diseases (Alessenko and Albi, 2020). Sphingomyelin (SM), sphinganin (Sphn), sphingosine (Sph), sphingosine-1-phosphate (S1P) and ceramide (Cer) are the most well-studied group of SphLs responsible for neurodegeneration, as well as derived molecules such as glucosylceramide or cerebroside (GCer) and galactosylceramide (GalCer) and finally more complex molecules such as as gangliosides.

Sphingomyelin metabolism: SM is a critical bioactive lipid that can quickly be converted into other SphLs starting from its degradation into Cer and phosphocholine because of the sphingomyelinase (SMase) action. The accumulated Cer is useful for the regeneration of SM when the cell needs it. SM has been proposed to regulate diverse pathophysiology processes; it is thought to be due to its intracellular localization (Alessenko and Albi, 2020). The lysosome SM is degraded by acid SMase (aSMase) and it is involved in apoptosis signaling. SM localized in the endoplasmic reticulum/Golgi apparatus as well as in the cell nucleus is metabolized by neutral SMase1 (nSMase1) in response to stress and degeneration. nSMase2 is specific for the inner leaflet of the plasma membrane SM and it is activated in many cell responses, such as cell growth arrest, exosome formation, and inflammatory response. nSMase3 catabolizes endoplasmic reticulum SM and it is involved in tumor necrosis factor-α mediated signaling, and tumorigenesis (Alessenko and Albi, 2020).

Sphingomyelin metabolism and neurodegeneration: Dysregulation of aSMase and nSMase1 enzymes is emerging as an important effector of neurodegeneration. Studies focusing on the relation between SM metabolism disorders and neurodegenerative disease pathogenesis were performed on the brain whole cells. Although the exact mechanism is still being defined, there is accumulating evidence supporting the role of SM in the regulation of cell physiological responses by altering the physico-chemical properties of the membranes (Insausti-Urkia et al. 2020). Thus, knowledge about the role of SM as an effector molecule in neuropathology is expanding. From recent international research findings, we believe that the manipulation of SM pathway may have interesting therapeutic implications for the neurodegeneration.

Nuclear sphingomyelin: Little attention is still paid to the implication of nuclear SM metabolism in neurodegeneration. There are only a few works showing the role of nuclear SphLs in both brain functions and development of various types of neurodegenerations (Kozireski-Chuback et al., 1999; Ledeen and Wu, 2004; Farooqui, 2012; Lucki and Sewer, 2012; Markevich and Kolomiytseva, 2014).

SM, the most abundant SphLs inside the nucleus, plays both structural and functional roles with multifactorial mechanisms. This finding is supported by many studies showing that nuclear SM is localized in nuclear membrane, nuclear matrix, nucleolus, and active chromatin with different roles (Albi, 2011). SM has been proposed to influence nuclear membrane and nuclear matrix fluidity (Albi, 2011). Furthermore, it has been speculated that SM localized in inner nuclear membrane forms lipid platforms which play a role in recruiting proteins and inducing receptor clustering for hormone and drug. Moreover, SM is essential for platforms useful for active chromatin anchoring and regulates gene expression and RNA transcription processes (Albi, 2011). SM acts in the structure/function of nucleic acids also in the nucleolus. The maintenance of the physiological levels of SM in the different subnuclear districts is due to a specific metabolism in the nucleus independent on the non-nuclear one. In fact, extranuclear and nuclear enzymes involved in SM metabolism, such as nSMase and SM-synthase, exhibit different physico-chemical properties (Albi, 2011). These results suggest that normal levels of SM in nucleus are crucial for cell physiology; and the changes could be responsible for numerous diseases.

Nuclear sphingomyelin in neurodegeneration: SM has been proposed to regulate diverse cellular processes, including neural cell proliferation, differentiation, inflammation, apoptosis, migration, cell adhesion, and intracellular trafficking by regulating gene expression (Kozireski-Chuback et al., 1999; Ledeen and Wu, 2004; Farooqui, 2012; Garcia-Gil and Albi, 2017). Thus the effort toward uncovering its role in neurodegeneration is really a promising new area of research.

Advances over the past three decades have improved our understanding of neural cell death in neurodegenerative diseases as a multifactorial process involving genetic and endogenous factors including lipid mediated neuroinflammation and oxidative stress, abnormal protein dynamics with defective protein degradation and aggregation, autoimmunity, and dysfunction, resulting in impaired energy metabolism. All these processes are controlled and regulated by the nucleus. Therefore, our opinion is that nuclear SM, by regulating gene expression and cell fate, plays an essential role in neurodegeneration.

One of the characteristics common to brain pathologies with neurodegenerative aspects is the compromise of the hippocampus with the consequent loss of memory. This is the saddest aspect of the disease, physically surviving the death of the mind. Patients forget their names, their story and relatives, and experience great suffering. Therefore, we focused the attention to our most recent studies on the hippocampus. We studied the behavior of nSMase in a mouse model of Niemann-Pick type A (NPA) disease, an autosomal recessive disorder characterized by a dramatic reduction in aSMase activity with developmental delay, hepatosplenomegaly and progressive neurodegeneration. We have found an evident increase of the nSMase expression and its shift at nuclear level in the *gyrus dentatus* (GD) of hippocampus where stem cells take place. Nuclear displacement of the nSMase is associated with gene and protein upregulation of (sex determining region Y)-box 2 (SOX2), a transcription factor that plays an important role in the maintenance of differentiation potential and self-renewal of pluripotent stem cells and of toll-like receptors (TLRs) whose defect is involved in neurodegeneration (Conte, 2019). We believe that increasing nuclear nSMase, with consequent reduction of SM levels in the neurogenic niches of the hippocampal GD, is critical for gene upregulation of proteins essential for stem cell differentiation and

protection from damage. In this way, the reduction of nuclear SM could represent a compensatory mechanism against the accumulation of lysosomal SM due to the aSMase deficiency and facilitate nuclear mechanisms that could limit memory loss. Differently, in the midbrain of mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to induce Parkinson's disease (PD), nSMase was reduced (Cataldi et al., 2017). Interestingly, in the TLR4-deficient mice treated with MPTP, nSMase increased significantly and delocalized from the cell membrane to the nucleus (Albi, 2019), probably always as a compensatory mechanism, suggesting a possible nSMase-TLRs cross-talk.

As a result of these studies, the role of SM in neurodegeneration is now better understood, with promise for development of new experimental tools, including the lipidomic analysis of SM species and of their derivates. In this regard, we have shown that the midbrain of mice contains more long chain fatty acid SM (16:0) than very long chain (20:0, 24:0) SM. Acute MPTP exposure induces a reduction of 16:0 SM, 20:0 SM, 22:0 SM, 22:1 SM, 22:2 SM, 24:0 SM 24:1 SM, 24:2 SM, 24:4 SM, it does not induce changes in 18:0 SM, and it induces an increase of 16:0, and 24:0 Cer species. Thus, an enrichment of saturated/unsaturated SM ratio can be found in PD (Albi, 2019). Since saturated fatty acids make the SM a more rigid molecule, our idea is that the prevalence of saturated SM on the unsaturated SM in cell membrane reduces neural plasticity. Moreover, saturated SM is able to bind non-esterified cholesterol present in the nucleus to enrich the inner nuclear membrane in lipid microdomains for active chromatin anchoring and regulation

Conclusion: Recent research is opening towards new horizons on the analysis of SphLs, including SM species, and the enzymes for their metabolism in neurodegenerative diseases. However, studies are carried out on brain tissue, on nerve cells in culture and, finally, in the blood looking for possible diagnostic targets. There are few studies of SphLs and in particular of SM in the nucleus and their relationship with gene expression. In our opinion, nuclear SM is emerging as an important molecule in the brain pathophysiology for its structural role in microdomains and functional role by generating lipid mediator of nuclear signaling because of the nuclear sphingomyelinase (**Figure 1**).

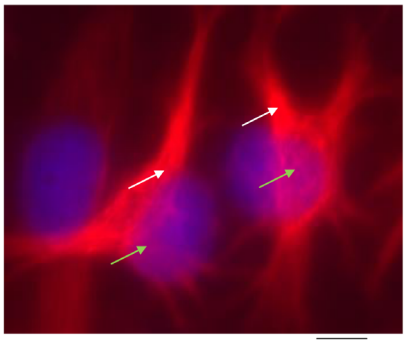

Figure 1 | **Image of ultra-thin sections of embryonic hippocampal cells induced to differentiate with 100 nM calcitriol.** Diamidino-2-phenylindole (DAPI) staining: nucler signal (blue) and neutral sphingomyelinase (red). Enzyme is present in both neurites (white arrows) and cell nucleus (green arrows). Original magnification, 40×. The figure is sourced from our unpublished paper.

In-depth lipidomics studies on nuclei isolated from different types of nerve cells can help understand how and why numerous genes and proteins are deregulated in different neurodegenerative diseases. It will also be important to analyze all molecules derived from nuclear SM metabolism in order to identify new possible molecules involved in neurodegeneration.

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