thematic review

Nuclear lipids: key signaling effectors in the nervous system and other tissues[1]

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Abstract **Lipids have long been recognized as quantitatively minor components of the nucleus, where they were initially thought to have little functional importance; but they now command growing interest, with recognition of their diverse signaling and modulating properties in that organelle. This applies to the lipid-poor compartments of the nucleoplasm as well as the relatively lipid-rich nuclear envelope. Phosphoglycerides and sphingomyelin, as the predominant lipids, have attracted the most interest among researchers, but some of the less-abundant lipids such as gangliosides, sphingosine, and sphingosine phosphate are now becoming recognized as functionally important nuclear constituents. Among recent advances in this emerging field are detailed findings on the metabolic enzymes that synthesize and catabolize nuclear lipids; the fact that these are localized primarily within the nucleus itself indicates considerable autonomy with respect to lipid metabolism. Current studies suggest several key processes involving RNA and DNA reactivity that are dependent on these lipid-initiated events. Neural cell nuclei have been the subject of such investigations, with results that closely parallel the more numerous studies on nuclei of extraneural cells. This review attempts to outline some of the major findings on nuclear lipids of diverse cell types; results with nonneural nuclei will hopefully provide useful guideposts to further studies of neural systems.**—Ledeen, R. W., and G. Wu. **Nuclear lipids: key signaling effectors in the nervous system and other tissues.** ***J. Lipid Res.*** **2004.** 45: **1–8.**

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Lipids are integral components of the nuclei from all cells examined to date, including those of the nervous system. Their function in that organelle was originally considered to be merely one of structural support for the nuclear envelope (NE), perhaps reflecting their relative paucity in other nuclear compartments. However, this concept has changed dramatically in the last decade or two with growing awareness of lipid presence in the various domains of the nucleoplasm and recognition of the powerful signaling and modulating roles of lipids and their metabolic products in all nuclear compartments. Although there have been relatively few systematic comparisons of nuclear lipids of different tissues and species, similar properties and derived mechanisms appear to apply in broad outline regardless of cellular origin. Lipid metabolism in the nucleus is now recognized as largely autonomous, although certain extracellular stimuli are able to induce lipid signaling in the nucleus only (1, 2) or in the nucleus as well as cytoplasm (3, 4). Early studies emphasized phospholipids (PLs), the predominant lipids of nuclei, and while that is still the major thrust of current research, other less-abundant lipids such as gangliosides and sphingosine/sphingosine phosphate are gaining recognition as nuclear constituents with important functional roles. Cholesterol occurs in the outer nuclear membrane (ONM), presumably in a structural role, and may also be present in a few select nucleoplasmic domains. This review will attempt to summarize some of the major findings in the area of nuclear lipid composition and function, with highlighting of neural cell nuclei where such data are available. For additional details, especially in regard to PL-related metabolism and signaling in diverse cells, the reader is referred to excellent reviews that have appeared in the last 2 to 3 years (5–8).

Abbreviations: DAG, diacylglycerol; ER, endoplasmic reticulum; INM, inner nuclear membrane; Ins(1,4,5)P_3, inositol trisphosphate; NE, nuclear envelope; NPC, nuclear pore complex; ONM, outer nuclear membrane; PI3K, PtdIns(4,5)P_2 3-kinase; PL, phospholipid; PLA_2, phospholipase A_2; PLase, phospholipase; PLC, phospholipase C; PLD, phospholipase D; SM, sphingomyelin; SMase, sphingomyelinase.

[1] Nomenclature of individual phospholipids is in comformity with the recommendations of the IUPAC-IUB Commission on Nomenclature of Lipids. Ganglioside nomenclature is that of Svennerholm (Svennerholm, L. 1964. *J. Lipid Res.* **5:** 145–155) and the JCBN recommendations (IUPAC-IUB Joint Commission on Biochemical Nomenclature. 1998. *Eur. J. Biochem.* **257:** 293–298).

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GENERAL NUCLEAR STRUCTURE AND SUBNUCLEAR DOMAINS

The nucleus is now recognized as a highly structured organelle enclosed within the double-membrane NE and possessing somewhat diffuse intranuclear domains. The latter are defined as structural compartments that are dynamically variable in relation to metabolic function (9). The ONM of the NE is directly continuous with the endoplasmic reticulum (ER) and shares certain properties with the latter, while the inner nuclear membrane (INM) has a distinctly different lipid and protein composition and is intimately associated with the nuclear lamina and chromatin. The nuclear lamina comprise a meshwork of intermediate filaments located on the inner surface of the INM. The two membranes of the NE are joined at the nuclear pores by the pore membranes, which are associated with the nuclear pore complexes (NPCs). The latter are distributed over the entire nuclear surface and consist of multiprotein assemblies of ~125 kDa size consisting of 30–50 different kinds of proteins, some occurring in multiple copies, for a total of about 1,000 polypeptides per nuclear pore complex. These NPCs allow passive transfer of small and middle-sized molecules (<50 kDa) between cytoplasm and nucleoplasm. Passage of larger molecules is energy driven and requires a nuclear localization signal. Lipids with very long chain fatty acids are associated with the pore membrane/NPC and appear to be essential for maintaining its function (10). The NE, for some purposes, is considered part of the nuclear matrix, whose general function is to organize chromatin within the nucleus. This matrix is operationally defined as the components that remain insoluble after extraction of the nuclei with nonionic detergents and salts and treatment with nucleases. Structural and functional links exist between the peripheral lamina and internal nuclear matrix (11). Some structural features of nuclei as currently conceived are summarized in **Fig. 1**.

ISOLATION OF NUCLEI AND MEMBRANE COMPONENTS

In ascribing biochemical properties to whole nuclei or nuclear components through use of the isolated organelle, the question of purity must be rigorously addressed. The high content of the combined protein and nucleic acids (>95%), with resultant high buoyant density, has facilitated isolation of nuclei from both tissues and cultured cells in relatively high purity. Various methods of isolation have been described, most of them employing differential and discontinuous-gradient centrifugation through high-density sucrose media; often two successive such gradients are employed. Procedures of this type have been utilized for nuclei from neurons and neuronal cell lines (12–15). Purity is confirmed by light or electron microscopy and assay of marker enzymes for potential contaminants, e.g., 5′-nucleotidase or Na/K-ATPase (plasma membrane), α-mannosidase or galactosyltransferase, (Golgi apparatus), cytochrome C oxidase (mitochondria), and glucose-6-phosphatase or NADPH-cytochrome C reductase (ER). The low activity often found for the latter enzymes does not necessarily indicate contamination, because, as mentioned, the ONM is continuous with the ER and shares many of its properties. The NE is obtained by treatment of isolated nuclei with DNase or DNase + RNase, followed by 6M NaCl to release DNA fragments. The fact that the INM is intimately associated with the peripheral nuclear lamina often results in portions of the latter copurifying with the NE (16). The ONM of the NE can be selectively removed from whole nuclei by treatment with 2% sodium citrate (17) or 0.2% Triton X-100 (18, 19). The INM is then liberated from the resulting nuclei by treatment with DNase/RNase (17).

LIPID COMPOSITION OF WHOLE NUCLEI AND MEMBRANE COMPONENTS

For nuclei of neural cells, as for those of other cell types, PLs comprise the large bulk of lipids, with lesser amounts of cholesterol, free fatty acids, diacylglycerol (DAG), sphingolipids, and perhaps others. These have been studied in whole nuclei as well as individual nuclear domains. Total PL content of rat liver nuclei was reported as 3.25% by weight (18) (compared with 74.6% for protein and 22.2% for DNA). It was recognized in early studies that most of this relatively small pool of nuclear lipids occurs in the NE (19), whose total lipid content was approximately half that of protein by weight (20). PLs were reported to comprise ~65% of NE lipids, whereas cholesterol was 10% (approximately three times that of ER); lesser amounts of other neutral lipids (cholesterol ester, DAG, triacylglycerol) were also detected (21). Although a relatively high concentration of free fatty acids (~15% of total lipid) was reported in the latter study, it is not known how much of this resulted from breakdown of PLs during isolation. The PL content (per mg protein) of the NE was reported as approximately nine times that of whole nuclei (21). Several studies of liver nuclei have shown phosphatidylcholine (PtdCho) to be the major PL, with lesser but still significant amounts of phosphatidylethanolamine (PtdEtn) and phosphatidylinositol (PtdIns) (18, 20–22). Phosphatidylserine (PtdSer) and sphingomyelin (SM) were detected at lower levels. Comparison with microsomes revealed NE to have significantly less PL/mg protein and correspondingly more cholesterol (20, 22). The cholesterol content, however, was significantly below that of plasma membranes. Despite the above-mentioned quantitative differences, the PL profiles (% composition) for NE and microsomes were similar. Analysis of fatty acid composition of individual PLs gave discrepant findings, but one such study that used antioxidants to minimize peroxidation showed the PLs of NE and ER to have similar fatty acid profiles with high levels of polyunsaturated fatty acids (principally 20:4 and 22:6) in the four major phosphoglycerides (22).

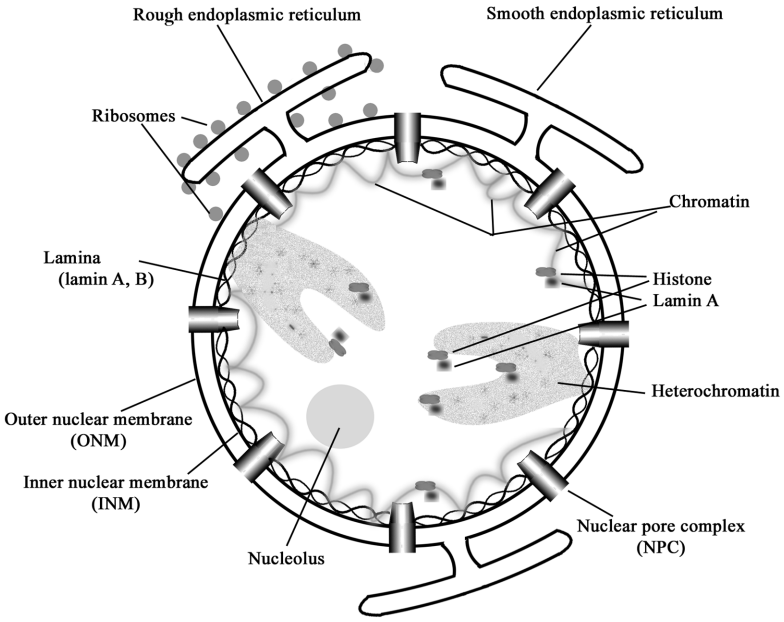

Fig. 1. Representation of nuclear structure with subnuclear domains, as presently conceived. The outer nuclear membrane is continuous with the endoplasmic reticulum, while the inner nuclear membrane is closely associated with the nuclear lamina and has unique lipid composition. These two membranes are joined at the nuclear pore complexes that are distributed over the nuclear surface and permit passive flow of small molecules between cytoplasm and nucleoplasm. The lumenal space between the two membranes of the nuclear envelope (NE) is a storage site for Ca^{2+}. In addition to the NE, lipids have been shown to occur in intranuclear compartments such as nucleolus, chromatin, and heterochromatin.

In contrast to intact NE, few studies have focused on the separated ONM and INM, although it is evident that they possess very different lipid compositions. One report, based on filipin-sterol interaction, found an unequal distribution of complexes that suggested higher cholesterol content in the ONM compared with the INM (23). In agreement, another study using a similar methodology reported filipin-sterol complexes only in the ONM (24). Differential localization of GM1 ganglioside has also been observed, this being detected in the INM of both neuronal and nonneuronal cells, in association with an Na^+/Ca^{2+} exchanger (see below). It is likely that more complete profiles of lipid composition and function for the two membranes will be forthcoming now that methods are available for their separate isolation (see above).

With regard to glycosphingolipids, the initial studies showed ganglioside presence in whole nuclei of rat liver (25) and bovine mammary (26) cells. In the latter study, the gangliosides were identified as GM3, GD3, and GT1b. More recently, nuclei from rat brain were shown to contain GM1, GD1a, GD1b, and GT1b, with lesser amounts of GM3 and c-series gangliosides; large nuclei had significantly higher concentrations of the same gangliosides, compared with small nuclei (15). A cytochemical study employing cholera toxin B subunit in conjunction with chemical analysis of isolated nuclei showed GM1, GD1a, and minor amounts of other gangliotetraose gangliosides to be present in the NE of rat central nervous system neurons and Neuro-2a neuroblastoma cells (13). GM1 was also detected in the NE of peripheral nervous system neurons and NG108-15 cells (27), their relative content increasing with onset of axonogenesis (28). Ganglioside GM1 at those sites, although an order of magnitude less than PLs, was clearly observable with cholera toxin B subunit linked to horseradish peroxidase (**Fig. 2**). Further study of localization placed GM1 on the INM in associa-

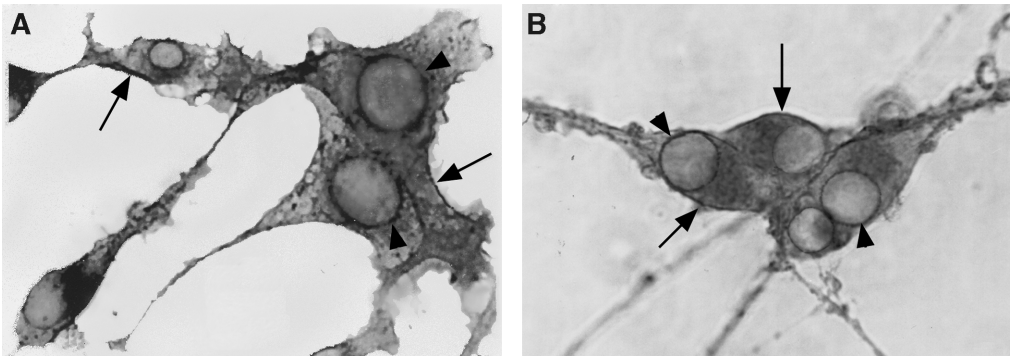

Fig. 2. Cytochemical evidence for the presence of ganglioside GM1 in the NE of neural cells. A: Neuro-2a neuroblastoma cells in culture were induced to differentiate and were stained with cholera toxin B subunit linked to horseradish peroxidase. B: Similar staining of cultured neurons from the superior cervical ganglion of embryonic rats. Arrows indicate staining of GM1 in the plasma membrane and arrowheads the NE. Fig. 2A is reproduced from Fig. 3 of ref. 13, with permission of the *Journal of Neuroscience*; Fig. 2B is reproduced from Fig. 4 of ref. 27, with permission from Elsevier.

tion with an Na^+/Ca^{2+} exchanger, whose exchange activity it potentiated (29); this proved to be a high-affinity association in that it survived SDS-PAGE and Western blot analysis. Location of the Na^+/Ca^{2+} exchanger-GM1 complex on the INM suggested a mechanism for maintaining Ca^{2+} homeostasis in the nucleoplasm through exchange transfer of elevated nuclear Ca^{2+} to the NE lumen. Similar Na^+/Ca^{2+} exchanger-GM1 complexes have been observed in the NE of C6 cells, astrocytes, and a number of non-neural cells (30). It remains to be determined whether GM1 also occurs, possibly with other gangliosides, in the ONM. The presence of gangliosides in intranuclear compartments has not been systematically studied, although there is a suggestion that such study may be warranted (see below).

Inositol-containing lipids within the nucleus have been of special interest, owing to their participation in multiple signaling reactions (see below). As mentioned, PtdIns was demonstrated in early studies to be a component of the NE (20–22). Phosphatidylinositol 4,5-bisphosphate [PtdIns(4,5)P_2], detected with specific monoclonal antibody, was shown to occur in the NE (31) and also within the nucleoplasm (32). The derived D-3 phosphoinositide, PtdIns(3,4,5)P_3, is also present and was shown to occur at the nuclear surface (33). It was transiently elevated in nuclei of PC12 cells subjected to nerve growth factor stimulation (34). Other minor lipids involved in signaling have been detected in nuclei; examples are DAG and phosphatidate, which increased during cell proliferation (35, 36), and sphingosine, which increased during mitosis (37) or apoptosis (38).

LIPIDS OF INTRANUCLEAR DOMAINS

While the NE was recognized from the beginning as the primary locus of nuclear lipids, a few early studies suggested the presence of limited intranuclear pools in the chromatin (39), nuclear matrix (40), and nucleolus (41). Use of gold-conjugated phospholipase (PLase) as a cytochemical tool demonstrated intranuclear PLs in the interchromatin spaces and in the nucleolar domain (42). Additional support for an endonuclear locus came from a combined histochemical and biochemical study of rat liver nuclei that ruled out contamination of endonuclear lipids by the NE; total PL content of the chromatin was shown to be approximately one-tenth that of whole nuclei (43). While the same PLs were present with similar fatty acid profiles, their relative concentrations differed. Each PL had a unique fatty acid profile that was generally the same whether the PL origin was chromatin or whole nuclei. However, recent work has revealed enrichment of PtdCho with a high degree of diacyl/alkylacyl chain saturation in nuclei of IMR-32 neuroblastoma cells localized in endonuclear compartment(s) (44). The latter study provided an estimate of the nuclear volume occupancy of such disaturated PtdCho species as ~10%, suggesting that these lipids may be present as large complex aggregates or even as liquid crystalline phases. Biosynthesis of these species of PtdCho was reported to occur endogenously in the nucleus (see below).

Cholesterol and SM were found to occur in similar amounts in rat liver nuclei, suggesting a complex of those lipids with proteins in the chromatin (45). PLs were found localized near the RNA in decondensed chromatin near the nucleoli and nuclear membranes (46, 47). Sequential treatment of isolated nuclei with DNase and RNase showed selective removal of PLs with the latter, PtdSer and SM being the most affected; this suggested functional linkage as well as colocalization of these (and perhaps other) PLs with RNA (48). An earlier cytochemical investigation had also indicated colocalization of nuclear PLs with RNA-containing structures (49). Further study of RNA-PL interaction suggested that SM might represent a bridge between the two RNA strands of double-stranded RNA, thereby protecting them from RNase action (50). Occurrence of phosphoinositides at intranuclear sites has been demonstrated with the use of a monoclonal antibody specific for PtdIns(4,5)P_2 that confirmed the presence of this key signaling inositide in the inner nuclear matrix of in situ matrix preparations (51). This correlated with the presence of both metabolizing and synthesizing enzymes for this PL at intranuclear sites (see below).

Glycosphingolipids, in particular gangliosides, were shown to occur in the NE (see above) and have also been considered in relation to intranuclear domains. Immunocytochemical evidence was presented for ganglioside GD3 colocalizing with nuclear chromatin in rat cultured cortical neurons subjected to β-amyloid peptide [25-35]; this occurred prior to the neurons entering S phase and apoptotic death (52). That GM1 may also be so situated was suggested in an earlier study of nuclei from mouse intestinal epithelial cells that showed binding of both cholera toxin and anti-GM1 antibodies in the heterochromatin of the nucleus (53).

LIPID-METABOLIZING ENZYMES AND LIPID SIGNALING IN THE NUCLEUS

The origin of nuclear lipids, originally thought to involve translocation of cytoplasmic products, came to be viewed in a new light with the discovery of lipid-metabolizing enzymes present in the nucleus proper. Although some of the relevant enzymes originate in the cytosol and are drawn to the nucleus in the course of physiological activity, many occur endogenously in one nuclear domain or another. One example is an acylation-deacylation cycle, affecting primarily the sn-2 position of nuclear PLs, which was found to increase in proliferating cells (54). This cycle, studied in the NE of neural cells, arises from the combined actions of acyltransferase (55, 56) and phospholipase A_2 (PLA_2) (57, 58). The latter activity in LA-N-1 neuroblastoma cells included two Ca^{2+}-independent enzymes, one active toward PtdEtn and the other toward plasmenylethanolamine, the plasmalogen analog (58). Both enzymes were strongly stimulated by exposure of the cells to retinoic acid, a neuronal-differentiating agent.

Some isoforms of PLA_2 translocate from the cytosol to the NE (59), where enzymes of eicosanoid generation are clustered (60). Isolated nuclei from LA-N-1 cells carried out synthesis of PtdCho, an activity that was enhanced by phorbol ester (14). Synthesis of highly saturated forms of chromatin-associated PtdCho was shown to occur in endonuclear compartment(s) of IMR-32 neuroblastoma cells in a manner spatially separate and compositionally distinct from that occurring in whole cells (44, 61). Membrane-free nuclei from these cells were indicated to contain the enzymes that comprise three reactions of the CDP-choline (Kennedy) pathway: *a*) choline + ATP → phosphocholine + ADP; *b*) phosphocholine + CTP → CDP-choline + PP_i; and *c*) CDP-choline + DAG → PtdCho + CMP.

The α isoform of CTP:choline-phosphate cytidylyltransferase, the principal regulatory enzyme in the above pathway, is confined to the nucleus throughout the cell cycle and was shown through temperature-sensitive mutation to be essential for cell survival (62). Precisely how the disaturated forms of PtdCho with the unusual acylation/alkylation pattern produced in this nuclear reaction sequence aid nuclear function and cell survival is not known, although these aspects appear consistent with the tight homeostatic control in evidence (44, 62). The above-mentioned study with LA-N-1 cells (14) also suggested the presence of phospholipase C (PLC) and phospholipase D (PLD) reactive toward PtdCho and the existence of a nuclear PtdCho cycle. A high level of PLD activity was detected in rat brain neuronal nuclei that was significantly greater than that detected in nuclei of glia or extraneural cells (63).

Nuclei also contain SM-metabolizing enzymes, with evidence of an SM cycle. Biochemical and immunocytochemical study of a well-defined isoform of neutral sphingomyelinase (SMase), nSMase1, showed this enzyme to occur in rat liver nuclei and cytosol, but not plasma membrane (64). Moreover, it was found associated with the nuclear matrix rather than the NE or chromatin. An apparently different SMase was reported to occur in rat liver chromatin, although this enzyme was not defined in molecular terms (65). That study reported PtdCho:ceramide phosphocholine transferase, or SM synthase, in the same fraction, as well as in the nuclear membrane, the two activities showing different enzyme properties (66). This would accord with the reported enrichment of SM in nuclear chromatin, amounting to 35% of that present in the entire nucleus (43). Activation of nuclear SMase can lead to apoptosis (67, 68) or regeneration/proliferation (65, 69). Other sphingolipid-metabolizing enzymes found in the nucleus include ceramidase (67) and sphingosine kinase (4). The presence of both ceramidase and SMase in the NE has suggested the presence of an SM cycle in that membrane system (70), consistent with the coexistence of SM synthase (66). The enzymatic properties of ceramidase in liver NE were shown to differ from those of other ceramidases (70).

The work of many laboratories has established the nucleus as endowed with a constitutive phosphoinositide cycle, the molecular details of which are now being elucidated. The first phosphoinositide-specific PLase to be studied was PLC-β1, detected in the nucleus of Swiss 3T3 cells (71), rat liver (72), and PC12 cells (73). This enzyme is phosphorylated by p42/44 MAP kinase, which enters the nucleus following IGF-I and other mitogenic signaling at the plasma membrane (74). The resulting rise in DAG attracts PKC-α to the nucleus, which may initiate a negative feedback mechanism. In an earlier study, four different forms of phosphoinositide-specific PLC were isolated from nuclei of rat ascites hepatoma AH7974 cells, all of which required Ca^{2+} for activity; these hydrolyzed PtdIns, PtdIns(4)P, and PtdIns(4,5)P_2, but not PtdCho or PtdEtn (75). Among the PLC isoforms detected in the nucleus, PLC-δ4 is one proposed as specific to that organelle (76, 77), although that has been questioned (78). Intranuclear localization of at least some (possibly most) PLC activity was indicated in the observation that membrane-deleted rat liver nuclei hydrolyzed inositol PLs as effectively as did membrane-containing nuclei (79). Selective extraction procedures similarly showed PLC to occur in the nuclear matrix (80). The latter approach, when applied in the same study to phosphoinositide-specific kinases, revealed PtdIns 4-kinase exclusively in the peripheral nuclear matrix and PtdIns(4)P 5-kinase in the internal matrix. That study also showed DAG kinase to be preferentially localized in the internal matrix.

DAG is potentially generated in the nucleus, as elsewhere, by two general pathways: *a*) phosphoinositide-specific PLC (see above); and *b*) hydrolysis of PtdCho, e.g., a different PLC or sequential action of PLD and phosphatidic acid phosphatase. The former produces a stearoyl-arachidonoyl-rich DAG that could serve as precursor to eicosanoids, while the latter would yield DAG with a different (more saturated) fatty acid composition. As mentioned, much of the endonuclear PtdCho is disaturated in the form of diacyl/alkylacyl species (44). A primary function of DAG in the nucleus is activation of PKC, and various isoforms of the latter, such as PKCα and PKCβII, are translocated to the nucleus following elevation of nuclear DAG. This phenomenon has been extensively studied in relation to the cell cycle [as reviewed in ref. (8)].

In addition to DAG, Ins(1,4,5)P_3 is also generated through the action of PLC on PtdIns(4,5)P_2, and this product has the potential for mobilizing Ca^{2+} via Ins(1,4,5)P_3 receptors on the INM of the NE (81). At that site, Ins(1,4,5)P_3 receptors are strategically located for regulating nuclear Ca^{2+} mobilization to nucleoplasm from the NE, a storage site for Ca^{2+} continuous with that of the ER. That Ca^{2+} mediates several key signaling reactions in the nucleus is well established, although the relative contributions of Ca^{2+} from the NE versus cytosolic compartments remains controversial (82, 83). Following release from PtdIns(4,5)P_2, Ins(1,4,5)P_3 can also be converted via successive kinases to $InsP_6$, which has been proposed to have a role in mRNA transport and regulation of the transcription of some genes (84, 85). Highly phosphorylated inositols have also been implicated in chromatin remodeling (86, 87).

Occurrence in the nucleus of D-3 phosphorylated inositol lipids such as PtdIns(3,4,5)P_3 has been demonstrated for neurons and several other cell types (5, 8). Unlike the "canonical" inositol PLs, this family is not susceptible to PLC. The kinase that forms the above molecule from PtdIns(4,5)P_2, type III PI3K, has been detected in the nucleus and was shown to translocate there in response to agonists (88). With PC12 cells, for example, stimulation by nerve growth factor causes translocation of PI3K to the nucleus, where it reacts with a recently discovered phosphoinositide kinase enhancer (PIKE) (89). The latter binds to the regulatory subunit of PI3K, with resulting activation of the p110 catalytic subunit. PIKE is expressed in a variety of tissues but most abundantly in brain. The other kinases that sequentially phosphorylate PtdIns and PtdIns4P (types I and II) have been proposed to occur in the nucleus, although not exclusively. A 3-phosphatase that acts on PtdIns(3,4,5)P_3, known as "phosphatase and tensin homolog deleted on chromosome 10" (PTEN), has been proposed to be partly nuclear and to have a role in neuronal differentiation (90).

Several in vitro effects of various phosphoinositides on DNA polymerase and other nuclear proteins have been summarized (6). A number of nuclear proteins contain a PtdIns binding consensus, which may explain the ability of proteins such as histones, DNA polymerase, RNA polymerase, and various transcription factors to bind to PtdIns(4,5)P_2 and certain other lipids (76). It was suggested that the activities of such enzymes are masked by the bound PL and reactivated by metabolic breakdown of the latter (6). As one example, PtdIns(4,5)P_2 binding to histone H1 reduces binding of the latter to DNA, thereby canceling the inhibition of RNA polymerase II by histone H1 (91). This PL has also been proposed to have a structural and/or regulatory function in RNA splicing (92).

The metabolic activities of glycosphingolipids in the nucleus have not yet been explored in detail, although one enzyme, sialidase, has been identified in the NE of brain cells (93). This enzyme was reactive toward oligosialogangliosides such as GD1a, a ganglioside that was shown to occur in that membrane (13). Its primary product when reacting with gangliotetraose gangliosides is GM1, and a speculated function of this enzyme is maintenance of an appropriate level of GM1 in the NE for activation of the Na^+/Ca^{2+} exchanger (29). Although glycolipid synthesis is generally regarded as confined to the Golgi apparatus and ER, the fact that cytidine 5′-monophosphate *N*-acetylneuraminic acid synthetase has been purified from rat liver nuclei (94) suggests that the nucleus may have some capacity of this kind as well.

CONCLUSIONS

Progress in defining the lipid composition of nuclear domains and the signaling and modulatory roles subserved by such lipids has been impressive. Nuclei of neural cells resemble those of other cell types with regard to lipid composition and functioning and in possession of autonomous lipid metabolism. Lipid characteristics of the NE are similar, although not identical, to those of the ER, the differences due in part to the unique lipid composition of the INM. The limited knowledge we have of the latter suggests a membrane deficient in cholesterol but possessing GM1 in association with an Na^+/Ca^{2+} exchanger that is thought to contribute to nuclear Ca^{2+} homeostasis. Although the various intranuclear compartments contain only small quantities of select lipids, these participate in numerous metabolic reactions based on colocalized enzymes that form the basis of a rich array of intranuclear signaling reactions. These include metabolic cycles involving SM-ceramide, ceramide-sphingosine, PL acylation-deacylation, and PLC-mediated breakdown of "canonical" phosphoinositides. The presence of disaturated forms of PtdCho in endonuclear compartment(s), giving rise to disaturated forms of DAG, has been noted. D-3 phosphorylated inositol lipids and the kinases that synthesize them are also present. In addition to influencing nuclear Ca^{2+} behavior and nuclear kinase activities, these various lipids and their metabolites are purported to modulate such primary nuclear mechanisms as histone binding, mRNA transport, RNA splicing, and DNA and RNA polymerases. Endonuclear lipids in particular, despite their quantitatively minor status, are gaining recognition as major contributors to the many functions indigenous to the nucleus. Much obviously remains to be learned about this relatively new and rapidly developing field, including such areas as nuclear lipid topology, autonomous metabolic reactions, and the rich diversity of signaling mechanisms now coming into focus.

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