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Review article

Glycerophospholipids – Emerging players in neuronal dendrite branching and outgrowth

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ABSTRACT

Dendrites are the input compartment of the neuron, receiving and integrating incoming information. Dendritic trees are often highly complex and branched. Their branch extension and distribution are tightly correlated with their role and interactions within neuronal networks. Thus, intense research has focused on understanding the mechanisms that govern dendrite elaboration. Recent reports highlight the importance of specific lipids for these processes. In particular, glycerophospholipids and several of their interacting proteins are involved in various steps of dendrite growth, including the initiation and elongation of dendritic branches and dendritic spines. The aim of this review is to provide a general overview about which particular lipids are involved in shaping dendrite morphology during neuronal differentiation. Additionally, it summarizes recent studies, which helped to gain insights into the mechanisms by which glycerophospholipids and their associated proteins contribute to establishing correct dendritic morphologies.

1. Introduction

Brain function relies on the proper establishment of neuronal connections. These are in large part represented by synaptic contacts between axons and dendrites of different neurons, leading to the formation of elaborate networks. Dendrites represent the input compartment of neurons. They collect sensory information or incoming signals from other neurons through specific functional contacts, the synapses, and transmit the information to the cell body. Control of dendrite branching and outgrowth is necessary to guarantee that connections of appropriate extent with the correct partners are formed within complex circuits (Jan and Jan, 2010). Thus, some types of neurons can form very large and highly branched dendritic trees by which the surface for reaching appropriate partners or distributed locations is provided together with ample possibilities for making synaptic connections with other neurons (Fig. 1A).

Neuronal networks are mostly assembled during embryonic and early postnatal stages in a process that involves extensive elongation and branching of neuronal processes. During development, neurons differentiate and form type-specific morphologies. In this phase of differentiation, neurons grow at first primary processes, which are also referred to as neurites. One of these will become the axon. The other neurites will become primary dendrites (Lyser, 1964; Stiess and Bradke, 2011). In a subsequent phase of differentiation, dendrite and axon branching and elongation give neurons their specific shape. The developmental process of dendritogenesis is very dynamic and includes the formation and retraction of filopodia-like dendritic branchlets. Only a fraction of these branchlets is stabilized into a dendritic branch and retained in the mature dendritic tree. Certain types of neurons display additionally up to hundreds of thousands of small dendritic spines on their dendrites (Fig. 1B) (Harris et al., 1992; Ziv and Smith, 1996). Those dendritic spines are often compartmentalized in a thin shaft and a bulky head receiving predominantly excitatory input from a presynaptic partner (Nimchinsky et al., 2002; Villa et al., 2016). The cytoskeleton and its regulators play a crucial role in the dynamic aspects that support the establishment of correct neuronal morphogenesis (Spence and Soderling, 2015). Additionally, recent studies highlight the importance of specific lipids and their interacting partners for proper branch initiation (Ammar et al., 2014; Cazzolli et al., 2006; Takenawa, 2010).

The thin and branched dendrites enable neurons to increase their surface without a large increase in cell volume, which in turn requires a high amount of membrane synthesis. Therefore, neurite growth also depends on *de novo* lipid synthesis that enables cells to expand their plasma membrane to sustain the elongation of their processes during development (Paoletti et al., 2011; Ziegler et al., 2017).

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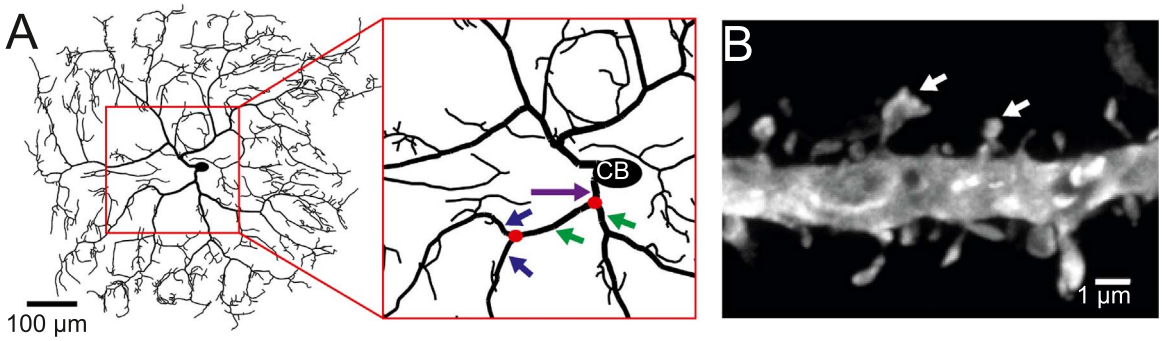

Fig. 1. (A) Traced dendritic tree of a CIVda neuron from a third instar *Drosophila melanogaster* larva. CB = cell body; red dots indicate branching points; purple arrow is pointing at a primary dendrite; green arrows are pointing at secondary dendrite branches; blue arrows at pointing at tertiary dendrite branches. **(B)** STED image of a PFA-fixed apical cortical dendrite labeled by Tyh1::GFP; arrows point at dendritic spines. Image 1B was kindly provided by Stefanie Poll and Martin Fuhrmann (DZNE, Bonn)

About 60% (in dry mass) of a human brain consists of lipids (Svennerholm et al., 1994). These have a polar head group and hydrophobic carbon side chains. In aqueous medium they tend to associate spontaneously into micelles or lipid bilayers. The most abundant lipids in the brain are phospholipids; in large part glycerophospholipids containing a glycerol backbone (Svennerholm et al., 1994). The glycerol backbone of these lipids comprises three carbons to which usually a saturated fatty acid is attached at position C_1 and an unsaturated fatty acid at position C_2 (Fig. 2A). The phosphate head group is linked to the C_3 position and can be further modified. Depending on the modification of the head group various glycerophospholipids can be synthesised. The most prominent ones in the human brain are (in order of abundance): phosphatidylcholine (PC), phosphatidylethanolamine (PE), ether PE (pPE), Phosphatidylserine (PS), Phosphatidylinositol (PI), ether PC (ePC), lysophospholipids, Phosphatidic acid (PA), Phosphatidylglycerol (PG), and lyso-bisphosphatidic acid (LBPA) (Chan et al., 2012).

Lipid head groups can carry an overall positive or negative charge (Fig. 2A). Especially the negatively charged head groups of phosphoinositides (PIPs), which are phosphorylated derivates of PI, are docking sites for actin cytoskeleton regulators such as the Wiskott-Aldrich syndrome protein (WASP) family members (Papayannopoulos et al., 2005; Saarikangas et al., 2010). They also recruit lipid-binding proteins including the Bin-amphiphysin-Rvs (BAR-) proteins. Those interact with the plasma membrane with their curved BAR-domain and force the membrane to curve (Nishimura et al., 2018; Peter et al., 2004). Some BAR domain containing proteins co-recruit actin regulators and thereby function as a linker between the plasma membrane and the actin cytoskeleton (Peter et al., 2004). This attribute makes BAR domain containing proteins being involved in neurite branching (Kessels and Qualmann, 2015). The involvement of PIPs in regulating neurite branching is described in Section 2 of this review.

With their different head groups and tails, lipids can also actively affect membrane curvature and distortion. While some lipids, like PC, have a uniform cylindrical shape, other lipids including PA have a rather small head group compared to the tail, and thereby support negative membrane curvature (Kooijman et al., 2003). Due to this property, PA synthesis stimulates vesicle fusion to the plasma membrane by exocytosis, a mechanism that guarantees membrane addition and supports neurite outgrowth (Zeniou-Meyer et al., 2007) (Section 3). The extension of a newly formed branch then relies on *de novo* lipid synthesis, which provides the building blocks necessary for neurite elongation (Paoletti et al., 2011; Ziegler et al., 2017). Sections 4 and 5 summarize metabolic and regulatory pathways for *de novo* membrane lipid synthesis.

2. Negatively charged glycerophospholipids and their involvement in dendritic branch initiation

The mechanisms that support the initiation of dendrite branch formation are not fully understood. However, it is well accepted that the production and localization of PIPs (Fig. 2A) represents an important factor. Although the amount of PIPs in the plasma membrane is essentially low, they play an extraordinarily important role in shaping dendritic morphology. Within a membrane, different lipid classes are not homogenously distributed. In particular PIPs that localize to the cytosolic leaflet of the plasma membrane can recruit Wiskott-Aldrich syndrome protein (WASP) family members and membrane bending factors of the BAR protein family (Lei et al., 2017; Papayannopoulos et al., 2005; Takenawa and Suetsugu, 2007). The events that lead to the production of PIPs or to their localization to specific sites of the plasma membrane are only partially known. Nonetheless, several pathways appear to converge downstream of PIP signaling towards the activation of the actin-related protein 2/3 (Arp2/3) complex, which is a key actin-nucleating factor (Fig. 3) (Egile et al., 2005; Kreishman-Deitrick et al., 2005; Qualmann et al., 1999; Saarikangas et al., 2015; Zhang et al., 2017). Those pathways will be described in the following sections.

2.1. Phosphoinositide signaling and its effects on cytoskeleton regulation in neuritogenesis

From PI, seven possible derivatives can be generated through phosphorylation at positions 3, 4, and 5 (Fig. 2A). Among the PIPs, Phosphatidylinositol 4,5-bisphosphate ($PI(4,5)P_2$), Phosphatidylinositol 3,4-bisphosphate ($PI(3,4)P_2$), and Phosphatidylinositol 3,4,5-triphosphate ($PI(3,4,5)P_3$) play a role in the spatiotemporal regulation of actin cytoskeleton organization (Saarikangas et al., 2010). They thereby function in dendritogenesis and dendrite maturation (Jaworski et al., 2005; Lei et al., 2017; Ueda and Hayashi, 2013; Zhang et al., 2017)

$PI(3,4)P_2$ for instance has been recently found to play an important role in neuritogenesis of cultured rat hippocampal neurons at early stages of differentiation (stage 1a and 1b), in which the growth of primary neurites is initiated. In that system, fluorescently labeled $PI(3,4)P_2$ co-localizes with accumulated F-actin labeled by phalloidin (Zhang et al., 2017). $PI(3,4)P_2$ is generated either from PI(4)P phosphorylation by the Phosphoinositide 3-kinase (PI3K) C2α or through dephosphorylation of $PI(3,4,5)P_3$ through the SH2 domain containing inositol 5-phosphatase 2 (SHIP2) (Fig. 2B) (Damen et al., 1996; Pirola et al., 2001). $PI(3,4)P_2$ produced by SHIP2/PI3K C2α can recruit neuronal N-WASP, which in turn locally stimulates actin polymerization by recruiting the Arp2/3 complex and thereby supports

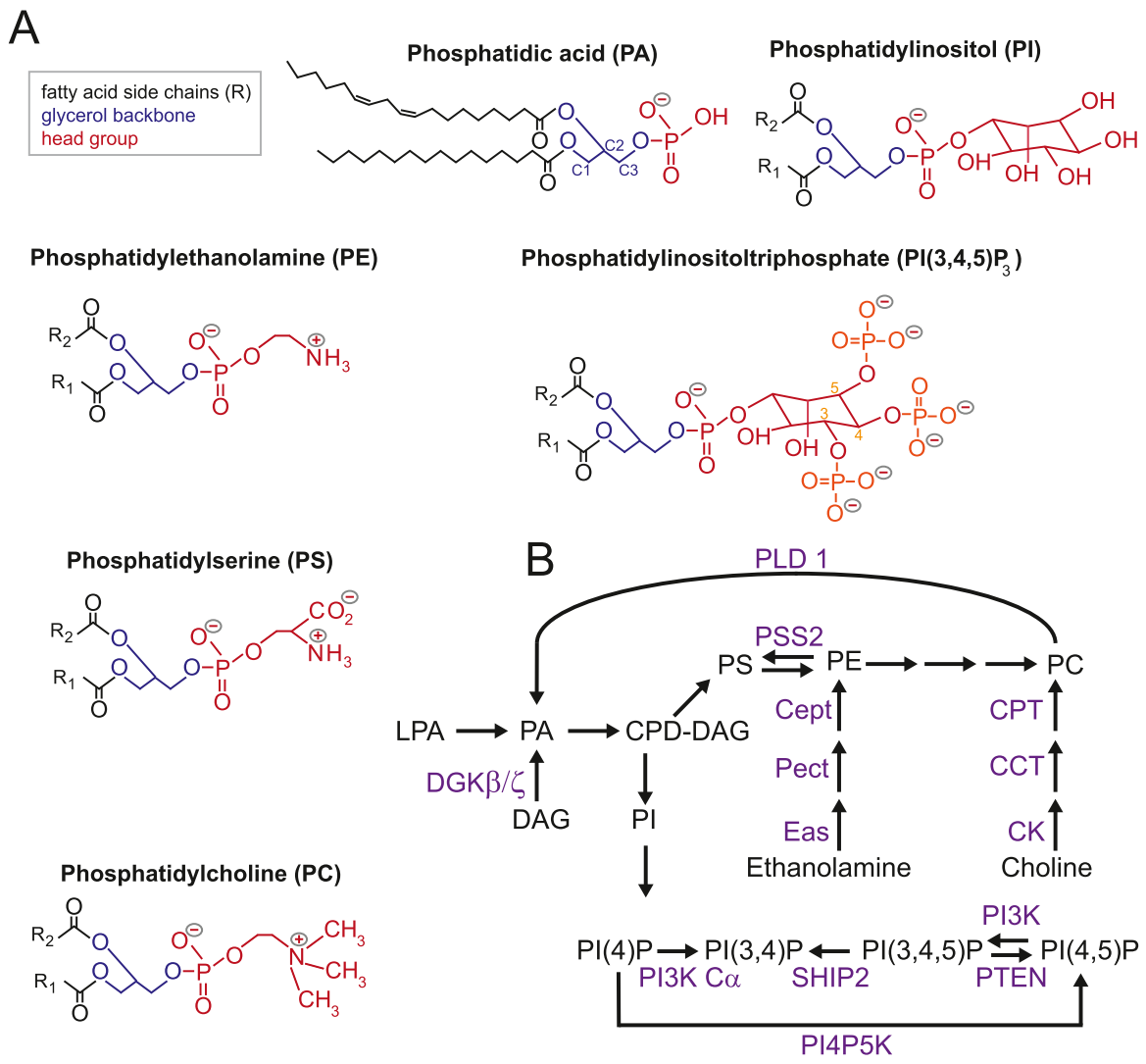

Fig. 2. Glycerophospholipids structures and metabolic pathways. **(A)** Structure of the major glycerophospholipids with their glycerol backbone in blue, fatty acid side chains in black, and head groups in red. The phosphate modifications on $PI(3,4,5)P_3$ are indicated in orange. Charge of the head groups is circled. **(B)** Scheme indicates the metabolic pathways of glycerophospholipids which are shown to be involved in neurite branching and outgrowth. Enzymes involved in those pathways and mentioned in this review are depicted in purple. Abbreviations: Cytidine Diphosphate Diacylglycerol (CPD-DAG), Diacylglycerol (DAG), Diacylglycerol kinase (DGK), Lysophosphaditic acid (LPA), Phospholipase D 1 (PLD1), phosphatidylserine synthases 1 (PSS2), Phosphoinositide 3-kinase (PI3K) C2α (PI3K α), SH2 domain containing inositol 5-phosphatase 2 (SHIP2), phosphatase and tensin homolog deleted on chromosome Ten (PTEN), Easily shocked (Eas), phosphoethanolamine cytidyltransferase (Pect), CDP-ethanolamine Phosphotransferase (Cept), Choline Kinase (CK), CTP:phosphocholine cytidylyltransferase (CCT), CDP-choline:1,2-diaglycerol cholinephosphotransferase (CPT), Phosphatidylinositol-4-phosphate 5-kinase (PI4P5K).

neurite branch formation (Fig. 3A). The direct interaction between $PI(3,4)P_2$ and N-WASP has been shown *in vitro* by co-immunoprecipitation of recombinant, purified N-WASP using PIP coated beads (Zhang et al., 2017). A lack of the $PI(3,4)P_2$ generating enzymes PI3K C2α or SHIP2, or a lack of N-WASP, or of the Arp2/3 complex members resulted in reduced dendrite complexity (Zhang et al., 2017). The cascade of events from the synthesis of $PI(3,4)P_2$ by SHIP2/PI3K C2α to the activation of Arp2/3 via N-WASP was further tested in a series of rescue experiments. In those, a lack of an upstream factor could be compensated by the overexpression of a component functioning further downstream in the cascade. For example the lack of either SHIP2 or PI3K C2α led to a loss of primary branches, but these defects could be rescued by the expression of a constitutive activeform of N-WASP targeted to the membrane via a CD8 domain (Zhang et al., 2017).

An additional regulator of PIP homeostasis found to be crucial for developing correct dendrite morphology is Phosphatase and Tensin Homolog Deleted on Chromosome Ten (PTEN). It dephosphorylates $PI(3,4,5)P_3$ to $PI(4,5)P_2$ (Fig. 2B) (Lee et al., 1999). PTEN function has been extensively investigated in cancer cells, a system in which it suppresses proliferation by inhibiting the PI3K/Akt signaling pathway (Knobbe et al., 2002; Neshat et al., 2001; Papa et al., 2014). In this pathway, $PI(3,4,5)P_3$ allosterically activates the membrane bound protein kinase B Akt, which responds to growth promoting hormones (Ebner et al., 2017). Stimulation of the Akt pathway by PI3K also stimulates dendrite growth of cultured rat hippocampal neurons and of *Drosophila* CIVda neurons *in vivo* (Jaworski et al., 2005; Lin et al., 2015). However, the production of $PI(4,5)P_2$ is under control of PI(4)P 5 Kinase (PIP4P5K) which phosphorylates PI(4)P. Therefore, it is thought that the major effect of PTEN is to counterbalance an excess of $PI(3,4,5)P_3$ and thereby to negatively regulate the strength of Akt signaling (Claret et al., 2014; Papa et al., 2014; Pinal et al., 2006). In agreement with this hypothesis, knock-down of *pten* expression in cultured hippocampal rat neurons at the end of the embryonic phase strongly increases dendritic branching (Jaworski et al., 2005; Wyatt et al., 2014). Additionally, a lack of Pten expression leads to larger somata and thickened dendritic and axonal processes (Backman et al., 2001; Jaworski et al., 2005; Kwon et al., 2006).

Embryonic stage 18 rat hippocampal neurons maintained in culture for 21 days display numerous dendritic spines. The spine shaft contains

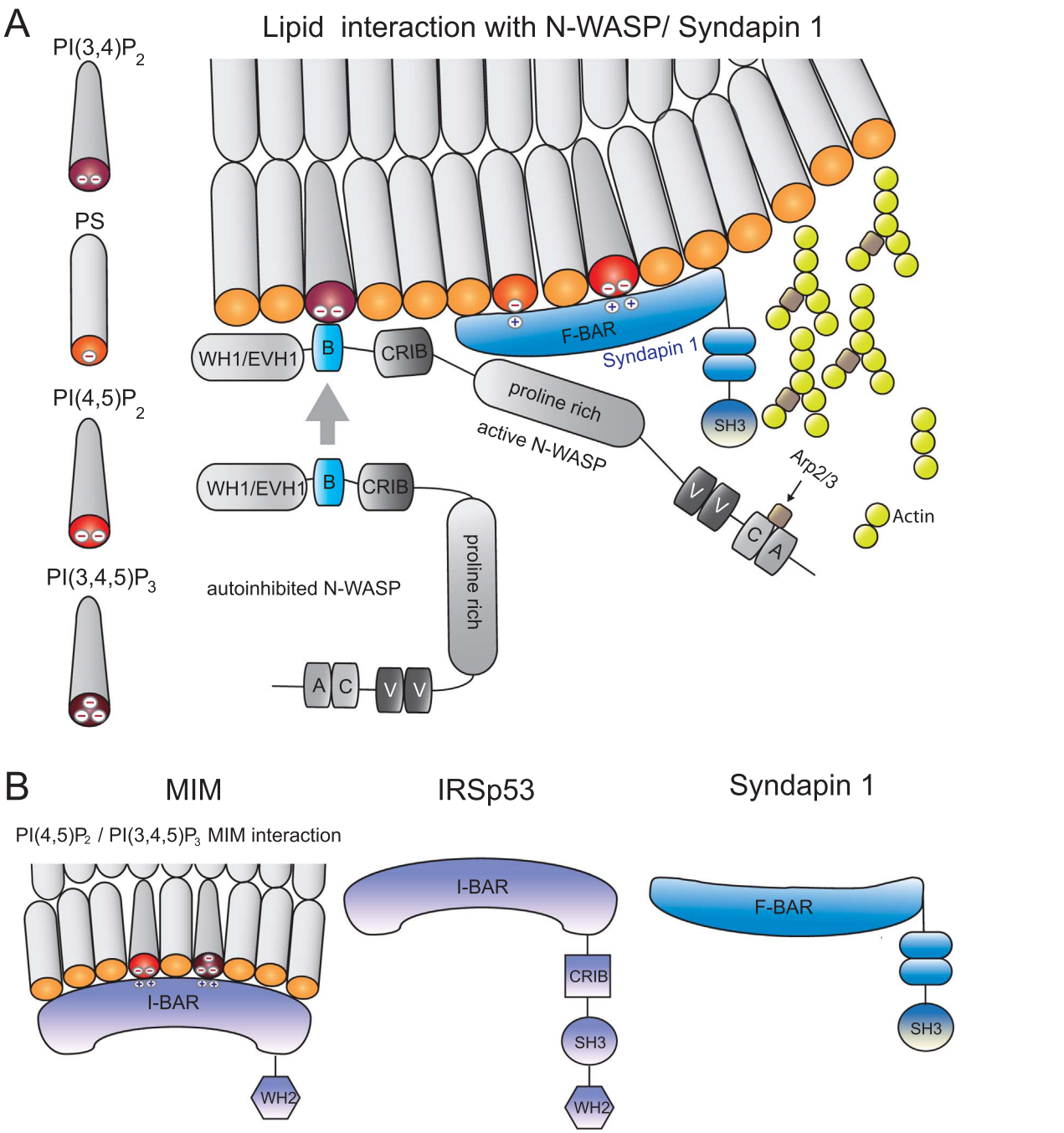

Fig. 3. PIP interactions with N-WASP and BAR-family members support neurite formation **(A)** Left: Legend of specific lipids. Right**:** neuronal Wiskott-Aldrich syndrome protein (N-WASP) is kept in an autoinhibited state. It binds to membrane bound $PI(3,4)P_2$ via a basic domain (B) and switches to an open and active state. It can further bind to the F-Bin-amphiphysin-Rvs (F-BAR) member Synpadin I, which induces positive membrane curvature by binding to PS and $PI(4,5)P_2$, via a proline rich region. The open conformation of N-WASP allows the recruitment of the Actin related protein 2/3 (Arp2/3) complex via its acidic extension (A) and connector domain (C). Arp2/3 polymerizes actin (yellow circles) and thereby supports the formation of new neurite branches. N-WASP has additional WASP-Homology 1 / Enabled/VASP homology 1(WH1/EVH1) and multiple WASP-Homology 2 domains (V) to bind and assemble actin monomers. **(C)** Scheme of BAR proteins with a known role in neurite branching. Missing in metastasis (MIM) docks to membrane bound $PI(3,4,5)P_3$ and $PI(4,5)P_2$. It induces negative membrane curvature and thereby forms a proto-protrusion. Insulin receptor tyrosine kinase substrate p53 (IRSp53) can equally induce negative membrane curvature and has multiple domains such as the Cysteine-rich protein domain (CRIB), Src homology 3 domain (SH3), and the WASP-Homology 2 domain (WH2), for protein-protein interaction. Syndapin 1 is the only F-BAR member known to support neurite branching.

mostly F-actin marked by fluorescent phalloidin while the spine head is enriched in G-actin revealed by anti-actin antibodies (Lei et al., 2017). The G-actin fraction within the spine head increases upon neuronal stimulation with the potassium channel blocker tetraethylammonium (TEA). This leads to an enlargement of the spine head volume and presumably to the maturation into a mushroom-like shape (Lei et al., 2017). LY294002 is a strong inhibitor for numerous proteins including PI3K (Searl and Silinsky, 2005; Vlahos et al., 1994). Blocking the production of $PI(3,4,5)P_3$ through pharmacological inhibition of PI3K using LY294002 reduced the spine head G-actin pool and consequently the size of the dendritic spine heads. Conversely, pharmacological inhibition of PTEN using SF1670, which should result in elevated $PI(3,4,5)P_3$ levels, increased G-actin concentration in spines and enlarged spine head size. The mechanism by which $PI(3,4,5)P_3$ might regulate G-actin enrichment and spine head maturation is not yet fully understood. However, $PI(3,4,5)P_3$ might contribute to retain a G-actin

pool in the spine head, which can be used to produce polymerized actin in response to neuronal stimulation. The interaction between PI(3,4,5)P_3 and G-actin is likely indirect and could involve the recruitment of Profilin-bound G-actin to WASP family proteins drafted through an interaction with PIPs to the plasma membrane (Lei et al., 2017; Takenawa and Suetsugu, 2007). Taken together, PI(3,4,5)P_3 and PI(3,4)P_2 seem to promote WASP dependent actin polymerization while PI(4,5)P_2 may suppress neurite growth by inhibiting the PI3K/Akt signaling pathway.

2.2. Involvement of BAR protein/PIP interaction in neuromorphogenesis

BAR domain proteins are curvature-generating proteins located at the interface between the plasma membrane and the cytoskeleton. A helix coiled-coil core that forms curved homo- or heterodimers gives BAR proteins their characteristic banana shape. Classical BAR domain proteins and extended FCH domain (F-BAR) family members introduce mostly convex/positive membrane curvature, while Inverse BAR domain (I-BAR) containing proteins induce a concave/negative membrane curvature (Fig. 3B) (Peter et al., 2004; Stanishneva-Konovalova et al., 2016). BAR domains interact with negatively charged membrane lipid head groups such as in phosphoinositides or phosphatidylserine (see Fig. 2) with appropriate positively charged residues within their BAR domain (Peter et al., 2004). Several BAR family members have been reported to shape dendrite morphology and their role within this process has been recently reviewed (Kessels and Qualmann, 2015). Therefore, we specifically focus in this review on only three BAR family members, whose function in dendritogenesis was studied in detail, namely, Missing-in-metastasis (MIM), the Insulin receptor tyrosine kinase substrate p53 (IRSp53) and the F-BAR member Syndapin I.

MIM and IRSp53 deform PI(4,5)P_2-rich membranes (Mattila et al., 2007). They are abundant in neurons and loss of their function is associated with learning and memory deficits, and behavioral abnormalities, such as altered locomotor behavior (Kim et al., 2009b; Saarikangas et al., 2015). MIM localizes to dendrites but not to the axons of a variety of rodent neurons, including hippocampal pyramidal neurons and Purkinje cells of the cerebellum. Within dendrites MIM localizes preferentially to spine heads and dendritic filopodia that give rise to spines prior to actin assembly. MIM binds specifically to PI(3,4,5)P_3 or PI(4,5)P_2 (Mattila et al., 2007). By dimerizing, it forms its characteristic bent I-BAR domain. The dimer then initiates a proto-protrusion at a future dendritic spine site (Fig. 3A) (Saarikangas et al., 2015). Additionally, the accumulation of MIM at spine initiation sites could prevent diffusion of PIPs away from the spine initiation site. Thus, MIMs can support the formation of PIP enriched membrane domains, which in turn could recruit actin regulatory factors capable of interacting with PIPs, such as N-WASP, and subsequently the Arp2/3 complex that supports dendritic spine outgrowth (Saarikangas et al., 2015, 2009; Zhao et al., 2013).

Dendritic filopodia initiation can take place even when actin assembly is inhibited using latrunculin B. However, in this condition the proto-protrusions induced by MIM do not grow and mature to dendritic spines. This suggests that MIM is a factor to mark future spine initiation sites (Saarikangas et al., 2015). In spite of the important role of MIM in dendritic spine formation, additional mechanisms might be involved in the initiation of dendrite spines, as loss of MIM in *MIM*$^{-/-}$ mice results in a reduction, but not a full loss of dendrite spines in cerebellar Purkinje cells and hippocampal neurons (Saarikangas et al., 2015). This reduction might have functional consequences as mice lacking MIM show motor behavior defects such as a decreased walking speed or decreased latency in the rotarod performance test (Saarikangas et al., 2015).

IRSp53 is especially abundant in neurons. It binds to negatively charged lipids, such as PI(4,5)P_2 and PS via its I-BAR domain (Futo et al., 2013). IRSp53 contains multiple domains for protein-protein interaction in addition to its I-BAR domain (Fig. 3B). It can thereby interact with actin filaments through its WH2 domain, with small GTPases such as Cell division control protein 42 (Cdc42) or Ras-related C3 botulinum toxin substrate 1 (RAC1) through its Cysteine-rich protein domain (CRIB) domain, with actin regulators such as WAVE2, N-WASP or enabled/Vasodilator-stimulated phosphoprotein (Ena/VASP) through its Src Homology3 (SH3) domain and trough its PDZ domain with scaffolding proteins such as postsynaptic density protein 95 (PSD-95) (Fig. 3A) (recently reviewed by Kang et al., 2016). It thus represents a complex hub for interactions. Depending on the binding partners IRSp53 can promote filopodia formation or inhibit filopodia outgrowth by supporting lamellipodia formation (Nakagawa et al., 2003). IRSp53 on its own slows down actin filament growth. However, upon GTP activation Cdc42 binds to IRSp53 and switches the action of IRSp53 from an inhibitor of actin filament assembly to a stimulator (Disanza et al., 2013). This stimulating effect is mediated by the ability of IRSp53 to bind WASP family members (Lim et al., 2008). RNAi mediated IRSp53 knock-down in cultured rat hippocampal neurons resulted in a reduction of dendritic spine density (Choi et al., 2005). Unexpectedly, spine density was not reduced in hippocampal CA1 pyramidal neurons of IRSp53$^{-/-}$ knock-out mice (Kim et al., 2009b).

BAR domains have a preference to bind to negatively charged lipids such as Phosphatidylserine (PS), the major anionic phospholipid (Dharmalingam et al., 2009; Futo et al., 2013) (Fig. 2A). In neurons, PS is synthesized mostly through phosphatidylserine synthases 1 or 2 (PSS1/PSS2), which exchange the head groups of either PC or PE with serine (Fig. 2B) (Kim et al., 2014; Tomohiro et al., 2009). However, PSS1 seems to be active rather in astrocytes while PS generated from PE by PSS2 seems to be of greater importance for neurons (Tasseva et al., 2011). Mice lacking either PSS1 or PSS2 develop normally and have unaltered PS brain levels. This suggests possible redundant roles between these two enzymes (Bergo et al., 2002; Steenbergen et al., 2006). The aminophospholipid translocase P4-ATPase localizes PS to the inner leaflet of the plasma membrane, where it serves as a docking site for various proteins including BAR-family members like Syndapin I (Coleman et al., 2009; Gordesky, 1973). Syndapin (also known as PACSIN1) was first shown to co-localize with PI(4,5)P_2 at the plasma membrane in *Drosophila* Schneider 2 cells (Takeda et al., 2013). However, in liposomes that have a defined lipid composition and a PS concentration of 10%, rat Syndapin I seemed to interact predominantly with PS. Only after the PS fraction in the liposomes was reduced to 5%, closer to the PS fraction in human brain membranes, addition of PI(4,5)P_2 enhanced binding of Syndapin I to the liposomes (Dharmalingam et al., 2009; O'Brien and Sampson, 1965). Syndapin I accumulates at dendritic branch initiation sites and in spine heads (Hou et al., 2015; Schneider et al., 2014). There, it recruits actin nucleation promoting factors of the WASP family, such as N-WASP and Cordon-bleu (Cobl) (Dharmalingam et al., 2009; Schwintzer et al., 2011). *In vitro* actin polymerization experiments suggested that interaction with Syndapin I could release N-WASP from its autoinhibited state and lead thus to actin polymerization via N-WASP and the Arp2/3 complex (Fig. 3A) (Dharmalingam et al., 2009; Qualmann et al., 1999).

The interaction of Synadapin I and Cobl was shown in mouse primary hippocampal neuron cultures, where the overexpression of either, Syndapin I or Cobl, increased the number of neurites, and simultaneous overexpression of Cobl and Syndapin I together even further increased dendrite numbers (Schwintzer et al., 2011). Conversely, reduction of those proteins via RNAi reduced the number of dendrites (Ahuja et al., 2007; Schwintzer et al., 2011).

Taken together, BAR family members bind to negatively charged phospholipids and are involved in shaping neurite morphology by the recruitment of cytoskeleton regulators of the WASP family which in turn lead to actin polymerization via the Arp2/3 complex.

3. The role of phosphaditic acid in dendrite growth

PA is the simplest naturally occurring phospholipid and contains only the unmodified phosphate head group (Fig. 2A). The small size of the head group gives PA a cone shape that promotes membrane curvature. Although PA represents only a small fraction of the cellular lipid content, it plays a central role in lipid metabolism since it is a precursor for most of the other glycerophospholipids (Fig. 2B). Furthermore, it controls multiple signaling pathways by modulating the catalytic activity or membrane attachment of several proteins (Liu et al., 2013). An additional important function of PA is its involvement in neurite elongation by promoting vesicle fusion for plasma membrane expansion (Ammar et al., 2014, 2015). PA can be generated via three different enzymatic reactions catalyzed by DAG kinases, Phospholipase D1 or Lysophosphatidic acid acyltransferases, with distinct implications for dendritogenesis (Fig. 2B).

3.1. Involvement of DAG kinases in the control of dendrite growth

PA can be generated by the addition of phosphate to diacylglycerol (DAG) through DAG kinases (DGK) (Pieringer and Kunnes, 1965). DAG acts as a lipid-derived second messenger molecule acting downstream of many G-Protein coupled receptors (GPCRs). Thereby DAG regulates the function of numerous enzymes including protein kinase C, chimerins, Munc13, and Ras guanyl nucleotide releasing protein (RasGRP). Through its action on these various downstream targets, DAG is involved in a complex network of signaling pathways that regulate diverse processes such as cytoskeletal dynamics, ntracellular membrane trafficking, neurotransmitter release, lipid signaling, and gene transcription (reviewed by Brose et al., 2004). By converting DAG to PA, DGKs are involved in terminating DAG signaling and in activating PA signaling (Kim et al., 2010; Sakane et al., 2007). Out of the ten DGK isoforms identified in mammals, a particular role on dendrite morphology has been attributed to DGKβ and DGKζ (Hozumi et al., 2009; K. Kim et al., 2009; Shirai et al., 2010).

DGKβ is predominantly expressed in neurons where it is preferentially targeted to dendrites (Adachi et al., 2005; Hozumi et al., 2009). In cultured rodent neurons, DGKβ immunolabeling overlaps with postsynaptic density protein-95 (PSD-95), an abundant scaffolding protein at excitatory synapses. Although experimental evidence was lacking, the co-localization with PSD-95 suggested a synaptic function of DGKβ. During differentiation, though, DGKβ also controls dendrite morphology as its overexpression at early developmental stages increased total dendrite length and number of mature dendritic spines (Hozumi et al., 2009). Conversely, cultured hippocampal neurons from DGKβ$^{-/-}$ KO mice formed on average less dendritic branches and spines. Consistently, KO animals had impaired cognitive functions, including defective learning and memory. But what is the molecular function of DGKβ? In agreement with its enzymatic activity, PA level was lower while the DAG content was higher in brains of mutant animals. However, how this lipid imbalance might lead to reduced dendritic spine formation remains unclear (Shirai et al., 2010).

Similarly, DGKζ localizes to dendritic spines in cultured hippocampal neurons where it is bound to PSD-95. While loss and gain of function experiments also indicate a role of DGKζ in sustaining dendritic spine density, time-lapse imaging strongly suggests that DGKζ is involved in the maintenance of dendritic spines rather than their formation (Kim et al., 2009a). Previous studies in N1E-115 neuroblastoma cells suggested that DGKζ can instead induce process outgrowth via its interaction with Rac1, a positive regulator of neurite growth (Woo and Gomez, 2006; Yakubchyk et al., 2005). However, in this system, neurite outgrowth could also be induced by kinase-dead DGKζ constructs. This indicates that DGK enzymatic activity might not be involved in promoting neurite outgrowth (Yakubchyk et al., 2005).

Taken together, while the function of some DGKs modulates dendrite and spine morphology, it is not clear to which extent termination of DAG signaling or rather enhanced PA levels contribute to the observed phenotypes (Kim et al., 2009a; Kim et al., 2010).

3.2. The role of PLD1-produced PA in the addition of new plasma membrane for neurite outgrowth

After the initial steps of outgrowth, dendrite branches elongate requiring continuous plasma membrane addition, which is supported by vesicle fusion to the plasma membrane via exocytosis (Peng et al., 2015). The formation of the rather rare lipid PA plays an extraordinarily important role in this process. PA can be synthesized by Phospholipase D1 (PLD1), a transphosphatidylase, which catalyzes the cleavage of choline from PC and yields PA (Fig. 2B) (Ponting and Kerr, 1996). PA produced by PLD1 is crucial for neurite outgrowth and maturation (Ammar et al., 2013). Primary cortical neuronal cultures obtained from *pld1*$^{-/-}$ knock-out mice exhibit fewer secondary and higher order branches and less dendritic spines (Ammar et al., 2013). The underlying mechanism was in parallel investigated in PC12 cells. In those cells, neuronal growth factor (NGF) triggered activation of PLD1 via phosphorylation by ribosomal S6 kinase 2 (RSK2). The direct visualization of dynamic PA distribution could offer essential insights into the role of PA in neurite elongation. A useful PA-sensor is “wild type-PA binding domain” (wtPABD). wtPABD was obtained by fusion of the PA binding domain of Sporulation-specific protein 20 (Spo20p), a yeast homolog of SNAP25, to green fluorescent protein (GFP) and enables the direct visualization of PA *in vitro* (Kassas et al., 2012; Nakanishi et al., 2004; Zeniou-Meyer et al., 2008). In cultured PC12 cells, wtPABD was used to visualize the site of PA production. Without growth stimulation wtPABD was detected in the nucleus. Only after NGF application, which stimulates neurite outgrowth, a significant PA fraction was visible at sites of exocytosis at the plasma membrane (Ammar et al., 2013). Next, a pH-sensitive GFP (pHlourin) fused to vesicle-associated membrane protein (VAMP) was used to label the site of exocytosis. pHlourin becomes brightly fluorescent only after the pHlourin containing vesicles fuse to the plasma membrane. This tool was used to show that RSK2 and PLD1 positively regulate vesicle fusion at the growing ends of neurites in PC12 cells (Ammar et al., 2015).

The mechanism, by which PLD1 promotes vesicle fusion to the plasma membrane, has been primarily investigated in non-neuronal cells (Huang et al., 2005). However, the current model may also hold true for neurons. In this model, exocytosis of vesicles requires the energy demanding fusion of the vesicle at the plasma membrane and thereby the generation of a pore in between both membranes (Grafmuller et al., 2009) (Fig. 4). The enrichment of cone shaped PA at the inner leaflet of the plasma membrane promotes a negative curvature of membranes and helps to overcome the energy demand for pore formation and thereby facilitates exocytosis (Fig. 4) (Grafmuller et al., 2009).

3.3. LPA receptors mediate developmental neuromorphological changes

The third pathway to synthesize PA utilizes Lysophosphatidic acid acyltransferases (LPAAT). Those use lysophosphaditic acid (LPA), which has only one hydrophilic fatty acid side chain, and add one more fatty acid side chain to produce PA (Eberhardt et al., 1997). Until now no role of LPAAT on dendrite morphology has been indicated. However, the substrate of LPAATs, LPA, is an important lipid messenger molecule that plays a role on establishing neuronal polarity during early phases of neuronal differentiation and induces neurite branch formation during later phases (Fukushima et al., 2002; Furuta et al., 2012; Yamane et al., 2010; Yung et al., 2015). In contrast to the other lipid metabolic pathways reviewed here, LPA is generated by an extracellular source and acts trough LPA receptors, which belong to the GPCR family (Hecht et al., 1996; Yung et al., 2015). LPA added to the medium of cultured mouse cortical neurons leads to the retraction of

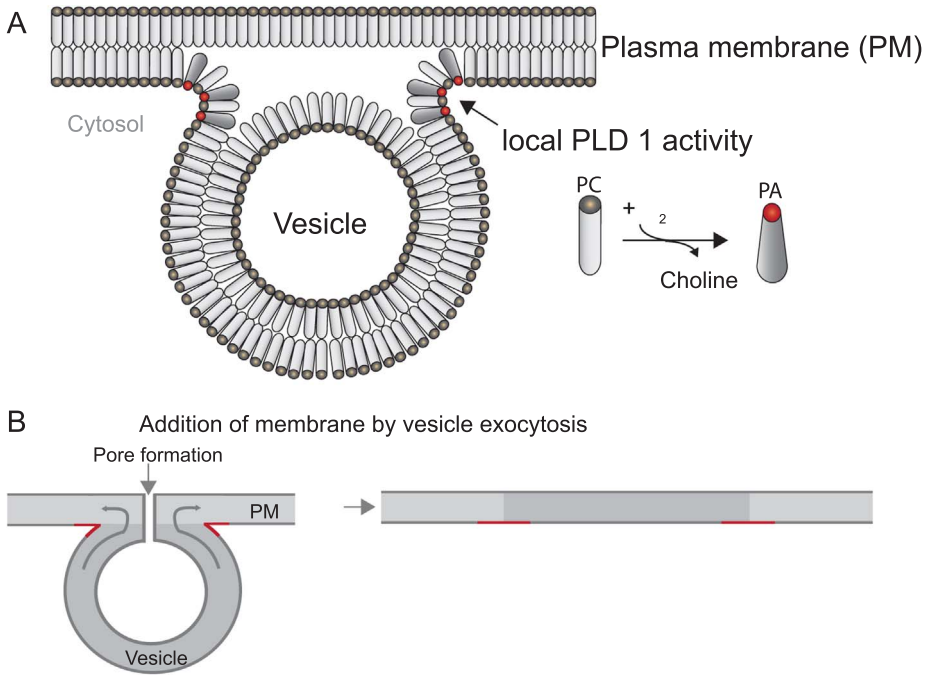

Fig. 4. Local PA production supports exocytotic vesicle fusion to the plasma membrane and neurite outgrowth. **(A)** Phospholipase D 1 (PLD1) catalyzes the formation of phosphatidic acid (PA) from phosphatidylcholine (PC). Local activity of PLD1 forms PA at sites of vesicle fusion. PA has a small head group compared to the fatty acid side chains and induces negative curvature into membranes (Modified after Cazzolli et al.,2006) **(B)** It thereby helps to overcome the energetically costly breakage of the plasma membrane (light gray) before vesicular lipids (darker shade) are added via exocytosis.

neuronal processes and thus leads to cell rounding (Fukushima et al., 2002). LPA signaling within the nervous system has been recently reviewed by Yung et al. (2015) and will only be briefly discussed here.

Six LPA receptors have been identified in mammals (LPA_{1-6}) (Hecht et al., 1996; Yung et al., 2015). Except LPA_3 all other studied LPA receptors have been implicated in mediating LPA dependent neurite retraction and growth cone collapse during very early stages of neuronal differentiation (Fukushima et al., 2002; Ishii et al., 2009; Noguchi et al., 2009). This effect is mediated by the Rho-associated protein kinase (ROCK) pathway (Tigyi et al., 1996). On the other hand LPA_3 is expressed at later neurodevelopmental stages and involved in axon sprouting. In cultured mouse hippocampal neurons (stage E17) axon branching could be enhanced when those neurons were incubated with the LPA agonist 1-oleoyl-2-O-methyl-rac-glycerophosphothioante (2(S)-OMPT). Knock-down of LPA_3 eliminated the enhanced axon branching after 2(S)-OMPT incubation. Axon branching was further blocked by G_q and Rho family GTPase 2 pathway inhibition (Furuta et al., 2012).

4. Endogenous lipid synthesis is required for neurite extension

The extension of neurites demands *de novo* synthesis of membrane lipids. The most abundant phospholipid in mammalian neurons is PC (O'Brien and Sampson, 1965; Svennerholm et al., 1994). It is mainly synthesized from choline in three enzymatic steps via the Kennedy pathway (Fig. 2B). Firstly, Choline Kinase (CK) phosphorylates choline to produce phosphocholine (P-choline) (Porter and Kent, 1990). Then, CTP: phosphocholine cytidylyltransferase (CCT) catalyzes the subsequent production of cytidine diphosphate (CDP)-choline (Friesen et al., 2001). The ultimate step in PC synthesis is catalyzed by the CDP-choline:1,2-diaglycerol cholinephosphotransferase (CPT) (Fig. 2B) (Kennedy and Weiss, 1956; Weiss et al., 1958).

Several independent reports have proven that the transition phase between cell proliferation and neuronal differentiation is accompanied by the up-regulation of PC synthesis to support the formation of new plasma membrane and thereby neurite outgrowth. This process has been thoroughly reviewed in (Paoletti et al., 2011) and will be discussed here only briefly. Most studies describing the role of the Kennedy pathway on neurite growth were performed using PC12 or neuroblastoma cells (Neuro-2a). The transition from their proliferating stage to a stage of neurite differentiation can be induced by stimulation with nerve growth factor (NGF) or retinoic acid (RA) (Greene and Tischler, 1976; Shea et al., 1985).

Mammalian genomes contain two CK encoding genes (*Chka* and *Chkb* encoding CKα and CKβ*)* (Aoyama et al., 2004). Although Neuro-2a cells express both genes, their differentiation after RA application was accompanied only by an upregulation of *Chka* expression level. Overexpression of CKα was also capable of inducing neurite formation in the absence of RA (Marcucci et al., 2010). Similarly, overexpression of CKα in embryonic rat hippocampal neurons enhanced neurite outgrowth and branching (Buchser et al., 2010).

Next to CK, CCT expression has also been linked to neurite outgrowth. Two CCT encoding genes (*Pcyt1a* and *Pct1b)* are present in mammalian genomes and encode for CCTα and CCTβ. In contrast to CK expression, CCT expression is up-regulated already before the visible outgrowth of neurites (Carter et al., 2003). While CCTα is ubiquitously expressed, CCTβ is enriched in the brain (Karim et al., 2003; Lykidis et al., 1999). PC12 cells, in which CCTβ expression has been knocked down, have an unaltered total neurite length. However, the amount of neurites per cell was significantly lower compared to the controls, indicating that mutant cells grow fewer but longer neurites (Carter et al., 2008).

The most abundant glycerophospholipid in insect neurons is not PC but PE (Guan et al., 2013). In the fruit fly *Drosophila melanogaster* dendritic arborization (da) neurons are used for *in vivo* studies of developmental dendrite formation and outgrowth (Jan and Jan, 2010). Da neurons are localized between a muscle layer and the epidermis and arborize in an almost two-dimensional fashion. Their dendrites can be labeled with fluorescent markers such as membrane-tethered GFP and imaged *in vivo* through the transparent cuticle of the animal (Grueber et al., 2002). The so-called class four (CIV) da neurons form particu-

larly extended and arborized dendritic processes with a total dendritic length of 20 mm and approximately 500–600 arborization points (Grueber et al., 2003; Ziegler et al., 2017). Recent data indicate that the growth of CIVda dendrites relies on PE generated from ethanolamine (Meltzer et al., 2017).

The first step in PE generation is catalyzed by an ethanolamine kinase called Easily shocked (Eas) which adds a phosphate group to ethanolamine to yield phosphoethanolamine (Pavlidis et al., 1994). It can be further processed by a phosphoethanolamine cytidyltransferase (Pect) to gain CDP-ethanolamine (Sundler, 1975). CDP-ethanolamine Phosphotransferase (Cept) catalyzes the final reaction to yield PE (Fig. 2B) (Kennedy and Weiss, 1956). RNAi mediated knock-down of all these three enzymes, as well as the usage of an *eas* knock-out mutant, led to reduced dendritic arborization patterns and reduced total dendritic length of CIV da neurons at the end of the larval developmental growth phase. While these experiments point to a role of PE abundance in the modulation of dendrite extension and complexity, it remains unclear whether reduced PE supplement to the plasma membrane or altered signaling related to the PE content are responsible for this defect (Meltzer et al., 2017). The involvement of this PE synthesis pathway in dendrite development has not yet been investigated in mammalian neurons.

5. Neuronal fatty acid synthesis supports developmental dendrite growth

An essential component of most lipids are the fatty acid side chains (Fig. 2A). Therefore, formation of new membrane lipids in neurons is accompanied by fatty acid *de novo* synthesis (Ziegler et al., 2017). Fatty acids can be produced by glia and provided to neurons in order to support their neurite outgrowth (Tabernero et al., 2001). However, some neurons including *Drosophila* da neurons rely on cell-autonomous fatty acid synthesis for their developmental dendrite outgrowth (Ziegler et al., 2017). Enzymes involved in fatty acid production, such as acetyl-CoA carboxylase (ACC) are essential for viability. Therefore, homozygous mutant cell clones of *acc* were generated in an otherwise heterozygous larva using the Mosaic analysis with a repressible cell marker (MARCM) technique (Lee and Luo, 2001). Homozygous *acc* mutant da neurons had significantly fewer and shorter dendrites, which suggested that dendrite development required cell-autonomous fatty acid synthesis in all investigated types of da neurons, from the morphologically simple CIda- to the highly arborized CIVda neurons (Ziegler et al., 2017).

In addition to this basic requirement of fatty acid synthesis in all da neuron classes, CIVda neurons with their particularly large and arborized dendritic trees (Fig. 1A) tune their fatty acid *de novo* synthesis further via a specific transcription factor (TF) (Ziegler et al., 2017). This TF is a member of the sterol regulatory element binding protein (SREBP) family. SREBPs are evolutionary conserved and mainly regulate the expression of genes related to lipogenesis (Bennett et al., 1995; Osborne and Espenshade, 2009). They are translated as inactive multidomain pre-proteins and are anchored in the endoplasmic reticulum. Under lipid deprivation, SREBPs translocate to the Golgi where their TF domain is liberated by a proteolytic cleavage mechanism. The activated TF domain travels into the nucleus and activates its downstream target genes (Eberle et al., 2004). The human genome comprises two *srebp* genes, *srebp1 and srebp2* (Osborne and Espenshade, 2009). Their downstream target genes are related to either fatty acid or sterol *de novo* synthesis, respectively (Amemiya-Kudo et al., 2002). Due to its central role for the body lipid metabolism, SREBPs function has been largely characterized in peripheral tissues (Eberle et al., 2004).

Drosophila melanogaster has only one *srebp* gene (Theopold et al., 1996). Its function resembles mammalian SREBP1 and it regulates *de novo* fatty acid synthesis (Dobrosotskaya et al., 2002; Seegmiller et al., 2002). Brains of *srebp* mutant *Drosophila* larvae have a significantly lower membrane lipid level. This lack of membrane lipid synthesis during the developmental growth phase correlated with simplified and overall shorter dendritic trees in CIVda neurons of *srebp* knock-out mutants. However, neurons with shorter and less complex dendritic trees, such as CIda or CIIIda neurons, were not affected by knock-down of *srebp* expression. This indicates that complex neurons, such as CIVda neurons, have the capacity of tuning up fatty acid production during the developmental growth phase to support the growth of their arborized dendrites (Ziegler et al., 2017).

6. Summary and outlook

The spatiotemporal production of lipids is important for proper neurite formation. This is especially true during the developmental growth phase in which dendritic and axonal processes are formed and synaptic circuits established. PC and PE are the most abundant lipids in the brain. A high synthesis rate of these lipids is especially important to maintain high rates of exocytotic addition of new membrane for dendrite elongation. In contrast PA, PS, and PIPs are present at lower levels. Nevertheless, they play equally important roles in shaping dendrite morphology. PA with its cone shape is generated at sites of exocytosis where it positively promotes the fusion between vesicles and the plasma membrane. Negatively charged PS and PIPs are docking sites for BAR family members and involved in dendrite branching or dendritic spine formation. Additionally PIPs can interact with N-WASP to support Arp2/3 mediated actin polymerization and thereby act on dendrite morphogenesis.

However, most studies have used cultured cells and cultured primary neurons for their investigations. In these experiments neurons did not grow in their natural environment where they are additionally surrounded by other cells such as glia, possible synaptic interaction partners or other cells they could interact with. Furthermore, they are not subject to systemic factors such as sensory input or nutrition. Future work might therefore focus more on studying the role of lipid production and lipid localization on neurite branching and growth by using *in vivo* models. Therefore, it will be of advantage to develop more genetically encoded lipid sensors, which enable the direct and *in vivo* visualization of newly produced specific lipid classes. Additionally, it will be high time to study the role of lipids in the development and progression of neurological diseases.

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