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Polyphosphoinositides in the nucleus: Roadmap of their effectors and mechanisms of interaction

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ABSTRACT

Biomolecular interactions between proteins and polyphosphoinositides (PPIn) are essential in the regulation of the vast majority of cellular processes. Consequently, alteration of these interactions is implicated in the development of many diseases. PPIn are phosphorylated derivatives of phosphatidylinositol and consist of seven species with different phosphate combinations. PPIn signal by recruiting proteins via canonical domains or short polybasic motifs. Although their actions are predominantly documented on cytoplasmic membranes, six of the seven PPIn are present within the nucleus together with the PPIn kinases, phosphatases and phospholipases that regulate their turnover. Importantly, the contribution of nuclear PPIn in the regulation of nuclear processes has led to an increased recognition of their importance compared to their more accepted cytoplasmic roles. This review summarises our knowledge on the identification and functional characterisation of nuclear PPIn-effector proteins as well as their mode of interactions, which tend to favour polybasic motifs.

1. Introduction

Polyphosphoinositides (PPIn) (nomenclature as detailed in (Michell *et al.*, 2006)) are phosphorylated derivatives of the glycerophospholipid phosphatidylinositol (PtdIns), composed of two hydrophobic fatty acyl tails esterified to a glycerol backbone, which is itself linked to the D-*myo*-inositol head group (Fig. 1A). Phosphorylation/dephosphorylation of the hydroxyl groups present on positions 3, 4 and 5 of the inositol head group by PPIn kinases and phosphatases can produce seven distinct PPIn, *i.e.* three monophosphorylated PPIn (PtdIns3*P*, PtdIns4*P* and PtdIns5*P*), three diphosphorylated (PtdIns(3,4)P_2, PtdIns(3,5)P_2 and PtdIns(4,5)P_2) and one triphosphorylated (PtdIns(3,4,5)P_3) (Balla, 2013). The presence of acyl chains allows PPIn to be embedded in membranes. On the other hand, the headgroup is exposed to the solvent where it can interact with proteins containing well-defined structured PPIn-binding domains or short polybasic motifs (Hammond and Balla, 2015; Pemberton and Balla, 2018). In both cases, interaction occurs through electrostatic interactions between basic residues and the phosphates displayed on the headgroup. Depending on the level and localisation of PPIn species, different proteins can be recruited to specific membrane locations in a timely manner, hence providing the cell with a PPIn-dependent signalling code.

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Abbreviations

ABP	actin-binding protein
BASP1	brain acid soluble protein 1
BAZ2B	BROMO domain adjacent to zinc finger 2B
CKIα	casein kinase Iα
DAG	diacylglycerol
EBP1	Erbb3 binding protein-1
FYVE	Fab1p, YOTB, Vac1 and EEA1
GAP43	growth associated protein 43
HDAC1	histone deacetylase 1
ING2	inhibitor of growth protein 2
IP_3	inositol 1,4,5-trisphosphate
IPMK	inositol polyphosphate multikinase
K/R	lysine/arginine motif following the motif K/R-(X_{3-7})-K-X-K/R−K/R
LRH-1	liver receptor homolog-1
MARCKS	myristoylated alanine-rich C-kinase substrate
NLS	nuclear localisation signal
NoLS	nucleolar localisation signal
N-WASP	neuronal Wiskott-Aldrich syndrome protein
OGT	O-linked beta-N-acetylglucosamine transferase
PBR	polybasic region
Pf1	PHD factor 1
PH	pleckstrin homology
PHD	plant homeodomain
PHF8	PHD finger protein 8
PI3K	phosphoinositide 3-kinase
PI4K	phosphatidylinositol 4-kinase
PIKE-L	PI3K enhancer-L
PIP_3BP	PtdIns(3,4,5)P_3 binding protein
PIPK	phosphatidylinositol phosphate kinase
PLC	phospholipase C
Pol I/II	RNA polymerase I/II
PPIn	polyphosphoinositide
PtdIns	phosphatidylinositol
PTEN	phosphatase and tensin homolog deleted on chromosome 10
RNP	ribonucleoprotein
SAP30	sin3A-associated protein 30
SAP30L	human SAP30-like protein
SF-1	steroidogenic factor-1
SHIP	src homology 2 (SH2) domain containing inositol phosphatase
TAF3	transcription initiation factor TFIID subunit 3
Topo IIα	DNA topoisomerase IIα
UBF	upstream binding factor
UHRF1	ubiquitin-like PHD and RING finger domain-containing protein 1

Since the 1950s when the PPIn cycle was discovered, research efforts have focused on the biochemical and functional characterisation of PPIn located at the plasma membrane and further on organelle membranes. It took at least another decade before the first studies demonstrated the existence of phospholipids (Manzoli *et al.*, 1977; Rose and Frenster, 1965) and then of PPIn within the confines of the nucleus, *i.e.* separate from the nuclear envelope (Cocco *et al.*, 1987; Payrastre *et al.*, 1992). Indeed, not only were PPIn detected in nuclei stripped of their nuclear envelope, but also their levels changed upon the addition of different cell stimuli (Clarke *et al.*, 2001; Cocco *et al.*, 1989; Divecha *et al.*, 1991). Since then, evidence has accumulated to detail the localisation of PPIn and the identification of effector proteins in the nucleus. This led to the recognition of PPIn being instrumental in a number of different nuclear processes such as splicing and chromatin remodelling (see recent reviews (Barlow *et al.*, 2010; Davis *et al.*, 2015; Fiume *et al.*, 2012; Hamann and Blind, 2018; Martelli *et al.*, 2011; Shah *et al.*, 2013)). Identifying which effector proteins these PPIn interact with and understanding their mode of interaction are key to deciphering the functions of these lipids in the nucleus. This review focuses on these two aspects.

2. Nuclear polyphosphoinositides and their metabolic enzymes

All PPIn, except PtdIns(3,5)P_2, have been detected in the nucleus by using different approaches (Table 1 and reviewed in (Fiume *et al.*, 2012; Shah *et al.*, 2013)). PtdIns3*P* has been detected in nuclei by the use of a specific probe consisting of two FYVE (Fab1p, YOTB, Vac1p and EEA1) domains and electron microscopy (Gillooly *et al.*, 2000). Mass levels of nuclear PtdIns4*P*, PtdIns5*P* and PtdIns(4,5)P_2 have been measured by radiolabelling (Clarke *et al.*, 2001). PtdIns(4,5)P_2 has also been identified in the nucleus using a PtdIns(4,5)P_2 specific probe, the pleckstrin homology (PH) domain of phospholipase C (PLC) δ1 combined with electron microscopy (Watt *et al.*, 2002). In addition, using immunostaining, PtdIns(4,5)P_2 was detected in nuclear speckles along with mRNA-processing components, in the newly described nuclear lipid islets as well as in nucleoli but as a minor detectable pool (Boronenkov *et al.*, 1998; Osborne *et al.*, 2001; Sobol *et al.*, 2013; Sobol *et al.*, 2018; Yildirim *et al.*, 2013). Using either a specific PtdIns(3,4,5)P_3 probe (the PH domain of general receptor of phosphoinositides 1) or antibodies, PtdIns(3,4,5)P_3 was shown to localise to the nucleoplasm and nucleolus (Karlsson *et al.*, 2016; Kumar *et al.*, 2010; Kwon *et al.*, 2010; Lindsay *et al.*, 2006).

Consistently, several PPIn metabolising enzymes are present in the nucleus, notably in discrete sub-nuclear areas common to the localisation of their respective PPIn substrate and/or product (Table 2 and Fig. 1B). In particular, strong evidence shows the presence of a PPIn metabolic cycle in nuclear speckles (alias inter chromatin granule clusters), hubs of mRNA processing in association with transcriptional events (Spector and Lamond, 2011) and the nucleolus, the ribosome factory (Pederson, 2011). The type III PtdIns4Kα and β isoforms, generating PtdIns4*P*, have been detected in nucleoli and nuclear speckles respectively (Kakuk *et al.*, 2006, 2008; Szivak *et al.*, 2006). The β form, in particular, was found in nuclear speckles when phosphorylated on Serine 496 or Threonine 504, while the Serine 294 phosphorylated enzyme is present on the Golgi (Szivak *et al.*, 2006). The type I phosphatidylinositol phosphate kinase (PIPKIα), which phosphorylates PtdIns4*P* to generate PtdIns(4,5)P_2, has also been found in the nucleolus in G1/S phase and shown to affect rRNA gene silencing through its physical association with H3K9me3 and heterochromatin protein 1α (Chakrabarti *et al.*, 2015). PIPKIα as well as PIPKIγ isoform 4, localise to nuclear speckles (Boronenkov *et al.*, 1998; Mellman *et al.*, 2008; Schill and

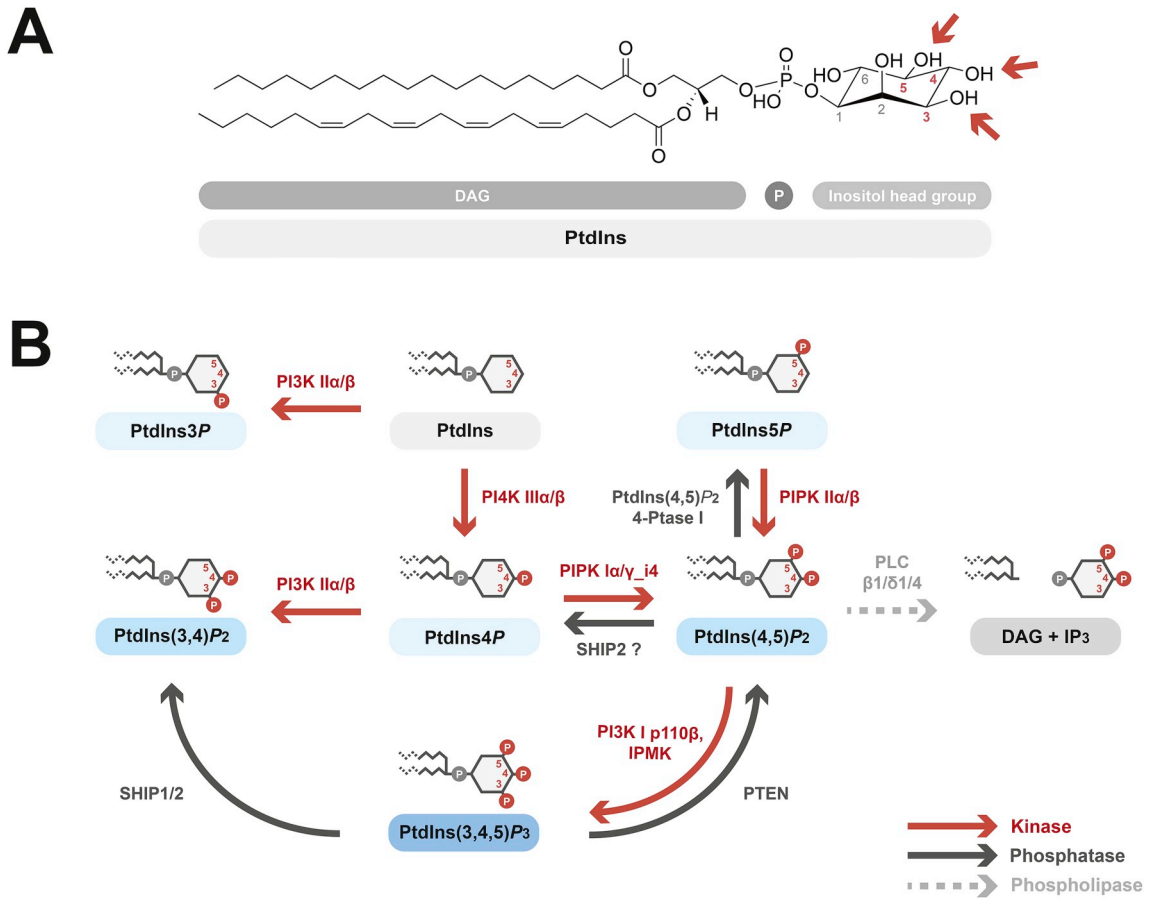

Fig. 1. Nuclear polyphosphoinositide metabolism. **A)** Phosphatidylinositol (PtdIns) structure PI(18:0/20:4 (5Z,8Z,11Z, 14Z)) downloaded from the LIPID MAPS structure database (LM ID: LMGP06010010) (Fahy *et al.*, 2009; Sud *et al.*, 2007). Hydroxyl groups that are sites of phosphorylation on the inositol head group are indicated with arrows and carbon atom numbers are shown in red. **B**) Nuclear polyphosphoinositide cycle. Polyphosphoinositide kinases and phosphatases as well as phospholipases known to reside in the nucleus are shown (see also Table 2). Abbreviations: 4-Ptase: 4-phosphatase, DAG: diacylglycerol, IP_3: inositol 1,4,5-trisphosphate, IPMK: inositol polyphosphate multikinase, P: phosphate group, PI3K: phosphoinositide 3-kinase, PI4K: phosphatidylinositol 4-kinase, PIPK: phosphatidylinositol phosphate kinase, PLC: phospholipase C, PTEN: phosphatase and tensin homolog deleted on chromosome 10, SHIP: src homology 2 (SH2) domain containing inositol phosphatase.

Table 1
Nuclear localisation of polyphosphoinositides.

PPIn	Sub-nuclear localisation (References)
PtdIns3*P*	Nucleolus (Gillooly *et al.*, 2000)
PtdIns4*P*	Nucleus (Clarke *et al.*, 2001; Kalasova *et al.*, 2016; Vann *et al.*, 1997)
	Nucleolus (Kalasova *et al.*, 2016)
PtdIns5*P*	Nucleus and chromatin enriched fraction, detected upon stress induction (Clarke *et al.*, 2001; Jones *et al.*, 2006)
PtdIns(3,4)P_2	Nuclear membrane (Watt *et al.*, 2004; Yokogawa *et al.*, 2000)
PtdIns(4,5)P_2	Interchromatin granules/Nuclear speckles (Boronenkov *et al.*, 1998; Osborne *et al.*, 2001)
	Nucleolus (Kalasova *et al.*, 2016; Osborne *et al.*, 2001; Sobol *et al.*, 2013; Yildirim *et al.*, 2013)
	Nuclear lipid islets (Sobol *et al.*, 2018)
PtdIns(3,4,5)P_3	Nuclear matrix (Kumar *et al.*, 2010; Kwon *et al.*, 2010; Lindsay *et al.*, 2006)
	Nucleolus (Karlsson *et al.*, 2016)

Anderson, 2009). These studies are consistent with the possible detection of PtdIns4*P* in nucleoli as well as nuclear speckles, as reported by Kalasova *et al.*, although no markers were used in the study (Kalasova *et al.*, 2016). In addition, the type II PIPKα and β, which phosphorylate PtdIns5*P* to generate PtdIns(4,5)P_2, are also present in nuclear speckles (Boronenkov *et al.*, 1998). PLCβ1, which metabolises PtdIns(4,5)P_2 to diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP_3), has also been found in the nucleus and in particular in nuclear speckles (Manzoli *et al.*, 1995; Martelli *et al.*, 1992; Tabellini *et al.*, 2003). Other isoforms are also known to be nuclear, such as PLCδ1 and δ4 (Kunrath-Lima *et al.*, 2018; Okada *et al.*, 2010). Finally, consistent with the presence of a PtdIns(3,4,5)

Table 2
Nuclear PPIn-metabolising enzymes, their substrates and nuclear localisation.

Nuclear PPIn kinases		
Enzyme	Substrate	Sub-nuclear localisation (References)
Type IIIα PI4K PI4K230	PtdIns	Nucleolus (Kakuk *et al.*, 2006, 2008)
Type IIIβ PI4K PI4K92	PtdIns	Nucleus (de Graaf *et al.*, 2002) > Nuclear speckles (Szivak *et al.*, 2006)
Type Iα PIPK	PtdIns4*P*	Nuclear speckles (Boronenkov *et al.*, 1998; Mellman *et al.*, 2008) Nucleolus (Chakrabarti *et al.*, 2015)
Type Iγ PIPK_i4	PtdIns4*P*	Nuclear speckles (Schill and Anderson, 2009)
Type IIα PIPK	PtdIns5*P*	Nucleus (Bultsma *et al.*, 2010) Nuclear speckles (Boronenkov *et al.*, 1998)
Type IIβ PIPK	PtdIns5*P*	Nucleus (Bultsma *et al.*, 2010; Ciruela *et al.*, 2000)
Class I PI3K, p110β	PtdIns(4,5)P_2	Nucleoplasm, chromatin, double stranded break foci (Kumar *et al.*, 2010, 2011; Marques *et al.*, 2009) Nucleolus (Karlsson *et al.*, 2016)
IPMK	PtdIns(4,5)P_2	Nucleus (Resnick *et al.*, 2005)
Class IIα PI3K	PtdIns, PtdIns4*P*	Nuclear speckles (Didichenko and Thelen, 2001)
Class IIβ PI3K	PtdIns, PtdIns4*P*	Nuclear matrix (Sindic *et al.*, 2001) Nuclear lamina (Banfic *et al.*, 2009)
Nuclear PPIn phosphatases		
Enzyme	Substrate	Sub-nuclear localisation (References)
PTEN	PtdIns(3,4,5)P_3	Nucleus (Deleris *et al.*, 2003; Shen *et al.*, 2007; Song *et al.*, 2008) Nucleolus (Li *et al.*, 2014), PTENβ (Liang *et al.*, 2017)
SHIP1	PtdIns(3,4,5)P_3	Nucleolus (Ehm *et al.*, 2015)
SHIP2	PtdIns(3,4,5)P_3 or PtdIns(4,5)P_2?	Nuclear speckles (Deleris *et al.*, 2003; Elong Edimo *et al.*, 2011)
Type I PtdIns(4,5)P_2 4-phosphatase	PtdIns(4,5)*P*2	Translocates to the nucleus upon cell stress (Zou *et al.*, 2007)
Nuclear phospholipase C		
Enzyme	Substrate	Sub-nuclear localisation (References)
PLCβ1	PtdIns(4,5)P_2	Nuclear speckles (Tabellini *et al.*, 2003)
PLCδ1	PtdIns(4,5)P_2	Nucleus (Okada *et al.*, 2010)
PLCδ4	PtdIns(4,5)P_2	Nucleus (Kunrath-Lima *et al.*, 2018)

Abbreviations: IPMK: inositol polyphosphate multikinase, PI3K: phosphoinositide 3-kinase, PI4K: phosphatidylinositol 4-kinase, PIPK: phosphatidylinositol phosphate kinase, PLC: phospholipase C, PPIn: polyphosphoinositide, PtdIns: phosphatidylinositol, PTEN: phosphatase and tensin homolog deleted on chromosome 10, SHIP: src homology 2 (SH2) domain containing inositol phosphatase.

P_3 pool in the nucleus and nucleolus, enzymes generating (class IA phosphoinositide 3-kinase (PI3K) p110β) or metabolising PtdIns (3,4,5)P_3 (phosphatase and tensin homolog deleted on chromosome 10 (PTEN) and src homology 2 (SH2) domain containing inositol phosphatase (SHIP) 1/2) have been detected in the nucleus. In particular, the PI3K catalytic subunit p110β harbours a nuclear

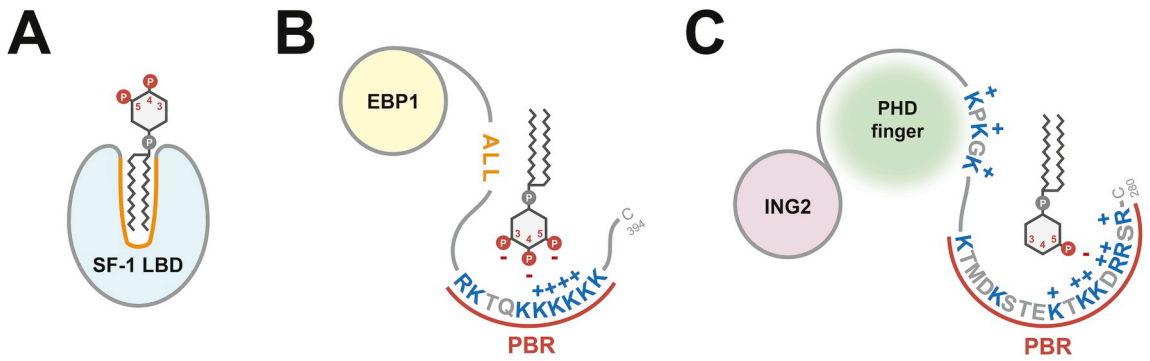

Fig. 2. Modes of protein interaction with polyphosphoinositides in the nucleus. Schematic representation of different modes of PPIn interaction in the following nuclear proteins in **A)** ligand binding domain (LBD) of steroidogenic factor-1 (SF-1) shielding the acyl chains of a representative PPIn (Blind *et al.*, 2014), **B)** Erbb3 binding protein-1 (EBP1) showing the human sequence of the C-terminal unstructured region including the K/R motif (Karlsson *et al.*, 2016) and **C)** Inhibitor of growth 2 (ING2), showing the human sequence of the plant homeodomain (PHD) with the polybasic region (PBR) (Gozani *et al.*, 2003; Huang *et al.*, 2007). Hydrophobic regions/interactions are indicated in orange. Basic residues are shown in blue. Basic residues which have been mutated and implicated in binding are indicated with +. Illustrations are not drawn to scale.

localisation signal (NLS) and was shown to be important for DNA replication, DNA repair and cell survival (Kumar *et al.*, 2010, 2011; Marques *et al.*, 2009). However, some of the reported nuclear functions of p110β have been shown to be kinase-independent (Kumar *et al.*, 2010; Marques *et al.*, 2009). Regarding a possible nucleolar role for p110β, one study showed that p110 (likely β) interacts, phosphorylates and activates the ribosomal DNA transcription factor, upstream binding factor (UBF), in the nucleus upon insulin growth factor-1 stimulation (Drakas *et al.*, 2004). This study did not however evaluate the lipid kinase activity of p110(β). Alternatively, inositol polyphosphate multikinase (IPMK), found in the nucleus, has PI3K activity (Maag *et al.*, 2011; Resnick *et al.*, 2005) and was shown to phosphorylate PtdIns(4,5)P_2-bound to steroidogenic factor-1 (SF-1) to PtdIns(3,4,5)P_3 (Blind *et al.*, 2012). The phosphatases PTEN and SHIP1/2, which dephosphorylate PtdIns(3,4,5)P_3 to produce PtdIns(4,5)P_2 and PtdIns(3,4)P_2 respectively, are also present in the nucleus (Deleris *et al.*, 2003; Ehm *et al.*, 2015; Elong Edimo *et al.*, 2011; Shen *et al.*, 2007). SHIP2 has been found in nuclear speckles when phosphorylated on Serine 132 and suggested to use PtdIns(4,5)P_2 as a substrate rather than PtdIns(3,4,5)P_3 *in vivo* (Deleris *et al.*, 2003; Elong Edimo *et al.*, 2011). The nuclear roles of PTEN are thought to be either dependent (Liu *et al.*, 2005) or independent of its lipid phosphatase activity (Lindsay *et al.*, 2006; Shen *et al.*, 2007; Song *et al.*, 2011). PTEN has also been found in promyelocytic leukaemia protein (PML) bodies, at the centromere and in nucleoli (Li *et al.*, 2014; Shen *et al.*, 2007; Song *et al.*, 2008). The class II PI3Ks α and β, which can produce PtdIns3*P* or PtdIns(3,4)P_2, are found in nuclear speckles or in the nuclear matrix in association with lamin A/C, respectively (Banfic *et al.*, 2009; Didichenko and Thelen, 2001; Sindic *et al.*, 2001).

One fundamental question about the presence of PPIn within the nucleus is how their hydrophobic tails are shielded from the aqueous environment. Although our understanding of the biophysical nature of these PPIn in the nucleus remains incomplete, several possibilities have been proposed. Recent elegant structural studies demonstrated the acyl chains to be buried in the hydrophobic ligand binding pocket of the nuclear receptors (NR) SF-1/NR5A1 ((Blind *et al.*, 2012, 2014), as represented in Fig. 2A) and liver receptor homolog-1 (LRH-1/NR5A2) (Sablin *et al.*, 2015), allowing the exposure of the inositol head group to the action of PPIn kinases and phosphatases (Blind *et al.*, 2012). Alternatively, the formation of micelles, perhaps with the abundant nuclear phospholipid phosphatidylcholine (Hunt *et al.*, 2001), has been suggested but not demonstrated so far (Barlow *et al.*, 2010; Irvine, 2006). Recently, a new type of nuclear structure referred to as nuclear lipid islets (NLIs) has been described as PtdIns(4,5)P_2 nuclear aggregates, possibly in the form of micelles with acyl chains facing inwards (Sobol *et al.*, 2018; Sztacho *et al.*, 2019). These structures are suggested to serve as platforms for RNA polymerase II (pol II) as an integral part for mRNA pol II transcription. Lipid droplets have also been documented in the nucleus (Layerenza *et al.*, 2013) as well as in expansions of the inner nuclear membrane (Romanauska and Kohler, 2018) and may act as reservoir of PPInin their monolayer. In whatever physico-chemical structure PPIn may be found in the nucleus, another issue is still unanswered: how is PtdIns transferred from its site of synthesis in the endoplasmic reticulum to the nucleus for the local action of PPIn kinases and phosphatases? Answering this question will in no doubt give the field of nuclear PPIn greater recognition.

3. Nuclear polyphosphoinositide functions

Elucidating interaction partners for nuclear PPIn is fundamental to understanding the role they play in the nucleus. Several studies have begun to shed light on nuclear PPIn effector proteins and the influence PPIn have on diverse key nuclear processes.

3.1. Nuclear PPIn in chromatin remodelling and gene transcription

PPIn have been linked to several aspects of chromatin remodelling and regulation of gene transcription. PPIn modulating the interaction of PPIn-binding proteins with chromatin is one potential mechanism by which PPIn influence these processes (Viiri *et al.*, 2012). Some of these interactions are regulated via PtdIns5*P*, which although normally found at low levels in cells, increases in the nucleus in response to different types of cellular stress (Clarke *et al.*, 2001; Jones *et al.*, 2006; Zou *et al.*, 2007). PtdIns5*P* binds to several nuclear proteins involved in chromatin remodelling harbouring a plant homeodomain (PHD)-type zinc finger. PHD zinc fingers can bind to methylated lysines in histone tails while other parts of the protein can recruit chromatin-remodelling complexes (Sanchez and Zhou, 2011). One of these proteins is the histone code reader, inhibitor of growth protein 2 (ING2), a component of the transcriptional co-repressor Sin3a-histone deacetylase 1 (HDAC1) complex (Bua *et al.*, 2013; Gozani *et al.*, 2003). PtdIns5*P* contributes to the localisation of ING2 in the nucleus where it associates with the chromatin (Gozani *et al.*, 2003; Jones *et al.*, 2006). This is indeed counteracted by the overexpression of the type II PtdIns5*P* 4-kinase β, which decreases the levels of PtdIns5*P*. Overexpression of ING2 induces p53 acetylation and p53-dependent induction of apoptosis and this activity was shown to be dependent upon an intact PPIn-binding motif (Gozani *et al.*, 2003; Zou *et al.*, 2007). In response to etoposide-induced DNA damage in particular, PtdIns5*P* was demonstrated to be required for the association of ING2 with target gene promoters leading to their transcriptional repression (Bua *et al.*, 2013). Interaction of all three mono-phosphorylated PPIn with the co-repressor sin3A-associated protein 30-like (SAP30L) was reported to decrease its association with chromatin *in vitro* and to reduce its transcriptional repression activity (Viiri *et al.*, 2009). Association of the basal transcription initiation factor TFIID subunit 3 (TAF3) with PPIn, including PtdIns5*P*, was shown to be required for TAF3-regulated gene transcription necessary for muscle differentiation (Stijf-Bultsma *et al.*, 2015). In plants, the extended PHD finger of *Arabidopsis* homolog of trithorax ATX1 binds selectively to PtdIns5*P*, which leads to its translocation from the nucleus to the cytoplasm, and a decrease in the transcriptional activity of ATX1 (Alvarez-Venegas *et al.*, 2006; Ndamukong *et al.*, 2010). Furthermore, interaction of Ubiquitin-like PHD and RING finger domain-containing protein 1 (UHRF1) with PtdIns5*P* leads to a conformational change allowing binding of UHRF1 to H3K9me3 (Gelato *et al.*, 2014).

Other nuclear factors are influenced by PtdIns(4,5)P_2. The role of this PPIn is associated with chromatin remodelling as it allows the retention of BRG1, a component of the SWI/SNF-like BRG/BRM-associated factors (BAF) chromatin-remodelling complex in the

nucleus and in particular on the chromatin (Zhao *et al.*, 1998). PtdIns(4,5)P_2 binds to a basic motif in the C-terminal part of BRG1 and enhances actin filament binding (Rando *et al.*, 2002). The functional consequence of this interaction is, however, not clear. What is known is that actin plays roles in transcription (Visa and Percipalle, 2010) and may hence influence the action of the BAF complex, and this, in turn, may be regulated by PtdIns(4,5)P_2.

Association of the myristoylated corepressor brain acid soluble protein 1 (BASP1) with PtdIns(4,5)P_2 is a requisite for HDAC1 binding at gene promoters regulated by Wilms' tumour 1 protein, and the subsequent repression of these genes (Toska *et al.*, 2012). The nuclear receptors SF-1 (Blind *et al.*, 2014) and LRH-1 (Sablin *et al.*, 2015) interact with PPIn via their hydrophobic ligand-binding pockets while leaving the inositol head group exposed to possible modification (Fig. 2A). Interestingly, the phosphorylation status of the PPIn associated with SF-1 has been shown to be critical for transcriptional activity, with phosphorylation of PtdIns(4,5)P_2 to PtdIns(3,4,5)P_3 by IPMK associated with higher transcriptional activity and dephosphorylation by PTEN to PtdIns(4,5)P_2 with reduced activity (Blind *et al.*, 2012). Alternatively, histones H1 and H3 themselves have also been identified as PtdIns(4,5)P_2-binding proteins and PtdIns(4,5)P_2 was identified to interacte with the C-terminal of H1 (Yu *et al.*, 1998). The authors further demonstrate that PtdIns(4,5)P_2 can alleviate the inhibition of mRNA pol II transcription imposed by H1 *in vitro*. Most recently, Choi *et al.* have shown that both nuclear PtdIns(4,5)P_2 and PIPKIα interact with the tumour suppressor p53, which increases its stability during cellular stress (Choi *et al.*, 2019).

3.2. PPIn in nucleolar processes

Several PPIn species have been detected in the nucleolus, including PtdIns3*P*, PtdIns(4,5)P_2, PtdIns(3,4,5)P_3 and perhaps also PtdIns4*P* (Gillooly *et al.*, 2000; Kalasova *et al.*, 2016; Karlsson *et al.*, 2016; Osborne *et al.*, 2001; Sobol *et al.*, 2013; Yildirim *et al.*, 2013). PtdIns(4,5)P_2 was shown to bind to RNA pol I and to be necessary for transcription at the rDNA promoter (Yildirim *et al.*, 2013). In addition, PtdIns(4,5)P_2 binds both to UBF and fibrillarin, which resulted in a reduction of binding of UBF to rDNA and altered mobility of the fibrillarin/snRNA complex, suggesting a possible competitive mode of action. Furthermore, PtdIns(4,5)P_2 engages with Pol I subunits and UBF during mitosis and co-localisation is maintained even when Pol I or II transcription is inhibited, suggesting that PtdIns(4,5)P_2 is part of the nucleolar organising region (NOR) complex of which the organisation is cell cycle dependent (Sobol *et al.*, 2013). Recently, PtdIns(4,5)P_2 has been shown to regulate the levels of H3K9me2 at the rDNA promoter by binding to and inhibiting the activity of the histone lysine demethylase PHD finger protein 8 (PHF8), likely resulting in a reduction in rRNA gene transcription (Ulicna *et al.*, 2018). Consistent with these studies showing a role for PtdIns(4,5)P_2 in nucleolar processes, PIPKIα, one of the PPIn kinases generating PtdIns(4,5)P_2 using PtdIns4*P*, was found in the nucleolus in the G1/S phase of the cell cycle (Chakrabarti *et al.*, 2015). PIPKIα associates with H3K9me3 and plays roles in rDNA gene silencing. Whether or not the action of PIPKIα is due to its lipid kinase acitivty was not investigated, but in light of the study of Ulicna *et al.*, this mechanism would be worth exploring.

3.3. Nuclear PPIn and cell survival

Nuclear PI3K activity and PtdIns(3,4,5)P_3 have been shown to mediate the anti-apoptotic response to nerve growth factor (NGF) together with the effector protein, nucleophosmin (alias B23) (Ahn *et al.*, 2004, 2005). Upon the addition of NGF, PtdIns(3,4,5)P_3 regulates the interaction of nucleophosmin with caspase-activated DNase (CAD), thereby preventing its nuclease activity and DNA fragmentation (Ahn *et al.*, 2005). The interaction between PtdIns(3,4,5)P_3 and nucleophosmin in particular was required for the prevention of cell death. Additionally, nucleophosmin associates with active Akt in the nucleus following NGF stimulation, which increases its stability and enhances cell survival (Lee *et al.*, 2008). The GTPase phosphatidylinositol 3 (PI3)-kinase enhancer (PIKE)-L (now known as Arf-GAP with GTPase, ANK repeat and PH domain-containing protein 2), is another nuclear protein which binds to PtdIns(3,4,5)P_3, and contributes to cell survival through activation of PI3K and Akt (Hu *et al.*, 2005).

3.4. PPIn in mRNA processing and export

Nuclear speckles (also known as interchromatin granule clusters) are nuclear hubs in which pre-mRNA splicing factors congregate, but also contain a variety of other proteins (Galganski *et al.*, 2017; Spector and Lamond, 2011). Localisation of PtdIns(4,5)P_2 to nuclear speckles was evident with its co-detection with speckle markers such as the splicing factor SC-35 or Sm proteins (Boronenkov *et al.*, 1998; Osborne *et al.*, 2001). Nuclear PtdIns(4,5)P_2 interacts with components of small nuclear ribonucleoproteins (RNP), the hyperphosphorylated form of the large subunit of RNA pol II and U1-U6 snRNAs (Osborne *et al.*, 2001). The same study also showed that its immunodepletion inhibited splicing of pre-mRNAs *in vitro*. Other nuclear speckle-associated proteins are also known to interact with PPIn. Aly (alias THO complex subunit 4), for example, can associate with PtdIns(4,5)P_2 and PtdIns(3,4,5)P_3 and mutation of key basic residues prevented PtdIns(3,4,5)P_3-binding and reduced Aly-mediated mRNA export activities and cell proliferation (Okada *et al.*, 2008). Moreover, PtdIns(3,4,5)P_3, produced by IPMK, was shown to regulate Aly-mediated recognition of specific mRNAs for nuclear export, particularly for those involved in homologous recombination DNA repair (Wickramasinghe *et al.*, 2013). Furthermore, a study searching for nuclear proteins interacting with the nuclear PIPKIα, identified the non-canonical poly(A) polymerase called nuclear speckle targeted PIPKIα regulated-poly(A) polymerase (Star-PAP), and showed that PtdIns(4,5)P_2 directly stimulates the polyadenylation activity of target mRNAs (Mellman *et al.*, 2008). Further studies from the same group demonstrated that casein kinase Iα (CKIα), which is also PtdIns(4,5)P_2-sensitive, is part of the Star-PAP complex together with PIPKIα and can regulate Star-PAP activity targeting the 3′-end mRNA processing of select mRNAs (Gonzales *et al.*, 2008).

Collectively, these studies clearly demonstrate the far-reaching influence that PPIn have on nuclear events via their interaction with an array of different effector proteins.

4. Mapping polyphosphoinositide-protein interactomes to understand their function

4.1. PPIn interactomic studies

To globally capture PPIn binding proteins, multiple studies have taken a proteomic approach ((Best, 2014; D'Santos and Lewis, 2012) and listed in Table 3). Affinity matrices containing synthetic PPIn followed by mass spectrometric fingerprinting have been used to isolate PtdIns(3,4,5)P_3-binding proteins in pig leukocytes (Krugmann *et al.*, 2002). A chemical proteomics method using cleavable lipid baits has also been used in macrophage whole cell extracts to identify mostly PtdIns(3,4)P_2 interacting proteins (Pasquali *et al.*, 2007). Other studies using PPIn pull downs to identify interacting proteins included bifunctional activity-based probes. In this approach, target proteins were labelled using PPIn head groups containing both a photo affinity tag to bind the proteins and a secondary tag for analysis (Rowland *et al.*, 2011). With the advancement of mass spectrometry, more quantitative methods have been employed. Bead immobilized or liposomes incorporated PPIn have been used to identify PtdIns3*P*, PtdIns(3,5)P_2, PtdIns(4,5)P_2 and PtdIns(3,4,5)P_3 target proteins in colorectal carcinoma cytosolic extracts (Catimel *et al.*, 2008, 2009, 2013). To discriminate specific PPIn binders from background proteins, quantitative approaches such as stable isotope labelling by amino acids in cell culture (SILAC) have been employed (Dixon *et al.*, 2011; Jungmichel *et al.*, 2014; Lewis *et al.*, 2011). Alternative strategies include the analysis of yeast cDNA libraries combined with FACS-dependent identification of fluorescent PPIn binding clones for the identification of PtdIns(4,5)P_2 and PtdIns(3,4,5)P_3 binding proteins (Bidlingmaier *et al.*, 2011).

4.2. Nuclear PtdIns(4,5)P_2 interactome

To map the nuclear PPIn-protein interaction networks, we established an approach allowing the enrichment of nuclear PPIn-interacting proteins by incubating nuclei with the polyamine neomycin (Lewis *et al.*, 2011). Due to the high affinity of neomycin for PPIn via electrostatic interactions (Gabev *et al.*, 1989; Schacht, 1976, 1978, 1979), neomycin was predicted to compete with proteins for binding to PPIn. By incubating isolated nuclei with neomycin, PPIn-binding proteins were displaced, allowing their collection and identification by quantitative mass spectrometry. Using this approach, 349 proteins specifically displaced by neomycin from intact nuclei were identified with enriched functions in DNA topological change, nucleosome positioning/assembly, chromatin assembly, ribosome biogenesis, rRNA processing, mRNA splicing and processing (Lewis *et al.*, 2011). Amongst them, a few known PPIn-effector proteins were identified such as Aly (Okada *et al.*, 2008), histone H1 (Yu *et al.*, 1998) and nucleophosmin (Ahn *et al.*, 2005) as well as several speckle-associated proteins with RNA splicing functions (Osborne *et al.*, 2001). However, many of the neomycin-displaced proteins had no previous history as nuclear PPIn-effector proteins and presented potentially novel roles for nuclear PPIn. PPIn

Table 3
PPIn interactomics studies.

PPIn interactome analysed	Method	Cell type/subcellular compartment	Reference
PtdIns(3,4,5)P_3	PPIn conjugated beads and MS	Pig leukocyte cytosolic extract	(Krugmann *et al.*, 2002)
Mostly PtdIns(3,4)P_2	PPIn conjugated to cleavable S-S bond biotin + streptavidin beads and MS	Primary macrophage cytosolic extract	(Pasquali *et al.*, 2007)
PtdIns(4,5)P_2	Biotinylated PPIn, streptavidine conjugated beads and MS	Secretory granules from bovine adrenal chromaffin cells	(Osborne *et al.*, 2007)
PtdIns(3,5)P_2 & PtdIns (4,5)P_2	PPIn conjugated beads or liposomes and MS	LIM1215 colon cancer cell cytosolic extract	(Catimel *et al.*, 2008)
PtdIns(3,4,5)P_3	PPIn conjugated beads or liposomes and MS	LIM1215 colon cancer cell cytosolic extract	(Catimel *et al.*, 2009)
PtdIns(4,5)P_2	PPIn conjugated beads and quantitative MS	Neomycin extracted nuclear proteins isolated from murine erythroleukemia cells	(Lewis *et al.*, 2011)
PtdIns(3,4)P_2	Stimulation of class I PI3K ± wortmannin, biotinylated PPIn coupled to streptavidin beads and SILAC-based quantitative MS	1321N1 astrocytoma membrane fractions	(Dixon *et al.*, 2011)
PtdIns(4,5)P_2 and PtdIns(3,4,5)P_3	yeast surface-displayed human protein fragment libraries + fluorescent PPIn	N/A	(Bidlingmaier *et al.*, 2011)
PtdIns(3,4,5)P_3	PPIn activity probe for click chemistry and MS	MDA-MB-435 cancer cell cytosolic extract	(Rowland *et al.*, 2011)
PtdIns3*P*	PPIn conjugated beads or liposomes and MS	LIM1215 colon cancer cell cytosolic, membrane and nuclear extracts	(Catimel *et al.*, 2013)
All PPIn	Triple SILAC-based quantitative MS	HeLa S3 whole cell extract	(Jungmichel *et al.*, 2014)

Table updated from (D'Santos and Lewis, 2012). SILAC: stable isotope labeling by amino acids in cell culture; MS: mass spectrometry; N/A: not applicable.

binding of DNA topoisomerase IIα (Topo IIα), for example, was validated and an inhibitory effect of PPIn on kDNA decatenation activity was demonstrated, suggesting a role for PPIn in the regulation of DNA topological changes (Lewis *et al.*, 2011). Other neomycin-extracted proteins were subsequently verified to interacte with PPIn and include Erbb3 binding protein-1 (EBP1, alias proliferation-associated protein 2G4, PA2G4) (Karlsson *et al.*, 2016), PHF8 (Ulicna *et al.*, 2018) and UHRF1 (Gelato *et al.*, 2014). Additionally, neomycin extracts were subjected to quantitative interactomics following PtdIns(4,5)P_2 lipid-pull down and this led to the identification of 34 PtdIns(4,5)P_2-binding proteins, 28 of which were annotated to the nucleus, and known to be involved in mRNA transcription regulation, mRNA splicing and protein folding/complex assembly (Lewis *et al.*, 2011). Two of these proteins were subsequently found common to the PtdIns(4,5)P_2-binding proteins identified by the PPIn interactomics study by Jungmichel *et al.* (2014),*i.e.* Elongation factor 1-delta and TBC1 domain family member 24.

5. Nuclear polyphosphoinositide-protein modes of interaction – polybasic regions lead the way

5.1. Diverse modes of interactions for PPIn-binding proteins

Proteins interact with PPIn via domains of diverse structure and PPIn binding specificities and affinities. They include the

Table 4
Polybasic motifs involved in polyphosphoinositide-protein interaction.

Actin-binding and membrane-binding proteins			
Sequence	Protein	Motif type	Reference
135-K**S**GL**K**Y**KK** 161-**K**LFQV**K**G**RR**	Gelsolin	K/R	(Yu *et al.*, 1992)
139-**K**LYQV**K**G**KK**	gCap39[a]	K/R	(Yu *et al.*, 1990, 1992)
112-**K**QGLVI**RK**	Villin	K/R	(Bazari *et al.*, 1988; Kumar *et al.*, 2004)
138-**R**LLHV**K**G**KR** 816-**K**QQNL**KKE**K			
13-**K**VFNDM**K**V**RK**	Cofilin	K/R	(Matsuzaki *et al.*, 1988; Yu *et al.*, 1992)
127-**K**CYEMAS**H**L**RR**	Profilin I	K/R-like	(Lassing and Lindberg, 1985; Skare and Karlsson, 2002; Lambrechts *et al.*, 2002)
151-**KKKKKR**FSF**KK**SF**K**LSGFSF**KK**N**KK**	MARCKS	K/R-like	(Wang *et al.*, 2001)
30-**K**AH**K**AATK**I**QASF**R**GHIT**RKKLK**GE**KK**	GAP43[b]	K/R-like	(Laux *et al.*, 2000)
183-**KE**K**KK**G**K**A**KKKR**LT**K**	N-WASP	PBR	(Papayannopoulos *et al.*, 2005)
Nuclear PPIn-binding proteins			
Sequence	Protein	Motif type	Reference
105-RRKKREQKK	Pf1	K/R, PBR	(Kaadige and Ayer, 2006)
123-RNRRKRK	SAP30	PBR	(Viiri *et al*, 2009)
85-RNK**RKR**K	SAP30L	PBR	(Viiri *et al*, 2009)
264-KTMDKSTE**K**T**KK**D**RRSR**	ING2	PBR	(Gozani *et al.*, 2003)
1-60 region including a polybasic motif[c]	BASP1 (alias NAP-22)	PBR	(Terashita *et al.*, 2002)
641-RTGKGKW**KRKS**AGGGPS	UHRF1	PBR	(Gelato *et al.*, 2014)
918-IKKD**KKH**K**KRK**HRAH	TAF3	PBR	(Stijf-Bultsma *et al.*, 2015)
27-**RGRGR** and 79-**RP**K	Aly	RG motif	(Okada *et al.*, 2008)
65-**KKE**K**E**MKK	EBP1[d]	Reverse K/R	(Karlsson *et al.*, 2016)
364-RKTQ**KKKKK**K	EBP1[d]	K/R	
PHD-BRD linker[e]	BAZ2B	K/R	(Kostrhon *et al.*, 2017)
827-**KSRPKKKK**	PHF8	K/R, PBR	(Ulicna *et al.*, 2018)
K194,K200 and **K228,K234**	NPM	PBR?	(Ahn *et al.*, 2005)
981-**KK**VRGKVWKQRISSPLFNTK	OGT	Reverse K/R	(Yang *et al.*, 2008)
1402-EEVRQKKSSRKRKRDS	BRG1	K/R, PBR	(Rando *et al.*, 2002)
370-**KSKK**GQSTS**RHKK**	p53	PBR	(Choi *et al.*, 2019)

Basic residues in bold indicate residues shown to be required for PPIn interaction. BASP1: brain acid soluble protein 1, BAZ2B: BROMO domain adjacent to zinc finger 2B, EBP1: Erb 3 binding protein-1, GAP43: Growth Associated Protein 43, ING2: inhibitor of growth protein 2, NPM: nucleophosmin, OGT: O-linked beta-N-acetylglucosamine transferase, Pf1: PHD factor 1, PHF8: PHD finger protein 8, N-WASP: neuronal Wiskott-Aldrich syndrome protein, SAP30: Sin3A-associated protein 30, SAP30L: human SAP30-like protein, TAF3: Transcription initiation factor TFIID subunit 3, UHRF1: E3 ubiquitin-protein ligase UHRF1. K/R: lysine/arginine motif following the motif K/R-(X_{3-7})-K-X-K/R—K/R, PBR-polybasic region.

[a] Recommended protein name: macrophage-capping protein.
[b] Recommended protein name: neuromodulin.
[c] The basic motif lies between aa 4–10 (1-MGG**KL**S**KKKK**GYNVN) of the first 60 aa shown to bind to PPIn.
[d] Isoform 1 also known as p48.
[e] PHD-BRD linker:1982-ASGQTL**KIKK**LHV**KGKK**TNES**KKGKK**VTLTGDTEDEDSASTSSSL**KR**GN**K**DL**KKRK**MEENTSINLSKQESFT.

following domains: PH, FYVE, PX (Phox homology), ENTH/ANTH (epsin amino-terminal homology), FERM (band 4.1, ezrin, radixin and moesin), PROPPIN and TRAF (Choy *et al.*, 2017; Hammond and Balla, 2015; Kutateladze, 2010; Pemberton and Balla, 2018). Alternatively, short polybasic PPIn-binding motifs or regions (PBR) have also been reported to interact with PPIn (Janmey *et al.*, 2018; McLaughlin and Murray, 2005; Yin and Janmey, 2003). These motifs consist of short stretches of basic amino acids, often denoted as lysine/arginine-rich patches/clusters or KR-motifs (K/R-(X_{3-7})-K-X-K/R−K/R), first identified in the actin-binding protein (ABP) gelsolin (Martin, 1998; Yu *et al.*, 1992). Gelsolin is a multifunctional protein involved in cytoskeletal remodelling by severing and capping actin filaments. This activity is regulated by PtdIns(4,5)P_2 interacting at the same site as the actin-binding site (Feng *et al.*, 2001; Yu *et al.*, 1992). KR-motifs have been identified in many PPIn-binding cytoskeletal proteins of the gelsolin family, such as gCap39, villin, cofilin and profilin and the Wiskott Aldrich syndrome protein (WASP) ((Janmey *et al.*, 2018) and Table 4). These motifs rely on electrostatic interactions between their basic residues and the negatively charged phosphate groups. In addition, hydrophobic residues can also contribute to the interaction to the acyl chains of PPIn, as shown for gelsolin and cofilin (Feng *et al.*, 2001; Gorbatyuk *et al.*, 2006; Janmey and Stossel, 1987). Some of these ABPs known to engage in PtdIns(4,5)P_2 interaction in the cytoplasm can also be found in the nucleus (reviewed in (Barlow *et al.*, 2010)). For example, profilin I, which binds to PtdIns(4,5)P_2 via two motifs, one of them overlapping with the actin binding site, is also present in nuclear speckles as well as cajal bodies, and has been implicated in mRNA splicing (Lambrechts *et al.*, 2002; Skare and Karlsson, 2002; Skare *et al.*, 2003). Other ABPs, such as N-WASP (Wu *et al.*, 2006), gCAP39 (Onoda and Yin, 1993; Onoda *et al.*, 1993), as well as cofilins (Munsie *et al.*, 2012), have also been detected in the nucleus in addition to the cytoplasm. To the best of our knowledge, the functional role(s) of the interaction with PPIn have however not been explored in the regulation of nuclear processes thought to be mediated by these proteins.

Another well characterized example of PPIn-binding motif can be found in the myristoylated alanine-rich C-kinase substrate (MARCKS) and growth-associated protein 43 (GAP43) proteins ((Laux *et al.*, 2000; Wang *et al.*, 2002) see Table 4). MARCKS and GAP43 anchor into the bilayer through an N-terminal myristate and two saturated acyl chains respectively, and bind electrostatically to a cluster of PtdIns(4,5)P_2 via a conserved effector domain, consisting of a K/R like PBR. The membrane interaction of MARCKS is regulated by phosphorylation of serine residues located within the effector domain by protein kinase C, resulting in a reduction of the electrostatic attraction between the protein and PPIn and causing MARCKS to dissociate from the plasma membrane and to translocate to the cytoplasm (McLaughlin and Murray, 2005; Ohmori *et al.*, 2000). Interestingly, MARCKS has also been detected in the nucleus due to its effector domain acting as an NLS (Rohrbach *et al.*, 2015).

Many small GTPases in the Ras and Rho families harbour C-terminal PBR consisting of four or more lysine or arginine residues, responsible for their association with the plasma membrane via PtdIns(4,5)P_2 and PtdIns(3,4,5)P_3 (Heo *et al.*, 2006). In the case of the small GTPase Rac1, the polybasic motif was demonstrated to also act as a functional NLS (Lanning *et al.*, 2003). The presence of canonical NLS sequences (K-K/R-x-K/R) in the polybasic motif of several Ras and Rho family members indicates a dual regulatory role in membrane binding and nucleo-cytoplasmic shuttling of these proteins (Williams, 2003).

5.2. Polybasic motifs as a mechanism for nuclear protein-PPIn interaction

In the case of *true* nuclear proteins, *i.e.* residing dominantly in the nucleus, only a few are known to interact with PPIn. via a structured domain. For example, basic residues in the PH domain of Tfb1 (p62), a subunit of the general transcription factor II H (TFIIH) interacts preferably with PtdIns3*P* and PtdIns5*P*, and interaction with PtdIns5*P* could potentially regulate its binding with the activation domain of VP16 due to an overlapping interaction site (Di Lello *et al.*, 2005). PtdIns(3,4,5)P_3 binding protein (PIP_3BP) binds to PtdIns(3,4,5)P_3 via two individual PH domains (Tanaka *et al.*, 1997, 1999). Consistently, in our study, only seven of the 349 proteins identified following neomycin displacement contained structured PPIn-binding domains, whereas 165 contained at least one basic PPIn-binding K/R motif (Lewis *et al.*, 2011). Furthermore, 19 of the 28 nuclear PtdIns(4,5)P_2 specific-binding proteins contained these motifs. Using mutational studies, we have subsequently verified the involvement of PBR or K/R motifs in PPIn binding in three proteins identified, namely EBP1 (Karlsson *et al.*, 2016), heterogeneous nuclear ribonucleoprotein U (hnRNP U) and Topo IIα (unpublished results). EBP1 harbours two K/R motifs, one localised in the unstructured C-terminus and a reversely orientated K/R motif in the N-terminus on a protruding loop (Table 4 (Karlsson *et al.*, 2016)). Both of these K/R motifs contributed to PPIn binding as site-directed mutations of lysine residues to alanines in both motifs were required to prevent PPIn binding of the full length protein (Karlsson *et al.*, 2016). The contribution of K/R motifs or PBRs in PPIn binding has also been demonstrated in a number of other nuclear proteins, hence underscoring the relevance of electrostatic interactions for PPIn-binding in the nucleus. These include ING2 (Bua *et al.*, 2013; Gozani *et al.*, 2003), PHD factor 1 (Pf1) (Kaadige and Ayer, 2006), SAP30L (Viiri *et al.*, 2009), UHRF1 (Gelato *et al.*, 2014), TAF3 (Stijf-Bultsma *et al.*, 2015), BAZ2B (Kostrhon *et al.*, 2017), PHF8 (Ulicna *et al.*, 2018) as well as p53 (Choi *et al.*, 2019) and all require basic residues for the interaction (see Table 4). For example, PHF8 contains two K/R motifs and one PHD, but only the most C-terminal K/R motif was found to bind to PtdIns(4,5)P_2. This binding was abolished by mutating all the lysine residues to alanine or glycine within the motif (Ulicna *et al.*, 2018). In the case of Pf1, a PBR located C-terminal of a PHD zinc finger was shown to be essential for PPIn binding while the PHD showed little contribution (Kaadige and Ayer, 2006). Basic residues have also been shown to be important for PPIn-binding in other nuclear proteins such as nucleophosmin, which binds via two lysine pairs within its C-terminus but in the absence of defined PPIn-binding motif (Ahn *et al.*, 2005). Another example is Aly, which binds via basic residues in a glycine-arginine-rich domain in its N-terminal (Okada *et al.*, 2008). O-linked beta-N-acetylglucosamine transferase (OGT), on the other hand, involves two lysines within a reverse K/R motif (Yang *et al.*, 2008).

In addition to electrostatic properties of the PBR, other features or structures can influence PPIn interaction with nuclear proteins. The contribution of hydrophobic regions is one of these features as shown in a number of nuclear PtdIns(3,4,5)P_3-binding proteins, as this permits interaction with acyl chains (Bidlingmaier *et al.*, 2011). NMR analysis of the C-terminal PBR of EBP1 showed that

hydrophobic interactions between non-polar residues upstream of the motif, particularly ^{356}ALL^{358}, and acyl chains of 16 carbons contributed to binding to PtdIns(3,4,5)P_3 in addition to electrostatic interactions ((Karlsson *et al.*, 2016), as illustrated in Fig. 2B). Consistently, a hydrophobic region upstream of the PBR is required for the ability of SAP30L to bind monophosphorylated PPIn, as the PBR alone was unable to bind PPIn unless this hydrophobic region was also present (Viiri *et al.*, 2009). In one instance, binding of the repressor BASP1 to PtdIns(4,5)P_2 requires the covalent binding of a myristoyl group within the region required for PPIn interaction (Terashita *et al.*, 2002; Toska *et al.*, 2012). Alternatively, PBR-mediated PPIn interaction can be influenced by the presence of a zinc finger of the PHD type, located N-terminal to the PBR. This is the case for ING2 as shown in Fig. 2C, as well as in ING1, ACF1 (alias BAZ1A), and TAF3, implying a common mechanism (Gozani *et al.*, 2003; Stijf-Bultsma *et al.*, 2015). Molecular modelling of the PHD-PBR of ING2 with PtdIns5*P* showed that, in at least one of the models, the PBR forms a PPIn binding pocket which encases the inositol ring while one of the acyl chains is oriented towards the PHD ((Huang *et al.*, 2007), as illustrated in Fig. 2C). The basic linker region between the PHD domain and the bromodomain of BROMO domain adjacent to zinc finger 2B (BAZ2B) interacts with PPIn via different K/R motifs and via the contribution of the proximal part of the PHD (Kostrhon *et al.*, 2017). Similarly, SAP30L, display an atypical zinc-finger followed by a PBR, which has also been recognised as a PPIn-interacting module, particularly to monophosphorylated PPIn (Viiri *et al.*, 2009). Interestingly, the zinc finger was shown to support PPIn interaction mediated by the PBR while the PBR was required for PPIn specificity. Again, the PBR of Pf1 and ING2 play a major role in direct PPIn binding particularly in determining PPIn specificity (Kaadige and Ayer, 2006). These studies emphasise that PBRs are key to PPIn binding and the environment and features around these regions can sometime influence binding, perhaps by shielding acyl chains.

As shown in Table 4, it is interesting to notice that many reported nuclear PPIn-binding proteins harbour K/R motifs that were initially shown as a binding site for both PtdIns(4,5)P_2 and actin in ABP. As discussed earlier, BRG1 is an example of a nuclear protein which harbours such a motif showing the same binding activity to PtdIns(4,5)P_2 and actin (Rando *et al.*, 2002). Considering the accumulating roles of both PPIn and actin in nuclear processes, it may be worth evaluating both their contribution when characterising the functions of PPIn-effector proteins in the nucleus.

5.3. Influence of PPIn-mediated interaction on nuclear localisation

A few different studies have indicated that PPIn can influence the nuclear localisation of some PPIn-interacting proteins due to the presence of basic residues in structured domains or short polybasic motifs. In particular, K/R motifs and PBRs bear resemblance to NLS, *i.e.* the bipartite NLS (KR-($X_{9\text{-}29}$)-KKK and monopartite K-K/R-X-K/R, and nucleolar localisation signals (NoLS), such as R/K-R/K-X-R/K (Emmott and Hiscox, 2009; McLane and Corbett, 2009). For example, the C-terminal K/R motif of EBP1 overlaps with a NoLS and was shown to be required for both nucleolar targeting and PPIn binding via four lysines (Karlsson *et al.*, 2016). The PBR in SAP30L and BASP1 serves both as a NLS and PPIn binding site (Terashita *et al.*, 2002; Toska *et al.*, 2012; Viiri *et al.*, 2009). The PPIn binding site within the PH domain of the nuclear protein PIKE-L is also a putative NLS (Hu *et al.*, 2005). Incidentally, disruption of PPIn binding can translocate nuclear effector proteins from the nucleus to the cytoplasm. Mutation of the PPIn binding site in the PH domain of PIKE-L causes its translocation to the cytoplasm (Hu *et al.*, 2005). Mutation of the PBR which binds PtdIns(4,5)P_2 in the C-terminal of p53 also caused an increased distribution of p53 to the cytoplasm (Choi *et al.*, 2019). As mentioned earlier, decreased levels of PtdIns5*P* releases ING2 from the chromatin leading to its translocation to the cytoplasm, suggesting that the localisation of ING2 is dependent upon PtdIns5*P* (Gozani *et al.*, 2003; Jones *et al.*, 2006). This was further substantiated by the effect of synthetic PtdIns5*P*, as well as other PPIn, on the sub-nuclear targeting of fluorescently labelled NLS-PHD finger of ING2, which was altered in the wild type but not in the PPIn binding mutant (Gozani *et al.*, 2005). Similarly, PIP_3BP, which harbours two PH domains, both necessary for PtdIns(3,4,5)P_3 binding, is translocated from the nucleus to the cytoplasm upon the introduction of constitutively active PI3K, which is prevented by loss of the PH domain binding to PPIn (Tanaka *et al.*, 1997, 1999). Another protein, OGT translocates from the nucleus to the plasma membrane upon serum stimulation in a PtdIns(3,4,5)P_3-dependent manner (Yang *et al.*, 2008).

Disruption of PPIn binding can also affect sub-nuclear localisation. For example, alteration of the basic motif of Aly prevents its localisation to nuclear speckles, redistributing it to the nucleoplasm (Okada *et al.*, 2008). Insulin receptor substrate 3 (IRS3) can localise both to the plasma membrane and to nuclear speckles and contains a PH domain which binds mostly to PtdIns3*P*, in contrast to the PH domains of IRS1 and 2 which demonstrate different PPIn specificities (Maffucci *et al.*, 2003; Razzini *et al.*, 2000). A point mutation in the PH domain, which abolishes PtdIns3*P* binding, decreases the localisation of full-length IRS3 to both the plasma membrane and the nuclear speckles (Maffucci *et al.*, 2003). PDZ (postsynaptic density protein-95, discs large, zonula occludens) domains, which can bind to PPIn, including PtdIns(4,5)P_2, have been suggested to localise zonula occludens 2 (ZO-2) to nuclear speckles (Meerschaert *et al.*, 2009) and syntenin-2 to nuclear speckles but most likely to nucleoli (Geeraerts *et al.*, 2013; Mortier *et al.*, 2005). Finally, the pericentric heterochromatin localisation of UHRF1 is dependent upon an intact PPIn-binding PBR, at least due to PtdIns5*P* (Gelato *et al.*, 2014).

These studies may implicate a role for nuclear PPIn to compete with interacting partners or induce conformation changes of effector proteins to allow their redistribution within the nucleus or even as far as to the cytoplasm and on the plasma membrane. The fact that PPIn can target the same protein on membranes as well as in membrane-less sub nuclear sites is, however, a paradox but appears to require similar binding strategies, as found in peripheral proteins and ABPs.

6. Conclusions

Mounting evidence have clearly shown that, just as cytoplasmic PPIn, nuclear PPIn can provide a signalling code allowing the regulation of diverse nuclear processes. Still, many questions are unanswered regarding their functional characterisation. Continuous

research efforts focusing on mapping the effector proteins of all known nuclear PPIn as well as deciphering their mode of interaction are needed to increase our understanding of PPIn signalling in the nucleus.

Conflicts of interest

The authors declare to have no conflict of interest with the publication of this manuscript.

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