4 The Multiple Functions of the PAQosome: An R2TP- and URI1 Prefoldin-Based Chaperone Complex

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Abstract

The PAQosome (Particle for Arrangement of Quaternary structure) is a large multisubunit chaperone complex that is essential for the assembly and stabilization of other macromolecular complexes. It also interacts with several chaperones including Hsp90, Hsp70, and CCT. The PAQosome is comprised of the R2TP complex, the URI1 prefoldin complex (also known as the non-canonical prefoldin-like complex), the RNA polymerase subunit RPB5, and the WD40 repeat protein WDR92. The R2TP complex is conserved among eukaryotes and has been comprehensively studied over the last 13 years. The R2TP complex is known for its involvement in the assembly and stabilization of L7Ae ribonucleoproteins, U5 small nuclear ribonucleoprotein, RNA polymerase II, phosphatidylinositol-3-kinase-related proteins (PIKKs), and the tuberous sclerosis complex (TSC1-TSC2). By contrast, the URI1 prefoldin complex has evolved exclusively in higher metazoans. Although the URI1 prefoldin complex was initially reported more than 15 years ago, little is known about its function and its role within the PAQosome. Given that URI1 is overexpressed in many types of cancer, it is surprising that the URI1 prefoldin complex has been overlooked. This chapter provides an update on the recent progress uncovering the physiological roles of each PAQosome subunit and provides an overview of the potential functions of the URI1 prefoldin complex.

Keywords

Molecular chaperones · R2TP · URI1 · PAQosome · RNA polymerase assembly · Non-canonical prefoldin complex · Quaternary structure · snoRNP biogenesis · PIKK stabilization · U5 snRNP · TSC

4.1 Overview

Molecular chaperones and their co-chaperones play key roles in maintaining proteostasis in response to environmental and stress conditions (Hartl et al. 2011). The R2TP chaperone complex (see Table 4.1 for nomenclature) was identified in a large-scale genomic and proteomic screen for Hsp90 co-factors in yeast (Zhao et al. 2005b), and it was subsequently shown to be conserved in

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N. Djouder (ed.), *Prefoldins: the new chaperones*, Advances in Experimental Medicine and Biology 1106, https://doi.org/10.1007/978-3-030-00737-9_4

Table 4.1 Nomenclature

αPFD	Alpha prefoldin domain
αMHC	Alpha myosin heavy chain
βPFD	Beta prefoldin domain
AAA+	ATPases associated with diverse cellular activities
AAR2	A1-Alpha2 repression
AhR	Aryl hydrocarbon receptor
AFMID	Arylformamidase
ALS2	Amyotrophic lateral sclerosis 2 protein
ANP	Atrial natriuretic peptide
AR	Androgen receptor
ART-27	Androgen receptor trapped clone 27 protein
Asa1	ASTRA-associated protein 1
ASTRA	Assembly of Tel, Rvb and Atm-like kinase
ATM	Ataxia-telangiectasia mutated
ATR	ATM- and RAD3-related
BAD	Bcl-2 associated death promoter
BAX	Bcl-2 associated X protein
Bcd1	Box C/D snoRNA accumulation 1
Bcl-2	B-cell leukemia/lymphoma 2
BNP	B-type natriuretic peptide
Bud27	Bud site selection protein 27
CCDC103	Coiled-coil domain containing 103
CCT	Complex containing TCP-1
CDC73	Cell division cycle protein 73 homolog
CDK1	Cyclin-dependent kinase 1
CHX	Cyclohexamide
CK2	Casein kinase 2
CLN3	Cyclin 3
CREB	cAMP responsive element binding protein
COP9	Constitutive photomorphogenesis 9
CS	CHORD domain-containing protein and Sgt1 domain
CSN2	COP9 signalosome 2
CTR9	Cln3 requiring 9
DKC1	Dyskerin
DMAP1	DNA methyltransferase associated protein 1
DNA-PK	DNA-dependent protein kinase
DNA-PKcs	DNA–protein kinase catalytic subunit
DNAAF1	Dynein axonemal assembly factor 1
DNAAF2	Dynein axonemal assembly factor 2
DNAAF4	Dynein axonemal assembly factor 4
DSCR1	Down syndrome critical region gene 1
ECD	Ecdysoneless homolog
EFsec	Selenocysteine-specific eukaryotic elongation factor
EFTUD2	Elongation factor tu GTP binding domain containing 2
EGFR	Epidermal growth factor receptor
eIF1A	Eukaryotic initiation factor 1A
ER	Estrogen receptor
EVI1	Ecotropic viral integration site 1
EZH1	Enhancer of zeste homolog 2
FBL	Fibrillarin
FOG2	Friend of GATA protein 2
FOXP3	Forkhead box P3
GAR1	Glycine arginine rich protein 1
GATA4	GATA binding protein 4
Gim1	GimC subunit 1
Gim4	GimC subunit 4
GimC	Genes involved in microtubule biogenesis complex
Gcn4	General control protein 4
HAAO	3-hydroxyanthranilate 3,4-dioxygenase
HBV	Hepatitis B virus
HBx	Hepatitis B virus X protein
Hit1	High temperature growth 1
HKE2	HLA class II region expressed gene KE2
Hsp70	Heat shock protein 70
Hsp90	Heat shock protein 90
HLE	Human hepatoma cell line
IL-6	Interleukin-6
INO80	Inositol biosynthesis genes 80
IP6K2	Inositol Hexakisphosphate kinase 2
KAP1	KRAB-associated protein 1
KNYU	Kynureninase
KMO	Kynurenine 3-monooxygenase
KRAB	Krüppel associated box
LEO1	RNA polymerase-associate protein left open reading frame 1
LINE-1	Long interspersed nuclear element 1
LOX-PP	Lysyl oxidase precursor protein
LLRC6	Leucine rich repeat containing 6
LRP16	Leukemia-related protein 16
MAPKAP1	Mitogen-activated protein kinase associated protein 1
Matα1	Methionine adenosyltransferase alpha 1
MAT I	Methionine adenosyltransferase I
MAT III	Methionine adenosyltransferase III
Mec1	Mitosis entry checkpoint 1
MEF	Mouse embryonic fibroblast
MDM4	Mouse double minute 4, human homolog of; p53 binding protein
MHC	Major histocompatibility
miR-214	MicroRNA 214

(continued)

Table 4.1 (continued)

MLST8	Mammalian lethal with SEC13 protein 8
MOT48	Motile flagella 48
MRE11	Meiotic recombination 11
MRN	Mre11-Rad50-Nbs1
mRNP	Messenger ribonucleoprotein
mTOR	Mammalian target of rapamycin
mTORC1	Mammalian target of rapamycin complex 1
mTORC2	Mammalian target of rapamycin complex 2
NAD+	Nicotinamide adenine dinucleotide
NAF1	Nuclear assembly factor 1
NBS1	Nibrin
NHP2	Non-histone protein 2
NKX2.5	NK2 Homeobox 5
NF-κB	Nuclear factor kappa beta
NOP1	Nucleolar protein 1
NOP10	Nucleolar protein 10
NOP56	Nucleolar protein 56
NOP58	Nucleolar protein 58
NUFIP1	Nuclear FMRP interacting protein 1
OCT1	Organic cation transporter 1
OGT	O-linked N-acetylglucosamine transferase 110 kDa subunit
OIP2	Opa-interacting protein 2
PAF1	RNA polymerase II-associated factor 1
PAQosome	Particle for arrangement of quaternary structure
PEP	Phosphoenolpyruvate
PDRG1	p53 and DNA damage regulated 1
PFDN1	Prefoldin subunit 1
PFDN2	Prefoldin subunit 2
PFDN3	Prefoldin subunit 3
PFDN4	Prefoldin subunit 4
PFDN4r	Prefoldin subunit 4-related
PFDN5	Prefoldin subunit 5
PFDN6	Prefoldin subunit 6
PIAS2	Protein inhibitor of activated STAT2
PIH1	PIH1 homology domain
Pih1	Protein interacting with Hsp90
PIH1D1	PIH1 domain-containing protein 1
PIH1D3	PIH1 domain-containing protein 3
PIKK	Phosphatidylinositol-3-kinase-related kinase
PKA	Protein kinase A
POLR2E	RNA polymerase II subunit E
POLR2M	RNA polymerase II subunit M
PP1γ	Protein phosphatase 1 catalytic subunit gamma
PP2A	Protein phosphatase 2A
PRAS40	Proline-rich Akt substrate
PRP8	Pre-mRNA-processing factor 8
PRP31	Pre-mRNA-processing factor 31
RAD50	Radiation sensitive 50
RSC	Remodel of the structure of chromatin complex
RSC4	Remodel of the structure of chromatin complex subunit 4
RMP	RNA polymerase II subunit 5-mediating protein
RNAP	RNA polymerase
RNP	Ribonucleoprotein
R2TP	Rvb1–Rvb2–Tah1–Pih1
Rpa190	DNA directed RNA polymerase I 190 kDa polypeptide
RPAP3	RNA polymerase II-associated protein 3
RPB1	RNA polymerase II subunit B1
RPB5	RNA polymerase II subunit B5
Rpc25	DNA-directed RNA polymerase III 25 kDa polypeptide
RPN8	Regulatory particle non-ATPase 8
Rsa1	Ribosome assembly protein 1
RuvBL1	RuvB-like AAA ATPase 1
RuvBL2	RuvB-like AAA ATPase 2
S6K1	Ribosomal protein S6 kinase beta-1
SARM	Selective androgen receptor modulator
SBP2	SECIS binding protein 2
SECIS	Selenocysteine insertion sequence
SHQ1	Small nucleolar RNAs of the box H/ACA family quantitative accumulation 1
SNCG	Gamma synuclein
SKP2	S-phase kinase-associated protein 2
SMN	Survival motor neuron
SMG-1	Nonsense-mediated mRNA decay associated phosphatidylinositol-3-kinase-related kinase
SNF5	Sucrose non-fermentable 5
snoRNA	Small nucleolar RNA
snoRNP	Small nucleolar ribonucleoprotein
snRNP	Small nuclear ribonucleoprotein
SNRNP200	Small nuclear ribonucleoprotein U5 subunit 200
SNU13	Small nuclear ribonucleoprotein 13
SPAG1	Sperm-associated antigen 1
Spt5	Suppressor of ty 5
STAP1	SKP2-associated alpha prefoldin 1
STAT2	Signal transducer and activator of transcription 2
Sth5	SNF two homolog
SUZ12	Suppressor of zeste 12 protein homolog

(continued)

Table 4.1 (continued)

SWI	Switching deficient
SWR1	SWI/SNF related protein
Tah1	TPR-containing protein associated with Hsp90
TBC1D7	Tre2-Bub2-Cdc16 domain family member 7
TERC	Telomerase RNA component
TERT	Telomerase reverse transcriptase
TDO2	Tryptophan 2,3-dioxygenase
TIP48	TBP-interacting protein 48
TIP49	TBP-interacting protein 49
TIP60	TAT-interactive protein 60 kDa
Tel1	Telomere maintenance 1
TEL2	Telomere maintenance 2
TFIIB	Transcription factor IIB
TFIIF	Transcription factor IIF
TNFα	Tumor necrosis factor alpha
TPR	Tetratricopeptide repeat
TRA1	Transcription-associated protein 1
TRRAP	Transformation/transcription domain-associated protein
TSC	Tuberous sclerosis complex
TTI1	TEL2 interacting protein 1
TTI2	TEL2 interacting protein 2
TTT	TEL2-TTI1-TT2
URI1	Unconventional prefoldin RPB5 interactor 1
UXT	Ubiquitously expressed transcript
UXT-AS1	Ubiquitously expressed transcript antisense strand 1
VHL	von Hippel–Lindau tumor suppressor
WAC	WW domain-containing adaptor protein with coiled-coil
WDR92	WD-40 repeat domain 92
ZNHIT2	Zinc finger HIT-type containing 2
ZNHIT3	Zinc finger HIT-type containing 3
ZNHIT6	Zinc finger HIT-type containing 6

humans (Boulon et al. 2008; Te et al. 2007). High-resolution mapping of the human RNAP II interaction network revealed that the R2TP complex associated with a URI1-containing prefoldin-like complex (also known as the non-canonical prefoldin-like complex) (Cloutier et al. 2009; Jeronimo et al. 2007) and with the RNA polymerase subunit RPB5 (POLR2E) and the WD40 repeat protein WDR92. The R2TP complex is involved in the assembly and stabilization of various macromolecular complexes including L7Ae RNPs (Boulon et al. 2008; Machado-Pinilla et al. 2012; Zhao et al. 2008), U5 snRNP (Cloutier et al. 2017; Malinova et al. 2017), RNAP II (Boulon et al. 2010), PIKK complexes (Horejsi et al. 2010), the MRN complex (von Morgen et al. 2017), and the TSC complex (Cloutier et al. 2017; Malinova et al. 2017). In addition, R2TP-like complexes have been hypothesized to mediate axonemal dynein assembly (Hartill et al. 2018; Li et al. 2017; Zur Lage et al. 2018). To emphasize its involvement in the assembly of macromolecular machinery, we have recently renamed the R2TP/URI1 prefoldin complex/RPB5/WDR92 to the PAQosome for Particle for Arrangement of Quaternary structure (Houry et al. 2018).

4.2 The PAQosome Subunits

The PAQosome contains eleven subunits. Nine subunits can be subdivided into two groups: the R2TP complex and the URI1 prefoldin complex (Fig. 4.1 and Table 4.2). The R2TP complex is comprised of RuvBL1, RuvBL2, RPAP3 and PIH1D1; while the URI1 prefoldin complex is comprised of URI1, UXT, PDRG1, PFDN2, and PFDN6. The two other PAQosome subunits are the RNAP subunit RPB5 and the WD40 repeat protein WDR92. RPB5 is likely associated with the URI1 prefoldin complex since it interacts with URI1 (Dorjsuren et al. 1998), whereas WDR92 is likely associated with the R2TP complex since it interacts with RPAP3 and PIH1D1 (Inoue et al. 2010; Ni et al. 2009) (Fig. 4.2).

The R2TP complex is essential for PAQosome-mediated assembly activities. R2TP is a conserved protein complex that has been identified in mammalian cells (Boulon et al. 2008; Te et al. 2007), Drosophila (Benbahouche Nel et al. 2014), Plasmodium (Ahmad et al. 2013), and yeast (Zhao et al. 2005b). In yeast, the R2TP complex is comprised of Rvb1, Rvb2, Pih1 and Tah1 (Fig. 4.1). RuvBL1/Rvb1 and RuvBL2/Rvb2 are highly conserved and are essential for

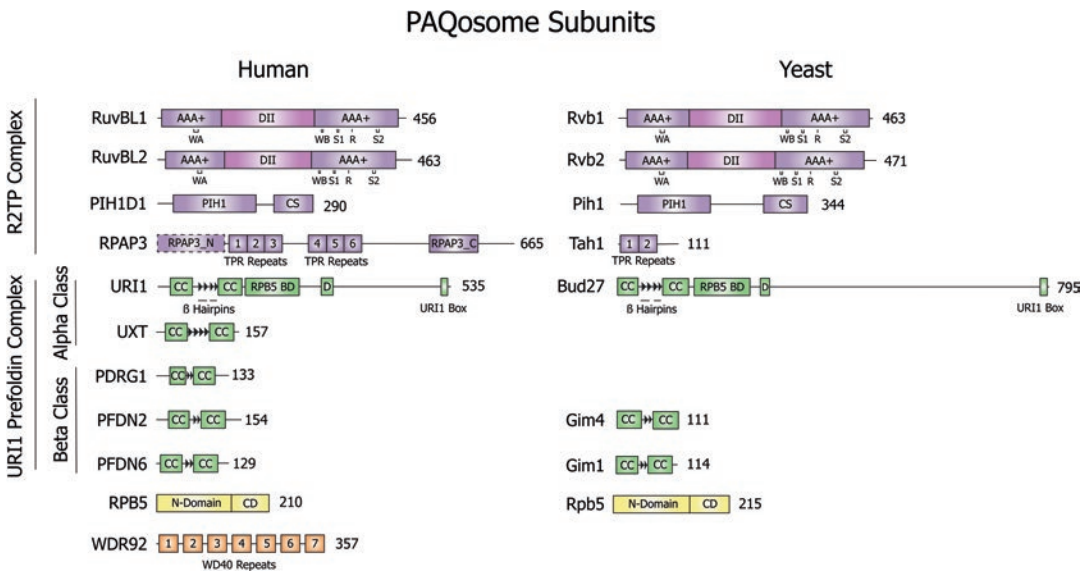

Fig. 4.1 Domain structure of the PAQosome subunits and yeast homologues
The domain organization of the human and yeast PAQosome subunits. WA, Walker A; WB, Walker B; DII, Domain II; S1, sensor 1; S2, sensor 2; RPAP3_N, possible N-terminal domain; RPAP3_C, RPAP3 C-terminal domain; CC, coiled-coil region; D, aspartic acid rich region; RPB5 BD, RPB5 binding domain; CD, C-Domain. RPAP3 isoform 1 and UXT isoform 2 are shown

Table 4.2 Summary of PAQosome subunit functions

Subcomplex	Subunit	Yeast ortholog	Function within the PAQosome	Functions outside the PAQosome
R2TP complex	RuvBL1/2	Rvb1/2	Client complex assembly and dissociation	Transcriptional regulation, DNA repair, mitotic spindle assembly
	PIH1D1	Pih1	Scaffold for adaptors and clients	Stress induced signaling, may be involved in exosome signaling
	RPAP3	Tah1	Flexible tether for Hsp90; stabilizes PIH1D1	Transcriptional regulation, DNA damage response, stem cell maintenance, circadian rhythm regulation
URI1 Prefoldin complex	URI1	Bud27	May regulate R2TP complex activity and localization; stabilizes RPB5	Nutrition signaling, transcriptional regulation
	UXT		May stabilize URI1 prefoldin complex	Male germ cell differentiation, transcriptional regulation
	PDRG1			Methionine adenosyl transferase regulation
	PFDN2	Gim4		Component of canonical prefoldin complex, transcriptional regulation within nervous system
	PFDN6	Gim1		Component of canonical prefoldin complex, adaptive immunity and cancer
None	WDR92		May stabilize RPAP3-PIH1D1 interaction	Dynein arm assembly within R2TP-like complexes
	RPB5	Rpb5	Scaffold for RNAP II	Component of all three RNAPs

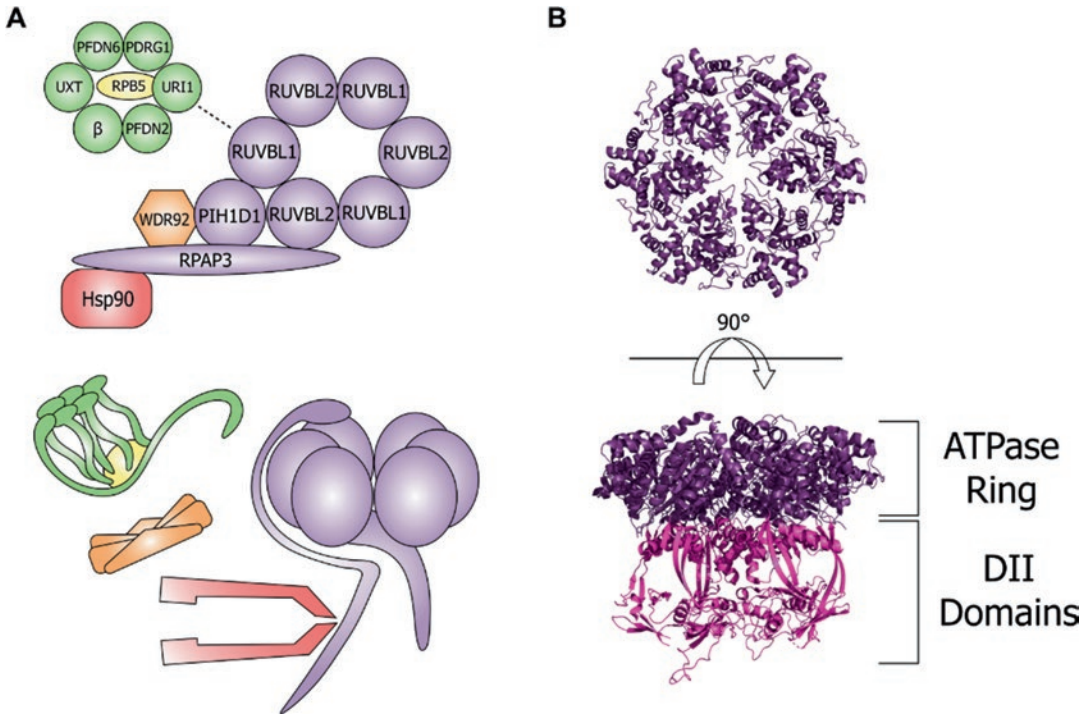

Fig. 4.2 Schematic of the PAQosome structure (**a**) R2TP complex (purple), URI1 prefoldin complex (green), RPB5 (yellow), WDR92 (orange) and Hsp90 (red) are shown based on previously reported protein interactions. The link between the URI1 prefoldin complex and the R2TP complex has not been reported (dotted line). β, possible duplicated beta subunit. (**b**) Structure of the RuvBL1/2 hetero-hexamer (PDB ID 5OAF). Top and side views of RuvBL1/2 (purple) are shown. DII residues (magenta) are omitted in the top view for clarity

viability (Bauer et al. 2000; Kanemaki et al. 1999; Qiu et al. 1998). By contrast, PIH1D1 and RPAP3 vary in size and domain composition relative to yeast Pih1 and Tah1, respectively, suggesting that they evolved to have more specialized roles and interacting partners. This is evidenced by the fact that PIH1D1 and RPAP3 interact with WDR92 (Inoue et al. 2010; Ni et al. 2009), whereas a functional ortholog of WDR92 in yeast is absent. Furthermore, Tah1 is a small protein (111 residues), while RPAP3 is much larger (665 residues).

In contrast to the R2TP complex, the URI1 prefoldin complex does not appear to play a significant role in most PAQosome-mediated processes. In fact, the URI1 prefoldin complex is present in humans, but is absent in yeast (Fig. 4.1). The yeast orthologs of URI1, PFDN2 and PFDN6 are Bud27, Gim4 and Gim1, respectively; whereas, yeast orthologs of UXT and PDRG1 have not been identified (Table 4.2). Both URI1 and Bud27 bind RPB5, an RNAP subunit common to all three RNAPs, suggesting that both URI1 and Bud27 have a conserved role in RNAP assembly. The physical link between the R2TP complex and the URI1 prefoldin complex has yet to be determined.

Below, the terms Rvb1, Rvb2, Pih1, Tah1, Bud27, Gim4 and Gim1 will be used when referring to yeast proteins, and the terms RuvBL1, RuvBL2, PIH1D1, RPAP3, URI1, PFDN2 and PFDN6 will be used when referring to mammalian proteins.

4.2.1 R2TP Subunits: Domains, Assembly and Functions

4.2.1.1 RuvBL1 (Pontin, TIP49, Rvb1) and RuvBL2 (Reptin, TIP48, Rvb2)

RuvBL1 and RuvBL2 are the catalytic components of the PAQosome. They are two paralogous members of the AAA+ superfamily. They contain one AAA+ domain with five highly conserved motifs: Walker A, Walker B, sensor 1, arginine finger, and sensor 2 (Fig. 4.1). The Walker A and Walker B motifs mediate the binding and hydrolysis of ATP, respectively, while the sensor 1, arginine finger and sensor 2 motifs mediate the conformational changes associated with ATP binding and hydrolysis (Miller and Enemark 2016).

Although both have intrinsic ATPase activity, RuvBL1 and RuvBL2 often function together in hexameric or dodecameric complexes. Homo-hexameric rings have been observed for RuvBL1 alone and RuvBL2 alone *in vitro* (Matias et al. 2006; Niewiarowski et al. 2010), hetero-hexameric rings have been observed for yeast Rvb1/2 (Gribun et al. 2008) and human RuvBL1/2 (Aramayo et al. 2018) (Ayala et al. 2018), and although their formation was proposed to be an artifact induced by histidine tags (Cheung et al. 2010), hetero-dodecameric complexes in yeast Rvb1/2 and human RuvBL1/2 have been observed under several experimental conditions (Ewens et al. 2016; Gorynia et al. 2011; Jeganathan et al. 2015; Lakomek et al. 2015; Lopez-Perrote et al. 2012; Martino et al. 2018; Puri et al. 2007; Silva-Martin et al. 2016; Torreira et al. 2008). Dodecameric assembly is mediated by the insertion domain present in both RuvBL1 and RuvBL2 called Domain II (DII) that protrudes out of the hexamer (Figs. 4.1 and 4.2) (Torreira et al. 2008).

The catalytic activity for RuvBL1 and RuvBL2 is presumably substrate and nucleotide driven (Fig. 4.3). It is reasonable to assume that before R2TP complex assembly, RuvBL1 and RuvBL2 exist as an ADP-bound hetero-hexamer or hetero-dodecamer (Martino et al. 2018). RPAP3 and PIH1D1 binding has been shown to disrupt RuvBL1/2 hetero-dodecamers into hetero-hexamers (Martino et al. 2018). The recent cryo-EM structure of human R2TP showed that the RPAP3 C-terminal binds to RuvBL2 on the AAA+ face opposite of the DII face (Fig. 4.2a) (Martino et al. 2018). The DII face is free to interact with client proteins or adaptors through an ATP-dependent or ATP-independent mechanism (McKeegan et al. 2009; Zhou et al. 2017a). In the presence of ATP, the R2TP complex is not stable. In yeast, the addition of ATP to R2TP caused the release of Pih1 and Tah1 (Kakihara et al. 2014; Prieto et al. 2015; Tian et al. 2017). These findings suggest that the PAQosome acts as a scaffold that loads client proteins onto RuvBL1/2 and Hsp90 (or other chaperone), and that ATP binding to RuvBL1/2 either initiates the assembly process independent from other PAQosome subunits, or that it terminates the PAQosome-client interaction after complex assembly (Fig. 4.3). To complete the cycle, ATP must be hydrolyzed before dodecamerization since ATP was also shown to disrupt Rvb1/2 dodecamers (Zhou et al. 2017a).

RuvBL1 and RuvBL2 also have essential roles outside of the PAQosome (reviewed in Nano and Houry 2013). They are key components of the chromatin remodeling INO80 (Jonsson et al. 2001; Shen et al. 2000) and SWR1 (Krogan et al. 2003) complexes, the histone acetyltransferase TIP60 complex (Ikura et al. 2000), the Fanconi anemia core complex, which is involved in DNA inter-strand cross repair (Rajendra et al. 2014; Rosenbaum et al. 2013), and several complexes involved in transcriptional regulation (Bauer et al. 2000; Gospodinov et al. 2009; Kim et al. 2005; Lopez-Perrote et al. 2014). In addition, RuvBL1 and RuvBL2 are essential for eukaryotic cell growth and development (Etard et al. 2005; Qiu et al. 1998; Rottbauer et al. 2002). RuvBL1 and RuvBL2 also promote cell survival and are overexpressed in various types of cancer (reviewed in Mao and Houry 2017). Furthermore, RuvBL1 and RuvBL2 have been implicated in mitotic spindle assembly since they associate with tubulin in the mitotic spindle apparatus and in the centrosome during mitosis

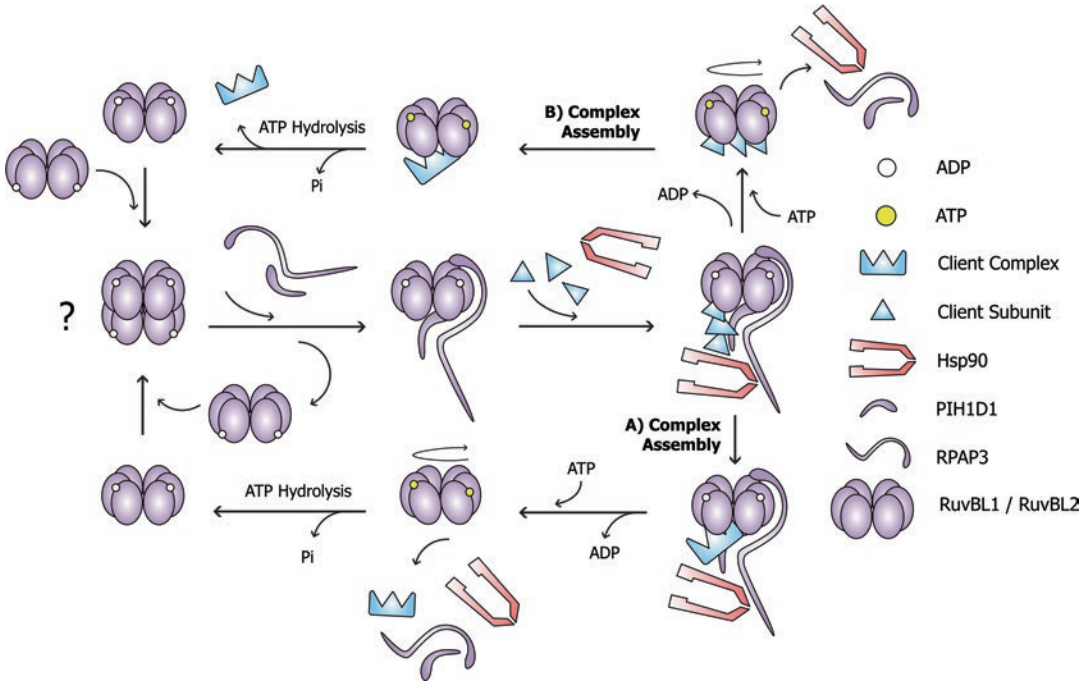

Fig. 4.3 Client complex assembly by R2TP (**a**) ATP-independent complex assembly and (**b**) ATP-dependent complex assembly mechanisms are shown. Symbols for proteins and nucleotides are shown on the right

(Ducat et al. 2008; Gartner et al. 2003; Sigala et al. 2005).

4.2.1.2 PIH1D1 (Pih1, Nop17)

PIH1D1 is primarily a scaffold protein that mediates PAQosome interactions with client complexes. PIH1D1/Pih1 contains a PIH1 domain and a CS domain (Fig. 4.1). The N-terminal of the PIH1 domain binds to several clients and assembly factors through a DpSDD/E motif that is dependent on the constitutively active CK2 kinase for serine phosphorylation (Grankowski et al. 1991; Horejsi et al. 2014; Mir et al. 2016; von Morgen et al. 2017). Within the PAQosome, the conformation of PIH1D1 is not well defined due to its inherent flexibility, but it is likely similar to Pih1 in yeast R2TP where it binds to multiple DII domains within an open basket formed by the Rvb1/2 hetero-hexamer (Fig. 4.2) (Martino et al. 2018; Rivera-Calzada et al. 2017; Tian et al. 2017). The central region of Pih1 mediates the recruitment of Pih1-Tah1 to the Rvb1/2 hetero-hexamer (Rivera-Calzada et al. 2017). The PIH1D1/Pih1 C-terminal contains a CS domain that also appears in the Hsp90 co-chaperones p23 and Sgt1 (Ali et al. 2006; Omran et al. 2008), and it interacts directly with Hsp90 (Zhao et al. 2005b, 2008; Quinternet et al. 2015). In yeast, the CS domain of Pih1 is unstable on its own and is stabilized upon interaction with the C-terminal domain of Tah1 (Eckert et al. 2010; Paci et al. 2012). When not bound to Tah1, Pih1 was found to interact with the proteasome lid subunit RPN8 to mediate its degradation in a ubiquitin-independent manner (Paci et al. 2016). In mammalian cells, PIH1D1 is also stabilized through RPAP3 binding (Yoshida et al. 2013).

PIH1D1/Pih1 may have additional roles independent of the PAQosome. Pih1 is not essential for cell viability in yeast, but its depletion caused a temperature-sensitive phenotype (Gonzales et al. 2005), and siRNA-mediated depletion of PIH1D1 sensitized U2OS cells to doxorubicin-induced apoptosis, suggesting a role for modulating stress induced pathways (Inoue et al. 2010). In addition, PIH1D1/Pih1 may have a regulatory

role for rRNA synthesis and processing. Pih1 was originally identified in yeast as an interactor of the exosome subunit Rrp43 that is involved in rRNA processing (Gonzales et al. 2005; Mitchell et al. 1997). Moreover, PIH1D1 associated with histone H4 to promote rRNA transcription through recruitment of RNAP I (Zhai et al. 2012), and it was also shown that knockdown of PIH1D1 in MCF-7 cells decreased rRNA transcription (Kamano et al. 2013). PIH1D1 may also be involved in regulating proteasomal degradation of certain proteins since its interaction with SNF5, a component of the SWI/SNF chromatin remodeling complex, was shown to attenuate SNF5 degradation (Zhai et al. 2009). Of note, an important caveat to consider with all these findings is that these processes may be dependent on PIH1D1 function within the PAQosome rather than on PIH1D1 function exclusively.

4.2.1.3 RPAP3 (Tah1, Spag1)

After the identification of the R2TP complex in yeast, an analysis of the human Hsp90 proteome identified human orthologs of Rvb1, Rvb2, and Pih1, but not for Tah1 (Te et al. 2007). From this analysis, Boulon and colleagues observed that the Drosophila TPR-containing protein Spag1 could be the Tah1 equivalent (Boulon et al. 2008). They observed that Spag1 was part of the human Hsp90 interactors and that Spag1 was previously shown to interact with Drosophila Hsp90 and Drosophila Pih1 in yeast two-hybrid screens (Boulon et al. 2008; Giot et al. 2003; Te et al. 2007). They showed that human Spag1 linked Hsp90 to PIH1D1, demonstrating that human Spag1 was the functional human equivalent of Tah1 (Boulon et al. 2008). Human Spag1 is more widely known as RPAP3 because a previous independent study identified human Spag1 in a survey of protein complexes that were associated with RNAP II components (Jeronimo et al. 2007).

RPAP3 is the largest subunit within the PAQosome. It contains a potential N-terminal domain, two TPR domains and an RPAP3 C-terminal domain (Fig. 4.1). The TPR domains likely bind Hsp90 and the C-terminal domain binds to RuvBL2 on the ATPase face of the RuvBL1/2 hexamer (Fig. 4.2a) (Martino et al. 2018). The long central segment spans the rim of the RuvBL1/2 ring to stabilize PIH1D1 while simultaneously providing a flexible tether for Hsp90 binding (Martino et al. 2018). Drosophila Spag1 has a similar domain architecture as RPAP3; however, in addition to Hsp90, Spag1 can also bind Hsp70 isoforms containing a C-terminal EEVD motif (Benbahouche Nel et al. 2014). In addition to its function in the PAQosome, there have been reports implicating RPAP3/Spag1 in transcriptional regulation (Shimada et al. 2011), adult stem cell maintenance (Chen et al. 2017) and circadian rhythm regulation (Means et al. 2015).

In contrast to RPAP3 and Spag1, Tah1 is much smaller (Fig. 4.1). It contains only one TPR domain consisting of two TPR repeats, followed by a C-helix and an unstructured region (Jimenez et al. 2012). The Tah1 TPR domain binds to yeast Hsp90 through the C-terminal MEEVD motif (Millson et al. 2008). Tah1 binds to Hsp90 in a 1:1 stoichiometric ratio (two Tah1 monomers: one Hsp90 dimer). The C-terminal tail of Tah1 contains an unfolded region that inserts into the CS domain of Pih1 (Back et al. 2013; Jimenez et al. 2012; Pal et al. 2014).

4.2.2 URI1 Prefoldin Complex Subunits

Members of the prefoldin family contain N- and C-terminal α-helical, coiled-coils connected by either one (β-class) or two (α-class) β hairpins (Fig. 4.1 and Table 4.2). Canonical prefoldin subunits (PFDN1-PFDN6) assemble into a α2β4 hexameric complex. In humans, the two canonical alpha subunits are PFDN3 and PFDN5, and the four canonical beta subunits are PFDN1, PFDN2, PFDN4 and PFDN6. The coiled-coil regions in the prefoldin complex form a jelly-fish like arrangement that binds its substrates with its tentacle-like structures (Martin-Benito et al. 2007; Siegert et al. 2000). The canonical prefoldin complex is best known for folding nascent cytoskeletal proteins actin, α-tubulin and γ-tubulin with the help of the CCT complex (Geissler et al. 1998; Martin-Benito et al. 2002;

Siegers et al. 1999; Vainberg et al. 1998). In addition, each prefoldin subunit may have a specialized function. For example, PFDN1 mutations in mice caused defects in lymphocyte development (Cao et al. 2008), whereas PFDN5 mutations caused photoreceptor degeneration, central nervous system abnormalities and male infertility (Lee et al. 2011).

In contrast to the canonical prefoldin complex, the function of the URI1 prefoldin complex is still not known. The URI1 prefoldin complex has been observed in humans and Drosophila (Cloutier et al. 2009; Giot et al. 2003; Gstaiger et al. 2003; Sardiu et al. 2008). The alpha subunits are URI1 and UXT, while the beta subunits are PDRG1 and the canonical subunits PFDN2 and PFDN6 (Fig. 4.1). The URI1 prefoldin complex may either be pentameric or hexameric with one of the beta subunits duplicated. It is presumed that the URI1 prefoldin complex has a jelly-fish like arrangement similar to the canonical prefoldin complex (Fig. 4.2). Aside from URI1, which takes part in mTOR signaling (Gstaiger et al. 2003), the URI1 prefoldin complex subunits act mainly in the nucleus as transcriptional regulators (Table 4.3).

4.2.2.1 URI1 (RMP, Bud27)

URI1 (535 residues) contains an α-type prefoldin domain and an elongated C-terminal domain that makes URI1 more than four times larger than α-type canonical subunits PFDN3 (193 residues) and PFDN5 (154 residues) (Fig. 4.1). The prefoldin domain interacts with and stabilizes UXT and PDRG1 (Gstaiger et al. 2003; Mita et al. 2013), while the central region interacts with and stabilizes RPB5 (Dorjsuren et al. 1998). The aspartic acid rich region of URI1 may stabilize RPB5 by acting as a DNA mimic (Chou and Wang 2015; Gstaiger et al. 2003). The C-terminal contains a URI1 box motif that is conserved in humans, Arabidopsis, Drosophila, *C. elegans*, and yeast (Gstaiger et al. 2003).

URI1 was initially reported as a transcription regulator through its association with RPB5 (Dorjsuren et al. 1998). It can outcompete viral proteins or transcription factors that share the same binding site on RPB5 (Dorjsuren et al. 1998; Yang et al. 2000; Zhou et al. 2015a). Human URI1 and yeast Bud27 also coordinate interactions between RPB5/RNAP II and other protein complexes (Le et al. 2005; Miron-Garcia et al. 2014; Wei et al. 2003; Yart et al. 2005). In yeast, Bud27 binds to phosphorylated forms of transcribing RNAP II to modulate its elongation dynamics (Miron-Garcia et al. 2014).

In addition to RPB5, URI1 regulates transcription through several other binding partners (Table 4.3). URI1 repressed steroid and aryl hydrocarbon receptor activity in prostate cancer cells and hepatocytes, respectively (Mita et al. 2011; Tummala et al. 2014). URI1 also repressed retrotransposon expression in prostate cancer cells through its interactions with PP2A and KAP1, suggesting that URI1 has a role in preventing DNA damage (Mita et al. 2016). In fact, URI1 was shown to be essential for maintaining DNA stability in *C. elegans* and Drosophila (Kirchner et al. 2008; Parusel et al. 2006). Moreover, URI1/Bud27 may also have a role in translation. Bud27 interacted with translation initiation factor eLF1A to promote 40S ribosome subunit formation (Deplazes et al. 2009). In addition, Gcn4 translation was derepressed in Bud27 knockout cells (Gstaiger et al. 2003).

Given the fundamental roles URI1 has on transcriptional regulation and DNA stability, it should come as no surprise that URI1 has been implicated in many types of cancers including ovarian cancer (Theurillat et al. 2011), multiple myeloma (Fan et al. 2014), endometroid adenocarcinoma (Gu et al. 2013), uterine carcinosarcoma (Wang et al. 2015b), cervical cancer (Gu et al. 2015; Xu et al. 2017), gastric cancer (Hu et al. 2016; Luo et al. 2016), colorectal cancer (Lipinski et al. 2016) and hepatocellular carcinoma (Gomes et al. 2016; Tummala et al. 2014, 2017; Wang et al. 2014; Yang et al. 2011, 2013; Zhang et al. 2015; Zhou et al. 2014, 2017b). Several oncogenic mechanisms in hepatocellular carcinoma have been reported for URI1. URI1 inhibits the transcription of genes needed for NAD+ metabolism, thereby causing early DNA damage (Tummala et al. 2014). URI1 also promotes epithelial-mesenchymal transition, which

Table 4.3 Summary of URI1 prefoldin complex subunit-mediated transcriptional regulation

Prefoldin subunits	Interactors	Target genes	Target gene functions	Mechanisms of action	References
Bud27	Rpb5	All genes transcribed by RNAP II		Regulates transcription elongation	Miron-Garcia et al. (2013)
Bud27	Sth1	All genes transcribed by RNAP II		Mediates RNAP II association with RSC complex	Miron-Garcia et al. (2014)
URI1	RPB5	HBx cell cycle targets	Proliferation, apoptosis	URI1 competitively binds RPB5, represses HBx-mediated gene expression	Dorjsuren et al. (1998)
URI1	HBV	HBx cell cycle targets	Proliferation, apoptosis	Represses apoptotic factor expression, enhances antiapoptotic factor expression	Wang et al. (2014)
URI1		HBV	Hepatitis B virus propagation	Represses transcription and replication	Zhou et al. (2015a)
URI1	TFIIB	All genes transcribed by RNAP II		URI1 competitively binds TFIIB, represses HBx-mediated gene expression, and most likely other genes	Yang et al. (2000)
URI1	TFIIF	All genes transcribed by RNAP II		Suppresses activated transcription	Wei et al. (2003)
URI1, UXT	AR	AR target genes	Proliferation, development, signaling, lipid metabolism	Represses transcription; stabilizes AR co-factor UXT; prevents AR recruitment to promoter sites	Mita et al. (2011)
URI1	ER	TDO2, AFMID, KMO, KNYU, HAAO	NAD+ metabolism	Represses transcription in hepatocellular carcinoma	Tummala et al. (2014)
URI1	AhR	TDO2, AFMID, KMO, KNYU, HAAO	NAD+ metabolism	Represses transcription in hepatocellular carcinoma	Tummala et al. (2014)
URI1	CDC73, PAF1, LEO1, CTR9	Cell cycle targets	Tumor suppression	Enhances transcription	Yart et al. (2005)
URI1	KAP1, PP2A	LINE-1	Retrotransposon	Activates KAP1 complex, represses transcription	Mita et al. (2016)
URI1	NF-κB	IL-6	B cell differentiation	Enhances transcription in multiple myeloma and hepatocellular carcinoma	Fan et al. (2014) and Zhang et al. (2015)
URI1	NF-κB	CSN2	Represses snail degradation	Enhances transcription in hepatocellular carcinoma	Zhou et al. (2017b)

(continued)

Table 4.3 (continued)

Prefoldin subunits	Interactors	Target genes	Target gene functions	Mechanisms of action	References
URI1		Snail	Transcriptional E-cadherin repressor	Enhances transcription in gastric cancer	Hu et al. (2016)
URI1		Vimentin	Intermediate filament	Enhances transcription in cervical cancer and gastric cancer	Gu et al. (2015) and Hu et al. (2016)
URI1		ATM	DNA damage repair	Enhances transcription in uterine carcinosarcoma	Wang et al. (2015b)
URI1		BAX	Tumor suppression	Represses transcription in hepatocellular carcinoma	Yang et al. (2013) and Zhou et al. (2014)
URI1		Bcl-2	Cell proliferation	Represses transcription in hepatocellular carcinoma	Yang et al. (2013) and Zhou et al. (2014)
URI1		p53	Tumor suppressor	Represses transcription	Lipinski et al. (2016)
URI1		CDK1	Cell proliferation	Enhances transcription in hepatocellular carcinoma	Yang et al. (2011)
URI1		Cyclin B	Cell proliferation	Enhances transcription in hepatocellular carcinoma	Yang et al. (2011)
UXT	AR	AR target genes	Proliferation, development, signaling, lipid metabolism	AR-mediated transcription regulator	Li et al. (2005), Markus et al. (2002), Nwachukwu et al. (2009) and Taneja et al. (2004)
UXT	AR, LRP16	AR target genes	Proliferation, development, signaling, lipid metabolism	LRP16 co-regulates AR-mediated transcription	Yang et al. (2009)
UXT	GATA4, FOG2, NKX2.5	ANP, BNP, αMHC	Cardiac specific functions	Represses transcription of cardiac genes during development	Carter et al. (2014)
UXT	EVI1	EVI1 target genes	Cell proliferation, development, transformation	Represses EVI1-mediated transcription	McGilvray et al. (2007)
UXT	EZH1, SUZ12	NF-κB target genes	Cell proliferation inflammation, immunity, development	Enhances transcription	Su et al. (2016)
UXT	NF-κB, LRP16	NF-κB target genes	Cell proliferation inflammation, immunity, development	Enhances transcription	Sun et al. (2007) and Wu et al. (2011)
UXT	VHL	AR target genes	Proliferation, development, signaling, lipid metabolism	Enhances transcription, mediates AR ubiquitination	Chen et al. (2013)
UXT	FOXP3	FOXP3 target genes	Immune suppression	Affects FOXP3 nuclear localization, represses transcription	Li et al. (2014)
UXT	ALS2	N.D.		May have an effect on NF-κB signaling	Enunlu et al. (2011)
UXT	MDM4	N.D.		Represses p53 activity, enhances NF-κB activity	Qi et al. (2015)

(continued)

Table 4.3 (continued)

Prefoldin subunits	Interactors	Target genes	Target gene functions	Mechanisms of action	References
UXT	ER	ER target genes	Proliferation, development, signaling, lipid metabolism	Represses transcription in breast cancer cells	Sanchez-Morgan et al. (2017)
UXT	LOX-PP	ER target genes	Proliferation, development, signaling, lipid metabolism	Mediates UXT ubiquitination, enhances transcription in breast cancer cells	Sanchez-Morgan et al. (2017)
UXT	PIAS2	N.D.		May have an effect on AR-mediated transcription	Kong et al. (2015)
UXT	Notch	Notch target genes	Cell proliferation, development, differentiation	Represses transcription	Zhou et al. (2015b)
UXT	DSCR1	N.D.		May have a role in regulating neurogenesis	Silveira et al. (2004)
PDRG1	MATα1	MATα1	S-adenosyl-methionine synthesis	Represses transcription, affects MATα1 nuclear localization, reduces DNA methylation	Perez et al. (2016)
PFDN2		SNCG	Maintains neurofilament network	Enhances transcription in mice	Chintalapudi et al. (2014, 2016)

N.D. - Not Determined

is a risk factor for metastasis (Zhou et al. 2017b). Furthermore, URI1 promotes the transcription of IL-6, which promotes metastasis (Fan et al. 2014; Mi and Gong 2017; Zhang et al. 2015).

4.2.2.2 UXT (Art-27, STAP1)

UXT is an α-type non-canonical prefoldin subunit, but in contrast to URI1, it is much smaller (Fig. 4.1). It was given its name because it was observed to be ubiquitously expressed in mouse and human tissues (Schroer et al. 1999). UXT is an X-linked gene that is transcribed in response to growth factor stimulation and CREB signaling (Nwachukwu et al. 2007). UXT is essential for mammalian cell growth and development (Carter et al. 2014; Schafler et al. 2018; Taneja et al. 2004; Zhao et al. 2005a). Recently, UXT deletion in somatic cells of mice was shown to be embryonic lethal (Schafler et al. 2018).

Two isoforms of UXT have been identified to have opposing roles in SARM-induced apoptosis (Sethurathinam et al. 2013); however, their roles in other contexts has not been well established. The non-coding antisense RNA UXT-AS1 was shown to regulate levels of each isoform through alternative splicing mechanisms of the UXT transcript (Yin et al. 2017). The first isoform UXT-V1 has 12 more amino acids at its N-terminus than the other isoform. It is localized in the cytoplasm and the mitochondria and is implicated in TNFα-induced apoptosis and antiviral signalosome formation (Huang et al. 2011, 2012). Most studies have focused on the second isoform, UXT-V2, which is located mainly in the nucleus where it is implicated in transcriptional regulation. We refer to UXT-V2 hereafter as UXT.

In the nucleus, UXT serves as a co-factor for multiple transcription factors and complexes involved in the regulation of cell proliferation, inflammation and differentiation (Carter et al. 2014; Chang et al. 2012; Chen et al. 2013; Enunlu et al. 2011; Kong et al. 2015; Li et al. 2014; Markus et al. 2002; McGilvray et al. 2007; Nwachukwu et al. 2009; Qi et al. 2015; Sanchez-Morgan et al. 2017; Silveira et al. 2004; Su et al. 2016; Sun et al. 2007; Taneja et al. 2004; Wu et al. 2011; Yang et al. 2009; Zhou et al. 2015b) (Table 4.3). UXT is largely involved in enhancing

NF-κB signaling through its interactions with MDM4 (Qi et al. 2015), the EZH1/SUZ12 complex (Su et al. 2016), and the NF-κB enhanceosome (Sun et al. 2007). By contrast, UXT also possesses inhibitor functions in certain growth pathways including EVI1-mediated transcriptional repression (McGilvray et al. 2007), cardiac gene downregulation during cardiac myocyte differentiation (Carter et al. 2014), and steroid receptor signaling (Li et al. 2005; Mita et al. 2011; Nwachukwu et al. 2009; Sanchez-Morgan et al. 2017). UXT was recently shown to regulate transcriptional programs governing male germ cell differentiation, presumably through its interaction with its co-factor URI1 and AR (Mita et al. 2011; Schafler et al. 2018).

4.2.2.3 PDRG1 (PFDN4r)

PDRG1 is a β-type non-canonical prefoldin subunit (Fig. 4.1). However, unlike URI1 and UXT, its function outside of the PAQosome is not well understood. In normal human tissues, PDRG1 expression was found to be highest in testis (Luo et al. 2003). PDRG1 is an oncogene that is downregulated by tumor suppressor p53, miR-214 and oleuropein (Luo et al. 2003; Wang et al. 2015a; Xu and Xiao 2017). By contrast, it is upregulated in response to UV-induced DNA damage, and genotoxic agents (Jiang et al. 2011; Saigusa et al. 2012). Following DNA damage, DNA-PK phosphorylates the stress sensor transcription factor OCT1 to promote PDRG1 transcription (Kang et al. 2009).

PDRG1 has a significant role in controlling epigenetic modifications. In the nucleus, PDRG1 interacts with MATα1, the catalytic subunit of methionine adenosyl transferases MAT I and MAT III, thereby inhibiting S-adenosylmethionine synthesis and subsequently reducing global DNA methylation (Perez et al. 2016). PDRG1 may also promote radioresistance in lung cancer (Tao et al. 2016). In response to irradiation, PDRG1 is upregulated and antagonizes apoptosis through the ATM-p53 signaling pathway (Tao et al. 2016). PDRG1 is also likely involved in cancers where miR-214 is downregulated including hepatocellular carcinoma, breast cancer, cervical cancer and bladder cancer (Perez et al. 2016; Wang et al. 2015a).

4.2.2.4 PFDN2

PFDN2 has been implicated in neurodegeneration through knock out studies and gene expression profiling, however, the pathogenic phenotypes are more likely due to aberrant canonical prefoldin complex assembly, and not PFDN2 itself (Abe et al. 2013; Broer et al. 2011; Filali et al. 2014; Takano et al. 2013; Tashiro et al. 2013). Interestingly, in mouse retinal ganglion neurons, PFDN2 has been reported to be an upstream regulator of γ-synuclein (Chintalapudi et al. 2014, 2016), and overexpression of γ-synuclein in mice caused severe age- and transgene dose-dependent neuropathology and motor deficits (Ninkina et al. 2009). Additionally, PFDN2 was upregulated in neuroblastoma, presumably as a neuroprotective response that prevented aggregate accumulation and dedifferentiation (Patil et al. 2015; Zhang et al. 2016). Moreover, PFDN2 was upregulated in mouse retinal neural cells, and in human skeletal muscle cells with Type II diabetes (Al-Khalili et al. 2014; Gao et al. 2009). PFDN2 autoantibodies were associated with Type II diabetes in a Southwest American Indian population (Chang et al. 2015, 2017); however, the significance of this finding is unknown.

4.2.2.5 PFDN6 (HKE2)

PFDN6 has been implicated in adaptive immunity and cancer. The PFDN6 encoding gene, *HKE2*, is located in the centromeric portion of the region encoding the genes of the MHC class II complex (Ostrov et al. 2007). Immunohistochemical analyses of human benign tissues and cancer tissues showed that PFDN6 was upregulated in colon, thyroid, breast, ovarian, and brain tumors (Ostrov et al. 2007). By contrast, a more recent study showed that PFDN6 was downregulated in dexamethasone-resistant acute lymphoblastic leukemia, suggesting that PFDN6 could participate in antigen processing in lymphocytes (Dehghan-Nayeri et al. 2017).

4.2.3 Other PAQosome Subunits

4.2.3.1 RPB5 (POLR2E)

RPB5 is a 23-kDa subunit present in all three RNAPs (Pati and Weissman 1989; Zaros et al. 2007). It has a bipartite structure that contains a eukaryotic-specific N-terminal domain and a C-terminal domain resembling the archaeal RNAP subunit H (Fig. 4.1) (Thiru et al. 1999; Todone et al. 2000). The N-terminal domain cross links with the DNA helix between positions +5 and + 15 (Kim et al. 1997), whereas the C-terminal domain contacts RPB1 (Cramer et al. 2000). RPB5 may be involved in RNAP assembly by providing a large interaction interface to most of the other subunits (Acker et al. 1997). Within the assembled RNAP II complex, RPB5 is not part of the catalytic domain (Armache et al. 2005; Bushnell and Kornberg 2003; Cramer et al. 2000; Gnatt et al. 2001). Rather, RPB5 is part of the lower jaw of the DNA binding cleft and is involved in the coordination of RNAP II opening and closing (Bushnell et al. 2002; Cramer et al. 2000; Zaros et al. 2007).

RPB5 has several roles as a transcriptional regulator. An early report in yeast suggested that RPB5 and RPB1-CTD have overlapping roles in transcription activation (Miyao and Woychik 1998). More recently, RPB5 was shown to modulate transcription elongation dynamics by influencing the phosphorylation state of the RPB1 CTD at Ser5 and Ser2, thereby affecting its association with elongation factor Spt5 (Martinez-Fernandez et al. 2018). In addition, RPB5 interacts with several transcription factors and gene specific regulators such as URI1 (Dorjsuren et al. 1998), TFIIB (Lin et al. 1997), TFIIF (Le et al. 2005; Wei et al. 2003), RSC4 (Soutourina et al. 2006), POLR2M (Jishage et al. 2012), and protein X of the Hepatitis B virus (Cheong et al. 1995).

4.2.3.2 WDR92 (Monad)

WDR92 is a WD40 repeat protein that contains seven WD40 sequences (Saeki et al. 2006; Xu and Min 2011) (Fig. 4.1). The WD40 repeats fold into a β-propeller architecture, a defining characteristic of all WD40 motifs (Neer et al. 1994; Xu and Min 2011). WDR92 was shown to interact directly or indirectly with PIH1D1 in mammalian cells (Inoue et al. 2010). In addition, WDR92 and RPAP3 are also proposed to interact (Itsuki et al. 2008; van der Voorn and Ploegh 1992). In human tissues, WDR92 and RPAP3 expression were shown to be highest in the testis (Itsuki et al. 2008; Saeki et al. 2006). Given that WDR92 is absent in yeast and that RPAP3 is approximately six times larger than yeast Tah1, WDR92 may have evolved to serve as a scaffold for protein-protein interactions, a common function for WD40 repeat proteins.

WDR92 may also have a tumor suppressor role since its overexpression in HEK293 cells potentiated CHX- and TNFα-induced apoptosis (Saeki et al. 2006). In addition, WDR92 binds to the exosome component OIP2, which is involved in pre-rRNA processing, and degrades amphiregulin mRNA encoding an EGFR ligand that increases tumor invasiveness (Saeki et al. 2013).

4.3 PAQosome-Mediated Complex Assembly

4.3.1 PAQosome-Mediated Assembly of L7Ae Ribonucleoprotein

The L7Ae family of RNA binding proteins are part of various RNP complexes that are essential for tRNA processing, translation, and RNA modification. The PAQosome has been implicated in the assembly of L7Ae RNPs involved in RNA modification, which include the snoRNP complexes (Watkins et al. 1998, 2000), the telomerase RNP complex (Watkins et al. 1998), the SECIS mRNPs (Allmang et al. 2002; Copeland et al. 2000), the U4 snRNP complex (Nottrott et al. 1999), and the U5 snRNP (Newman 1997). The PAQosome recognizes specific prospective client RNP complexes through various adaptor proteins.

The assembly of snoRNP complexes and their localization to the nucleolus is essential for pre-rRNA maturation. snoRNPs contain snoRNA that can be classified into several types based on

conserved sequence elements including: box C/D snoRNA and box H/ACA snoRNA. The snoRNA sequences are complementary to rRNA sequences to guide nucleotide modification in the nucleolus. The core proteins of box C/D and box H/ACA process pre-rRNA through site-specific 2'-O-methylation and pseudoridylation, respectively. Binding of core proteins to snoRNA also protects snoRNA from exonuclease-mediated degradation (Kufel et al. 2000).

4.3.1.1 Box C/D snoRNP Assembly

The box C/D snoRNP complex is comprised of box C/D snoRNA, L7Ae protein SNU13, the methyltransferase FBL, and the core proteins NOP56 and NOP58 (Snu13, Nop1, Nop56, and Nop58 in yeast, respectively) (Fig. 4.4a). The first study to demonstrate a functional role for yeast R2TP showed that it was required for box C/D snoRNA accumulation and for pre-rRNA processing (Zhao et al. 2008), suggesting a possible role of R2TP in box C/D snoRNP assembly. These findings were supported by additional studies, which demonstrated that Pih1 interacted and stabilized box C/D snoRNP component Nop58 (Gonzales et al. 2005; Zhao et al. 2008), and that Rvb1 and Rvb2 associated with an *in vitro*-assembled mouse U14 snoRNP complex (Newman et al. 2000). In addition, PIH1D1 knockdown in mammalian cells caused a global reduction of box C/D snoRNA levels (McKeegan et al. 2007). Furthermore, Rvb1, Rvb2 and Pih1 deletion yeast strains had reduced box C/D snoRNA levels and had mislocalized box C/D snoRNP proteins, especially when cells were grown under stress conditions (Gonzales et al. 2005; Kakihara et al. 2014; King et al. 2001).

In addition to the proposed scaffolding action of Pih1, the R2TP complex recruits pre-box C/D snoRNP components using assembly factors. NUFIP1 (Rsa1 in yeast) was identified in a yeast two-hybrid screen using SNU13 as bait (Boulon et al. 2008). NUFIP1 contains a zinc finger domain and a conserved PEP domain that is essential for SNU13 binding (Boulon et al. 2008). In yeast, the interaction between Snu13 and Rsa1 was essential for cell growth and snoRNP formation (Rothe et al. 2014a). NUFIP1 was also shown to bind FBL, NOP56, and NOP58 to bridge interactions between partially reconstituted pre-box C/D snoRNP complexes (McKeegan et al. 2007). It was subsequently shown that RuvBL1/2 hexamers could also bridge interactions between the core box C/D proteins more efficiently than NUFIP1, and that these interactions were dependent on ATP binding (McKeegan et al. 2009). NUFIP1 was also shown to bind to RuvBL1 and RuvBL2, suggesting that NUFIP1 connected pre-box C/D snoRNP complexes to the R2TP complex (McKeegan et al. 2007). Indeed, an *in vivo* systematic quantitative stable isotope labeling proteomic study showed that NUFIP1 existed in a protein-only pre-snoRNP complex containing RuvBL1, RuvBL2, SNU13, NOP58 and two other assembly factors, ZNHIT3 and ZNHIT6 (Fig. 4.4a) (Bizarro et al. 2014).

ZNHIT3 and ZNHIT6 (Hit1 and Bcd1 in yeast, respectively) also facilitate box C/D snoRNP assembly by acting as scaffolds or by stabilizing complex intermediates. They contain zinc finger domains comprised of seven cysteines and one histidine, called the HIT domain. In yeast, Hit1 binds to Rsa1 and contributes to *in vivo* box C/D snoRNA stability and pre-RNA maturation kinetics (Rothe et al. 2014a). Moreover, the Hit1-Rsa1 heterodimer can interact with Snu13 to make a heterotrimer, which can subsequently bind to box C/D snoRNA and Nop58 to form a complex intermediate *in vitro* (Rothe et al. 2014b). Bcd1 was identified as an essential protein in yeast that interacts with Rsa1, Rvb1, and Rvb2 to maintain box C/D snoRNA levels in an ATP-dependent manner (McKeegan et al. 2007, 2009; Peng et al. 2003).

4.3.1.2 Box H/ACA snoRNP Assembly

The box H/ACA snoRNP complex is comprised of box H/ACA snoRNA, L7Ae protein NHP2, the pseudouridine synthase DKC1, and the core proteins GAR1 and NOP10 (Fig. 4.4b). Assembly of box H/ACA snoRNP complex is dependent on the assembly factors SHQ1, NAF1 and the R2TP complex. SHQ1 binds DKC1 in a vicelike grip prior to its assembly with NHP2, NOP10 and NAF1 (Grozdanov et al. 2009). PIH1D1 interacts

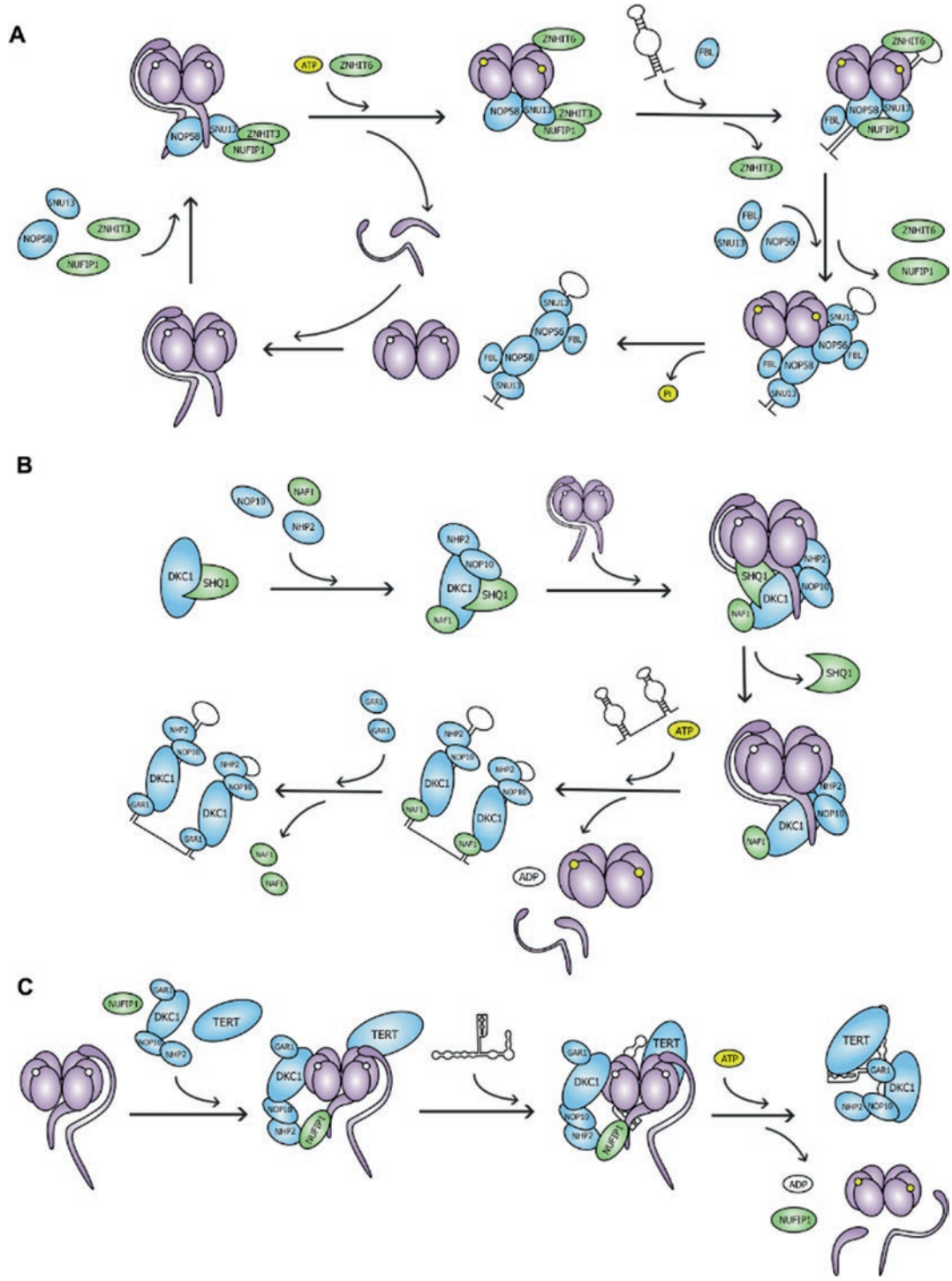

Fig. 4.4 snoRNP complex assembly
R2TP-mediated assembly of (**a**) box C/D snoRNP, (**b**) box H/ACA snoRNP and (**c**) telomerase RNP. R2TP subunits (purple), assembly factors (green), snoRNP complex protein subunits (blue), nucleotides (ATP, yellow circles; ADP, white circles), and RNA are shown

with DKC1 to recruit DKC1-SHQ1 to the R2TP complex where RuvBL1 and RuvBL2 interact with DKC1-SHQ1 in an ATP-independent manner (Machado-Pinilla et al. 2012). Alternatively, NHP2 could be recruited to the R2TP complex through a PIH1D1-NUFIP1-NHP2 interaction (Boulon et al. 2008). Dissociation of SHQ1 from DKC1 requires the entire R2TP complex and additional cytosolic factors, but not RuvBL1/2 or Hsp90 ATPase activity (Machado-Pinilla et al. 2012). However, an earlier study in yeast showed that Rvb2 ATPase activity was required for box H/ACA snoRNA production (King et al. 2001). ATP binding and hydrolysis may be needed for the dissociation of DKC1 from the R2TP complex during snoRNP maturation. NAF1 then escorts the pre-box H/ACA complex to nascent H/ACA RNA (Darzacq et al. 2006; Grozdanov et al. 2009). Lastly, the complex is shuttled to the nucleoli where NAF1 is replaced by GAR1 (Darzacq et al. 2006).

4.3.1.3 Telomerase Assembly

The telomerase RNP complex adds DNA repeats, known as telomeres, to the ends of chromosomes after DNA replication. It is comprised of L7Ae protein NHP2, pseudouridine synthase DKC1, core proteins GAR1 and NOP10, reverse transcriptase TERT, and the RNA component TERC (Fig. 4.4c). NUFIP1/PIH1D1 was shown to bind NHP2, and this interaction may facilitate RuvBL1 binding to DKC1 (Boulon et al. 2008; Venteicher et al. 2008). In addition, RuvBL1 and RuvBL2 ATPase activities were required for TERC accumulation, suggesting that RuvBL1/2 facilitates the binding of TERC to NHP2-NOP10-DKC1-GAR1 (Venteicher et al. 2008). Moreover, RuvBL1 was shown to bind TERT and may therefore bridge the interactions between TERT and the rest of the telomerase RNP complex (Venteicher et al. 2008).

4.3.1.4 SECIS mRNP Assembly

Selenoproteins are enzymes involved in antioxidant defence, redox homeostasis and immune responses (Lu and Holmgren 2009). Transcribed selenoprotein mRNAs associate with selenoprotein mRNPs for translational recoding of a UGA codon which enables the insertion of selenocysteine (Berry et al. 1991). Selenoprotein mRNPs are comprised of selenoprotein mRNA, L7Ae protein SBP2 and the elongation factor EFsec (Copeland et al. 2000; Fagegaltier et al. 2000). SBP2 binds to NUFIP1, and it has recently been shown that SBP2 also interacts with the SMN complex (Boulon et al. 2010; Gribling-Burrer et al. 2017). Similar to U4 snRNP assembly, R2TP/NUFIP1 may directly interact with the SMN complex and SBP2 to facilitate SPB2 binding to selenoprotein mRNA.

4.3.1.5 U4 snRNP Assembly

The U4 snRNP has a regulatory role within the spliceosome machinery and is comprised of U4 snRNA, L7Ae protein SNU13 and the pre-mRNA splicing component PRP31 (Fig. 4.5a). The assembly of the U4 snRNP is dependent on NUFIP1/R2TP and the heptameric SMN complex that loads snRNA onto snRNP complexes (Bizarro et al. 2015). PRP31 associates with SNU13, ZNHIT3 and NUFIP1/R2TP within Cajal bodies; however, the exact role of R2TP is not clear. Since RuvBL1 and RuvBL2 interacted with PRP31 in a yeast two-hybrid screen, the role of PIH1D1/NUFIP1 may be to recruit PRP31-SNU13 to RuvBL1/2, RPAP3 and Hsp90 to mediate their proper folding and assembly (Bizarro et al. 2015). The PRP31-SNU13-ZNHIT3-NUFIP1-R2TP complex subsequently associates with the SMN complex, with NUFIP1 making direct interactions with SMN subunits Gemin3 and Gemin6 (Bizarro et al. 2015). The SMN complex facilitates U4 snRNA loading to PRP31 and SNU13 (Bizarro et al. 2015). Upon maturation, ZNHIT3-NUFIP1-R2TP dissociate from the complex (Fig. 4.5a).

4.3.2 U5 snRNP Assembly

The U5 snRNP is also part of the spliceosome machinery and is involved in aligning two exons for ligation (Newman 1997). It is comprised of U5 snRNA, the GTPase EFTUD2, the helicase SNRNP200, and the mRNA processing factor PRP8 (Fig. 4.5b). EFTUD2 and PRP8 are assem-

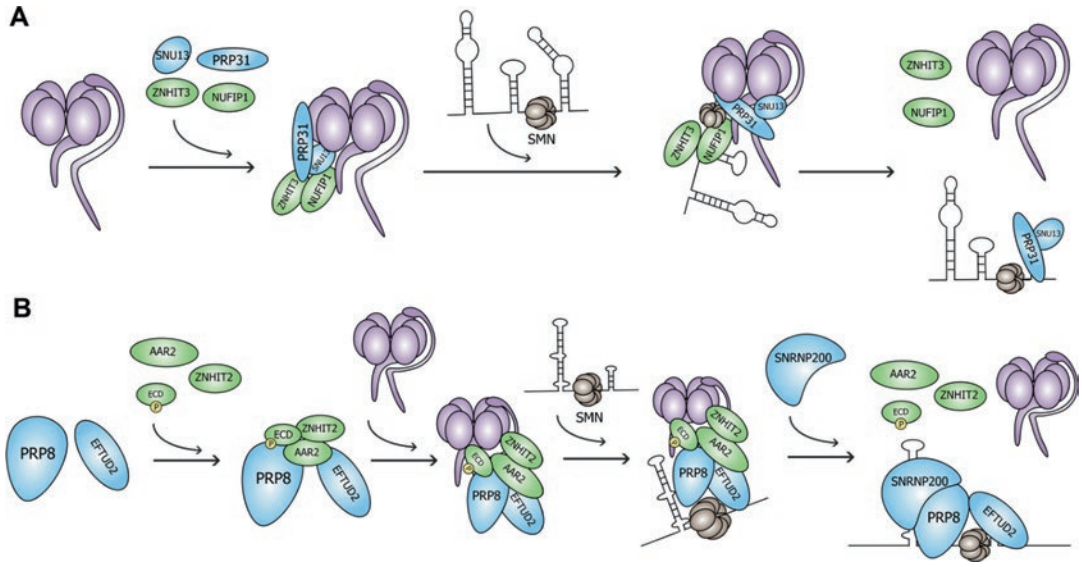

Fig. 4.5 snRNP complex assembly
R2TP-mediated assembly of (**a**) U4 snRNP and (**b**) U5 snRNP. R2TP subunits (purple), assembly factors (green), snRNP complex protein subunits (blue), SMN complex (grey), and RNA are shown

bled into a subcomplex by the AAR2 chaperone (Boon et al. 2007; Gottschalk et al. 2001). EFTUD2-PRP8 associate with U5 snRNA and then translocate to the nucleus where AAR2 is replaced by SNRNP200 (Boon et al. 2007). EFTUD2 and PRP8 regulate SNRNP200 activity, which unwinds the U4/U6 duplex to activate the spliceosome.

The R2TP complex was found to associate with PRP8 and EFTUD2 in the cytoplasm, and with SNRNP200 in the nucleus (Malinova et al. 2017). ZNHIT2 was identified as a putative U5 snRNP assembly factor when it was shown to associate with GFP-AAR2 (Malinova et al. 2017). ZNHIT2 was subsequently shown to associate with all U5 snRNP protein components and with all PAQosome subunits, except PDRG1 and RPB5 (Malinova et al. 2017), suggesting that ZNHIT2 bridges the interactions between U5 snRNP components and the PAQosome. ZNHIT2 was found to bind to RuvBL2 (Cloutier et al. 2017).

Although EFTUD2 can interact with PIH1D1, its phosphorylation, which is essential for U5 snRNP maturation, causes its interaction with PIH1D1 to become weaker (Malinova et al. 2017). Additionally, depletion of PIH1D1 enhanced PRP8 interaction with R2TP (Malinova et al. 2017). Furthermore, ZNHIT2 knockdown in HEK293 cells had reduced levels of RuvBL1 and RuvBL2 in PRF8- and EFTUD2-based purifications, while all other PAQosome subunits were not detected (Cloutier et al. 2017). These findings confirm that ZNHIT2 bridge interactions between U5 snRNP and RuvBL1/2 and suggest that only RuvBL1/2 are needed for later stages of U5 snRNP assembly.

Proper U5 snRNP assembly was also shown to depend on ECD, which interacts with the R2TP complex (Cloutier et al. 2017). ECD can bind to PIH1D1 in a phosphorylation-dependent manner and to RuvBL1 in a phosphorylation-independent manner (Horejsi et al. 2014; Mir et al. 2015). In addition, ECD interacted with AAR2 and with all components of the U5 snRNP (Claudius et al. 2014). Therefore, along with ZNHIT2, ECD bridges interactions between the R2TP complex and U5 snRNP (Mir et al. 2016).

4.3.3 PAQosome–Mediated Assembly of RNAP II

The RNAP II complex, which synthesizes mRNAs and capped noncoding RNAs, is comprised of 12 subunits that assemble in a stepwise fashion partly through PAQosome interactions (Fig. 4.6) (Boulon et al. 2010). Quantitative proteomics using SILAC on cells treated with RPB1 inhibitor α-amanitin and RPB1 nuclear exportin inhibitor leptomycin B revealed that cytoplasmic RPB1 and RPB8 formed a tight subcomplex that associated with PAQosome components RPAP3, PFDN2, and UXT (Boulon et al. 2010). Yeast two-hybrid and co-immunoprecipitation experiments confirmed RPB1 interactions with UXT and RPAP3 (Boulon et al. 2010). The RPB1-RPB8 subcomplex was stabilized through an RPAP3-mediated Hsp90 interaction (Boulon et al. 2010). Another study showed that RPB5 binds to and is stabilized by the non-canonical prefoldin subunit URI1 (Mita et al. 2013), suggesting that the RPB5-URI1 prefoldin complex may act as a scaffold for RPB1-RPB8 recruitment to RPAP3-Hsp90.

The SILAC proteomic analysis also showed that another subcomplex, comprised of RPB2-RPB3-RPB10-RPB11-RPB12, was also present after cells were treated with α-amanitin and leptomycin B (Boulon et al. 2010). When GFP-RPAP3 was used as bait, RPAP3 co-purified with RPB2, suggesting that RPAP3 may also mediate the interaction between the RPB1-RPB8 subcomplex and the RPB2-RPB3-RPB10-RPB11-RPB12 subcomplex (Boulon et al. 2010). To complete RNAP II assembly, RPB4-RPB7-RPB6 and RPB9 are integrated into the complex (Fig. 4.6). Finally, RNAP II nuclear translocation is mediated through its association with RPAP2 (Forget et al. 2013).

The PAQosome may also be involved in RNAP I and RNAP III assembly. In yeast, Bud27 interacted with RNAP I- and RNAP III-specific subunits, Rpa190 and Rpc25, respectively (Miron-Garcia et al. 2013). Bud27 mutant strains exhibited cytoplasmic accumulation of all RNAPs, and this defect was rescued by Rpb5 overexpression (Miron-Garcia et al. 2013). URI1/Bud27 may facilitate the correct assembly of Rpb5 with Rpb6, both of which are common to all three RNAPs (Miron-Garcia et al. 2013). In mammalian cells, affinity purification coupled to mass spectrometry experiments have also shown that R2TP/URI1 prefoldin subunits interact with components of all three RNAPs (Cloutier et al. 2009, 2017). These findings suggest that the PAQosome may have a general role for RNAP assembly.

4.3.4 PAQosome-Mediated Assembly of PIKK Complexes

The PIKK family of kinases and kinase-related proteins are essential for several fundamental biological processes such as DNA damage repair (ATM, ATR, DNA-PKc) (Shiloh 2003), nutrient signaling (mTOR) (Wullschleger et al. 2006), non-sense mediated mRNA decay (SMG-1) (Yamashita et al. 2005), and chromatin remodel-

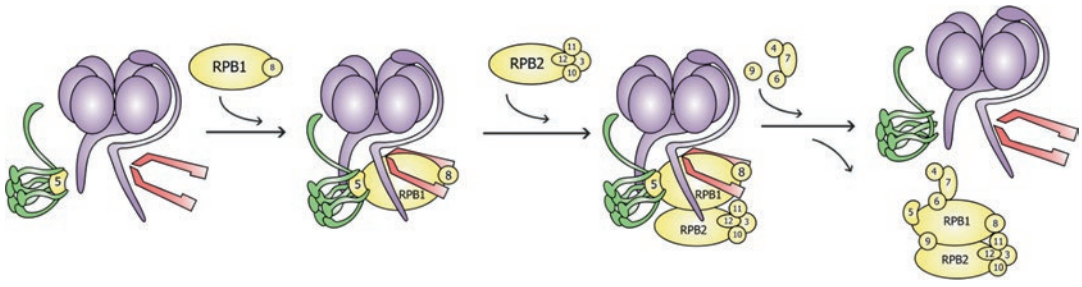

Fig. 4.6 RNAP II complex assembly and stabilization PAQosome-mediated assembly of RNAP II. R2TP subunits (purple), URI1 prefoldin subunits (green), RNAP II subunits (yellow) and Hsp90 (red) are shown. WDR92 has been omitted for clarity

ing (TRRAP) (McMahon et al. 2000). In response to energy status and metabolic stress, the R2TP complex regulates cell growth and proliferation by affecting PIKK protein levels, assembly, stabilization and signaling (Horejsi et al. 2010; Izumi et al. 2010, 2012) (Fig. 4.7). Similar to RNAP II, PIKK complex assembly and stabilization is also dependent on Hsp90 activity (Izumi et al. 2012; Takai et al. 2010).

The adaptor TTT complex, comprised of TEL2, TTI1 and TTI2, plays an essential role in R2TP-mediated PIKK assembly and stabilization (Fig. 4.7) (Horejsi et al. 2010; Hurov et al. 2010; Kaizuka et al. 2010; Takai et al. 2007, 2010). The TTT complex itself is essential and each subunit was shown to depend on another for stability (Hurov et al. 2010). In MEF cells grown under nutrient-rich conditions, the TTT complex was found to interact with RuvBL1/2 to assemble and stabilize active dimeric mTORC1 (mTOR, Deptor, MLST8, Raptor, PRAS40) at the lysosome (Kim et al. 2013; Yip et al. 2010). Interactions between mTOR and RuvBL1/2 are mediated by the adaptor protein WAC and PIH1D1 (David-Morrison et al. 2016; Kamano et al. 2013). In MCF-7 cells, PIH1D1 knockdown decreased mTORC1 assembly (Kamano et al. 2013).

The N-terminal of PIH1D1 was revealed to interact with TEL2 in a CK2-phosphorylation dependent manner (Horejsi et al. 2014, 2010; Pal et al. 2014). Phosphorylated TEL2 at S487 and S491 is required for PIH1D1 binding, and alanine mutations at these sites resulted in unstable mTOR and SMG-1 in MEF cells (Horejsi et al. 2010). In myeloma cells grown under nutrient-depleted conditions, CK2 phosphorylated TEL2 at S485 and TTI1 at S828 to facilitate their Fbxo-9 mediated-ubiquitination and proteasomal degradation when in complex with mTORC1 (Fernandez-Saiz et al. 2013) (Fig. 4.6).

In addition to mTORC1, the TTT complex and presumably R2TP are also essential for the assembly and stability of all other PIKKs. TEL2 deletion in MEFs reduced levels of PIKKs and affected the stability of ATM and mTOR (Takai et al. 2007). Hsp90 inhibition in HeLa cells affected TEL2 interactions with PIKKs and resulted in unstable ATR, mTORC1 and mTORC2 (mTOR, Deptor, MLST8, MAPKAP1, Rictor, Proctor) complexes (Takai et al. 2010). In HEK293T cells, TTI1 interacted with and stabi-

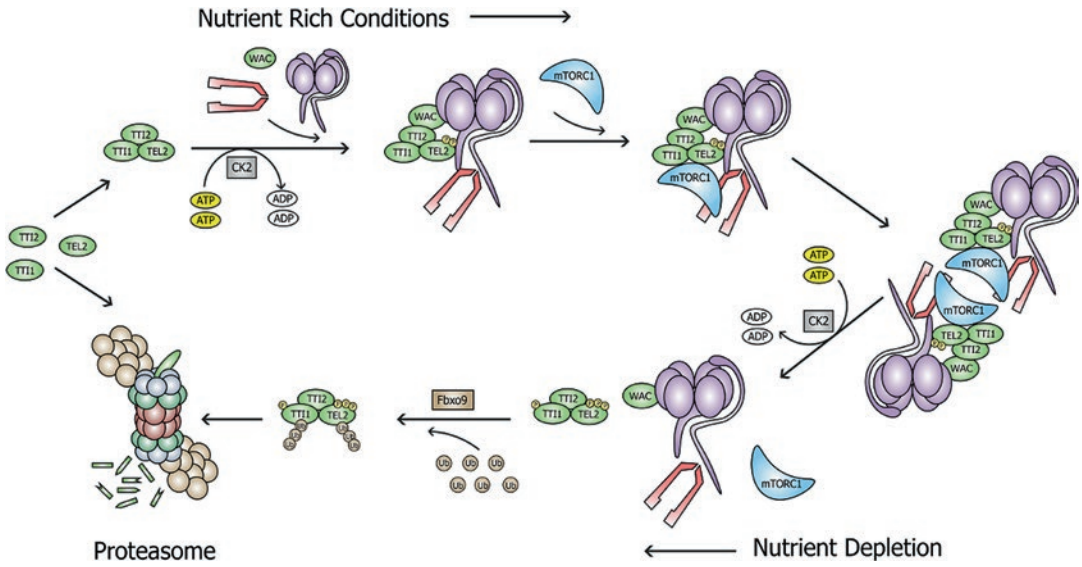

Fig. 4.7 Nutrient-dependent mTORC1 complex assembly and stabilization
R2TP-Hsp90-mediated assembly, stabilization and dimerization of the mTORC1. R2TP subunits (purple), Hsp90 (red), mTORC1 assembly factors (green), mTORC1 (blue), ubiquitin (brown circles), Fbxo9 (brown box), CK2 (grey box) and nucleotides (ATP, yellow ovals; ADP, white ovals) are shown

lized all six members of the PIKK family, and knockdown of TTI and TEL2 caused disassembly of mTORC1 and mTORC2 (Kaizuka et al. 2010). In addition, TTI1 can be phosphorylated by IP6K2 to enhance its ability to bind and stabilize DNA-PKcs and ATM (Rao et al. 2014). In yeast, Tti2 depletion resulted in decreased expression of Tra1 (TRRAP), Tel1 (ATM), and Mec1 (ATR), affected their localization, and inhibited stress responses (Hoffman et al. 2016; Kim et al. 2013). Furthermore, in addition to the TTT-Pih1 interaction, the TTT complex interacted with Asa1-Rvb1-Rvb2 to stabilize Tel1 and Mec1 (Goto et al. 2017).

4.3.5 PAQosome-Mediated Assembly of the MRN Complex

The MRN complex is essential for sensing and repairing DNA double strand breaks (Cannavo and Cejka 2014; Paull and Gellert 1998). The complex is comprised of exonuclease MRE11, DNA repair protein RAD50, and DNA damage sensor and PIKK scaffold protein NBS1. The complex associates with TRRAP and activates ATM and ATR as part of the DNA damage response (Buis et al. 2008; Robert et al. 2006; Zhong et al. 2005). Mutations in MRE11 and NBS1 have been linked to ataxia-telangiectasia-like disorder and Nijmegen breakage syndrome, respectively (Stewart et al. 1999; Varon et al. 1998), while mutations in both have been found in patients with breast and colon cancer (Chubb et al. 2016; Heikkinen et al. 2006).

The MRN complex may be stabilized by the PAQosome through the direct interaction between MRE11 and PIH1D1 (von Morgen et al. 2017). The interaction motifs on MRE11 are similar to the DpSDD/E CK2-phosphorylation dependent motifs on TEL2 (Horejsi et al. 2014; von Morgen et al. 2017). In addition, MRE11 must also be phosphorylated by CK2 at S688 and S689 before binding to PIH1D1 (von Morgen et al. 2017). In contrast to TEL2, MRE11 is further stabilized by additional phosphoserine sites. Point mutations in MRE11 at S688 and S689 caused a significant reduction in PIH1D1 binding, whereas additional mutations at S558, S561 and S649 completely abolished PIH1D1 binding (von Morgen et al. 2017).

4.3.6 PAQosome-Mediated Assembly of the TSC Complex

The TSC complex, comprised of TSC1, TSC2 and TBC1D7, acts as a tumor suppressor by inhibiting mTORC1 activity (Dibble et al. 2012; Huang and Manning 2008; Inoki et al. 2002). *TSC1* and *TSC2* mutations have been linked to tuberous sclerosis (Inoki et al. 2002; Kandt et al. 1992; van Slegtenhorst et al. 1997), which is a rare genetic disorder that causes non-malignant tumors to form in many different organs. TSC1 and TBC1D7 each have regulatory roles within the TSC complex. TSC1 stabilizes TSC2 to prevent its ubiquitin mediated degradation (Benvenuto et al. 2000), while TBC1D7 stabilizes the TSC1-TSC2 interaction (Dibble et al. 2012). TSC2 is a GTPase activating protein that targets G-protein Rheb and induces the dissociation of Rheb-GDP from mTORC1, resulting in the inactivation of mTORC1 (Inoki et al. 2003; Tee et al. 2003; Zhang et al. 2003).

The TSC complex may be stabilized through its interactions with PAQosome subunits. TSC1 and TSC2 were shown to associate with ectopically expressed URI1 and RPAP3 in HeLa cells (Cloutier et al. 2017). Another study showed that the N-terminal domain of PIH1D1 pulled down all three subunits of the TSC complex (Malinova et al. 2017). TAP-MS of all components of the TSC complex showed associations with RuvBL1, RuvBL2, WDR92, PIH1D1, RPAP3 and URI1 (Cloutier et al. 2017).

The significance of TSC complex interactions with the PAQosome are uncertain at this time. TSC1- and TBC1D7-based purifications did not yield high levels of TSC2, suggesting that TSC1 and TBC1D7 form a subcomplex (Cloutier et al. 2017). Therefore, binding of TSC1-TBC1D7 to TSC2 may be mediated by the PAQosome. Moreover, TSC1 was recently shown to be an Hsp90 co-chaperone that inhibits Hsp90 chaper-

one function, suggesting that the PAQosome may also function as a scaffold that bridges the interaction between TSC1 and Hsp90 (Woodford et al. 2017). Alternatively, the PAQosome may bind to the TSC complex as a way to block its inhibitory effect on mTORC1, during PAQosome-mediated mTORC1 stabilization (Huang and Manning 2008).

4.3.7 PAQosome-Mediated Assembly of Axonemal Dynein Arm Assembly

Cilia are small microtubule-based organelles that have roles in cell and fluid motility. Non-motile cilia consist of a ring of nine microtubule doublets called the axoneme. By contrast, motile cilia consist of an axoneme, as well as a central pair of microtubules in a 9 + 2 arrangement. In addition, the peripheral microtubules are attached to one another through dynein arms that provide the force needed for cilia movement. The dynein arms are preassembled in the cytoplasm before they are transported into the ciliary axoneme.

It has recently been demonstrated that RuvBL1 and RuvBL2 facilitate axonemal dynein arm assembly through R2TP-like complexes (Hartill et al. 2018; Li et al. 2017). Loss of function mutants of RuvBL1 and RuvBL2 in zebrafish, and a conditional knockout mouse model of RuvBL1 showed cilia motility defects (Li et al. 2017). Additionally, RuvBL2 interaction with dynein arm assembly factor LRRC6 was essential for cilia motility in zebrafish (Zhao et al. 2013). Furthermore, the dynein assembly factor DNAAF1 was shown to interact with RuvBL1/2 to facilitate axonemal dynein arm assembly during zebrafish cardiac development (Hartill et al. 2018).

RuvBL1/2 also associate with dynein assembly factors that show sequence similarities to PIH1D1 and RPAP3. The dynein arm assembly factors PIH1D2, PIH1D3 and DNAAF2 have the PIH1 domain (Omran et al. 2008; Yamaguchi et al. 2018), whereas DNAAF4 has both PIH1 and TPR domains (Tarkar et al. 2013). Similar to Tah1, DNAAF4 can also bind to Hsp90 (Chen et al. 2009). In zebrafish, mutations in PIH1- containing proteins PIH1D1, PIH1D2, PIH1D3 and DNAAF2 resulted in dynein arm loss and abnormal sperm motility (Yamaguchi et al. 2018). In addition, mutations in PIH1D3 caused defects in dynein arm assembly in mouse sperm and have been associated with X-linked primary ciliary dyskinesia in humans (Dong et al. 2014; Olcese et al. 2017).

WDR92 is also essential for dynein arm assembly. In humans, WDR92 is highly expressed in motile ciliated cells (Saeki et al. 2006), and WDR92 was required for the correct assembly of motile cilia in *S. Mediterranea* (Patel-King and King 2016). Moreover, WDR92 was essential for dynein arm assembly in Drosophila and associated with Spag1 (Zur Lage et al. 2018). In mammalian cells, WDR92 binds to RPAP3, potentially through the RPAP3 C-terminal domain (Itsuki et al. 2008). This domain is also present in an RPAP3-like protein named SPAG1 (not the RPAP3 Drosophila ortholog), as well as the ciliary dynein assembly factor CCDC103 (Chintalapudi et al. 2016; Knowles et al. 2013). Mutations in each of these proteins are associated with primary ciliary dyskinesia (Knowles et al. 2013; Panizzi et al. 2012). WDR92 was shown to interact with SPAG1, most likely as part of an R2TP-like complex that exclusively mediates dynein arm assembly (Cloutier et al. 2017).

Furthermore, SPAG1 was recently demonstrated to be part of an R2TP-like complex named R2SP which stands for RuvBL1-RuvBL2-SPAG1-PIH1D2 (Maurizy et al. 2018). Components of this novel complex were highly enriched in testis, suggesting a potential role in motile cilia formation (Maurizy et al. 2018). Similar to the R2TP complex, the R2SP complex also displayed chaperone activity. The R2SP complex was required for the assembly of complexes containing the scaffolding protein liprin-α2 (Maurizy et al. 2018). Interestingly, quaternary protein folding and assembly was strongest at 32°C, the optimal temperature for testis function (Maurizy et al. 2018).

4.4 The Potential Roles of the URI1 Prefoldin Complex

The role of the canonical prefoldin complex has been well established, whereas the role of the URI1 prefoldin complex has remained elusive since its initial discovery in 2003 (Gstaiger et al. 2003). The canonical prefoldin complex is known to be a chaperone mainly for cytoskeleton proteins actin, α-tubulin, and γ-tubulin (Geissler et al. 1998; Martin-Benito et al. 2002), suggesting that the URI1 prefoldin complex may have a related role in cytoskeleton protein complex assembly. Surprisingly, RNAi depletion of URI1, UXT, and PDRG1 in Drosophila sensory neurons and spermatocytes had no effect on ciliary dynein arm assembly (Zur Lage et al. 2018). Alternatively, similar to the recruitment mechanism between the canonical prefoldin complex and the CCT complex (Vainberg et al. 1998), the URI1 prefoldin complex may recruit client proteins to R2TP; however, a PAQosome client that binds specifically to the URI1 prefoldin complex has not been identified.

Studies investigating the non-nuclear roles of URI1 have provided some insight for potentially more specialized roles of the URI1 prefoldin complex and its effects on the R2TP complex. URI1 is the most structurally diverse subunit within the prefoldin family and likely mediates most URI1 prefoldin complex functions and interactions (Figs. 4.1 and 4.2). This is supported by the fact that the other URI1 prefoldin subunits do not have any significant roles outside of the nucleus.

One potential role for the URI1 prefoldin complex may be that it acts as a scaffold for RNAP II assembly. URI1 was initially reported as an RPB5 binding protein (Dorjsuren et al. 1998). Additionally, UXT was shown to interact with RPB1 in a yeast two-hybrid screen (Boulon et al. 2010). Although a scaffolding function for the URI1 prefoldin complex is probable, the URI1 prefoldin complex more likely evolved for more specialized roles since URI1 is conserved in yeast, while UXT and PDRG1 are absent.

Canonical prefoldin subunits stabilize and protect each other from ubiquitin-mediated degradation, and it was shown that PFDN2 and PFDN6 have longer half-lives than the other canonical prefoldin subunits, most likely because of their association with the URI1 prefoldin complex (Gstaiger et al. 2003; Simons et al. 2004). In a similar fashion, another possible role for the URI1 prefoldin complex may be to simply stabilize and protect each subunit of the complex from ubiquitin-mediated degradation before they are imported into the nucleus where they function as transcriptional regulators (Table 4.3). Indeed, URI1 was shown to affect the stability of UXT, PDRG1 and RPB5 (Mita et al. 2011, 2013). However, this hypothesis does not explain why the URI1 prefoldin complex associates with the R2TP complex.

The URI1 prefoldin complex may regulate the cellular localization of the PAQosome (Fig. 4.8). URI1 was reported to act as an effector of mTOR nutritional signaling (Gstaiger et al. 2003), and our group had demonstrated that localization of the R2TP complex depends on nutritional status (Kakihara et al. 2014). In yeast grown under nutrient rich conditions, the R2TP complex was localized in the nucleus, whereas under nutrient limiting conditions, the R2TP complex was localized in the cytoplasm (Kakihara et al. 2014). When URI1 was overexpressed in HLE hepatoma cells, it interacted with DMAP1 to facilitate its nuclear import (Delgermaa et al. 2004); however, when URI1 was overexpressed in prostate cancer cells, it failed to interact or colocalize with DMAP1 (Mita et al. 2013). Nevertheless, a proteomic analysis identified all subunits of the PAQosome as nuclear URI1 interactors (Mita et al. 2013).

URI1 may also be involved in the nuclear import of PAQosome-bound RNAP II (Fig. 4.8). siRNA-mediated URI1 silencing in pulmonary fibroblasts resulted in the cytoplasmic accumulation of RPB1 (Miron-Garcia et al. 2013). Furthermore, mutant yeast strains lacking Bud27 resulted in the cytoplasmic accumulation of all three RNAPs (Miron-Garcia et al. 2013). When prostate cancer cells were treated with a compound that stalled RNAP II on DNA, but did not

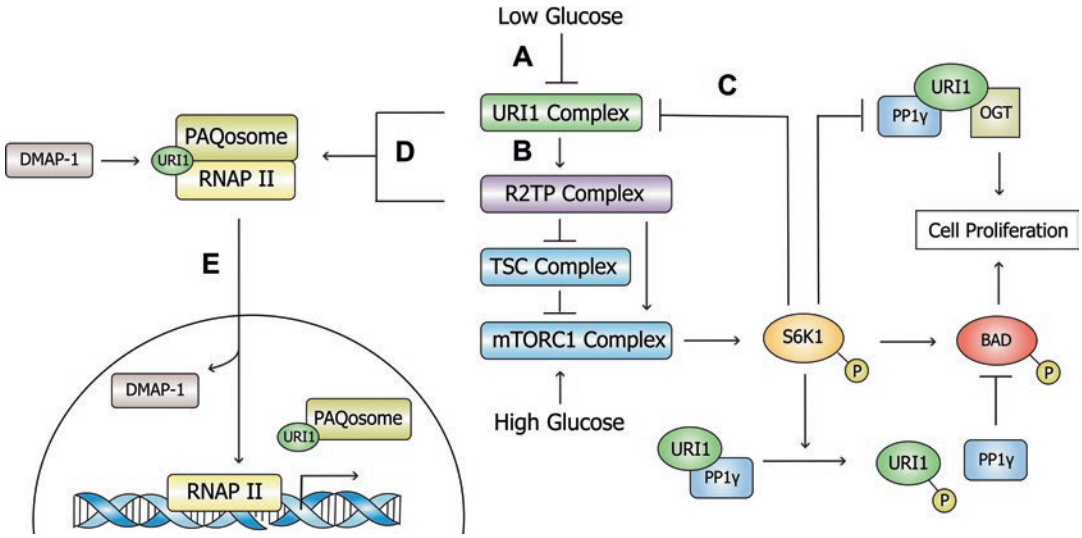

Fig. 4.8 Overview of pathways involving the URI1 prefoldin complex
Letters indicate specific roles of the URI1 prefoldin complex. (**a**) URI1 is phosphorylated in nutrient depleted conditions which may affect URI1 prefoldin complex assembly. (**b**) URI1 prefoldin complex may stabilize or enhance R2TP activity through scaffolding client proteins. (**c**) The URI1 prefoldin complex may regulate R2TP complex activity through a negative feedback mechanism involving R2TP client complex mTORC1 and its effector S6K1. Activation of S6K1 enhances cell proliferation, which is also regulated through negative feedback mechanisms. (**d**) URI1-RPB5 may mediate RNAP II assembly by folding and stabilizing RPB5, or by acting as a scaffold for RPB1. (**e**) DMAP-1 interacts with URI1, which may mediate PAQosome-RNAP II nuclear localization. See text for more details

induce its disassembly, URI1 was mostly nuclear (Mita et al. 2013), suggesting that the PAQosome could potentially stabilize RNAP II during transcription. URI1 was shown to interact with the nuclear exportin CRM1, the same exportin used by RNAP subunits, to facilitate its export into the cytosol (Fornerod et al. 1997; Mita et al. 2013). Taken together, these findings suggest that in addition to a scaffolding role, the URI1-RPB5 interaction may be essential for PAQosome nuclear localization and its continued stabilization within the nucleus.

If the URI1 prefoldin complex indeed stabilizes the R2TP complex, then the PAQosome may regulate itself through a negative feedback mechanism that depends on cellular energy status (Fig. 4.8). Under nutrient limited conditions, URI1 is phosphorylated by PKA at S371 and cannot bind PP1γ (Buren et al. 2016). Under nutrient rich conditions, non-phosphorylated URI1 is bound to PP1γ and OGT, which subsequently enhances c-myc levels to promote cell growth (Buren et al. 2016). URI1 phosphorylation may therefore affect the structural integrity of the PAQosome. Many other post-translational modification sites on URI1 have been identified, but their significance is unknown (Mita et al. 2013).

URI1 may play a key role in R2TP-mediated assembly pathways related to cell proliferation and survival (Fig. 4.8), which would explain why URI1 is perhaps the most overexpressed PAQosome subunit in cancer (Fan et al. 2014; Gomes et al. 2016; Gu et al. 2013; Gu et al. 2015; Hu et al. 2016; Lipinski et al. 2016; Luo et al. 2016; Theurillat et al. 2011; Tummala et al. 2014, 2017; Wang et al. 2014, 2015b; Xu et al. 2017; Yang et al. 2011, 2013; Zhang et al. 2015; Zhou et al. 2014, 2017b). In response to growth factors, the R2TP complex stabilizes the mTORC1 complex at the lysosome (Kim et al. 2013; Takai et al. 2007, 2010). R2TP may also bind to the TSC complex to prevent its inhibitory effect on mTORC1 (Cloutier et al. 2017; Malinova et al. 2017). The mTORC1 complex activates S6K1, which subsequently activates antiapoptotic factor

BAD to promote cell survival (Djouder et al. 2007; Harada et al. 2001; Theurillat et al. 2011) (Fig. 4.8). Activation of S6K1 also phosphorylates URI1 which could inhibit the PAQosome (Djouder et al. 2007; Theurillat et al. 2011). In addition, URI1 phosphorylation releases URI1 bound PPIγ to inactivate BAD through a negative feedback mechanism (Djouder et al. 2007) (Fig. 4.8). When URI1 is upregulated in cancer, it acts as an oncogene through excessive PPIγ phosphatase binding and PAQosome-mediated mTORC1 stabilization, which leaves BAD constitutively active, even under low growth factor conditions (Theurillat et al. 2011). Altogether, these findings suggest that URI1 acts as the signal integrator within the PAQosome.

4.5 Concluding Remarks

Since the R2TP complex was first identified in 2005, remarkable progress has been made in understanding the role of R2TP in macromolecular complex assembly. The recently reported high resolution cryo-EM structures of both yeast and human R2TP are beginning to shed light on this complicated system (Martino et al. 2018; Rivera-Calzada et al. 2017; Tian et al. 2017). A thorough understanding of the R2TP assembly mechanisms would be extremely useful for identifying new ways of targeting R2TP client complexes that are involved in cancer such as the MRN, TSC and mTOR complexes.

In contrast to the R2TP complex, the URI1 prefoldin complex has gone unnoticed. As we have mentioned above, the PAQosome likely functions as a single unit in which the URI1 prefoldin complex acts as the regulatory module, whereas the R2TP complex acts as the catalytic component. In order to gain a deeper understanding of how the R2TP complex functions and how it is assembled, the role of the URI1 prefoldin complex warrants further investigation.

Acknowledgements We thank members of the Houry group for careful reading of the manuscript. This work was funded by the Canadian Institutes of Health Research grant MOP-93778 to WAH.

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