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The Arabidopsis Nuclear Pore and Nuclear Envelope

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The nuclear envelope is a double membrane structure that separates the eukaryotic cytoplasm from the nucleoplasm. The nuclear pores embedded in the nuclear envelope are the sole gateways for macromolecular trafficking in and out of the nucleus. The nuclear pore complexes assembled at the nuclear pores are large protein conglomerates composed of multiple units of about 30 different nucleoporins. Proteins and RNAs traffic through the nuclear pore complexes, enabled by the interacting activities of nuclear transport receptors, nucleoporins, and elements of the Ran GTPase cycle. In addition to directional and possibly selective protein and RNA nuclear import and export, the nuclear pore gains increasing prominence as a spatial organizer of cellular processes, such as sumoylation and desumoylation. Individual nucleoporins and whole nuclear pore subcomplexes traffic to specific mitotic locations and have mitotic functions, for example at the kinetochores, in spindle assembly, and in conjunction with the checkpoints. Mutants of nucleoporin genes and genes of nuclear transport components lead to a wide array of defects from human diseases to compromised plant defense responses. The nuclear envelope acts as a repository of calcium, and its inner membrane is populated by functionally unique proteins connected to both chromatin and—through the nuclear envelope lumen—the cytoplasmic cytoskeleton. Plant nuclear pore and nuclear envelope research—predominantly focusing on Arabidopsis as a model—is discovering both similarities and surprisingly unique aspects compared to the more mature model systems. This chapter gives an overview of our current knowledge in the field and of exciting areas awaiting further exploration.

INTRODUCTION

The nucleus is the most prominent compartment of any eukaryotic cell, and home to its genetic information. The nucleoplasm is surrounded by a double membrane system, termed the nuclear envelope (NE). The two lipid bilayers each form a flat, spheroid membrane sheet. The two sheets are juxtaposed by a perinuclear space of an apparently even separation of ca. 30 to 50 nm (Hetzer et al. 2005). The outer nuclear membrane (ONM) is continuous with the ribosome-associated endoplasmic reticulum (ER), thus allowing for direct insertion of NE membrane proteins and translocation of proteins into the perinuclear space (Hetzer and Wente 2009). The inner nuclear membrane (INM) has a distinct protein composition and specialized functions. The nuclear envelope has several main functions. It separates the biochemical environment of the nucleus from that of the cytoplasm, and mediates and regulates the selective exchange of molecules between the nucleus and cytoplasm (nucleocytoplasmic transport) (Carmody and Wente 2009; Terry et al. 2007).

The INM and ONM are fused at specific sites to form aqueous pores. Inserted at these sites are the nuclear pore complexes (NPCs), which occupy these pores. NPCs are large protein conglomerates responsible for the selective import and export of macromolecules traversing the envelope (Brohawn et al. 2009; D'Angelo and Hetzer 2008). Both the nuclear pores and the nuclear envelope act as anchoring sites for chromatin and this chromatin association is involved in gene activation and repression (Akhtar and Gasser 2007; Capelson and Hetzer 2009; Kalverda et al. 2008). In higher organisms, the NE plays a role in the dissociation and re-formation of the nucleus during cell division (Kutay and Hetzer 2008). Proteins interacting in the NE lumen connect the nucleoplasm and cytoplasm through the nuclear envelope, thereby transmitting information from the cytoskeleton and giving rise to nuclear mobility (Burke and Roux 2009). Like the ER, the NE lumen acts as a repository of calcium, and ion transporters in both the ONE and INE are involved in signal transduction (Bootman et al. 2009; Erickson et al. 2006).

Signal transduction chains frequently include a nuclear import step that can be rate limiting or regulated (for an example from plants, see Lee et al. 2008). Similarly important are the nuclear export of proteins and of the different RNAs, including mRNA, tRNAs and the diverse regulatory small RNAs (Kohler and Hurt 2007). In yeast, components of the NPC are directly involved in mRNA quality control prior to export, preventing for example the export of incompletely spliced mRNAs (Fasken and

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Corbett 2009). Together, the nuclear envelope and NPCs are at the crossroad of communication between nucleus and cytoplasm. In this chapter, we give an overview of composition and structure, biological activities and regulatory roles, and the connection to many aspects of the plant life cycle of these important cellular components, particularly in Arabidopsis.

NUCLEAR PORES

Nuclear Pore Complexes

Macromolecules enter and exit the nucleus by trafficking through NPCs. The complexity of these large, 40-60 MDa protein complexes has for decades limited their detailed structural analysis. More recently, however, structural biologists have taken advantage of the intrinsic modularity of the NPC, and are making progress toward deciphering this nanomachine in detail. Structures of several of the stable building blocks of the NPC have been solved, and several models for their assembly have been proposed (Brohawn et al. 2009; Elad et al. 2009). To approximate the molecular architecture of the yeast NPC, a diverse set of biophysical and proteomic data was collected and used to model localization of the NPC's 456 constituent proteins. The proposed structure shows that roughly half of the NPC is composed of a core scaffold, with structural similarity to vesicle-coating complexes. This scaffold coats the curved surface of the nuclear envelope membrane. The selective barrier for transport is formed by disordered repeat regions of proteins (FG-repeats) that line the inner face of the scaffold. Accordingly, the NPC consists of only a few structural modules and is organized in a 16-fold repetition of 'columns' (Alber et al. 2007).

The FG-nucleoporins (FG-Nups) coordinate and potentially regulate translocation through the NPC. The extensive repeats of phenylalanine-glycine (FG) in each FG-Nup directly bind to shuttling transport receptors moving through the NPC. The exact mechanism of the path through the pore and its biochemistry and biophysics have not been clarified, but much progress has been made recently to refine our understanding of the roles of the FG-Nups. Several elegant approaches show that selective pores can be reconstituted from defined components *in vitro* and that the selectivity is largely due to FG-Nups that form hydrogels that reseal upon translocation of molecules through the pore (Frey and Gorlich 2007; Frey et al. 2006; Jovanovic-Talisman et al. 2008). For a recent review on the different models of nuclear pore transversion, see Walde and Kehlenbach (2010).

Until recently, NPCs were viewed as relatively static structures, embedded in the NE and controlling the molecular trafficking between nucleus and cytoplasm. Now, it has become evident that nuclear pore complexes are instead highly dynamic and are involved in diverse cellular processes, which range from the organization of the cytoskeleton to gene expression. Enzymatic activities at the NPC regulate nucleocytoplasmic transport and use the NPC as a regulatory scaffold, while nucleoporins may regulate gene expression by contacting chromatin. Thus, discriminating between the effects of individual nucleoporins on transport, scaffolding, or gene expression is a major challenge in understanding the role of the NPC (D'Angelo and Hetzer 2008; Xylourgidis and Fornerod 2009).

Plant Nuclear Pore Structure

For many years, plant biologists have relied on images of yeast and vertebrate NPCs informing about the high-resolution organization of the NPC. Reviews about the plant NPC tended to cite the early study by Roberts and Northcote (Roberts and Northcote 1970) as the most recent high-resolution ultrastructure work on the plant NPC. This situation has now changed with the 2009 publication by Fiserova et al. (Fiserova et al. 2009) providing an in-depth view of the tobacco BY2 cell and onion root cell NE and NPC structure and organization. The authors used in-lens feSEM (field emission electron scanning microscopy) to visualize the NPC from both the nuclear and the cytoplasmic surface of the NE, and have compared NPC ultrastructure in quiescent and dividing BY2 cells. They show that the plant NPC closely resembles the known yeast and vertebrate NPCs and that its diameter falls somewhat between those (plant ~105 nm, *Xenopus laevis* ~110-120 nm, yeast ~95 nm). Plant NPCs appear to be surprisingly densely spaced (~ 50 NPCs per μm^2 compared to 60 NPCs per μm^2 for *X. laevis* oocytes, considered very rich in NPCs). Interestingly, the NPCs are not randomly distributed but rather aligned in rows, similar to other higher eukaryotes, but different from yeast (Belgareh and Doye 1997; Maeshima et al. 2006).

Plant Nucleoporins

In earlier studies, several candidate plant nucleoporins (Nups) were described. A 100 kD carrot nuclear matrix protein associates closely with the NPC, and is recognized by antibodies against mammalian and yeast nucleoporins (Scofield et al. 1992), but the identity of this protein remains unknown. Eight proteins associated with the tobacco NE were identified through their *N*-acetylglucosamine (GlcNAc) modification (Heese-Peck et al. 1995). The association of these proteins with the plant NPC and their potential function have not been tested. More recently, several proteins with significant similarity to animal and yeast nucleoporins have been identified in forward genetic screens for diverse pathways. In addition, reverse genetic approaches with Nup homologs have revealed impairment of flowering-time regulation and overall plant development. Some of the phenotypes are shared with mutants in components of the protein import and RNA export machinery (Table 1).

Putative Arabidopsis Nup160 and Nup96 were identified as suppressors of *auxin-resistant 1* (*axr1*), SUPRESSOR OF AXR1 1 and 3 (SAR1 and SAR 3) (Parry et al. 2006). In *sar1* and *sar3*, the morphological and molecular phenotypes of *axr1* are partially restored. Among other defects in nucleocytoplasmic trafficking found in *sar1* and *sar3*, nuclear import of the repressor IAA17 was affected. This suggests that reduced nuclear import of transcriptional Aux/IAA repressors might counteract their over-accumulation based on reduced proteolysis in the *axr1* background. A defect in Nup160/SAR1 was also found to sensitize plants to chilling stress and disrupt acquired freezing tolerance (Dong et al. 2006).

R proteins are intracellular immune sensors, typically of the NB (nucleotide binding)-LRR (leucine-rich repeat) type, that act as regulatory signal transduction switches upon sensing isolate-specific pathogen effectors. A gain-of-function mutation in the Arabidopsis *SNC1* R gene leads to constitutive SNC1 activity and constitutive

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Table 1. Categories of characterized plant NE/NPC-associated proteins

Protein	Plant Species	Localization	Related Process	Reference
Nucleoporins				
Nup160/ SAR1	*Arabidopsis thaliana*	NE/NPC	mRNA export Flowering time control Auxin response Cold stress response	Dong et al., 2006; Parry et al., 2006
Nup96/ MOS3/ SAR3	*Arabidopsis thaliana*	NE/NPC	Immune response (basal and R protein-mediated) Protein nuclear import mRNA export Auxin response	Parry et al., 2006; Zhang and Li, 2005
Nup88/ MOS7	*Arabidopsis thaliana*	NE/NPC	Immune response (basal and R protein-mediated) Protein nucleocytoplasmic transport Protein stability	Cheng et al., 2009
Nup133	*Lotus japonicus*	NE/NPC	Calcium spiking Rhizobial and fungal symbiosis	Kanamori et al., 2006
Nup85	*Lotus japonicus*	NE/NPC	Calcium spiking Bacterial and fungal symbiosis	Saito et al., 2007
NUA/ AtTPR	*Arabidopsis thaliana*	INE/NPC	mRNA export miRNA homeostasis Auxin response Flowering time control	Xu et al., 2007b Jacob et al., 2007
Putative Nucleoporins				
WIP1, 2, 3	*Arabidopsis thaliana*	ONE/NPC	RanGAP NE localization	Xu et al., 2007a
WIT1, 2	*Arabidopsis thaliana*	NE/NPC Nucleus	RanGAP NE localization SUMO homeostasis Heat stress response	Zhao et al., 2008; Brkljacic et al., unpublished
gp210	*Arabidopsis thaliana*	POM	Unknown	Cohen et al., 2001
NDC1	*Arabidopsis thaliana*	POM	Unknown	Xu and Meier, 2008
Nuclear matrix protein/Nsp1, Nup62-like	*Daucus carota*	Nuclear pore	Unknown	Scofield et al., 1992
NE-associated proteins				
WPP1, 2 LeMAF1	*Arabidopsis thaliana* *Solanum lycopersicum*	NE/NPC Cell plate	WIT1 localization	Patel et al., 2004 Brkljacic et al., 2009
NMCP1 LINC1, 2	*Daucus carota* *Arabidopsis thaliana*	INE/Nuclear periphery Nucleoplasm	Nuclear size and morphology	Masuda et al., 1997 Dittmer et al., 2007
AtSUN1, 2	*Arabidopsis thaliana*	INE	Nucleo-cytoskeletal bridging*	Graumann et al., 2010
LeFPP1-7	*Solanum lycopersicum*	Unknown	Unknown	Gindullis et al., 2002
CASTOR	*Lotus japonicus*	Chloroplast ONE or INE	Cation channel	Imaizumi-Anraku et al., 2005 Charpentier et al., 2008
POLLUX DMI1	*Lotus japonicas* *Medicago truncatula*	Chloroplast ONE and INE	Cation channel	Imaizumi-Anraku et al., 2005 Charpentier et al., 2008 Riely et al., 2007
Spc98p	*Arabidopsis thaliana*	Nuclear periphery	MT nucleation*	Erhardt et al., 2002
GCP4	*Arabidopsis thaliana*	Unknown	MT nucleation	Kong et al., 2010
Histone H1	*Nicotiana tabacum cv. BY2*	Nuclear periphery Nucleus Mitotic spindle	MT nucleation	Hotta et al., 2007 Nakayama et al., 2008
TPX2	*Arabidopsis thaliana*	Nucleus Nuclear periphery Mitotic spindle	NEBD Spindle assembly	Vos et al., 2008

(Continued)

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Table 1. (continued)

Protein	Plant Species	Localization	Related Process	Reference
Rae1	*Nicotiana benthamiana*	Nuclear periphery PPB Mitotic spindle Cell plate	mRNA export Mitosis Spindle assembly Chromosome segregation	Lee et al., 2009
LOS4	*Arabidopsis thaliana*	NE	mRNA export Cold stress response	Gong et al., 2005
ESD4	*Arabidopsis thaliana*	Nuclear periphery Nucleus	SUMO homeostasis Flowering time control	Reeves et a., 2002 Murtas et al., 2003
Ran cycle components				
Ran1, 2, 3	*Arabidopsis thaliana* *Triticum aestivum* *Oryza sativa*	ONE/Nuclear periphery	Mitosis Auxin response ABA response Salt stress response Osmotic stress response	Wang et al., 2006; Zang et al., 2010
NTF2a, b	*Arabidopsis thaliana*	NE Nucleus Cytoplasm	Protein nuclear import	Zhao et al., 2006b
RanBP1a, b, c	*Arabidopsis thaliana*	Nuclear periphery	Mitosis Auxin response	Kim et al., 2001 Cho et al., 2008
RanGAP1	*Arabidopsis thaliana*	ONE/NPC PPB CDS Cell plate	Cytokinesis	Rose and Meier, 2001 Jeong et al., 2005 Xu et al., 2008
RanGAP2	*Solanum tuberosum* *Nicotiana benthamiana* *Arabidopsis thaliana*	NE	Immune response Cytokinesis	Sacco et al., 2007 Tameling and Baulcombe, 2007 Rairdan et al., 2008 Sacco et al., 2009 Brkljacic et al., unpublished
Nuclear transport receptors				
MOS6/ Importin α3	*Arabidopsis thaliana*	Nucleus	Immune response	Palma et al., 2005
Importin α4	*Arabidopsis thaliana*	Unknown	Nuclear import of T-DNA	Bhattacharjee et al., 2008
Importin α1	*Arabidopsis thaliana*	Nuclear periphery Nucleus Cytoplasm	Protein nuclear import	Smith et al., 1997
SAD2/ Importin β	*Arabidopsis thaliana* *Oryza sativa*	Nucleus	Protein nuclear import ABA response Osmotic stress response Cold stress response UV-B response	Verslues et al., 2006 Zhao et al., 2007 Gao et al., 2008 Jiang et al., 1998
XPO1a, b/ Exportin 1	*Arabidopsis thaliana*	Unknown	Gametophyte development	Haasen et al., 1999 Blanvillain et al., 2008
TRN1/ Transportin 1	*Arabidopsis thaliana*	Unknown	Protein nuclear import	Ziemienowicz et al., 2003
HASTY/ Exportin 5	*Arabidopsis thaliana*	Unknown	miRNA export	Bollman et al., 2003 Park et al., 2005
PAUSED/ Exportin-t	*Arabidopsis thaliana* *Oryza sativa*	Nucleus/ Cytoplasm	t-RNA export	Hunter et al., 2003 Park et al., 2005 Yao et al., 2008

* Indicates putative function. Abbreviations: CDS-cortical division site; INE-inner nuclear envelope; NE-nuclear envelope; NEBD-nuclear envelope breakdown; NPC-nuclear pore complex; ONE-outer nuclear envelope; POM-pore membrane nucleoporin; PPB-preprophase band.

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defense response. Suppressors of *snc1* (*modifiers of snc1, mos*) include MOS3 (Nup96), which is identical to SAR3 (Zhang and Li 2005), MOS6 (Importin alpha 3) (Palma et al. 2005) and MOS7, (Nup88) (Cheng et al. 2009).

Two loss-of-function alleles of putative Nup133 and Nup85 affect nodulation and mycorrhiza in *Lotus japonicus* (Kanamori et al. 2006; Saito et al. 2007). The two *Lotus* Nups are required for nucleus-associated calcium spiking during symbiotic signal transduction, suggesting a role in transducing a calcium signal at the nuclear pore. Calcium-mediated structural changes have been shown at the *X. laevis* NPC and a function for the NPC as a gated ion channel has been proposed (Bustamante 2006; Stoffler et al. 1999). Currently, the molecular mechanism underlying the Nup-dependent calcium spiking in *Lotus* is not known.

An additional Nup mutant with an extremely early-flowering phenotype was identified in a reverse genetic study targeting Arabidopsis nuclear long coiled-coil proteins (Xu et al. 2007b). NUA (Nuclear Pore Anchor) is a long coiled-coil protein located at the inner nuclear envelope, consistent with the association with the inner nuclear basket of its human and its yeast homologs Tpr (Translocated Promoter Region) and Mlp1/Mlp2 (Myosin-like proteins 1 and 2), respectively (Cordes et al. 1997; Strambio-de-Castillia et al. 1999; Xu et al. 2007b). NUA was also identified in a screen for mutants that suppress the expression of the floral repressor FLC (Flowering Locus C) (Jacob et al. 2007). In yeast, the TREX-2 complex, involved in mRNA export, is associated with the NPC through binding the nucleoporin Nup1. Orthologs of several TREX-2 components, as well as Nup1 have recently been identified in Arabidopsis (Lu et al. 2010).

While the plant nuclear pore proteome still awaits full identification, it is interesting that already now likely plant-specific components have been found. A group of putative plant specific Nups are the members of the WIP and WIT protein families. They share a function of anchoring RanGAP to the NE and a structure with a coiled-coil protein interaction domain adjacent to a C-terminal transmembrane domain (CC-TMD proteins). Both the WIP and the WIT proteins families likely reside at the nuclear pore and have no counterparts outside the land plant lineage (Xu et al. 2007a; Zhao et al. 2008).

NUCLEOCYTOPLASMIC TRAFFICKING

The Ran Cycle

The small GTP-binding protein Ran is a crucial component of nuclear import and export. GTPase activating protein (RanGAP) and Ran binding proteins 1 and 2 (RanBP1 and RanBP2) are localized to the cytoplasmic side of the NPC, whereas the nucleotide exchange factor for Ran, named RCC1, is localized inside the nucleus. These localizations are thought to establish a gradient of high RanGDP in the cytoplasm and high RanGTP in the nucleus, which determines the directionality of nucleocytoplasmic transport. RanGTP dissociates imported cargo from import receptors, but stabilizes complexes between export receptors and their cargo. After an export receptor/cargo complex reaches the cytoplasm, it in turn is dissociated due to hydrolysis of Ran-bound GTP to GDP ((Stewart 2007) and therein). Ran has been cloned from several plant species and plant Ran proteins suppress the *pim1* mutation in *Schizosaccharomyces pombe*, demonstrating that they are functional (Ach and Gruissem 1994; Merkle et al. 1994). Overexpression of wheat Ran1 in rice and Arabidopsis was shown to cause meristem changes, alterations in mitotic progress, and an altered sensitivity to auxin (Wang et al. 2006). Overexpression of rice Ran2 in rice and Arabidopsis was shown to cause hypersensitivity to salinity and osmotic stress (Zang et al. 2010). The molecular causes of these phenomena and their connection to nucleocytoplasmic trafficking are not known. In addition, Arabidopsis Ran2 has been found in a yeast two-hybrid screen as an interactor of a phragmoplastin-interacting protein and was shown to be localized in the perinuclear region with the highest concentration at the nuclear envelope (Ma et al. 2007). In another yeast two-hybrid screen, Arabidopsis Ran3 was found to interact with a methyl CpG-binding protein, and both proteins were found localized in the nucleus during interphase and primarily around chromatin during mitosis (Yano et al. 2006). Arabidopsis RanBP1a and RanBP1b are about 60% similar to mammalian and yeast RanBP proteins and antisense of Arabidopsis RanBP1c renders transgenic roots hypersensitive to auxin and alters auxin-induced root growth and development by arresting mitotic progress (Cho et al. 2008; Haasen et al. 1999a; Kim et al. 2001; Kim and Roux 2003). Arabidopsis has two copies of RanGAP, and Arabidopsis and Medicago RanGAPs were shown to complement the yeast RanGAP mutant *rna1* (Pay et al. 2002). *Nicotiana benthamiana* and potato RanGAP2 have been found to interact with the NB-LRR resistance protein Rx of Potato Virus X and found required for extreme resistance to Potato virus X, as discussed in more detail below (see The Role of the NPC in Plant Innate Immunity). No plant homologs of RCC1 have been identified yet.

The domain organization of RanGAP differs significantly across kingdoms, with metazoan and plant RanGAPs containing specific, distinct NE targeting domains at their C-terminus and N-terminus, respectively (Rose and Meier 2001). Metazoan RanGAPs have a C-terminal, sumoylated, unique domain that binds the nucleoporin RanBP2/Nup358. No RanBP2/Nup358 homolog appears to exist in plants. Plant RanGAPs share a plant-specific N-terminal WPP domain. The WPP motif within the WPP domain is required for the NE targeting. The WPP domain of plant RanGAPs has sequence similarity with a small plant protein family named WPP-domain proteins. Other than the WPP-domain that resembles the N-terminus of RanGAP, this group of proteins has no other functionally recognizable domains. WPP-domain proteins are also associated with the NE (Patel et al. 2004).

Two families of proteins were identified that target Arabidopsis RanGAP to the NE. WPP-domain interacting proteins (WIPs) were identified in a yeast two-hybrid screen using Arabidopsis RanGAP1 as bait. They contain a coiled-coil domain and a C-terminal putative transmembrane domain (TMD). This domain structure was named CC-TMD for coiled-coil-transmembrane domain. No WIP-like proteins have been identified from non-plant species (Xu et al. 2007a). Using Arabidopsis WPP1 and WPP2 as baits for tandem-affinity purification coupled with mass spectrometry, a second, related class of CC-TMD proteins was identified (WIT1 and WIT2). Like WIP1, 2a and 3, WIT1 and WIT2 are necessary for RanGAP association with the NE in root tip cells (Zhao et al. 2008). Neither WIP nor WIT proteins appear to be conserved outside the plant lineage, indicating that RanGAP targeting to the NE has evolved at least twice, in plants and animals, utilizing different domains and interaction partners.

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Protein Nuclear Import

Proteins to be imported into the nucleus generally contain small peptide sequence motifs recognized by import receptors. The best understood signal is the classical nuclear localization signal (NLS), which typically consists of one or two clusters of basic amino acid residues. In animals and yeast, nuclear import receptors (karyopherins) of the importin β type (also called karyopherin β) are the main nuclear import receptors. While importin β type karyopherins can directly bind to many NLS-containing cargos, often importin α adaptors bind the cargo protein and importin β then binds to importin α. Additional nuclear import signals include the M9 domain (recognized by transportin) and the IBB domain. For a more thorough overview of non-plant karyopherins and nuclear localization signals, see the excellent recent reviews in the field (Lange et al. 2007; Stewart 2007; Wagstaff and Jans 2009).

Homologs of both importin α and importin β have been identified in plants. The Arabidopsis importin α1 homolog binds *in vitro* to all three types of animal NLS (Hicks and Raikhel 1993; Hicks et al. 1995). Arabidopsis has eight putative importin α genes, seven of which code for proteins containing all functional domains, and 17 importin β-like nuclear transport receptors, whereas the human genome encodes at least 21 importin β-like proteins (Kanneganti et al. 2007; Merkle 2009). Characterized plant importin β-like proteins (including exportins) include SAD2 (RanBP7/8) (Zhao et al. 2007), rice imp β (Jiang et al. 1998), Exportin 2 (Haasen and Merkle 2002), Transportin 1 (Ziemienowicz et al. 2003), Exportin 1 (Haasen et al. 1999b), Exportin T (Hunter et al. 2003) and Exportin 5 (Bollman et al. 2003; Park et al. 2005). For the adaptors, MOS6 (Palma et al. 2005) and IMPα-4 (Bhattacharjee et al. 2008) have been investigated. Interestingly, all plant importin α proteins appear to fall into the imp α1-like clade, while in metazoans, imp α1, α2, and α3 clades exist (Mason et al. 2009). The functional significance of the loss of imp α2 and α3 and the expansion of the α1 clade in plants are currently not known. It will be interesting to investigate potential cargo specificity of the eight Arabidopsis importin α proteins.

One striking difference between plant and animal nuclear import is that permeabilized plant protoplasts cannot be depleted of cytoplasmic factors involved in nuclear import. Also, nuclear transport in plant systems is not inhibited by low temperature, as is nuclear import in HeLa cells (Hicks et al. 1996; Merkle et al. 1996). This experimental difference, which caused plant importins to be analyzed in mammalian *in vitro* import systems rather than plant systems (Hubner et al. 1999), might point to fundamental differences in the organization or mechanisms of plant nuclear import receptors *in vivo*. Interestingly, an Arabidopsis importin α co-localizes in the cytoplasm with microtubules and microfilaments, and is redistributed when these cytoskeletal structures are depolymerized (Smith and Raikhel 1998).

Ran-Dependent Nuclear Export

In general, the nuclear protein export machinery appears to be well conserved between species. As mentioned above, the Arabidopsis genome contains 17 genes that code for importin β-like nuclear transport receptors and some of these might function in protein export. The best-characterized protein exporter from Arabidopsis is Exportin 1, the homolog of the vertebrate and yeast nuclear export receptors CRM1/XPO1. There are two genes in Arabidopsis that produce two very similar proteins (XPO1a, XPO1b) with high sequence similarity. Arabidopsis XPO1 interacts with RanGTP and confers nuclear export of proteins that contain a leucine-rich nuclear export signal (NES; Haasen et al. 1999b). The HIV Rev NES is recognized by Arabidopsis XPO1 and confers nuclear export of a plant protein. XPO1a and XPO1b both contain the conserved cysteine residue that is the site of modification by leptomycin B (LMB) (Haasen et al. 1999b; Kudo et al. 1999). If this residue is mutated, LMB sensitivity is lost (Haasen et al. 1999b; Merkle 2009). Exportin 1 genes are essential for the development and function of gametophytes in Arabidopsis (Blanvillain et al. 2008).

The second Arabidopsis exportin that was functionally characterized is Exportin 2, a homolog of CAS (Cellular Apoptosis Susceptibility Protein). CAS is the importin α exporter. Of the eight Arabidopsis importin α homologs, four (Impα1-4) interact with Arabidopsis CAS, which also binds to Ran, indicating functional conservation of this function in plants (Haasen and Merkle 2002).

Two Arabidopsis exportins were identified in forward genetic screens. Exportin-t (Xpo-t), the Arabidopsis ortholog of the export receptor for tRNAs, was identified in genetic screens for mutants in different developmental pathways (Li and Chen 2003), and was designated PAUSED (PSD). Arabidopsis PSD/Xpo-t shares high sequence similarity with its vertebrate and yeast orthologs, interacts with Ran and complements a temperature-sensitive allele of Los1, the gene encoding yeast Xpo-t (Hunter et al. 2003). A putative PAUSED gene was also reported from rice (Yao et al. 2008).

The exportin 5 gene was also identified in a genetic screen for developmental mutants and was designated HASTY (HST), because of the accelerated change from juvenile to adult phase in the mutant (Bollman et al. 2003). Human Exportin 5 is the export receptor for double stranded RNA (dsRNA) molecules including precursor microRNAs (pre-miRNAs). HST binds Ran, binds dsRNA, and is involved in miRNAs nuclear export (Bollman et al. 2003; Park et al. 2005), again indicating conservation in plants.

Apart from these five proteins that were experimentally characterized as exportins, there are three more proteins of the Arabidopsis importin β family that might also act as nuclear export receptors, based on similarity to human proteins (Merkle 2009). One of them is similar to human Exportin 4, the export receptor for eukaryotic translation initiation factor eIF5A (Lipowsky et al. 2000), one to Exportin 7 (Mingot et al. 2004), and one to Importin 13/RanBP13 that also acts as an export receptor for eIF1A (Mingot et al. 2001). So far, none of these proteins have been experimentally characterized (Merkle 2009).

mRNA Nuclear Export

Proteins involved in mRNA export are unrelated to the karyopherins discussed above and to the Ran cycle. In humans, TAP (for Tip-Associated Protein)/NXF1 (for Nuclear RNA Export Factor 1) and p15/NXT1 (for NTF2-like Export Factor 1) form heterodimers to facilitate export of mRNA out of the nucleus (Cullen 2003; Rodriguez et al. 2004). In yeast, the respective proteins are Mex67 and Mtr2 (mRNA Transport Regulator 2). TAP/Mex67 and p15/Mtr2 have NTF2-like domains named after NTF2 (Nuclear Transport

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Factor 2), the nuclear import receptor for RanGDP (Ribbeck et al. 1998; Smith and Raikhel 1998; Suyama et al. 2000). In contrast to NTF2, p15 does not form homodimers and does not interact with RanGDP, but binds to TAP (Katahira et al. 2002; Wiegand et al. 2002). TAP has an NTF2-like domain for binding p15 and an RMM RNA-binding domain, as well as leucine-rich repeats (LRRs), and the so-called TAP-C domain. This C-terminal domain is, together with the NTF2-like domain, important for binding to FG repeat-containing nuclear pore proteins (Fribourg et al. 2001; Levesque et al. 2006). Directionality of nuclear export of mRNA is not driven by the Ran gradient but the RanGTP gradient is needed for the mRNA export factors (Izaurralde et al. 1997). There is no obvious homolog of TAP in the Arabidopsis genome. Arabidopsis contains three genes encoding NTF2-like proteins, two of which interact with Ran (termed NTF2a and NTF2b). The third one, termed NTL for NTF2-like does not interact with Ran (Zhao et al. 2006b). The function of this protein is uncharacterized to date, and it is a candidate for the Arabidopsis homolog of vertebrate p15/NXT1.

Recently, components of the THO-TREX complex have been identified in plants, indicating that this part of the pathway from transcription to mRNA export appears to be conserved. A mutant of the gene for TEX1, a THO-TREX complex subunit, was found in a screen for siRNA biogenesis, suggesting an involvement in processing or transport of a long RNA precursor (Yelina et al. 2010). In an unrelated screen for suppressors of the *erecta* locus, the homolog of another THO complex component, Hpr1 was found, and several other THO complex subunits were identified, and found essential in Arabidopsis (Furumizu et al. 2010). A homolog of Thp1, a component of the TREX-2 complex was found in another unrelated screen, and the loss-of-function mutant shows retention of nuclear mRNA (Lu et al. 2010). These new findings indicate that plant TREX-like activities are functioning in RNA processing/export and - as mentioned above - connected to the nuclear pore via AtNUP1.

Proteins binding to the 5' CAP as well as to the 3' poly(A) tail have also been implicated in mRNA export, for example the poly(A)-binding protein (PABP) Pab1. Yeast has one and humans have three genes encoding PABPs, while Arabidopsis contains a small gene family of eight members (Belostotsky 2003). Arabidopsis PAB3 binds to RNA and PAB2, 3, and 5 rescue the yeast *pab1*Δ mutant, suggesting that PABP function in mRNA biogenesis and export is conserved (Chekanova and Belostotsky 2003). Arabidopsis has homologs of the large and the small subunit of the Cap-binding complex (CBC, termed CBC80 and CBC20, respectively) (Kmieciak et al. 2002). Mutations in CBP80 confer abscisic acid (ABA)-hypersensitivity, suggesting that mRNA processing factors act as negative regulators for ABA signaling. Interestingly, another RNA-binding protein is implicated in ABA signaling (Razem et al. 2006), as well as CBC20 (Papp et al. 2004). Proteomic studies of the Arabidopsis nucleolus identified SR proteins as well as components of the exon-junction complex that functions in mRNA export and surveillance (Pendle et al. 2005). In addition, Arabidopsis also contains four homologs of vertebrate ALY/REF proteins (Uhrig et al. 2004), RNA binding proteins that recruit TAP/p15 to the mRNA (Stutz et al. 2000; Stutz and Izaurralde 2003).

Mutants in several nuclear pore-associated proteins in Arabidopsis have defects in mRNA export, as indicated by a strong increase of intranuclear signal in *in situ* hybridizations with an oligo-dT probe. They include the nuclear basket protein NUA (Tpr in mammals, Mlp1/2 in yeast, Megator in Drosophila), Nup160, Nup96 and AtNUP1 (Lu et al. 2010; Jacob et al. 2007; Parry et al. 2006; Xu et al. 2007b; Zhang and Li 2005). In addition, the *cryophyte/los4-2*, a temperature-sensitive allele of a DEAD-box RNA helicase, leads to nuclear poly(A) RNA accumulation (Gong et al. 2005). LOS4 is an Arabidopsis homolog of yeast Dbp5, which associates with mRNA early in the nucleus and accompanies it to the cytoplasmic side of the NPC, where it participates in mRNA export. The ATPase activity of Dbp5 is activated by interaction with Gle1, an RNA export factor that is also associated with the cytoplasmic side of the NPC, and inositol polyphosphate IP_6. This activity leads to mRNP re-modeling and probably constitutes a crucial step for dissociation of specific RNP factors to impose directionality on mRNP export (Carmody and Wente 2009; Tran et al. 2007). Whether a similar mechanism also operates in plants is currently not known.

THE NUCLEAR ENVELOPE

Over the last decade, the nuclear envelope (NE) has emerged as a key component in the organization and function of the nuclear genome. As many as 100 different proteins are thought to specifically localize to this double membrane that separates the cytoplasm and the nucleoplasm of eukaryotic cells. Selective portals through the NE are formed at sites where the inner and outer nuclear membranes are fused, and the coincident assembly of approximately 30 proteins into nuclear pore complexes occurs. These nuclear pore complexes are essential for the control of nucleocytoplasmic exchange (see Nucleocytoplasmic Trafficking). Many of the NE and nuclear pore proteins are thought to play crucial roles in gene regulation and are increasingly linked to human diseases (Hetzer and Wente 2009).

Lamins

A mesh of intermediate filament proteins, the nuclear lamins, lines the mammalian inner nuclear membrane. Lamins bind DNA and chromatin, and are depolymerized during mitosis in response to phosphorylation. Lamins are thought to provide scaffolding structures within interphase nuclei, and to mediate the attachment of chromatin to the nuclear envelope during interphase and chromatin detachment during mitosis (Grant and Wilson 1997). A-type lamins (lamins A and C), encoded by the *LMNA* gene, are major protein constituents of the mammalian nuclear lamina. The lamina acts as a scaffold for protein complexes that in turn regulate nuclear structure and functions. Interest in these proteins has increased significantly in recent years with the discovery that *LMNA* mutations cause a variety of human diseases which are collectively termed laminopathies and which include progeroid syndromes and disorders that primarily affect striated muscle, adipose, bone, and neuronal tissues. Recent research effort supports the concept that mammalian lamins and lamina-associated proteins regulate gene expression in health and disease by connecting various signal transduction pathways, transcription factors, and chromatin-associated proteins (Andres and Gonzalez 2009).

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Early electron microscopy (EM) studies revealed a structure similar to the vertebrate nuclear lamina in the nuclei of higher plant cells (Galcheva-Gargova and Stateva 1988). Immunohistochemical studies suggested the existence of lamin-like proteins in plant nuclei (Li and Roux 1992; McNulty and Saunders 1992; Minguez and Moreno Diaz de la Espina 1993), but no sequence information from the antigens detected in these studies is available, and no lamin-coding genes seem to be present in the fully sequenced plant genomes. Similarly, despite earlier reports of lamin-like proteins in yeast, the fully sequenced *Saccharomyces cerevisiae* genome also contains no lamin genes (Georgatos et al. 1989; Mewes et al. 1998). It is therefore likely that non-animal eukaryotes have a distinct set of nuclear envelope proteins that functionally replace the lamins.

Somewhat similar, yet significantly larger long coiled-coil proteins do exist in plants and might be candidates for lamin-like proteins. A plant-specific insoluble nuclear protein was identified in carrot (*Daucus carota*), called Nuclear Matrix Constituent Protein1 (NMCP1), which contains extensive coiled-coil domains and localizes to the nuclear periphery (Masuda et al. 1997). This 134-kD carrot protein fractionated with an insoluble nuclear fraction and localized exclusively to the nuclear periphery. Two NMCP1-related nuclear proteins were described in Arabidopsis, LITTLE NUCLEI1 (LINC1) and LINC2. A mutation in either gene caused reduced nuclear size and changes in nuclear morphology. A double mutant had an additive effect. These results suggest that LINC coiled-coil proteins are important determinants of plant nuclear structure (Dittmer et al. 2007).

Another class of plant proteins with a possible role as nuclear envelope structural proteins are the filament-like plant proteins (FPP1 - FPP7; (Gindullis et al. 2002). Like lamins and the NMCP1-related proteins, they contain extended coiled-coil domains. Two indirect lines of evidence connect them to the nuclear envelope. First, the tomato homolog LeFPP was identified as a yeast-two hybrid interactor of LeMAF1, a NE-associated protein (Gindullis et al. 1999; Gindullis et al. 2002). Second, a pea protein with similarity to AtFPP3 was identified with an antibody against Lamin B (Blumenthal et al. 2004). Interestingly, the AtFPP family stands out as a plant-specific family of long-coiled coil proteins in a cluster analysis of long coiled-coil proteins of 22 genomes (Rose et al. 2005) and is characterized by four highly conserved sequence motifs of unknown function (Gindullis et al. 2002). The subcellular location of the Arabidopsis proteins is currently not known.

In addition, Fiserova et al. (Fiserova et al. 2009) offer a new view on the plant nuclear lamina. Using feSEM, the authors reveal the meshwork of filaments underlying the inner NE in tobacco BY-2 cells, closely resembling the animal nuclear lamina both in terms of organization and filament thickness. These data should re-ignite the interest in plant lamin-like proteins, especially in light of the numerous new findings from both animals and yeast, indicating that the inner NE has crucial regulatory functions, a role attributed in vertebrates at least in part to the nuclear lamina (Heessen and Fornerod 2007).

Inner Nuclear Envelope Proteins

The number of known inner nuclear envelope (INE) proteins from animals is growing, in part due to the newly awakened interest in such proteins as targets of human genetic diseases (Ellis 2006; Wheeler and Ellis 2008; Worman and Bonne 2007). Such proteins include lamin B receptor (LBR), lamina-associated polypeptide-1 (LAP1), LAP2, emerin, MAN1, otefin, and nurim (Wagner and Krohne 2007). In addition, proteome analyses have added significantly to the list of proteins associated with the nuclear envelope, which are now available for functional investigation (Schirmer and Gerace 2005). Very few of these proteins have an identifiable homolog in the plant databases. These findings, though negative, underscore the possibility that the plant nuclear membrane has a unique protein composition, and that plants evolved unique solutions to nuclear architectural problems such as chromatin organization and nuclear structure.

The characterization of two novel plant INE proteins, AtSUN1 and AtSUN2 has recently been reported (Graumann et al. 2010). The proteins are the Arabidopsis homologs of a group of animal and yeast INE proteins containing a well-conserved SUN (Spindle architecture defective 1/UNC84 homology) domain. In animals, SUN-domain proteins interact in the lumen of the NE with KASH-domain proteins (located at the outer NE) to form protein complexes that connect the nucleus to the cytoplasmic cytoskeleton during interphase. SUN-KASH protein complexes are involved in attaching centrosomes to the nuclear periphery, alignment of homologous chromosomes, and their pairing and recombination in meiosis. They have been implicated in the regulation of apoptosis, the maturation and survival of the germline, nuclear location, and in human diseases such as laminopathies and Emery Dreifuss muscular dystrophy (Burke and Roux 2009; Fridkin et al. 2009; Hiraoka and Dernburg 2009).

Both Arabidopsis SUN proteins share a similar domain layout with their animal counterparts and interact with each other as indicated by fluorescence resonance energy transfer. Confocal microscopy of fluorescent protein fusions and electron microscopy suggest localization at the plant INE. Deletion of either the SUN domain or a nuclear localization signal abolished this localization. It will be interesting to study their *in planta* functions, and to investigate whether there are plant KASH-domain proteins, or whether SUN-domain proteins have other interaction partners in plants.

THE PLANT NUCLEAR PERIPHERY AND THE CELL CYCLE

Microtubule Nucleation at the Plant Nuclear Envelope

During nuclear division, the genetic material is distributed into two daughter nuclei by the action of the spindle apparatus. Formation of the mitotic spindle originates at microtubule organizing centers (MTOCs), which are the cytoplasmic centrosomes in animal cells and the NE-embedded spindle pole bodies in yeast cells. One of the main differences in cell division between higher plant cells and other eukaryotic cells is the absence of centrosomes or spindle pole bodies. Instead, the plant NE plays an important role in plant microtubule nucleation. A finding that isolated maize nuclei are capable of nucleating microtubules *in vitro* (Stoppin et al. 1994) gave early evidence for the association of microtubules with the nuclear surface in a plant cell. While the nuclear surface might not be the only site for microtubule nucleation in plants cells, it is especially active in the G2 phase of the cell cycle before NE breakdown (reviewed by Canaday

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et al. 2000), suggesting that its microtubule-nucleating activity might be under cell-cycle control. Microtubule-associated proteins (MAPs) modulate the nucleating activity of the plant nuclear surface (Stoppin et al. 1996).

Using the microtubule end binding protein AtEB1a fused to green fluorescent protein (GFP), it was shown that at the onset of cell division, a focused pattern of the plus end comets grows away from sites associated with the nuclear periphery. In cells with a preprophase band (PPB), EB1 was found at the nuclear periphery, segregating into two polar caps, perpendicular to the PPB, before nuclear envelope breakdown (NEBD). These polar caps then marked the spindle poles upon NEBD. Interestingly, in cells without PPBs, no prepolarization at the nuclear envelope was seen, and the bipolar spindle only emerged clearly after NEBD. In those cells, both spindle and phragmoplast orientation were more variable, suggesting that the PPB triggers a polarization that is perceived by the early developing spindle poles at the nuclear periphery (Chan et al. 2005).

γ-tubulin is centrally involved in microtubule (MT) nucleation and organization in eukaryotic cells (Wiese and Zheng 2006). Together with five proteins it forms the γ-tubulin ring complex, or TuRC, which binds to and stabilizes MT minus ends (Job et al. 2003). In fungal and animal cells, components of the TuRC concentrate at the MT organizing centers (MTOCs) (Raynaud-Messina and Merdes 2007). γ-tubulin patterns differ somewhat in plant cells, with a punctate distribution pattern on all MT arrays during mitosis (Liu et al. 1995; Liu et al. 1993). However, γ-tubulin along MTs has also been found in spindles and midbodies in animal cells (Lajoie-Mazenc et al. 1994; Luders and Stearns 2007). In contrast, γ-tubulin is highly concentrated in MTOCs like the plastid surface and polar organizers at spindle poles in early land plants (Brown et al. 2004; Shimamura et al. 2004). The large variety of MTOCs in non-vascular plants might inform about the evolution of the typical diffuse acentrosomal plant spindle.

In yeast, the γ-TuRC consist of the spindle pole proteins Spc98p and Spc97p that form a complex with γ-tubulin, which in turn binds to the large coiled-coil protein Spc110p of the spindle pole body at the NE (Job et al. 2003; Knop and Schiebel 1997; Moritz and Agard 2001). Plant homologues of Spc98p have been reported to colocalize with γ-tubulin at the nuclear surface in plant cells (Erhardt et al. 2002). Microtubule nucleation in plant cells depends on the presence of both γ-tubulin and Spc98p, and GFP-labeled plant Spc98p localizes within the nucleus, at the NE and close to the plasma membrane, strengthening the hypothesis of multiple nucleation sites in plant cells (Seltzer et al. 2003).

Vertebrate γ-TuRC contains several proteins not present in yeast cells but conserved in plants. Human 76p, also known as GCP4 (γ-tubulin complex protein 4), was identified as a component of an isolated γ-tubulin complex and localizes to the centrosomes and the spindle poles. It has an orthologue in higher plants and the moss *Physcomitrella patens*, but appears to be absent in yeast (Fava et al. 1999). Murphy and colleagues reported the finding of the two remaining components of the γ-tubulin complex in mammalian cells, GCP5 and GCP6, and identified the Arabidopsis counterparts of h76p/GCP4 and the GCP5/6 family by sequence comparison (Murphy et al. 2001). It is not understood how GCP4-GCP6 are involved in acentrosomal MT nucleation in plant cells. However, Kong et al. (2010) showed that GCP4 is associated with γ-tubulin in Arabidopsis. Downregulating GCP4 expression caused a reduced γ-tubulin signal at the mitotic spindle and the phragmoplast. MTs did not converge at unified spindle poles, the phragmoplast was disorganized, and cytokinesis was defective, as indicated by the presence of cell wall stubs. These data thus suggest that GCP4 is important for MT nucleation and organization in plant cells, as well (Kong et al. 2010).

Two papers have recently been published that add a novel dimension to the question of plant MTOCs on the NE and bring an unanticipated player into the picture. Mizuno and coworkers (Hotta et al. 2007; Nakayama et al. 2008) have used a biochemical approach to purify and identify a microtubule-organizing activity from tobacco BY2 cell nuclei. Raising an antibody against the MTOC-enriched fraction they identified an isoform of histone H1 and showed that recombinant histone H1 indeed had a microtubule-organizing activity. The same antibody was able to inhibit MT nucleation on isolated nuclei. Interestingly, immunolabeling demonstrated that a fraction of H1 is associated with the nuclear rim, outside of the extension of DAPI-stained chromatin. In a second accompanying paper the group showed that H1 can form ring-shaped complexes with tubulin and that these complexes nucleate and elongate radial microtubules (Hotta et al. 2007). These new data would place histone H1 at the plant NE MTOC and suggest that aspects of its composition radically differ from animal and yeast MTOCs. In addition, this raises the question of where exactly the non-DAPI overlapping H1 is located, if there is any evidence for H1 on the outer surface of the nucleus, and how its location might change at the onset of mitosis and NE breakdown. These are all very exciting questions that can now be further addressed.

Targeting protein for Xklp2 (TPX2) is a key regulator of vertebrate spindle assembly. In vertebrates, both a centrosome-based and a chromosome-based spindle assembly mechanism operate. In the chromosome-based mechanism, the RanGTPase in its GTP-bound form acts as a signal for the location of the chromatin. In the vicinity of a high RanGTP concentration, NLS-containing cargo proteins are released from importin β. TPX2 is activated by release from importin β and induces microtubule nucleation at the kinetochores and around the chromosomes. Activated TPX2 also localizes the mitotic kinase Aurora A to the spindle and activates it. Aurora A, among other functions, activates microtubule nucleation from the centrosomes. In *X. laevis* oocytes, that operate only with the chromosome-based mechanisms, TPX2 depletion leads to aberrant spindles or block of spindle formation. In HeLa cells, that have centrosomes, TPX2 depletion leads to aberrant centrosomes-based asters that do not connect (e.g., see (Bayliss et al. 2003; Gruss and Vernos 2004; Kawabe et al. 2005).

Vos et al. (Vos et al. 2008) have characterized the role of Arabidopsis TPX2. They show that AtTPX2 is predominantly nuclear during interphase, like vertebrate TPX2, but is actively exported before NE breakdown. AtTPX2 accumulates in the nucleoplasm in interphase and prophase, with a clear elevation at the NE and accumulates in the vicinity of the prospindle upon prospindle formation. AtTPX2 can induce microtubule assembly in *X. laevis* egg extracts and binds importin α, consistent with its proposed role. Microinjection of anti-TPX2 antibodies into stamen hair cells of *Tradescantia virginiana* blocks NE breakdown and prospindle formation, consistent with a role of TPX2 in plant prospindle formation.

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Rae1/mrnp41 in metazoans, Gle2p in *S. cerevisiae*, and Rae1 in *S. pombe* is an mRNA export factor associated with the NPC. It binds polyadenylated mRNA and associates with the nucleoporin Nup98. Rae1 mutants accumulate nuclear poly(A) RNA (Pritchard et al. 1999). In addition, Rae1 has cell-cycle functions and Rae1 mutants are arrested at the G2/M transition (Whalen et al. 1997). Rae1 operates as a mitotic spindle checkpoint component in conjunction with Bub3 and forms a complex with Nup98 and the Cdh1-activated anaphase promoting complex (APC), preventing degradation of Securin before anaphase (Babu et al. 2003; Whalen et al. 1997). Tobacco Rae1 was identified in a functional genomics screen for growth arrest and abnormal leaf development (Lee et al. 2009). Both GFP-tagged and HA-tagged Rae1 was found enriched at the nuclear periphery. Virus-induced gene silencing (VIGS) of Rae1 caused nuclear accumulation of poly(A) RNA. In addition, mitosis was affected, with reduced CDKA activity, reduced expression of cyclin B1, CDKB1-1 and histones H3 and H4. Differentiated leaf cells showed an increased degree of ploidy. Tobacco Rae1 was found associated with mitotic microtubules and capable of binding to microtubules *in vitro*. Estradiol-inducible RNAi in tobacco BY2 cells affected spindle organization, leading to multipolar spindles and defects in chromosome segregation. Together, these data suggest that plant Rae1 plays a role both in mRNA export and mitosis, too, and that its mitotic role is connected to spindle assembly and function (Lee et al. 2009).

A Connection between the NPC and the Preprophase Band

The plane of cell division in higher plants is defined by the assembly of the preprophase band (PPB), a ring of microtubules and F-actin that appears during G2 phase, and the migration of the premitotic nucleus into the plane defined by the PPB. During mitosis, the site of the former PPB becomes the cortical division zone (CDZ), which remains "marked" in an unknown way and which is thought to guide the phragmoplast and the outwardly growing new plasma membrane. The molecular nature of the CDZ has long been enigmatic, and only recently the first molecular markers have been described (reviewed in Muller et al. 2009).

As discussed above, RanGAP is associated with the outer surface of the NPC in plants and animal interphase cells, where it is involved in the directionality of nucleocytoplasmic transport. During mitosis in vertebrates, the Ran cycle takes on additional roles, like the localized activation of spindle promoting factors such as TPX2. Nothing is currently known about plant Ran cycle functions during cell division. Xu et al. (Xu et al. 2008) have now shown that Arabidopsis RanGAP1 accumulates at the PPB and remains associated with the site of division through mitosis and cytokinesis. RanGAP1 persistence at the CDZ depends on the two mitotic kinesins POK1 and POK2. Inducible depletion of Arabidopsis RanGAP in seedling roots leads to misplaced cell walls similar to other mutants with division plane defects, suggesting an involvement of the Ran cycle in this process.

During animal mitosis and cytokinesis, the general theme is that a high local concentration of RanGTP promotes microtubule growth. This is based on the release from inhibition of NLS-containing spindle assembly factors (such as TPX2). Thus, RanGAP could assist in the disassembly of the PPB by keeping local RanGTP levels low and thereby favoring depolymerization over polymerization of microtubules at this site. In addition to microtubule stability, RanGTP has been shown to affect the polarity of microtubule motor activities. Wilde et al. (Wilde et al. 2001) showed that RanGTP increases plus end-directed motor activity and decreases minus-end directed activity. During plant cytokinesis, the microtubule arrays of the phragmoplast are oriented with the plus ends toward the growing cell plate and deliver vesicles presumably by plus end-directed motor activity (Jurgens 2005). RanGAP1 might therefore cause reduced plus end growth of the phragmoplast microtubules and/or reduced plus-end motor activity. Such a regulatory function could conceivably fine-tune phragmoplast and vesicle delivery dynamics and thereby contribute to the overall precision of the processes underlying cell plate synthesis and positioning.

MEIOTIC TETHERING OF TELOMERES TO THE NUCLEAR ENVELOPE

Homologous chromosome synapsis, which allows for meiotic recombination is the hallmark of meiotic prophase. It is accompanied by the clustering of telomeres at the NE in a bouquet arrangement that is unique to meiosis (reviewed by Scherthan 2001). This NE association of the telomeres occurs adjacent to the centrosome or, in yeast, the spindle pole body. While plant cells do not have these structures, plant telomeres do cluster in a bouquet at the NE during meiotic prophase (Bass et al. 1997; Cowan et al. 2001; Harper et al. 2004; Martinez-Perez et al. 1999). A connection has been visualized between the synaptonemal complex of meiotic chromosomes and their NE attachment site. An anti-calf-centrosomes antibody was found to decorate both the NE and the synaptonemal complex in plants (Schmit et al. 1996), which suggests a link between these structures. In rye and maize, asynaptic mutants have been studied. They are defective both in formation of synaptonemal complexes and in clustering telomeres into bouquets (Bass 2003; Golubovskaya et al. 2002; Mikhailova et al. 2001). Interestingly, not all plant species show the typical bouquet arrangement at the NE. For example, Arabidopsis telomeres appear to cluster in the nucleoplasm during meiosis, most likely attached to the periphery of the nucleolus (Armstrong et al. 2001). This suggests a degree of diversity of patterns in nuclear organization during meiosis among plant species.

Very little is known about which factors control these processes. In particular, cytological studies have been used to study nuclear organization during meiosis in plants for decades; however, essentially nothing is known about the genes that regulate the movement of chromosomes and chromatin reorganization during early meiosis in plants. The nuclear pores have been discussed as candidates for telomere attachment sites (Tham and Zakian 2000). However, meiotic telomere attachment to the NE occurs in regions that are distinct from nuclear pore-dense areas in mammalian cells (Scherthan et al. 2000). The yeast proteins Taz1 (telomere-associated 1) in *S. pombe* and Ndj1p (nondisjunction 1) in *S. cerevisiae* are required for the bouquet formation at the spindle pole body during meiosis, and it has been suggested that they might function in tethering meiotic chromosomes to the nuclear periphery (Cooper et al. 1998; Trelles-Sticken et al. 2000). However, no homologues of these proteins are currently known in either plants or animals.

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Recent mutant analysis has shown that in plants the bouquet is required neither for homologous pairing nor synapsis. However, it appears to allow both to progress more rapidly and more efficiently. While the initiation of bouquet formation is independent of the initiation of recombination, it appears that the progression through recombination and synapsis are needed for the exit from the bouquet stage. The data indicate that the mechanism of telomere clustering is an active process (Carlton et al. 2003; Harper et al. 2004).

It has been show that the Arabidopsis SKP1 homolog ASK1 is essential for early nuclear reorganization events including the clustering of telomeres and the release of contacts between chromosomes and the nuclear membrane. *ask1-1* plants show alterations in pairing of homologous chromosomes, nucleolus migration and the mis-segregation of chromosomes, and these might be caused by the inability of chromosomes to release properly from the nuclear membrane and the nucleolus. ASK1 is therefore an interesting candidate for a protein that controls a regulator of early meiotic progression, possibly through the ubiquitin-mediated proteolysis of proteins by the proteasome (Yang et al. 2006; Zhao et al. 2006a).

A REGULATORY ROLE OF THE ARABIDOPSIS NUCLEAR ENVELOPE

Two major subcellular compartments in a eukaryotic cell—the nucleus and the cytoplasm are functionally compartmentalized. Nevertheless, the processes that require traffic in and out of the nucleus must occur in a dynamic and continuous fashion to maintain cellular functions. Our understanding of the many steps that control the regulation of gene expression (beginning with transcription in the nucleus and ending with a specific function at a specific site in the cell) is constantly increasing; so is our appreciation of the nuclear envelope as a selective barrier that separates and links the two compartments. While mRNAs have to traverse the NPC in order to reach their cytoplasmic destination to be translated, many proteins have to reach the nucleus to play their regulatory or enzymatic roles. By controlling the flow of nuclear import of proteins and nuclear export of mRNAs, tRNAs, miRNAs and proteins, NPCs regulate growth, development and the responses of Arabidopsis to environmental signals. The processes known to be affected by components of the NE or NPC are illustrated in Figure 1. The list is not final, as the community constantly discovers new roles attributed to the NE and NPC.

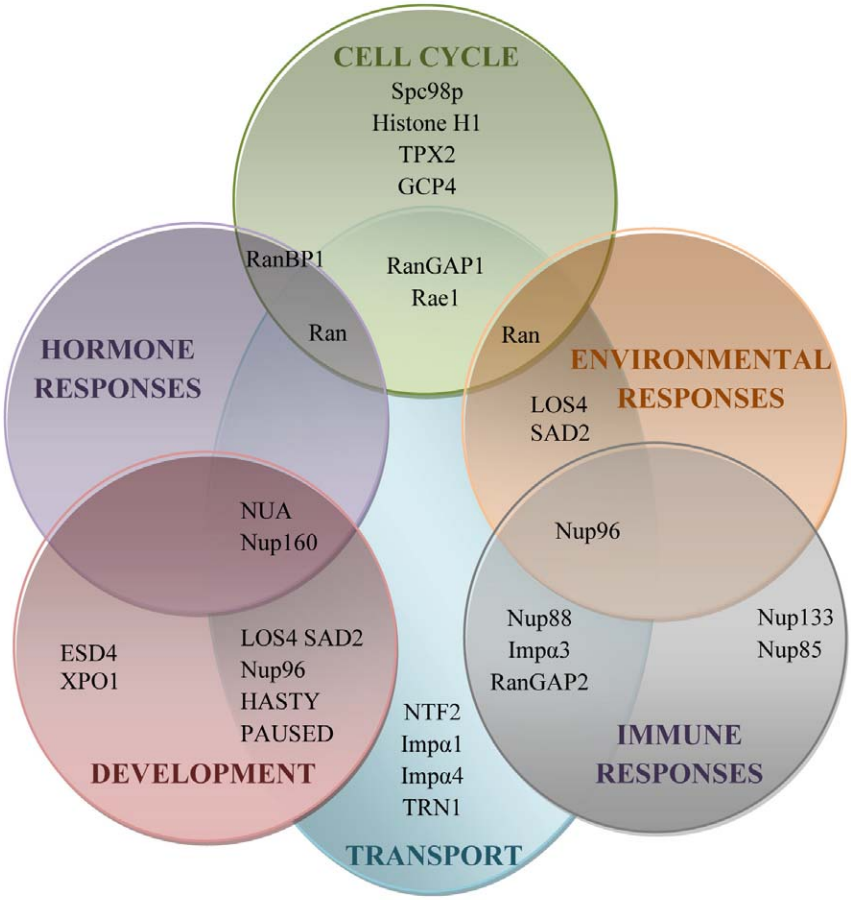

Figure 1. Categories of observed impairment in mutants of plant NE/NPC-associated components.

Hormone responses: Auxin, ABA; Environmental responses: cold, heat, osmotic, salt, UV-B; Development: flowering time control, gametophyte development, SUMO homeostasis; Immune responses: interaction with microbes and immune responses; Transport: protein import and export; T-DNA import, mRNA export, tRNA export, miRNA homeostasis and export; Cell cycle: MT nucleation, NEBD, spindle assembly, mitosis, chromosome segregation, cytokinesis. Refer to Table 1 for abbreviations and protein names. Proteins with mere structural roles, cation channels and anchors of RanGAP1 are not included.

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Secondary Messengers at the NE

Aside from a cytoplasmic source of Ca^{2+} ions that enters the nucleus through the nuclear pore complexes, the nuclear envelope itself represents a depot of Ca^{2+} that can be released into the nucleus. There, it controls various processes, such as gene expression, phosphorylation, dephosphorylation, to name a few (Xiong et al. 2006). In animals, changes in free Ca^{2+} concentration are enabled by Ca^{2+} channels that traverse the nuclear envelope and allow mobilization of accumulated Ca^{2+} from the NE lumen and replenish the Ca^{2+} store within the same compartment (Bkaily et al. 2006; Gerasimenko and Gerasimenko 2004). The channels are activated by secondary messengers such as inositol-1,4,5-triphosphate (IP_3), which is generated by the activity of phosphoinositide-dependent phospholipase C (PI-PLC) (Gerasimenko and Gerasimenko 2004).

In plants, there is both electrophysiological and localization evidence that place Ca^{2+} pumps or channels at the NE (Bunney et al. 2000; Downie et al. 1998). Several physiological responses to environmental stimuli, such as wind, mechanical stimulation or temperature changes include changes in the concentration of Ca^{2+} in the nucleus (van Der Luit et al. 1999; Xiong et al. 2004). The process that has been studied in most detail and includes periodic release and re-uptake of Ca^{2+} in the nucleus is known as calcium spiking. Nod factors, produced by endosymbiotic rhizobia in response to flavonoids, cause rapid influx of Ca^{2+} ions at the plasma membrane of the cells at the root hair tip and subsequent perinuclear Ca^{2+} spiking in legumes (Ehrhardt et al. 1996). CASTOR and POLLUX were identified in mutant screens in *Lotus japonicus* for nodulation defects and impaired perinuclear Ca^{2+} spiking. Although they were also shown to be localized in chloroplasts, both proteins are targeted to the NE and have electrophysiological properties of cation channels, with a preference for potassium (Charpentier et al. 2008). It was hypothesized that they could either function as counter-ion channels, or change the electric potential across the NE that could possibly activate the still unknown calcium channels. DMI1 (Doesn't Make Infections 1), the *Medicago truncatula* homologue of POLLUX is associated with the NE, too (Riely et al. 2007). Interestingly, a homologue of CASTOR and POLLUX is predicted in the Arabidopsis genome (encoded by At5g49960), although its function has yet to be revealed, since Arabidopsis is an asymbiotic species (Imaizumi-Anraku et al. 2005). A role for the NE in Ca^{2+} spiking does not end here. In *Lotus japonicus*, Nup85 and Nup133, both components of the Nup107-Nup160 NPC subcomplex, were shown to be required for Ca^{2+} spiking and nodule formation (Kanamori et al. 2006; Saito et al. 2007).

Another example for the role Ca^{2+} plays in signal transduction at the NE comes from heat stress studies. Liu and colleagues have shown that heat stress is followed by elevated cytoplasmic levels of calcium ions (Liu et al. 2006; Liu et al. 2003), released from intracellular Ca^{2+} depot membranes, such as the endoplasmic reticulum or NE. An increased Ca^{2+} level leads to the increased expression and accumulation of calmodulin (CaM), which has multiple levels of action in response to the heat shock. CaM promotes the DNA-binding activity of the heat shock transcription factor HSF in maize (Li et al. 2004; Sun et al. 2000). In Arabidopsis, it was shown that CaM interacts with a protein phosphatase PP7, which regulates the expression of heat shock protein genes (Liu et al. 2007). CaM also activates calmodulin-binding protein kinase 3 (AtCBK3), which in turn promotes phosphorylation of Arabidopsis HSFA1a and subsequent expression of the heat shock protein genes (Liu et al. 2008).

In legumes, pharmacological studies suggest the involvement of both phospholipase D and phospholipase C upstream of Ca^{2+} spiking (den Hartog et al. 2003; Engstrom et al. 2002). Phospholipase D also activates the phospholipids PA (phosphatidic acid) and PIP_2 (phosphatidylinositol 4,5-biphosphate) and causes relocation of PIP_2 to the NE, among other subcellular localizations. These phospholipids are known as mediators of signaling pathways involved in signal transduction during heat, cold, osmotic, salt, pathogen and wounding stress (Mishkind et al. 2009), illustrating that a series of signaling events, mediating stress responses, take place at the NE.

Signal Transduction of External Stimuli—the Role of the NE/NPC

Temperature stress

Signal transduction pathways leading to a response to elevated temperature have been studied for decades in various eukaryotic species, ranging from yeast to mammals. However, the knowledge gained using Arabidopsis as a model is surprisingly scarce compared to other species, including plants. As in other organisms, heat shock proteins (HSPs) act as chaperones to protect proteins from heat-induced denaturation. Their expression is strictly heat-induced and their genes are activated by a number of heat shock transcription factors (HSFs). Mammalian HSF1 shuttles between the cytoplasm and the nucleus in the absence of heat stress (Vujanac et al. 2005). The retention of HSF1 upon heat stress is caused by the inactivation of nuclear export (Vujanac et al. 2005), preceded by its phosphorylation and sumoylation (Hong et al. 2001). Like mammalian HSF1, many plant HSFs were found to contain both an NLS and an NES, suggesting they might also shuttle between the two compartments. Constitutively expressed HsfA1 has been shown to be required for heat-shock response in tomato (Mishra et al. 2002). Similar to mammalian HSF1, tomato HsfA1 is equally distributed between the cytoplasm and the nucleus at normal temperature. However, after heat shock the protein becomes predominantly nuclear. In contrast, the expression of a second tomato HSF, HsfA2 is heat-induced, and the protein is predominantly found in the cytoplasm. When co-expressed with HsfA1, both proteins localize in the nucleus after heat shock, indicating the involvement of HsfA1 in the nuclear import of HsfA2 in response to heat stress (Scharf et al. 1998). While both proteins contain an NLS, HsfA2 also contains a functional NES, as shown by nuclear localization of the protein in the presence of the XPO1 inhibitor leptomycin B under normal temperature. Leptomycin B treatment had no effect on the localization of HsfA2 after heat shock. Together, these data indicate that nuclear export is involved in its cytoplasmic location under normal temperature, and that, in addition, the NLS on HsfA2 must be inactivated after heat shock (Heerklotz et al. 2001). In summary, the data suggest that the nuclear partitioning of HsfA1 and HsfA2 is regulated by the ratio of nuclear import and export as well as by protein-protein

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interactions between the two HSFs. The complexity of this isolated system allows only a glimpse of the potential complexity of the role of nucleocytoplasmic partitioning in heat shock regulation, given the large number of heat-shock factors found in most plant species and the presence of NLS and NES motifs in many of them. Although the level of complexity of the HSFs is similar in Arabidopsis and tomato, no functional homolog of HsfA1 has been identified in Arabidopsis and no information about the localization of Arabidopsis HSFs is available (Baniwal et al. 2004).

A mutation in CRYOPHYTE/LOS4, a NE-localized DEAD-box RNA helicase, was shown to cause sensitivity to heat stress, further suggesting the involvement of the NE and/or nucleocytoplasmic transport in the regulation of this process. Interestingly, the same mutation also has an effect on the increased tolerance to chilling and freezing, most likely due to the enhanced cold-stress induction of CBF2, a transcription factor that controls the expression of many cold-responsive genes (Gong et al. 2005). A mutation in another protein shown to be associated with the NE, the putative nucleoporin Nup160/SAR1, was also found to sensitize plants to chilling stress and disrupt acquired freezing tolerance (Dong et al. 2006). Since both *sar1-1* and *los4-2* accumulate mRNA in the nucleus, it was proposed that impaired mRNA export, rather than protein nucleocytoplasmic transport, causes the modulated responses to cold in both cases. However, it still remains unclear why these two mutations cause the opposite effects to cold tolerance, while both show similar mRNA export defects. It is possible that there is an additional defect in case of *atnup160-1*. It was shown that the nuclear import of ICE1, an upstream regulator of CBF3, was unchanged in *atnup160-1* (Dong et al. 2006). It is possible that ICE1 sumoylation, shown to be required for freezing tolerance (Miura et al. 2007), might be disrupted in *atnup160-1*, causing downstream changes in cold responses.

Salt and osmotic stress

A recent report of Zang et al. (Zang et al. 2010) suggests a novel link between the efficiency of Ran-dependent nucleocytoplasmic transport and the perception of two types of abiotic stresses – salt and osmotic stress (Zang et al. 2010). The overexpression of *Ran* from rice, OsRAN2, caused an increased sensitivity to osmotic and salt stress, both in rice and in Arabidopsis. In addition, experiments with a nuclear import marker, the maize transcription factor Lc fused with YFP, suggested that co-expression of OsRAN2 causes partial retention of Lc-YFP in the cytoplasm, indicating a disruption of protein import. Endogenous OsRAN2 expression was temporarily reduced in response to both stress treatments (Zang et al. 2010). Together, these data suggest that Ran-dependent protein import might be reduced for some time after salt and osmotic stress treatments, which eventually enables the plant to cope with these two stresses. In plants, salt stress is followed by elevated cytoplasmic levels of Ca^{2+} ions (Bressan et al. 1998). In permeabilized HeLa cells, nuclear import becomes Ran-independent at high Ca^{2+} concentrations (Sweitzer and Hanover 1996). It is tempting to speculate that increased Ca^{2+} concentration induces the activation of a Ca^{2+}-dependent, Ran-independent nuclear import pathway in plants, as well. Therefore, constitutive expression of Ran would perturb the balance between Ran-dependent and Ran-independent protein transport, which might be one of the signals downstream of Ca^{2+} that enables plants to sense various stresses. It would be interesting to explore the consequences of a disruption of Ran-dependent nucleocytoplasmic transport in other ways to confirm this hypothesis.

Light signaling and photomorphogenesis

Three classes of photoreceptors are known to exist in plants to transmit signals in response to different wavelengths of the light spectrum. The family of phytochromes transmits signals predominantly in response to light in the red part of the visible spectrum, cryptochromes and phototropins respond to the blue/UV-A light range, and a yet unidentified photoreceptor plays a role in the perception of UV-B light (Briggs and Olney 2001; Lin and Shalitin 2003; Quail 2002). There are five phytochrome genes in Arabidopsis, *PHYA-PHYE*, which together with the phytochromobilin component represent phyA-phyE holoproteins. They exist in two forms – inactive, red light-absorbing Pr and functionally active, far-red light-absorbing Pfr form. phyB and phyA are required to tranduce continuous red- and far-red light signal, respectively (Quail et al. 1995). Biologically active phyB-GFP was shown to be predominantly cytoplasmic in etiolated seedlings but nuclear in light-grown seedlings (Gil et al. 2000; Yamaguchi et al. 1999). Nuclear import of phyB was induced by red light and could be reversed by far-red light, which inactivates phyB (Kircher et al. 1999). In contrast, phyA-GFP was imported into the nucleus in response to short pulses of blue, red or far-red light or by continued irradiation with far-red light (Kim et al. 2000). The rate of nuclear import of phyB was at least one order of magnitude slower than the very rapid one shown for phyA, suggesting a different mechanism of the nuclear import of these two major phytochromes.

The mechanism of nuclear import of phyB is not completely understood yet. Although the C-terminal domain of phyB was shown to be sufficient to provide nuclear localization with a characteristic speckled pattern, it failed to complement the corresponding phyB mutant and, unlike phyB, nuclear transport was not light-dependent (Matsushita et al. 2003). In contrast, the N-terminal domain of phyB was able to partially complement the same mutation, even more so in the presence of an NLS, suggesting that the N-terminus contains signal-transducing property. Based on this and other results, it was concluded that the N-terminus might contain a weak NLS that might act in addition to a yet unidentified NLS at the C-terminus or that phyB protein import is NLS-independent (Kevei et al. 2007). Unlike phyB, phyA requires FHY1 (Far-red elongated hypocotyl 1) and partially redundant FHL (FHY1 like) to enter the nucleus (Hiltbrunner et al. 2006; Hiltbrunner et al. 2005). FHY1 has been shown to directly interact with the active Pfr form of phyA (Hiltbrunner et al. 2005). FHY3 (Far-red elongated hypocotyl 3) and FAR1 (Far-red impaired Response 1) indirectly control phyA nuclear accumulation by regulating the transcription of *FHY1* and *FHL* (Desnos et al. 2001; Lin et al. 2007). Both FHY1 and FHY3 become functionally dispensable when phyA is constitutively expressed in the nucleus (Genoud et al. 2008). A model proposed by Genoud and coauthors attempts to explain why the nuclear import mechanism of phyA is specific and unique. Far red light illumination causes conversion of most of the Pfr form of

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phyA to the Pr form. However, about 2% of phyA remains in the Pfr form, capable of interacting with FHY1 in the cytoplasm. The phyA-FHY1 complex is proposed to enter the nucleus and dissociate to the Pr form of phyA and free FHY1, the latter of which is recycled back to the cytoplasm for the new round of import. It is not yet clear whether the remaining 2% of the nuclear pool of the Pfr form of phyA or the nuclear phyA-FHY1 complex is responsible for phyA-specific downstream signaling. Although the piggyback nuclear import mechanism is not without a precedent, the finding that it is conformation-dependent and that the required proteins have no other functions, makes it unique (Genoud et al. 2008). On the other hand, the function of phyA in phototropic responses has recently been shown to require its cytoplasmic pools (Rosler et al. 2007), demonstrating the importance of the balance of the two pools for the proper functioning of phyA signaling.

The blue light receptors CRY1 and CRY2 are both found in the nucleus. While CRY1 was reported to shuttle between the nucleus and the cytoplasm in response to light, CRY2 was found primarily in the nucleus (Cashmore et al. 1999; Guo et al. 1999; Kleiner et al. 1999; Yang et al. 2001). A recent study showed that all blue-light dependent responses of CRY2, including phosphorylation and subsequent phosphorylation-dependent degradation, as well as downstream signaling leading to the inhibition of hypocotyl elongation, occur in the nucleus (Yu et al. 2007). This demonstration, together with the ones described above for phytochromes, underscores the role of nucleocytoplasmic partitioning in providing the appropriate cellular environment for the function of the proteins involved in light signaling.

The etiolation response of Arabidopsis seedlings germinating in the dark is in part mediated by COP1 (Constitutively Photomorphogenic 1), a RING-finger E3 ubiquitin ligase that represses light-induced development (Osterlund et al. 2000). The absence of COP1 therefore causes a constitutive light-grown morphology, even in the dark (Deng et al. 1991). Function of COP1 in repressing light-regulated genes has been associated with its nuclear localization in the dark, which becomes cytoplasmic after light exposure. This light-dependent shuttling requires a single bipartite NLS and the cytoplasmic localization signals (CLS) for the nuclear import and export, respectively (Stacey et al. 1999; Stacey et al. 2000). As reported recently, the interaction of the coiled-coil domain of COP1 and the N-terminus of a subunit of the COP9 signalosome, CSN1, is necessary and sufficient for the nuclear localization of COP1. Since the coiled-coil domain of COP1 partially overlaps with its CLS, it was hypothesized that COP1-CSN1 interaction prevents the action of the CLS and therefore causes nuclear retention of COP1 (Wang et al. 2009). However, this hypothesis needs to be confirmed and the complete mechanism of COP1 light-regulated compartmentalization remains to be fully understood.

Hormone-Regulated Signal Transduction

Cytokinin signaling

Cytokinins are plant hormones involved in root and shoot cell division, vascular differentiation, root, shoot and inflorescence growth and branching, leaf senescence, apical dominance and chloroplast biogenesis. Cytokinin signaling resembles the bacterial two-component signaling, but consists of multiple steps, initiated by the interaction of cytokinin receptors with a cytokinin molecule and leading to a series of phosphorylation events (Sheen 2002). There are eight histidine kinases (AHK) in the Arabidopsis genome, three of which have been confirmed as cytokinin receptors. Upon binding of cytokinin, AHKs are auto-phosphorylated at a His residue within the kinase domain, which phosphorylates an Asp residue in the receiver domain (Ferreira and Kieber 2005). The phosphoryl group is then transferred to one of the six histidine phosphotransfer proteins (AHP), some of which are translocated to the nucleus after phosphorylation (Hwang and Sheen 2001). The phosphorylation of the type-B response regulator (ARR) in the nucleus leads to the de-repression of the transcriptional activation function of this type of ARR, which in turn activates the transcription of downstream genes responsible for cytokinin responses (Muller and Sheen 2007). Type-B ARRs also induce the expression of type-A ARRs, negative regulators of cytokinin responses, thus creating a negative feedback loop. The components of the nucleocytoplasmic transport machinery responsible for the cytokinin-induced nuclear import of AHP1 and AHP2 have not been identified yet (Hwang and Sheen 2001). Cytokinin response factors (CRFs) belong to the AP2 group of transcription factors, with targets and a function that partially overlap with those of type-B ARRs. Cytokinin-dependent nuclear translocation of CRF2 depends on AHKs and AHPs (Rashotte et al. 2006). CRFs and AHPs therefore represent two examples of cytokinin-dependent proteins involved in cytokinin signaling that require protein import, although the mechanisms still remain unclear.

Gibberellin signaling

Gibberellins (GAs) have been long known as essential regulators of several different aspects of plant development, including seed germination, stem elongation, leaf expansion and trichome development, flowering time and floral development (Olszewski et al. 2002; Schwechheimer 2008). Mutants in GA biosynthesis or signaling have poor germination rate, are dwarf and late flowering. Several nuclear proteins involved in GA signaling show GA-dependent redistribution between the nucleus and the cytoplasm following GA application. However, as shown for DELLA repressor proteins, in some cases the redistribution of the signal is due to protein degradation rather than to regulated nucleocytoplasmic transport (Schwechheimer 2008), and such examples are not further discussed here.

RSG (Repression of shoot growth) is a basic leucine zipper (bZIP) transcription factor that transcriptionally activates Arabidopsis *GA3*, encoding ent-kaurene oxidase, one of the enzymes of the GA biosynthetic pathway (Fukazawa et al. 2000). In the absence of GA, RSG is distributed equally between the nucleus and the cytoplasm. Using leptomycin B, an inhibitor of nuclear export, Igarashi et al. (Igarashi et al. 2001) showed that shuttling of RSG between the two compartments is responsible for this localization pattern (Igarashi et al. 2001). After GA application, RSG is excluded from the nucleus (Ishida et al. 2004). The GA-dependent sequestration of RSG in the cytoplasm relies on its binding for a 14-3-3 signaling protein, which occurs after phosphorylation of RSG (Igarashi et al. 2001; Ishida et al. 2004). Ca^{2+}-dependent protein kinase (CDPK1) was identified as the kinase that promotes 14-3-

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3 interaction with RSG by phosphorylation (Ishida et al. 2008). It remains to be seen whether CDPK1-mediated phosphorylation of RSG occurs in the nucleus, after which the RSG-14-3-3 complex gets exported more efficiently, or in the cytoplasm, where 14-3-3 binding would prevent the nuclear import of RSG.

Brassinosteroid signaling

Brassinosterioids (BR) are polyhydroxylated steroid hormones that play essential role in several developmental processes, such as seed germination, stem elongation, leaf expansion and xylem differentiation (Bishopp et al. 2006). Brassinazole-resistant 1 (BZR1) and brassinazole-resistant 2 (BZR2)/bri1-EMS-suppressor 1 (BES1) are two transcription factors that act downstream of the BR receptors BRI1 and BAK1, which perceive the BR signal. BR signals cause the dephosphorylation of BZR1 by BRI1 suppressor 1 (BSU1) and subsequent BR-specific activation of gene expression (Gendron and Wang 2007). BIN2, a glycogen synthase kinase-3 (GSK3)–like kinase phosphorylates BZR1. Phosphorylation causes the inactivation of the transcriptional activation capability of BZR1. Until recently, it was believed that the phosphorylation status of BZR1 alone controls its signaling activity (Vert and Chory 2006). Two independent studies now convincingly show that the subcellular localization plays a crucial role in the function of BZR1 (Gampala et al. 2007; Ryu et al. 2007). Like RSG1, the phosphorylation of BZR1 promotes binding of 14-3-3 protein, which causes its cytoplasmic retention and inactivation (Gampala et al. 2007). In addition, another phosphorylation domain of BZR1 is required for its nuclear export (Ryu et al. 2007). 14-3-3 proteins are emerging as regulators of many developmental processes (Oecking and Jaspert 2009). Therefore, it is not surprising to find a common theme in GA and BR signaling pathways, where phosphorylation, binding of 14-3-3 and export to the cytoplasm play a critical role in mediating corresponding hormone signals.

Abscisic acid signaling

Abscisic acid (ABA) has the most important function in plant responses to various abiotic stresses that cause dehydration. A mutant in SAD2 (Sensitive to ABA and drought 2), a member of the Arabidopsis importin β family, was identified in a screen for mutants altering the expression of *RD29A:LUC* reporter after cold, osmotic or cold stress treatment (Verslues et al. 2006). The *sad2-1* mutant was hypersensitive to ABA in inhibiting seed germination and seedling growth, leading to the hypothesis that a SAD2 cargo might be a negative regulator involved in ABA signaling. A mutation in the importin β gene most closely related to *SAD2* did not show ABA hypersensitivity, suggesting that individual members of the 17-member importin β family in Arabidopsis (Merkle 2003) might have different cargo specificities and preferences. Interestingly, *sad2-1* was also more tolerant to UV-B radiation, due to the less efficient nuclear import of the transcription factor MYB4 (Zhao et al. 2007). As a consequence, MYB4 repression of the gene for cinnamate 4-hydroxylase (*C4H*) is released, which leads to the upregulation of *C4H* expression, resulting in the accumulation of more UV-absorbing pigment. Different mutations in SAD2 also disrupt trichome initiation, although neither the mechanism, nor the cargo has been identified (Gao et al. 2008). Overexpression of rice *OsRAN2* was reported to lead to ABA hypersensitivity in transgenic Arabidopsis seedlings, most likely due to impaired nuclear import (Zang et al. 2010; see Salt and Osmotic Stress). A demonstration that changes in the expression level of two independently identified components of the nucleocytoplasmic transport machinery, importin β and Ran, lead to ABA hypersensitivity, suggests that the ABA response is one of the most sensitive plant responses to a change in the efficiency of this transport.

Auxin signaling

Auxin is a plant hormone well-known for its function in cell division, cell elongation, phototropic and gravitropic response. Auxin controls the vast majority of plant developmental responses, such as apical dominance, lateral root formation, vascular tissue differentiation, leaf abscission, floral and fruit development. The first report providing a connection between the nuclear envelope/nuclear pore and auxin responses showed that antisense suppression of Arabidopsis *RanBP1* causes auxin hypersensitivity (Kim et al. 2001). The authors proposed that impaired protein import of Aux/IAA transcriptional repressors causes the observed phenotype. This study was followed by the identification of SAR1 and SAR3 (Suppressor of auxin resistance 1 (AXR1) 1 and 3) as homologs of nucleoporins Nup160 and Nup96 (Parry et al. 2006). AXR1 is a subunit of a heterodimeric RUB-activating enzyme, implicated in the RUB modification of cullin, necessary for the formation of a functional SCF (Skp1-Cul1/Cdc53-F-box) complex involved in the auxin-dependent degradation of the Aux/IAA repressors (del Pozo et al. 2002). In *sar1* and *sar3*, the morphological and molecular phenotypes of auxin resistance observed in *axr1* are partially restored, but RUB-modified cullin levels are still reduced, as in *axr1*. Based on the changed localization of IAA17, one of the auxin Aux/IAA transcriptional repressors, it was proposed that the reduced nuclear import of IAA17 found in *sar1* and *sar3* counteracts its over-accumulation based on reduced proteolysis in the *axr1* background, as mentioned above. These two examples illustrate how the redistribution of a nuclear repressor to the cytoplasm based on diminished protein import causes significant changes in downstream nuclear responses. Although a mutation in the nuclear basket-associated protein NUA/AtTpr was also able to suppress the auxin resistant phenotype of *axr1*, the mechanism behind this observation was not examined further (Jacob et al. 2007). An auxin hypersensitivity phenotype was also detected in Arabidopsis overexpressing wheat *TaRAN1* (Wang et al. 2006). Interestingly, the overexpression of *TaRAN1* and *OsRAN2* renders Arabidopsis hypersensitive to auxin and ABA, respectively (Wang et al. 2006; Zang et al. 2010), suggesting that these two signaling pathways might be particularly sensitive to perturbing components of nucleocytoplasmic trafficking.

The Role of the NPC in Plant Innate Immunity

In an evolving arms race against their microbial and viral pathogens, plants deploy two different, yet converging defense strategies that include two groups of immune receptors. The first class

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consists of membrane-associated extracellular receptors that recognize pathogen-associated molecular patterns (PAMPs), which set off the PAMP-triggered immunity (PTI) response. The PTI signal is further transmitted to activate the mitogen-activated protein kinase (MAPK) signaling pathways and downstream transcriptional responses, mediated to a large part by WRKY transcription factors. The second class is represented by resistance proteins (R) that specifically recognize the presence of pathogen effector proteins, secreted into the cell by Type III secretion systems, resulting in effector-triggered immunity (ETI). ETI is characterized by the response that results in the programmed cell death at the site of infection, called hypersensitive response (HR), as well as by the systemic signals that provide a long distance defense response of uninfected tissues, named systemic acquired resistance (SAR). A resistance response activated by virulent pathogens on susceptible hosts is considered a basal defense response and includes PTI and weak ETI caused by weak recognition of pathogen effectors (Jones and Dangl 2006).

Salicylic acid (SA) is required for the initiation of SAR and the expression of pathogenesis-related (PR) genes. NPR1 (Nonexpressor of PR genes 1) is one of the major regulators of both basal defense and SAR (Dong 2004). *npr1* mutants are characterized by abolished SAR, due to insensitivity to SA, leading to a failure to express PR genes (Cao et al. 1994). NPR1 represents one the first examples of a protein involved in plant defense against pathogens for which it was shown that the function requires the partitioning between the nucleus and the cytoplasm. The localization of NPR1-GFP, which was able to rescue the *npr1* mutant, was shown to be different in the absence and the presence of SA. NPR1-GFP signal was found evenly distributed between nucleus and cytoplasm under non-inducing conditions, but was exclusively nuclear after treatment with SA. Nuclear accumulation of NPR1 was found to be necessary, but not sufficient for PR gene expression and SAR (Kinkema et al. 2000). It was demonstrated that NPR1 exists predominantly in the form of oligomers in the cytoplasm and that due to a change in the cellular redox potential, the majority of NPR1 becomes monomeric and moves to the nucleus upon SA induction (Mou et al. 2003). Recently, it was shown that the nuclear function of NPR1 as a co-regulator of the transcription of PR genes is proteasome-dependent (Spoel et al. 2009). This degradation is dependent upon phosphorylation of NPR1 after activation of PR gene transcription. Both phosphorylation and degradation of NPR1 are required for NRP1-mediated activation of target genes and disease resistance. This study clearly demonstrates how different levels of regulation of localization, posttranslational modification and degradation of NPR1 are orchestrated to control its function.

Two types of R proteins share a central nucleotide binding (NB) and a C-terminal leucine-rich repeat (LRR) domains and differ based on the presence of the N-terminal Toll interleukin receptor (TIR) or a coiled-coil (CC) domain. TIR-NB-LRR proteins require EDS1/PAD4 (Enhanced disease susceptibility 1/Phytoalexin deficient 4) and EDS1/SAG101 (Senescence-associated gene 101) complexes as their downstream signaling component (Feys et al. 2005). Interestingly, nucleocytoplasmic trafficking of EDS1 and PAD4 was proposed as one of the possible mechanisms explaining the requirement of EDS1/PAD4 complex partitioning in its defense signaling function (Wiermer et al. 2005). CC-NB-LRR proteins, on the other hand, commonly use the membrane protein NDR1 (Non race-specific disease resistance 1) in their downstream signal transduction pathways (Century et al. 1997). EDS1- and NDR1-dependent pathways converge at the downstream step of SA synthesis, which provides a signal necessary for basal defense and SAR. A gain of function mutation in the Arabidopsis TIR-NB-LRR R gene, *SNC1* (*Suppressor of npr1-1, constitutive 1*) leads to constitutive SNC1 activity and constitutive defense response (Zhang et al. 2003). Suppressors of *snc1* (*Modifiers of snc1, mos*) include MOS6 (importin α3), MOS3 (Nup96/SAR3) and MOS7 (Nup88) (Cheng et al. 2009; Palma et al. 2005; Zhang and Li 2005). Since all three MOS proteins represent either a component of the NPC or of nuclear import, it was proposed that the impaired nucleocytoplasmic transport of several candidates is responsible for the suppression phenotype of *snc1*. These include EDS1, PAD4, SAG101, the transcription factor bZIP10, NPR1 and SNC1 itself (Wiermer et al. 2007). That this is indeed the case was demonstrated in *mos7-1*, a partial loss of function mutant in which nuclear accumulation of SNC1 was reduced substantially (Cheng et al. 2009). In addition, both overall and nuclear levels of EDS1 and NPR1 were reduced in the mutant background, suggesting a role of MOS7/Nup88 in the stability of these two proteins. It is possible that both decreased nuclear import and enhanced nuclear export of SNC1 in *mos7-1* contribute to its decreased nuclear accumulation.

In the past few years, there has been a burst of publications describing the absolute requirement of nuclear localization or trafficking through the nucleus of several other R proteins for their activity. A fraction of CC-NB-LRR type MLA R proteins from barley was found in the nucleus (Bieri et al. 2004; Shen et al. 2007). Nuclear accumulation of MLA10 was increased upon fungal infection and its function was lost when an NES was added to prevent its nuclear localization. The interaction of MLA10 with WRKY transcription repressors in the nucleus was dependent on the presence of its fungal effector A10. Based on genetic analysis, it was concluded that A10-dependent MLA10/WRKY repressor interaction causes the activation of the defense genes expression by inhibiting WRKY repressor function, established during PTI (Shen et al. 2007; Shen and Schulze-Lefert 2007). The most exciting finding from this study was a demonstration that ETI and PTI converge in the nucleus, acting on the same set of WRKY transcription factors. This indicates that ETI can act as an amplification loop to increase the severity of PTI responses.

The tobacco TIR-NB-LRR R protein N, which provides resistance to Tobacco mosaic virus (TMV) fails to achieve this function when fused to an NES. Although the interaction between N and its viral effector p50 TMV replicase occurs in the cytoplasm, it was proposed that this interaction activates N, enabling its translocation to the nucleus and subsequent interaction with SPL transcription factors, required for TMV disease resistance (Burch-Smith et al. 2007; Shen and Schulze-Lefert 2007). The Arabidopsis TIR-NB-LRR protein RPS4, which confers resistance to *Pseudomonas syringae* strains expressing the effector AvrRps4, also requires nuclear localization for its function in disease resistance (Wirthmueller et al. 2007). Unlike MLA and N, RPS4 was shown to contain a functional bipartite NLS, necessary for nuclear import and immunity. However, a recent prediction of nuclear localization estimates that many more R proteins contain a nuclear localization signal. This indicates that the function of R proteins in the nucleus might be a rule rather than an exception (Liu and Coaker 2008). An-

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other interesting example is the Arabidopsis TIR-NB-LRR protein RRS1 that induces resistance to *Ralstonia solanacearum*. RRS1 interaction with the bacterial effector PopP2, which possesses a bipartite NLS, causes its translocation to the nucleus. In addition to nuclear localization, the C-terminal WRKY domain of RRS1 is also required for PopP2-induced ETI (Deslandes et al. 2003). Therefore, RRS1 represents yet another case where R protein function inside the nucleus provides a direct modulation of the transcription of genes involved in defense responses.

RanGAP2 has been shown to specifically interact with a coiled-coil domain of the CC-NB-LRR protein Rx, which confers resistance to PVX (potato virus X), as well as with the coiled-coil domains of Rx-like proteins Rx2 and Gpa2, the last being required for resistance against nematode *Globodera pallida* (Sacco et al. 2009; Sacco et al. 2007; Tameling and Baulcombe 2007). It has been demonstrated that RanGAP2 was required for both Rx-mediated and Gpa2-mediated resistance to their corresponding pathogens (Sacco et al. 2009; Sacco et al. 2007; Tameling and Baulcombe 2007). Interestingly, neither GAP activity nor NE localization of RanGAP2 seem to be important for this capability, since RanGAP1 does not interact with Rx-like proteins and the WPP/AAP mutant of RanGAP2 retains the ability to induce HR in the presence of Rx (Sacco et al. 2007). Although the mechanism by which RanGAP2 plays a role in disease resistance remains unknown, it has been confirmed that it mediates an initial recognition of a pathogen effector through the interaction with a coiled-coil domain of a Rx-like protein, while a LRR domain provides further recognition specificity (Rairdan et al. 2008; Sacco et al. 2009).

A general mechanism of a defense strategy of plants against viruses that includes neither RNA silencing nor gene-for-gene resistance was recently discovered (Carvalho et al. 2008). It was demonstrated that a ribosomal protein rpL10A represents a substrate and a downstream effector of the NSP-interacting kinase (NIK). NIK kinase activity causes translocation of rpL10A to the nucleus, where it either functions to directly induce defense responses or to attenuate general protein synthesis. Although geminivirus nuclear shuttle protein (NSP) inhibits NIK-mediated phosphorylation of rpL10A, it was proposed that this mechanism might act to protect the host against other viruses by inhibiting plant growth and development. As all of the examples mentioned above illustrate, translocation of proteins in and out of the nucleus is becoming an emerging theme in the pathogen resistance field, thus obtaining the level of appreciation it deserves.

OUTLOOK

The field of nuclear pore and nuclear envelope research has all but exploded in the past decade and our view of the structure and function of this selective intracellular barrier has been much refined. While most breakthroughs in yeast and animal models have contributed to a very detailed understanding of the arrangement and specific function of many NPC and NE components, plant research also brought some unexpected and exciting findings to the table. Contrary to expectations, several aspects of the plant nuclear pore turned out to be unique and plant-specific, both in terms of composition and in terms of the processes most sensitive to its changes. A number of developmental pathways and stress responses have been found sensitive to defects in the plant nuclear pore composition. At the same time, nuclear envelope components long sought for in plants—such as the nuclear lamina—may have finally been found. One of the next big challenges for the plant field is to systematically identify all the components of the plant NPC, place them in a structural model and analyze them functionally, with plant-specific properties in mind. For the nuclear envelope, the most exciting next step will be to unravel its capacity to connect the nucleoplasm with the cytoplasm through interactions in the nuclear envelope lumen, and to decipher the capacity of these connections for regulated nuclear mobility and signaling. These efforts are not only expected to bring the field to the level of yeast and animal systems, but also to add a currently still underexplored field to the growing toolbox of plant cellular components ready for future genetic engineering and synthetic biology.

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