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The edge of the nucleus: Variations on a theme

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The plant nuclear lamina utilizes distinct and highly divergent proteins to mediate chromatin interactions at the nuclear edge. In this issue of *Developmental Cell*, Tang et al. show that members of PNET2, a family of inner nuclear membrane proteins in *Arabidopsis*, are capable of binding histones and are involved in large-scale genome organization.

A principal regulatory hub in the nucleus is the surface defined by the exterior rim of its chromatin core and the inner leaf of the nuclear envelope. Functional dissection of the proteins that reside and act at this interface has been a fruitful entrée to understand how chromatin regulation is integrated with nuclear architecture and dynamics. Work in this area is more advanced in animals compared to fungi and plants, but the report of Tang et al. (2021) in this issue joins other recent studies in plants that are beginning to close the gap. Using proximity labeling and subtractive proteomics approaches in *Arabidopsis*, the lead author's team has identified an expanding number of previously uncharacterized proteins that are located in or near the inner nuclear envelope (Tang et al., 2020), and in the process, they have begun to reveal the enormous complexity of the plant nuclear lamina (NL).

The nuclear lamina is comprised of several types of proteins. In animals, lamins are the best-studied class, and while plants lack lamins, they have analogs of long coiled-coil domain proteins (NMCP/CRWN) that form fibril networks under the inner nuclear membrane (INM) (Masuda et al., 2021). Tang et al. describe a successful search for plant counterparts of a second type of NL protein, which is located in the INM and interacts with both lamins and chromatin. In animals and yeast, LEM-D (LAP2-emerin-MAN1 domain) proteins play this role (Barton et al., 2015) by binding with BAF (barrier-to-autointegration factor), which, in turn, interacts with chromatin. BAF-independent connections to chromatin also operate, and some proteins (like NEMP1; Mamada et al., 2009) interact with BAF through other domains. Plants have orthologs of both MAN1 and NEMP1, but these proteins lack BAF-interaction motifs, as expected from the absence of BAF in plants. Tang et al. demonstrate that the plant MAN1 is an INM protein whose proxitome includes CRWNs, as well as transcription factors and chromatin modifiers.

However, it is the second protein family identified in this study that takes center stage: the three PNET2 paralogs, which are orthologs of animal NEMP1. The A and B paralogs of PNET2 reside in the INM, where they lie in close proximity to core histone subunits and interact with known NL components KAKU4 and CRWN1. At least some of PNET2 interactions with the core histones are direct, and, interestingly, the PNET2_A and PNET2_B proxitomes contain a non-overlapping subset of H2A and H2B subunits, giving some indication of the different chromatin micro-environments that might exist at the NL. The PNET2_A proxitome includes H2A.W.6 and H2A.Z.9 that occupy constitutive and facultative heterochromatin, respectively, consistent with docking of silent chromatin at the nuclear periphery (Lei and Berger, 2019). Despite their different complements of proximal proteins, the A and B paralogs overlap functionally, as only combinations of *pnet2_a* and *pnet2_b* mutations lead to developmental phenotypes.

The phenotype of the *pnet2_abc* triple mutant is severe (these plants do not survive past the seedling stage) and is associated with widespread changes in gene expression, involving roughly one-quarter of the protein-coding genes. The authors summarize these changes as a tip in the balance toward stress gene induction at the expense of expression of genes involved in growth and development. Several plausible mechanisms could link loss of PNET2s to altered gene expression, including changes in transcription factor interactions at the NL or perturbation of epigenetic codes due to mistargeted chromatin modifiers. Although local epigenomic profiling remains to be done on these mutants, the authors report shifts in three-dimensional genome folding patterns, assessed by Hi-C analysis, in *pnet2_abc* mutants, including a reduction in inter-chromosomal and longer range intra-chromosomal interactions. Interestingly, these trends differ from those observed in other *Arabidopsis* NL mutants (i.e., *crwn1* and *crwn4*) (Grob et al., 2014), pointing to qualitative differences in the way that specific components of the NL interact with the genome.

The molecular mechanisms that underlie expression changes in *pnet2* mutants may also lie beyond transcription factors and chromatin mis-regulation. For example, disruption in nuclear envelope integrity can affect nuclear pore complex (NPC) function, which could ultimately alter transcriptional regulation. In human fibroblasts of HGPS patients (Hutchinson Gilford progeria syndrome, caused by lamin A/C mutations), nuclear import of Nup153 is hindered because of cytoplasmic retention of nuclear importer TNPO1 (Transportin-1). Restoring the normal nuclear transport ameliorates HGPS symptoms, showing that defects in the nuclear lamina act partially via altering nuclear transport (Larrieu et al., 2018). In *Arabidopsis*, the nucleoporin CPR5 is required to maintain both normal nuclear morphology and defense

responses, suggesting that nuclear envelope integrity, nuclear transport, and immune response converge on nucleoporin activity (Gu et al., 2016). Although the PNET2 proxitomes do not include any nucleoporins, the proximity labeling of KAKU4 shows that this NL protein lies close to Nup82 and Nup136, which are required to elicit salicylic acid defense responses (Tamura et al., 2017). Also included is Nup155, which interacts with CPR5. Given that PNET2_A interacts with KAKU4, it is possible that mutations in *PNET2* genes trigger immune responses by disrupting NPCs.

It is unknown if disruption of different nuclear envelope proteins will culminate in similar consequences or elicit specific phenotypes. On one hand, loss of PNET2s, CPR5, or CRWNs all lead to ectopic defense responses. However, mutations in other nuclear envelope proteins are not obviously related to defense responses. Although fluorescent images of nuclear envelope and NL proteins are generally localized to the entire rim of the nuclear periphery, each protein may reside in microenvironments with specific interactors. In future studies, it will be important to dissect how the expanding number of validated nuclear envelope and NL proteins regulate different signaling pathways and gene expression programs in plants. These studies will also provide a fuller understanding of both the conservation and the diversity of the machinery and regulatory mechanisms deployed in different eukaryotic kingdoms to manage the genome from the nuclear edge.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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