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NUCLEAR ORGANIZATION

NUP-tial binding to super-enhancers

> “the interaction between the NUPs and cell type-specific super-enhancers occurs at the NPC”

Components of the nuclear envelope (NE) and the nuclear pore complexes (NPCs) associate with the genome to affect genome organization and cell type-specific gene expression; whereas the NE is largely underlaid with heterochromatin, the NPCs are associated with genomic regions that are devoid of heterochromatin. Although it has been observed that NPC components can positively or negatively regulate transcription, in human cells NPC–genome interactions and their implications remain largely unknown. Hetzer and colleagues now show that the human nucleoporins NUP93 and NUP153 bind to regulatory DNA regions, more specifically to super-enhancers, to control the expression of cell type-specific genes.

The NPC, which comprises ~30 different types of NUP, is formed by NE-embedded rings and two peripheral structures: the cytoplasmic filaments and the nuclear basket.

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NUP93 is part of the ring scaffold, whereas NUP153 is a component of the nuclear basket. When using the DamID (DNA adenine methyltransferase identification) technique to identify NE–genome interactions in human osteosarcoma-derived U2OS cells, the authors identified a large number of local genome interaction sites with NUP153 and NUP93 (1,851 and 1,021, respectively). These sites were enriched for histone modifications that are associated with active transcription, such as histone H3 Lys4 trimethylation (H3K4me3), and for H3K27 acetylation, which marks putative transcriptional enhancers, indicating that these NUPs interact with genomic regions that regulate transcription.

When examining the distribution of NUP153- and NUP93-interacting sites in the genome, the authors found that they accumulated at cell type-specific super-enhancers — clusters of enhancers that drive the transcription of key cell identity genes — both in U2OS cells and in IMR90 primary lung fibroblasts. In U2OS cells, these NUPs interacted with super-enhancers associated with the regulation of genes that are implicated in bone formation; whereas in IMR90 cells they interacted with super-enhancers that are associated with genes involved in lung development and cell adhesion.

NUP93 is stably embedded in the NPC, whereas NUP153 can shuttle between the NPC and the nucleoplasm; however, DNA fluorescent *in situ* hybridization analyses revealed that NUP153- and NUP93-associated super-enhancers were preferentially localized at the periphery of the nucleus but were excluded from lamina-associated domains (which underlie the NE). This result indicates that the interaction between the NUPs and cell type-specific super-enhancers likely occurs at the NPC.

Lastly, knockdown of *NUP153* and *NUP93* in U2OS and IMR90 cells resulted in the alteration of transcriptional profiles and these changes were particularly severe for genes that are regulated by super-enhancers.

Together, these results show that NPC components are important for the accurate expression of genes that are involved in cell-type specification and that gene regulation occurs at the cell periphery, presumably where the NPC can provide a stable platform for complex interactions. Whether NUP–genome interactions that occur in the nuclear interior have similar or different functions remains to be determined.

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