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Spotlight

Nuclear Pore Complexes: A Scaffold Regulating Developmental Transcription?

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Nuclear pore complexes (NPCs) have a conserved, but poorly understood, role in transcriptional regulation. Recently, in *Developmental Cell*, Raices *et al.* argued that tissue-specific nuclear pore proteins (Nups) act as scaffolds that recruit the transcription factor Mef2C to the NPC, promoting transcription of NPC-associated genes during muscle development.

The NPC is a large, selective channel of approximately 110 MDa, comprising ≥30 different Nups. NPCs act as highly selective, bidirectional transporters between the cytoplasm and nucleoplasm. In addition to this role, NPCs also physically interact with chromatin, impacting the positioning of genes within the nucleus and influencing transcriptional regulation and chromatin structure. In budding yeast, hundreds of active genes interact with the NPC [1]. This interaction leads to positioning of genes to the nuclear periphery and, in several cases, has been shown to promote stronger expression [2,3]. Likewise, in *Drosophila* and mammals, thousands of genes interact with Nups and these interactions have both positive and negative effects on transcription [4]. However, in flies and mammals, Nup interactions occur both at the NPC and in the nucleoplasm, with soluble Nups. It has been unclear whether these two types of interaction are functionally equivalent and whether the yeast system reflects the spatial organization of transcription in metazoans.

In mammalian cells, the composition of NPCs varies among different cell types and tissues, raising the possibility that different tissues utilize functionally distinct forms of the NPC to facilitate differentiation. For example, Nup210, an integral membrane Nup, is expressed only in a subset of differentiated tissues, such as neurons and muscle cells [5]. Knockdown of Nup210 downregulates several genes and prevents myogenic differentiation. Nup210-dependent expression is independent of nucleocytoplasmic transport through NPCs [5]. This suggests that NPCs directly modulate gene expression to promote differentiation.

Using zebrafish muscle differentiation and mouse C2C12 myoblast cell line as models, Raices *et al.* explored how Nup210 promotes muscle differentiation [6]. Knockdown of Nup210 in zebrafish led to shortened muscle fibers and progressive accumulation of actin at the myoseptum due to a defect in myofiber maturation and muscle growth during development. These phenotypes correlated with changes in gene expression, including defects in activation of muscle-specific transcriptional programs. The same phenotypes are associated with loss of a transcription factor necessary for muscle development, Mef2C. The transcriptional changes were highly correlated with the binding of Nup210, and co-immunoprecipitation and *in vivo* assays revealed a physical interaction between Mef2C and Nup210, through the adaptor protein Trip6, at the NPC (Figure 1A). This finding suggests that Nup210 is required for Mef2C-mediated transcriptional activation. DNA-FISH in C2C12 cells showed that Nup210/Mef2C-regulated genes localize at the nuclear periphery, suggesting that transcriptional activation is occurring at the NPC. Thus, Nup210 recruitment of Mef2C to the NPC promotes expression of Mef2C target genes and proper muscle development.

Although many active genes localize at the nuclear periphery and physically interact with the NPC in budding yeast, repressed genes also interact with the NPC and, in other eukaryotes, positioning at the nuclear periphery frequently correlates with transcriptional silencing. Certainly, interactions with the nuclear lamina are associated with transcriptional silencing and heterochromatin [7]. However, the work by D'Angelo *et al.* highlights an important role for NPCs in promoting gene expression during vertebrate development. Likewise, some superenhancers that have critical roles in development interact with the NPC [8]. Therefore, the nuclear periphery is a complex environment and physical interactions between genes and the NPC can both promote or inhibit transcription. Furthermore, the molecular outputs of NPC–gene interactions appear to have been conserved from yeast to human and likely represent a fundamental mechanism of regulation of gene expression.

Nup210 may anchor a variety of genes and transcription factors in different cell types, because Nup210 is also involved in neural differentiation (Figure 1B [5]). However, it is unclear how the target genes get to the NPC; in quiescent myoblasts that do not express Nup210, Nup210 target genes localize at the nuclear periphery. This suggests that these genes are positioned at the nuclear periphery either through another NPC interaction or through a non-NPC interaction. In yeast, transcription factor binding is both necessary and sufficient for gene localization to nuclear periphery and many different transcription factors mediate the repositioning of different genes [2,9]. Given that Nup210 is required for proper binding of Mef2C, this suggests that Nup210 functions as a scaffold to facilitate Mef2C binding to NPC-associated genes. Perhaps Nup210 target genes are positioned at the NPC by transcription factors other than Mef2C. If so, then transcription factors could control either gene positioning, gene expression, or both. This would be

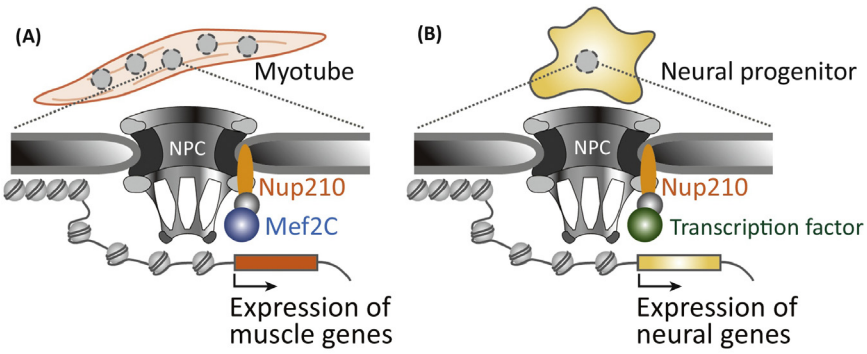

Figure 1. The Nuclear Pore Complex (NPC) As a Regulatory Scaffold for Developmental Gene Expression. (A) Model for nuclear pore protein 210 (Nup210) regulation of Mef2C. In myoblasts, expression of Nup210 recruits Mef2C through interaction with the adaptor protein Trip6. Mef3C binds to enhancers associated with genes critical for muscle development, activating their expression. (B) Hypothetical Nup210 regulation of neural genes. Nup210 is required for the differentiation of neural progenitor cells and, akin to its role in muscle development, could function as a scaffold to recruit transcription factors to NPC-associated genes involved in neural differentiation.

consistent with work in yeast showing that enhancers that control gene positioning are not always the same enhancers that control transcription [2]. This suggests that there are adaptive advantages to controlling these two phenomena separately.

Some exciting questions remain. Mef2C localizes both at nuclear periphery and in the nucleoplasm, indicating that some genes regulated by Mef2C are expressed independently on Nup210. What are the mechanistic differences between the transcription occurring at the NPC and in the nucleoplasm? Global expression analysis showed that loss of Nup210 or Mef2C resulted in both upregulation and downregulation of mRNA levels. Similar results have been obtained with other Nups [10]. What explains these two distinct classes? Are genes both activated and repressed by interactions with the NPC? Along these lines, are all Nup210-containing NPCs functionally equivalent or are there functional differences between them? Finally, do cell type-specific Nups function as determinants of cell identity or simply as generic cofactors for transcription factors? If the former, what determines the specificity of their function? The answers to these questions are bound to alter our perspective on the molecular and cellular drivers of developmental gene expression.

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