Report

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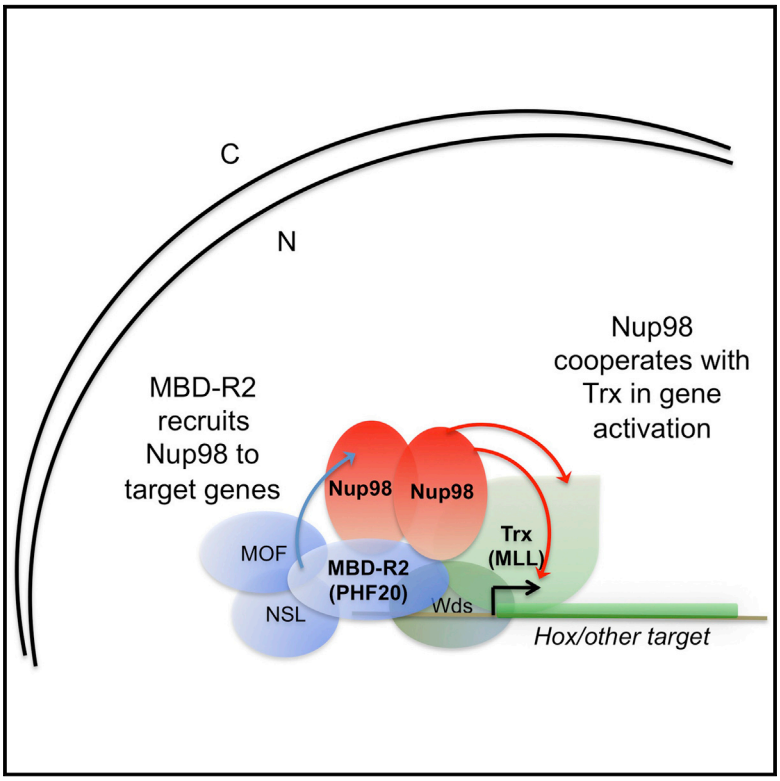
Nucleoporin Nup98 Associates with Trx/MLL and NSL Histone-Modifying Complexes and Regulates Hox Gene Expression

Graphical Abstract



Highlights

Nup98 associates and colocalizes with the MBD-R2/NSL and Trx complexes

MBD-R2 is required for recruitment of Nup98 to chromatin at a number of genes

Nup98 regulates transcription of Trx targets, the Hox genes, in development

Nup98 overexpression exhibits a homeotic transformation phenotype

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In Brief

Nuclear pore proteins regulate nuclear transport but have also been implicated in the regulation of transcription and chromatin. Pascual-Garcia et al. now report a physical and functional interaction between Nup98 and histone-modifying complexes NSL and Trx. The authors identify a component of the NSL complex, MBD-R2, as targeting Nup98 to active gene promoters, providing mechanistic insight into the connection between nuclear pores and chromatin state.

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Nucleoporin Nup98 Associates with Trx/MLL and NSL Histone-Modifying Complexes and Regulates Hox Gene Expression

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SUMMARY

The nuclear pore complex is a transport channel embedded in the nuclear envelope and made up of 30 different components termed nucleoporins (Nups). In addition to their classical role in transport, a subset of Nups has a conserved role in the regulation of transcription via direct binding to chromatin. The molecular details of this function remain obscure, and it is unknown how metazoan Nups are recruited to their chromatin locations or what transcription steps they regulate. Here, we demonstrate genome-wide and physical association between Nup98 and histone-modifying complexes MBR-R2/NSL and Trx/MLL. Importantly, we identify a requirement for MBD-R2 in recruitment of Nup98 to many of its genomic target sites. Consistent with its interaction with the Trx/MLL complex, Nup98 is shown to be necessary for Hox gene expression in developing fly tissues. These findings introduce roles of Nup98 in epigenetic regulation that may underlie the basis of oncogenicity of Nup98 fusions in leukemia.

INTRODUCTION

The nuclear pore complex (NPC) is a massive macromolecular protein complex embedded in the nuclear envelope (NE). Its classically characterized function is to mediate the selective transport between the nucleus and the cytoplasm. The NPC consists of multiple copies of ~30 different proteins termed nucleoporins (Nups), which include the scaffold Nups that form the core ring-like structure of the NPC and the peripheral Nups that regulate its selectivity barrier (D'Angelo and Hetzer, 2008) and can move dynamically on and off the pore (Rabut et al., 2004). Mutations in Nups are responsible for several human disorders, most notably cases of acute myelogenous leukemia (AML), caused by oncogenic fusions of Nup98 to a number of different partners (Gough et al., 2011; Xu and Powers, 2009). Metazoan Nups have been shown to affect tissue-specific development such as neural and muscle differentiation (D'Angelo et al., 2012; Lupu et al., 2008), yet the mechanisms by which NPC components can lead to tissue-specific pathologies and phenotypes remain unknown.

In addition to their classical role as transport channels, NPCs have been demonstrated to regulate transcriptional programs via physical binding to specific genes. In yeast, peripheral Nups has been shown to bind and promote expression of the nutritionally inducible genes INO1 and GAL1 (Cabal et al., 2006; Light et al., 2010; Schmid et al., 2006; Taddei et al., 2006). Remarkably, this Nup-gene interaction was also required for transcriptional memory of the gene's active state, assisting its subsequent reactivation after several cell divisions (Brickner, 2009; Tan-Wong et al., 2009). A similar role for Nups in epigenetic transcriptional memory has been recently described in human cells, where interferon γ (IFN-γ)-inducible genes are activated more robustly with repeated exposure to IFN-γ, but this remembered response is lost upon depletion of Nup98 (Light et al., 2013).

In *Drosophila,* genome-wide methods of polytene chromosome staining, chromatin immunoprecipitation (ChIP), and DamID demonstrated that several of the peripheral Nups, including Nup98, were recruited to genes undergoing developmentally induced transcriptional activation (Capelson et al., 2010; Kalverda et al., 2010; Vaquerizas et al., 2010). In line with the mobile behavior of peripheral Nups, it was found that such Nup-gene contacts commonly occur in the nucleoplasm, away from the NE-embedded NPCs. Human Nup98 has been similarly detected at genes undergoing robust activation during neural differentiation of embryonic stem cells (Liang et al., 2013). Together, these findings implicate Nups in direct regulation of developmental transcription programs, yet the molecular mechanism by which Nups affect transcription or its memory remains obscure.

To begin unraveling this mechanism, we identified interacting partners of *Drosophila* Nup98, which include proteins implicated in gene activation and epigenetic memory. Importantly, we pinpoint the chromatin-binding complex that is able to recruit Nup98 to active genes and uncover a role for Nup98 in maintaining developmental expression of Hox genes. These findings expose the link between NPC components and epigenetic regulators of tissue-specific gene expression, which may also be central to the oncogenic roles of Nups in leukemia.

RESULTS AND DISCUSSION

Identification of Chromatin-Associated Interacting Partners of Nup98

To address the molecular mechanism of the role of Nups in transcription and development, we aimed to identify proteins that