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NUCLEAR TRANSPORT

Cell-cycle-regulated mRNA traffic

> "…NUP96 dosage can differentially regulate the export of specific sets of mRNAs, including … cell-cycle regulators…"

The NUP107–160 complex, the largest component of the nuclear pore complex (NPC), has a key role in mRNA export. Chakraborty *et al.* now report that the levels of NUP96, a subunit of NUP107–160, are cell-cycle regulated. In turn, NUP96 controls the differential expression of key cell-cycle regulators, which are ultimately responsible for ensuring proper cell-cycle progression.

Immunoblot analysis of HeLa cell extracts obtained from different cell-cycle phases revealed that the levels of NUP96 were downregulated in early mitosis, whereas the levels of other constituents of the NUP107–160 complex did not change to the same degree. This downregulation does not occur at the mRNA level, but instead NUP96 is downregulated by ubiquitin-mediated proteolysis that involves the mitosis-specific E2 enzyme UBCH10 (also known as UBE2C). Overexpression of NUP96 had little or no effect in mitosis but resulted in a significant delay in G1–S-phase progression. Conversely, cells from *Nup96*$^{+/-}$ mice, which express low levels of NUP96, showed increased proliferation resulting from accelerated cell-cycle progression.

BANANASTOCK

But how might changes in the levels of NUP96 control cell-cycle progression and proliferation? The authors found that low levels of NUP96 in *Nup96*$^{+/-}$cells in G1 phase did not affect the levels of various mRNAs, including those of key G1-phase cell-cycle regulators, such as cyclin D3 and CDK6. However, the nuclear/cytoplasmic (N/C) ratio of some mRNAs, including cyclin D3 mRNA, was decreased in *Nup96*$^{+/-}$ cells in G1 phase, which led to an increase in protein levels. Remarkably, the ratio of some other mRNAs was increased, which suggests that NUP96 can both facilitate and inhibit nuclear export of selected mRNAs.

In addition, Chakraborty *et al.* showed that G2 cells had a lower N/C ratio of bulk mRNAs than G1 cells, which indicates that mRNA distribution is cell-cycle dependent. Furthermore, in G2 phase certain mRNAs, including cyclin D3 mRNA, were preferentially localized in the nucleus of *Nup96*$^{+/-}$ cells compared with *Nup96*$^{+/+}$ cells, whereas other mRNAs did not show a preference.

So, NUP96 dosage can differentially regulate the export of specific sets of mRNAs, including those that encode key cell-cycle regulators, in a cell-cycle regulated manner, thereby setting the cell up for proper cell-cycle regulation.

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ORIGINAL RESEARCH PAPER Chakraborty, P. *et al.* Nucleoporin levels regulate cell cycle progression and phase-specific gene expression. *Dev. Cell* **15**, 657–667 (2008)