Introduction

Nucleoli are the sub-nuclear “stress-sensing” centers that respond to diverse cellular insults, ranging from molecular damage (e.g. DNA) to metabolic dysregulation and infection. Nucleoli provide a survival advantage in many types of cancers, including leukemia, breast, pancreatic, post and lung carcinomas. Migration of nucleolar proteins from nucleoli to metabolic dysregulation and infection. Nucleoli provide a non-prognostic and reduced survival in a variety of cancers. Our research focus is to dissect NCL regulation of cellular DDR through post-transcriptional and post-translational mechanisms. We use multiple cellular models of osteosarcoma, breast, prostate and pancreatic cancers to study NCL mediated DDR.

“In-situ” insights

Fig. 3 (A, B) NCL exit from nucleoli is a cue for cellular stress-like conditions: NCL phosphorylation by CK2 regulates this event

(A) NCL is predominantly nucleolar (punctate) under normal conditions
(B) NCL-6/S*A, hyper-phosphorylated mutants is prominent in the nucleoplasm (diffuse) even under ‘non-stress’ conditions

(C-F) NCL translocation upon DNA damage (DD) requires wt-p53

(C) NCL only translocated to nucleoplasm when wt-p53 is functional
(D) NCL migrates to nucleoplasm (diffuse) under DNA damage conditions
(E) Differentiation treatment generally triggers ‘stress-mimic’ conditions and NCL translocation, as seen in Chls.
(F) Even so, p53 mutants cells resist NCL translocation upon DNA damage.

“In-vitro” analyses

Fig. 4 (A-C) Distinct NCL phosphorylation profile during normal cell cycle and upon DNA damage

(A) NCL is differentially phosphorylated during normal cell cycle
(B) NCL is hyper-phosphorylated during DNA damage and upon CK2 inhibition

(D-H) Post-translationally modified NCL controls gene-expression post-transcriptionally

(D) NCL-5/S*A expression mimics cellular stress conditions resulting in SAPPINK and c-Jun phosphorylation, increases in p53, PUMA and caspases expression
(E) NCL-WT enhances PARN destabilization activity to keep its target mRNAs (e.g. TP53) levels low under normal conditions

“In-silico” modeling

Fig. 5 NCL interacts with many RNA species through its RNA binding domains

Relevant Literature:


Goals and Significance

Post-translational modifications on NCL are predominantly ignored while studying its RNA-binding properties and physiological functions. In this study, we collectively explore the roles of NCL in DDR by defining its sub-cellular location, altered phosphorylation status and its roles in regulating RNA metabolism.

Materials and Methods

Fig. 2 Modular structure of NCL protein: The hNAP1, tRNA-RNA binding (RBDs) and RUS/GAR domains, CK2-hypers (5′-S*A, 6′-S*A, 6′-S*E), additional putative CK2 sites (blue lines), & CKD1 sites (red lines) are diagrammed.

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For further information

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Fig. 1 Cellular response to DNA damage: A Nucleolar Story A) Post-transcriptional modifications on NCL (B) Post-transcriptional regulation by NCL in DDR (Xiao, 2014, Zhang, 2018).

Fig. 6 NCL-RBDs confers specificity for RNA targets

NCL-mediated gene-expression in DDR

- Nucleolin sub-cellular localizations from nucleus, nucleolosome, cytoplasm and at the cell membrane are depicted in a numbered black circle (4F, #3-4). The white circles with numbers indicate cellular insults (e.g. DD, DNA damage, AD, cellular processes (#7-12) and resulting different cellular factors (#10-12) during the DDR.

“Stressed out” nucleolar proteins: Nucleolin (NCL) phosphorylation in RNA binding and gene expression

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- Gene expression; Drug for cancer therapeutics

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