RNA Biology 10:8, 1231-1232; August 2013; © 2013 Landes Bioscience

Landes Highlights

CRM1 and NMD3 localize to the nucleolus and affect rRNA synthesis

Baoyan Bai, Henna M Moore, and Marikki Laiho

CRM1 is an export factor that, together with its adaptor NMD3, transports numerous cargo molecules from the nucleus to cytoplasm through the nuclear pore. In previous studies, CRM1 and NMD3 were also detected in the nucleolus, but their localization with subnucleolar domains or participation in the activities of the nucleolus remain unclear. A new study by Dr Marikki Laiho and colleagues confirmes that CRM1 and NMD3 co-localize with nucleolar marker proteins in the nucleolus. In particular, they found that nucleolar localization of these two proteins is markedly increased by inhibition of RNA polymerase I (Pol I) transcription. CRM1 nucleolar localization was shown to be dependent on its activity and the expression of NMD3, whereas NMD3 nucleolar localization was independent of CRM1. This suggests that NMD3 provides nucleolar tethering of CRM1. While inhibition of CRM1 by leptomycin B inhibited processing of 28S rRNA, depletion of NMD3 did not, suggesting that their effects on 28S rRNA processing are distinct. Markedly, depletion of NMD3 and inhibition of CRM1 reduced the rate of pre-47S rRNA synthesis. However, their inactivation did not lead to nucleolar disintegration, a hallmark of Pol I transcription stress, suggesting that they do not directly regulate transcription. Taken together, the study results indicate that CRM1 and NMD3 have complex functions in pathways that couple rRNA synthetic and processing engines and that the rRNA synthesis rate may be adjusted according to proficiency in rRNA processing and export.
http://www.landesbioscience.com/journals/nucleus/article/25342/

Reference

Bai B, et al. Nucleus 2013; 4:315-25; PMID:23782956; http://dx.doi.org/10.4161/nucl.25342

mRNA secondary structure correlates with protein function and domains

Lee Vandivier, Fan Li, Qi Zheng, Matthew Willmann, Ying Chen, and Brian Gregory

RNAs fold into intricate structures that are determined by specific base pairing interactions encoded within their primary sequences, and similar to proteins, folding into specific confirmations is essential for RNAs to function properly. Few studies have addressed the transcriptome-wide significance of structure in mRNA regulation and function, thus a team of researchers led by Dr Brian Gregory sought to fill this gap by applying a high-throughput, sequencing-based, structure mapping approach to measure folding patterns of every detectable transcript in unopened flower buds of *Arabidopsis thaliana*. The authors applied this technique in conjunction with sequencing of a number of different RNA populations to survey the functional relevance of structure across the Arabidopsis transcriptome. They showed that the regulatory significance of Arabidopsis RNA secondary structure is revealed specifically through high-throughput, sequencing-based, structure mapping data, not by computational prediction. Additionally, they found that transcripts with similar levels of secondary structure in their 5' or 3' untranslated regions (UTRs) or coding sequence (CDS) tend to encode proteins with coherent functions. Finally, portions of mRNAs encoding predicted protein domains were significantly more structured than those specifying inter-domain regions. In total, the study findings show the utility of high-throughput, sequencing-based, structure-mapping approaches and suggest that mRNA folding regulates protein maturation and function.
http://www.landesbioscience.com/journals/10/article/24301/

Reference

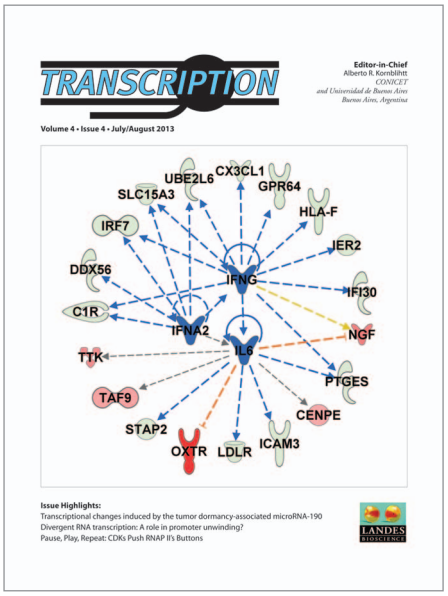
Vandivier L, et al. Plant Signal Behav 2013; 8:e24301; PMID:23603972; http://dx.doi.org/10.4161/psb.24301

Transcriptional changes induced by tumor dormancy-associated microRNA-190

Nava Almog, Christine Briggs, Afshin Beheshti, Lili Ma, Kathleen Wilkie, Edward Rietman, and Lynn Hlatky

Tumor dormancy is a highly prevalent stage in cancer progression. In this stage, small cancerous lesions remain occult and asymptomatic until they eventually switch to become fast-growing, clinically apparent, and potentially lethal cancer. Dr Nava Almog and colleagues previously generated and characterized in vivo experimental models of human tumor dormancy in which micro-tumors remain occult until they spontaneously shift into rapid tumor growth. They showed that the dormant micro-tumors undergo a stable microRNA (miR) switch during their transition from dormancy to a fast-growing phenotype and reported the identification of a consensus signature of human tumor dormancy-associated miRs (DmiRs). MiRNA-190 (miR-190) is among the most upregulated DmiRs in all dormant tumors analyzed. Upregulation of miR-190 led to prolonged tumor dormancy in otherwise fast-growing glioblastomas and osteosarcomas. In a new study, the same authors investigated the transcriptional changes induced by miR-190 expression in cancer cells and showed similar patterns of miR-190-mediated transcriptional reprogramming in both glioblastoma and osteosarcoma cells. They found that miR-190-mediated effects rely on an extensive network of molecular changes in tumor cells and that miR-190 affects several transcriptional factors, tumor suppressor genes, and interferon response pathways. The molecular mechanisms governing tumor dormancy described in this work may provide promising targets for early prevention of cancer and could lead to novel treatments to convert the malignant tumor phenotype into an asymptomatic dormant state.

http://www.landesbioscience.com/journals/transcription/article/25558/



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Almog N, et al. Transcr 2013; 4:177-91; PMID:23863200; http://dx.doi.org/10.4161/trns.25558

Ribonuclease binase: A potential anticancer therapeutic

Nadezhda L Mironova, Irina Y Petrushanko, Olga A Patutina, Aexandra V Sen'kova, Olga V Simonenko, Vladimir A Mitkevich, Oleg V Markov, Marina A Zenkova, and Alexander A Makarov

Exogenous ribonucleases are known to inhibit tumor growth via apoptosis induction in tumor cells, and can therefore be considered as potential anticancer drugs for clinical application. A recent study by Dr Marina Zenkova and colleagues evaluated the antitumor potential of a bacterial RNase called binase in vivo. The mechanism of the cytotoxic effect of binase on tumor cells was comprehensively studied in vitro. Tumoricidal activity of binase was investigated using three murine tumor models of Lewis lung carcinoma (LLC), lymphosarcoma RLS40 and melanoma B-16. Intraperitoneal injection of binase resulted in retardation of primary tumor growth up to 45% in LLC and RLS40. Metastasis formation was inhibited up to 50% in LLC and RLS40, and up to 70% in B-16 melanoma. Binase did not exhibit overall toxic effects and displayed general systemic and immunomodulatory effects. Further, treatment of RLS40-bearing animals with binase together with polychemotherapy revealed that binase decreases the hepatotoxicity of polychemotherapy while maintaining its antitumor effect. The authors could demonstrate that the cytotoxic effect of binase is realized via the induction of the intrinsic and extrinsic apoptotic pathways. The activation of the intrinsic apoptotic pathway was manifested by a drop of mitochondrial potential, increase in calcium concentration, and inhibition of respiratory activity. Subsequent synthesis of TNF-α in the cells under the influence of binase triggered the extrinsic apoptotic pathway through the binding of TNF to cell-death receptors and activation of caspase 8. Taken together, the study suggests that binase is a potential anticancer therapeutic inducing apoptosis in cancer cells.

http://www.landesbioscience.com/journals/cc/article/25164/

Reference

Mironova NL, et al. Cell Cycle 2013; 12:2120-31; PMID:23759588; http://dx.doi.org/10.4161/cc.25164