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Landes Highlights

Distinct roles for Btf and TRAP150 in regulating mRNA distribution

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Transcription of protein-coding genes in mammalian cells is coordinated with pre-mRNA (pre-mRNA) processing as well as the assembly and nuclear export of messenger ribonucleoprotein particles (mRNPs). Btf (BCLAF1) and TRAP150 (THRAP3) were previously reported to associate with in vitro spliced mRNPs and also as a part of the spliceosome, suggesting they are involved in pre-mRNA processing. Btf and TRAP150 are serine-arginine-rich (SR) proteins with significant sequence similarity, but the extent of their functional overlap is not yet clear. A recent study by Dr Paula Bubulya and coworkers shows accumulation of both Btf and TRAP150 at a constitutively active β-tropomyosin (BTM) reporter locus as well as at an activated U2OS 2-6-3 gene locus. At transcription sites, Btf and TRAP150 showed the most precise overlay with each other and with the exon junction complex (EJC) protein Magoh. Since EJC components have roles in nuclear export, the authors examined nuclear/cytoplasmic mRNA distribution after Btf or TRAP150 knockdown. Btf depletion caused an increase of β-tropomyosin minigene reporter transcripts in the cytoplasm as well as global increase of endogenous polyadenylated RNA in the cytoplasm, while TRAP150 depletion did not. In summary, these data show that Btf has functions distinct from TRAP150 in mRNA metabolism, and that modulating the expression of a single protein, Btf, has global impact upon the nuclear/cytoplasmic distribution of mRNAs in human cells.

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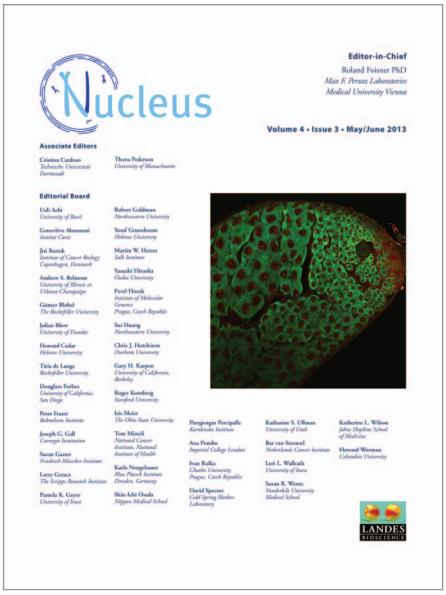

Reference

Varia S, et al. Nucleus 2013; 4:229-40; PMID:23778535; http://dx.doi.org/10.4161/nucl.25187

Epigenetic and transcriptional features of the novel human imprinted lncRNA GPR1AS

Hisato Kobayashi, Eikichi Yanagisawa, Akihiko Sakashita, Naoko Sugawara, Shiori Kumakura, Hidehiko Ogawa, Hidenori Akutsu, Kenichiro Hata, Kazuhiko Nakabayashi, and Tomohiro Kono

Long non-coding RNAs (lncRNAs), transcribed from the intergenic regions of animal genomes, play important roles in key biological processes. In mice, *Zdbf2linc* was recently identified as a lncRNA isoform of the paternally expressed imprinted *Zdbf2* gene. The functional role of *Zdbf2linc* remains undefined, but it may control parent-of-origin-specific expression of protein-coding neighbors through epigenetic modification in cis, similar to imprinted Nespas, *Kcnq1ot1* and *Airn* lncRNAs. In a recent study, Dr Tomohiro Kono and colleagues identified a novel imprinted long-range non-coding RNA, termed *GPR1AS*, in the human *GPR1-ZDBF2* intergenic region. Although *GPR1AS* contains no human *ZDBF2* exons, this lncRNA is transcribed in the antisense orientation from the *GPR1* intron to a secondary, differentially methylated region upstream of the *ZDBF2* gene (*ZDBF2* DMR), similar to mouse *Zdbf2linc*. Interestingly, *GPR1AS/Zdbf2linc* is exclusively expressed in human/mouse placenta with paternal-allele-specific expression and maternal-allele-specific promoter methylation (*GPR1/Gpr1* DMR). The paternal-allele-specific methylation of the secondary *ZDBF2 DMR* was established in human placentas as well as somatic lineage. Meanwhile, the *ZDBF2* gene showed stochastic paternal-allele-specific expression, possibly methylation-independent, in placental tissues. Overall, the authors demonstrated that epigenetic regulation mechanisms in the imprinted *GPR1-GPR1AS-ZDBF2* region are well-conserved between human and mouse genomes without the high sequence conservation of the intergenic lncRNAs. The study findings also suggest that lncRNAs with highly conserved epigenetic and transcriptional regulation across species arose by divergent evolution from a common ancestor, if they do not have identical exon structures.

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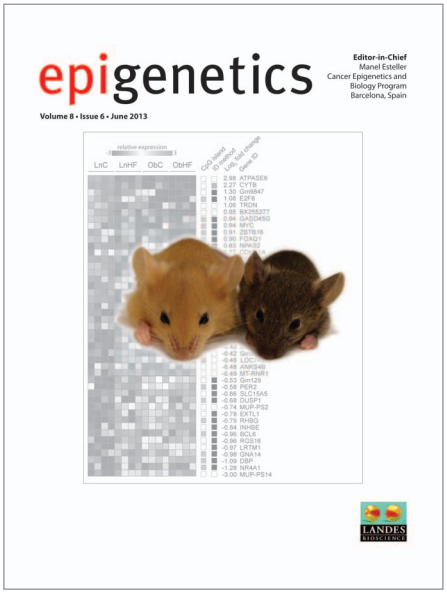

Reference

Kobayashi H, et al. Epigenetics 2013; 8:635-45; PMID:23764515; http://dx.doi.org/10.4161/epi.24887

A ribosomal shunting mechanism of translation initiation for BACE1 mRNA

Dora Koh, Gerald Edelman, and Vincent P. Mauro

Cleavage of the Amyloid Precursor Protein (APP) by cellular proteases gives rise to various peptides, including a set of 38–43 amino acid peptides (Aβ) that are generated when APP is cleaved by the β-site APP cleaving enzyme 1 (BACE1) and γ-secretase. In Alzheimer's disease, elevated levels of the BACE1 enzyme are correlated with increased production of Aβ and disease pathology. Previous studies indicate that the increase in BACE1 levels is not due to an increase in its mRNA levels, but rather involves post-transcriptional mechanisms including altered translation efficiency. Translation of *BACE1* mRNA was found to be cap-dependent. As ribosomal subunits move from the cap-structure to the initiation codon, they fail to recognize several AUG codons in the 5' leader. In a new study, Dr Vincent Mauro and coworkers looked for physical evidence of the mechanism underlying ribosomal scanning or shunting along the *BACE1* 5' leader by investigating structural stability in the 5' leaders of endogenous mRNAs in vivo. To perform this analysis, the authors probed RNAs using lead(II) acetate, a cell-permeable chemical that induces cleavage of unpaired nucleotides having conformational flexibility. The data revealed that the ≈440-nt 5' leader was generally resistant to cleavage except for a region upstream of the initiation codon. Cleavage continued into the coding region, consistent with destabilization of secondary structures by translating ribosomes. Evidence that a large segment of the *BACE1* 5' leader was not cleaved indicates that this region is structurally stable and suggests that it is not scanned. The results of this study support a mechanism of translation initiation in which ribosomal subunits bypass (shunt) part of the *BACE1* 5' leader to reach the initiation codon. The authors suggest that a nucleotide bias in the 5' leader may predispose the initiation codon to be more accessible than other AUG codons in the 5' leader, leading to an increase in its relative utilization.
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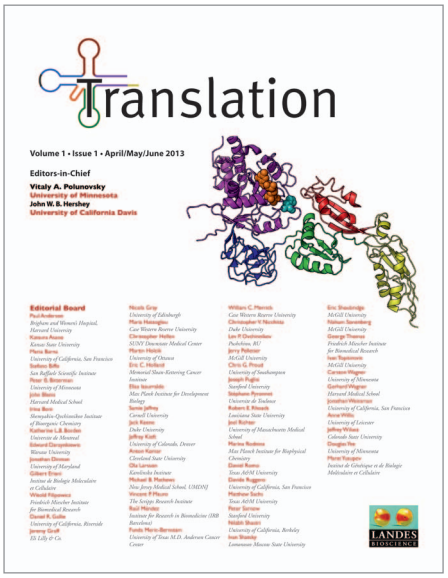

Reference

Koh D, et al. Translation 2013; 1:e24400; http://dx.doi.org/10.4161/trla.24400

Oncogenic miR-181a/b affect DNA damage response in breast cancer

Andrea Bisso, Michela Faleschini, Federico Zampa, Valeria Capaci, Jacopo De Santa, Libero Santarpia, Silvano Piazza, Vera Cappelletti, Mariagrazia Daidone, Reuven Agami, and Giannino Del Sal

Breast cancer is a heterogeneous tumor type characterized by a complex spectrum of molecular aberrations, resulting in a diverse array of malignant features and clinical outcomes. In order to improve patient management, it is essential to decipher the molecular mechanisms that fuel breast cancer development and act as determinants of aggressiveness. Among other alterations, aberrant expression of microRNAs has been found in breast cancer and other human tumors, where they act as either oncogenes or tumor suppressors by virtue of their ability to finely modulate gene expression at the post-transcriptional level. In a recent study, Dr Giannino Del Sal and colleagues describe a new role for miR-181a/b as negative regulators of the DNA damage response in breast cancer, impacting on the expression and activity of the stress-sensor kinase ataxia telangiectasia mutated (ATM). The authors found that miR-181a and miR-181b are overexpressed in more aggressive breast cancers, and their expression correlates inversely with ATM levels. Deregulated expression of miR-181a/b was found to determine the sensitivity of triple-negative breast cancer cells to poly-ADP-ribose-polymerase1 (PARP1) inhibition, a potentially effective therapy for certain cancers. The study results suggest that monitoring the expression of miR-181a/b could be helpful in tailoring more effective treatments based on inhibition of PARP1 in breast and other tumor types.
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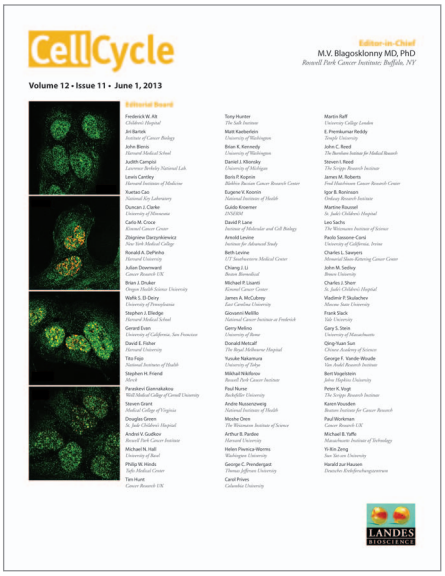

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Bisso A, et al. Cell Cycle 2013; 12:1679-87; PMID:23656790; http://dx.doi.org/10.4161/cc.24757