ΔΗΜΟΚΡΙΤΕΙΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΡΑΚΗΣ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΤΜΗΜΑ ΜΟΡΙΑΚΗΣ ΒΙΟΛΟΓΙΑΣ ΚΑΙ ΓΕΝΕΤΙΚΗΣ

ΕΡΓΑΣΤΗΡΙΟ ΓΟΝΙΔΙΑΚΗΣ ΕΚΦΡΑΣΗΣ,
ΜΟΡΙΑΚΗΣ ΔΙΑΓΝΩΣΗΣ
& ΣΥΓΧΡΟΝΩΝ ΘΕΡΑΠΕΥΤΙΚΩΝ ΜΕΣΩΝ

Antonis Giannakakis, PhD

Ass. Professor of Computational Molecular Biology (MBG-DUTH)

DarkMatters Research Group

RNA salon, July 2024

Biography

Dr. Antonis Giannakakis' scientific fields are experimental molecular biology and bioinformatics with an emphasis on multi-omics approaches to study the biology of so-called "dark" systems, such as non-coding RNAs, exosomes, and oxidative stress. His scientific research focuses on the crosstalk between molecular biology, bioinformatics, translational medicine, and endocrinology in human health research and diseases such as cancer and autoimmune diseases. He works as an Assistant Professor in the Department of Molecular Biology and Genetics at DUTH. He is the PI of the DarkMatters Research Group (http://theranostics.mbg.duth.gr/), integrated into the Laboratory of Gene Expression, Molecular Diagnostics, and Modern Therapeutic Means (https://theranostics.edu.gr/).

References

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2. **Giannakakis A.**, Tsifintaris M., Gouzouasis V., Ow GS., Aau MY., Papp C., Ivshina AV., and Kuznetsov VA#. (2024) KDM7A-DT induces genotoxic stress, tumorigenesis, and progression of p53 missense mutation-associated invasive breast cancer. Frontiers in Oncology, 2(14), 1227151.
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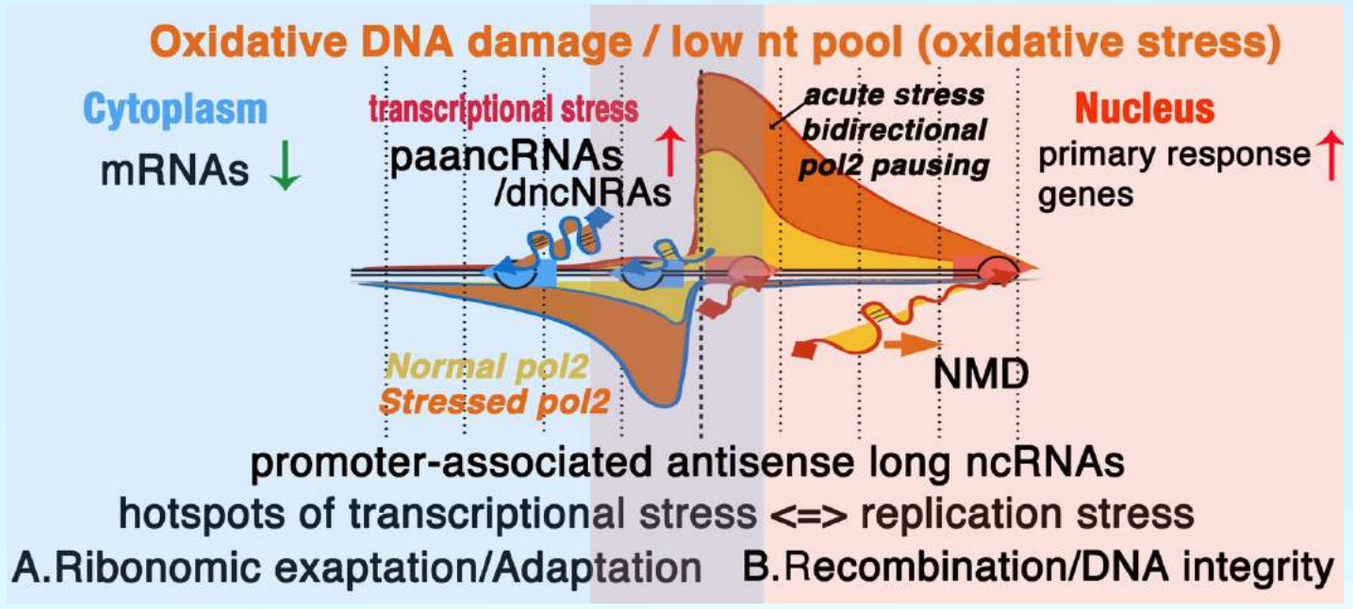
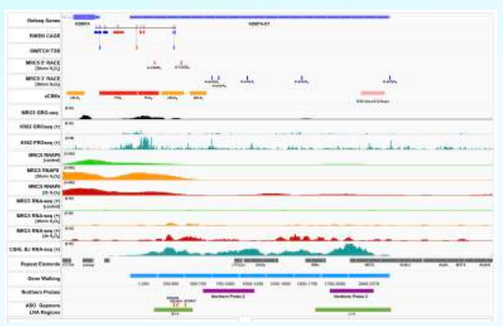
4. Mourtzi N, Siahanidou T, Tsifintaris M, Karamichali E, Tasiopoulou A, Sertedaki A, Pesmatzoglou M, Kapetanaki A, Liosis G, Baltatzis G, Vlachakis D, Chrousos GP, and **Giannakakis A** (2021) lncRNA NORAD is consistently detected in breastmilk exosomes, and its expression is downregulated in mothers of preterm infants. International Journal Molecular Medicine. 48(6), 216.
5. Vlachakis D, Mitsis T, Nicolaides N, Efthimiadou A, and **Giannakakis A**, Bacopoulou F, Chrousos GP. Functions, pathophysiology and current insights of exosomal endocrinology (2020). Molecular Medicine Reports. 23(1), 26.
6. **Giannakakis, A.**, Zhang, J., Jenjaroenpun, P. et al. Contrasting expression patterns of coding and noncoding parts of the human genome upon oxidative stress (2015). Sci Rep 5, 9737

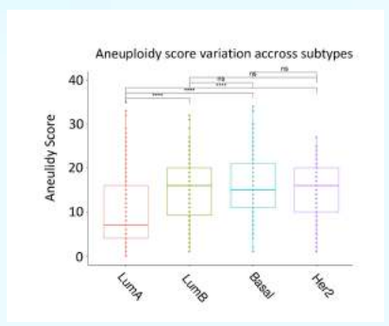
Lecture title: **Stress-induced cancer-causing lncRNAs** -The hidden «hand» of the non-coding genome for cellular stress response in cancer (and other diseases)

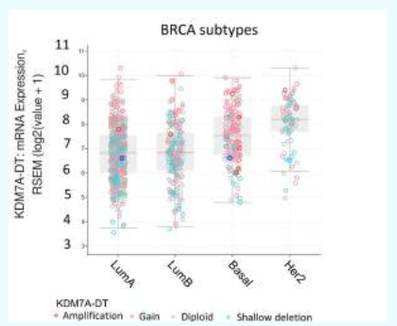
1. **Discovery of si-paancRNAs**: By employing a (similar to yeast studies) systems-level analysis of gene expression changes in human fibroblasts exposed to acute OS, we observed that a transient but robust burst in non-coding transcription at hotspot sites of divergent transcription is associated with a novel bidirectional pol2-promoter pausing phenomenon. Stress-induced promoter-associated and antisense lncRNAs (si-paancRNAs) originate from a reservoir of oxidative stress (OS)-specific promoters. Unlike yeast cells, which have a small and compact genome with only few hundred of lncRNAs present, we show that the genome of human cells responds to OS by a genome-wide but stress-specific transcriptional pulse generating transiently thousands of si-paancRNAs (and other si-lncRNA types). This increase in antisense transcription during chronic stress may acclimate the cellular RNP milieu to facilitate the cell's survival switch from proliferation or development to a stress protection/adaptation response. si-paancRNAs and other categories of si-lncRNAs are associated with polysomes under OS, but even if they don't, we show that they increase their association with free-RNPs and have the potential to elicit an RNA-mediated DDR activation and cell cycle exit. This observation may potentially change the way we understand the stress core response in human cells and generate novel oncogenic si-lncRNAs, as it happened with many classical mRNA oncogenes, which were first discovered in cellular core stress response studies in normal fibroblasts and since then were found to be induced by a plethora environmental stimuli and play critical roles in cancer progression. [**doi.org/10.1038/srep09737**]

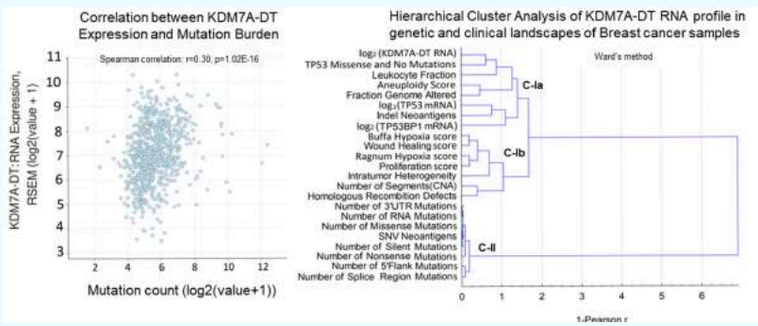


2. **The role of KDM7A-DT si-paancRNA in genotoxic stress during BrCa development:** Several studies have shown that the KDM7A divergent transcript gene (KDM7A-DT), is overexpressed in some cancer types. However, the mechanisms of this overexpression and its corresponding roles in oncogenesis and cancer progression are poorly understood. We found that KDM7A-DT expression is correlated with highly aggressive cancer types and specific inherently determined subtypes (such as ductal invasive breast carcinoma (BRCA) basal subtype). Its regulation is determined by missense TP53 mutations in a subtype-specific context. KDM7A-DT transcribes several intermediate-sized ncRNAs and a full-length transcript, exhibiting distinct expression and localization patterns. Overexpression of KDM7A-DT upregulates TP53 protein expression and H2AX phosphorylation in nonmalignant fibroblasts, while in semi-transformed fibroblasts, OS superinduces KDM7A-DT expression in a TP53-dependent manner. KDM7A-DT knockdown and gene expression profiling in the TP53-missense mutated luminal A BRCA variant, which is abundantly expressed, indicate its significant role in cancer pathways. Endogenous over-expression of KDM7A-DT inhibits DNA damage response/repair (DDR/R) via the TP53BP1-mediated pathway, reducing apoptosis and promoting G2/M checkpoint arrest. Higher KDM7A-DT expression in BRCA is associated with KDM7A-DT locus gain/amplification, higher histologic grade, aneuploidy, hypoxia, immune modulation scores, and activation of the cmyc pathway. Higher KDM7A-DT expression is associated with relatively poor survival outcomes in patients with luminal A or Basal subtypes. In contrast, it is associated with favorable outcomes in patients with HER2+ER- or luminal B subtypes. KDM7A-DT levels are coregulated with critical transcripts and proteins aberrantly expressed in BRCA, including those involved in DNA repair via nonhomologous end joining and epithelial-to-mesenchymal transition pathway. KDM7A-DT and its si-lncRNA exhibit several intrinsic biological and clinical characteristics that suggest essential roles in invasive BRCA and its subtypes. KDM7A-DT-defined mRNA and protein subnetworks offer resources for identifying clinically relevant RNA-based signatures and prospective targets for therapeutic intervention.[**doi.org/10.3389/fonc.2024.1227151**]









Weighted Kappa Correlation
Genome Copy Number Alteration and Somatic Mutations in TP53

Gene pair		P-value	ES	WK
KDM7A-DT	BCL2	9.43E-05	2.49	0.085
KDM7A-DT	TP53	1.68E-03	1.29	0.041
KDM7A-DT	TP53BP1	1.14E-03	2.57	0.064
BCL2	TP53	2.07E-15	1.86	0.094
TP53BP1	TP53	3.34E-03	1.47	0.025
TP53BP1	BCL2	>0.5	-	-

P-value: 2-sided, p<0.005 (N=2,583)
ES; Enrichment Score
WK; Weighted kappa (degree of dependence)