Editorial

Long non-coding RNA and messenger RNA—the meeting of two worlds

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Long non-coding RNAs (lncRNAs), defined as transcripts without protein-coding potential, have recently emerged as key mediators in numerous biological functions. LncRNAs act as regulators of gene expression at different levels including transcriptional and post-transcriptional regulation as well as chromatin organization. Through these actions, lncRNAs have been implicated in several cellular processes as proliferation, differentiation, migration, apoptosis and their misregulations have been found to be associated to several human disorders including cancers (1).

The advent of DNA arrays and next generation sequencing technologies has revealed that a larger part of the genome is transcribed into RNAs than previously assumed. About 70% of the genome is transcribed but only 2% of the human genome codes for proteins (2). However, until now, messenger RNAs and lncRNAs world remained quite distinct.

Recently, Grelet *et al.* demonstrated that *PNUTS* gene can generate a regular PNUTS mRNA but also a non-coding isoform (3). In PNUTS pre-RNA, the authors identified an alternative splice site in exon 12 generating a premature termination codon. Even if a potential truncated protein could be formed, the authors failed to detect this product and assume that alternative spliced RNA forms a lncRNA. *PNUTS* (protein phosphatase 1 nuclear targeting subunit), also known as protein phosphatase 1 regulatory subunit 10 (*PPP1R10*) gene encodes a protein phosphatase 1 binding protein. This protein plays a role in many cellular processes including cell cycle progression (4), DNA repair (5) and apoptosis (6) by regulating the activity of protein phosphatase 1 as well as PTEN (7).

In their work, Grelet *et al.* demonstrate that binding of heterogeneous nuclear ribonucleoprotein E1 (hnRNP E1) in PNUTS pre-RNA mediates its alternative splicing. Indeed, they showed that hnRNP E1 knock-down favours PNUTS lncRNA expression without change in PNUTS mRNA expression. The hnRNP E1 was previously identified as being able to interact with particular secondary structures consisting of stem-loop structure located in 3' UTR of mRNAs (8). The group of PH Howe has found such structure able to interact with hnRNP E1 close to the alternative splice site. The downregulation of hnRNP E1 binding on pre-RNA after TGFβ treatment and E1 phosphorylation (8) or after cytoplasmic translocation or transcription inhibition increases PNUTS lncRNA. So, they showed that binding of hnRNP E1 to pre-RNA controls splicing probably by masking this alternative splice site. Interestingly, the authors showed that PNUTS lncRNA could act as a competing endogenous RNA. The PNUTS lncRNA possesses seven miR-205-5p binding sites and the authors demonstrated an effective binding of miR-205-5p in PNUTS lncRNA. The miR-205 is well-known to regulate ZEB proteins and epithelial-mesenchymal transition (EMT). Authors demonstrated that miR-205 binding to

PNUTS lncRNA decreases miR-205 bioavailability and subsequently stabilizes ZEB mRNAs leading to E-cadherin down-regulation. By this mechanism, the PNUTS lncRNA regulates EMT. PNUTS lncRNA favours mammospheres formation and tumorigenesis in mice after limiting dilution injection. In addition, PNUTS lncRNA increases lung metastasis. All these results indicate that PNUTS lncRNA display an oncogenic role.

Interestingly, the authors showed that miR-205 binds preferentially PNUTS lncRNA rather than normal mRNA. Thus, when hnRNP E1 is present, the PNUTS mRNA is translated and the miR-205 degrades the ZEB1 mRNAs leading to the mesenchymal markers repression, whereas when the binding of hnRNP E1 to the PNUTS pre-RNA is repressed, the PNUTS lncRNA depletes the miR-205 allowing expression of ZEB1 and EMT. PNUTS lncRNA could transiently enhance the effect of TGFβ on EMT. Collectively, these data indicate that PNUTS lncRNA exhibits different properties than PNUTS mRNA.

PNUTS lncRNAs appear overexpressed in breast tumor compare to the normal counterpart, and could be involve in cancerous phenotype. In addition, as transcription inhibition is associated with PNUTS lncRNA expression, this lncRNA could participate to drug resistance through its ability to enhance EMT. The authors demonstrate that PNUTS lncRNAs is probably submitted to nonsense mediated mRNA decay (NMD). However, it is still able to deplete the miR-205 and impair its action. This article shows that an mRNA with premature termination codon leading to the lack of protein production remains able to exert cellular function even if NMD mechanism is functional.

The number of lncRNAs increases exponentially. Many are located in intergenic regions, but some of them are encoded concomitantly with mRNA. In addition, alternative splicing of regular mRNA could generate lncRNA or circular RNA. In cancer, probably due to aberrant protein expression or loss of regulation mechanisms, this phenomenon is increased (9,10). Thus, it is likely that the regulation described by Grelet *et al.* for the gene PNUTS can be extended to many loci. In their paper, the authors demonstrate the competing endogenous effect of PNUTS lncRNA by squelching miR-205 activity. An lncRNA or circular RNA can interact with miR (11) but also with proteins (12) and it is possible that the concept of competition can be associated with miR or protein depletion.

In summary, the article of Grelet and colleagues provide new information on the role of PNUTS lncRNA on establishment of EMT. More interestingly, this work suggests that a gene should no longer be considered as a locus producing messenger RNA but as a locus potentially capable of producing different RNAs including mRNA, lncRNA or competing endogenous RNA (ceRNA) with potentially antagonistic roles. Results obtained in this paper suggest that PNUTS lncRNA can be used as biomarkers or therapeutic targets in cancers. Indeed, PNUTS lncRNA is overexpressed in cancer cells showing the value of this lncRNA as a new molecular target in cancer. A variety of approaches have already been developed to modulate the alternative splicing (10). Such approaches could be used to inhibit the formation of PNUTS lncRNA. Alternatively, the specific degradation of this lncRNA could be used to impair EMT and drug resistance. In conclusion, the discovery of this new lncRNA may open up new opportunities for innovative therapeutic strategies.

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Footnote

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References

1. Angrand PO, Vennin C, Le Bourhis X, et al. The role of long non-coding RNAs in genome formatting and expression. Front Genet 2015;6:165.
2. Bertone P, Stolc V, Royce TE, et al. Global identification of human transcribed sequences with genome tiling arrays. Science 2004;306:2242-6.
3. Grelet S, Link LA, Howley B, et al. A regulated PNUTS mRNA to lncRNA splice switch mediates EMT and tumour progression. Nat Cell Biol 2017;19:1105-15. Erratum in: Nat Cell Biol 2017;19:1443.
4. Fisher LA, Wang L, Wu L, et al. Phosphatase 1 nuclear targeting subunit is an essential regulator of M-phase entry, maintenance, and exit. J Biol Chem 2014;289:23745-52.
5. Landsverk HB, Mora-Bermúdez F, Landsverk OJ, et al. The protein phosphatase 1 regulator PNUTS is a new component of the DNA damage response. EMBO Rep 2010;11:868-75.

6. Lee SJ, Lim CJ, Min JK, et al. Protein phosphatase 1 nuclear targeting subunit is a hypoxia inducible gene: its role in post-translational modification of p53 and MDM2. Cell Death Differ 2007;14:1106-16.
7. Kavela S, Shinde SR, Ratheesh R, et al. PNUTS functions as a proto-oncogene by sequestering PTEN. Cancer Res 2013;73:205-14.
8. Brown AS, Mohanty BK, Howe PH. Identification and characterization of an hnRNP E1 translational silencing motif. Nucleic Acids Res 2016;44:5892-907.
9. Kristensen LS, Hansen TB, Venø MT, et al. Circular RNAs in cancer: opportunities and challenges in the field. Oncogene 2018;37:555-65.
10. Song X, Zeng Z, Wei H, et al. Alternative splicing in cancers: From aberrant regulation to new therapeutics. Semin Cell Dev Biol 2017. pii: S1084-9521(17)30261-6. [Epub ahead of print].
11. Tay Y, Rinn J, Pandolfi PP. The multilayered complexity of ceRNA crosstalk and competition. Nature 2014;505:344-52.
12. Marchese FP, Raimondi I, Huarte M. The multidimensional mechanisms of long noncoding RNA function. Genome Biol 2017;18:206.

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