Cours du 21-10-2013

Longévité cérébrale
Charity begins at home: non-coding RNA functions in DNA repair

Dipanjan Chowdhury, Young Eun Choi and Marie Eve Brault

Nature Reviews Molecular Cell Biology
2013 vol. 14 (3) pp. 181–9

Small non-coding RNAs mount a silent revolution in gene expression
Antti P Aalto and Amy E Pasquinelli

![Diagram showing DNA repair mechanisms](image-url)
Extracellular miRNAs: the mystery of their origin and function

Turchinovich A, Weiz L, Burwinkel B

1. Pre-miRNA transcription
2. Pre-miRNA processing
3. Dicer complex
4. RISC complex

- Vesicles-free miRNA
- Apoptotic body-enclosed miRNA
- Shedding vesicles and exosomes packaged miRNA

- Specific secretion?
- Passive secretion

- Extracellular space
- Cytoplasm
- Nucleus

- Release after cell death
- Specific secretion?
Membrane vesicles as conveyors of immune responses

Clotilde Théry, Matias Ostrowski and Eliodie Segura

Figure 1 | Different types of secreted membrane vesicles. Intracellular trafficking
miRNA response to DNA damage

Guohui Wan¹, Rohit Mathur¹, Xiaoxiao Hu¹, Xinna Zhang² and Xiongbin Lu¹

Trends in Biochemical Sciences, September 2011, Vol. 36, No. 9

Table 1. miRNAs target key genes involved in the DNA damage response

<table>
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<tr>
<th>Targets</th>
<th>Function in DNA damage response</th>
<th>miRNAs</th>
<th>Refs.</th>
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<tbody>
<tr>
<td>ATM</td>
<td>Mediator/transducer</td>
<td>miR-421</td>
<td>[27]</td>
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<tr>
<td>H2AX</td>
<td>Mediator, DNA repair</td>
<td>miR-24</td>
<td>[28]</td>
</tr>
<tr>
<td>RAD52</td>
<td>DNA repair</td>
<td>miR-210, miR-373</td>
<td>[63]</td>
</tr>
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<td>RAD23B</td>
<td>DNA repair</td>
<td>miR-373</td>
<td>[63]</td>
</tr>
<tr>
<td>MSH2</td>
<td>DNA mismatch repair</td>
<td>miR-21</td>
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</tr>
<tr>
<td>BRCA1</td>
<td>DNA repair</td>
<td>miR-182</td>
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</tr>
<tr>
<td>p53</td>
<td>Cell cycle checkpoint, apoptosis</td>
<td>miR-504, miR-125b</td>
<td>[30,31]</td>
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<tr>
<td>p63</td>
<td>Transcription factor</td>
<td>miR-92, miR-302</td>
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<tr>
<td>E2F</td>
<td>Transcription factor</td>
<td>miR-17-92, miR-20a, miR-34a</td>
<td>[66,67]</td>
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<td>p21</td>
<td>Cell cycle</td>
<td>miR-17, miR-20a/b, miR-106a/b, miR-93, miR-215, miR-192</td>
<td>[35,68]</td>
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<tr>
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<td>Cell cycle</td>
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<td>CDK6</td>
<td>Cell cycle</td>
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<td>[71–73]</td>
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<td>Cdc25A</td>
<td>Cell cycle checkpoint</td>
<td>miR-21, miR-449a/b</td>
<td>[73,74]</td>
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<td>Cdc42</td>
<td>Cell cycle checkpoint</td>
<td>miR-29</td>
<td>[75]</td>
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<td>Cyclin E</td>
<td>Cell cycle</td>
<td>miR-15a, miR-16</td>
<td>[76,77]</td>
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<tr>
<td>Cyclin D</td>
<td>Cell cycle</td>
<td>miR-15a, miR-16</td>
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<td>Cyclin G1</td>
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<td>miR-122</td>
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<td>Wee1</td>
<td>Cell cycle checkpoint</td>
<td>miR-195</td>
<td>[80]</td>
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<td>p27</td>
<td>Cell cycle</td>
<td>miR-221/222, miR-181</td>
<td>[81,82]</td>
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<td>p57</td>
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<td>[81]</td>
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<td>miR-16</td>
<td>[61]</td>
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<td>Bcl-2</td>
<td>Apoptosis</td>
<td>miR-15a, miR-16-1</td>
<td>[83]</td>
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Charity begins at home: non-coding RNA functions in DNA repair

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**Junk DNA as an evolutionary force**

**LINE-1 retrotransposons:** modulators of quantity and quality of mammalian gene expression?

**PIWI-interacting small RNAs: the vanguard of genome defence**

**Beyond transposons: the epigenetic and somatic functions of the Piwi-piRNA mechanism**
Beyond transposons: the epigenetic and somatic functions of the Piwi–piRNA mechanism

Peng JC, Lin H

Current Opinion in Cell Biology
2013 vol. 25 (2) pp. 190–4

DNA methylation

transposon loci
Rasgrf1 imprinting locus
Aplysia CREB2 promoter

Nuage: piRNA biogenesis & transposon RNA degradation

gene regulation, transposon repression, genome protection

Canalization

Piwi phosphorylation?

translation inhibition & mRNA degradation

mRNAs w/ stopped polysomes
A LINE-1 component to human aging do LINE elements exact a longevity cost for evolutionary advantage?
St Laurent G, Hammell N, McCaffrey TA

Mech Ageing Dev
2010 vol. 131 (5) pp. 299–305

Activation of transposable elements during aging and neuronal decline in Drosophila

Nat Neurosci
2013 vol. 16 (5) pp. 529–31

L1 retrotransposition in nongrowing and primary human somatic cells
Kubo S, Selmeczi MC, Soifer HS, Perez JL, Moran J, Kazazian HH, Kasahara N

Proc Natl Acad Sci USA
2006 vol. 103 (23) pp. 8036–41

Active human retrotransposons: variation and disease
Hancks DC, Kazazian HH

Current Opinion in Genetics & Development
2012 vol. 22 (3) pp. 191–203

Somatic expression of LINE-1 elements in human tissues
Belancio VP, Ray-Engel AM, Pochampally RR, Deininger P

Nucleic Acids Research
2010 vol. 38 (12) pp. 3909–22

DICER1 deficit induces Alu RNA toxicity in age-related macular degeneration

Nature
2011 vol. 471 (7338) pp. 325–30

A Role for Neuronal piRNAs in the Epigenetic Control of Memory-Related Synaptic Plasticity

Cell
2012 vol. 149 (3) pp. 693–707

Transcriptional activation of short interspersed elements by DNA-damaging agents
Rudin CM, Thompson CS

Genes Chromosomes Cancer
2001 vol. 30 (1) pp. 64–71

L1 mobile element expression causes multiple types of toxicity
Wallace NA, Belancio VP, Deininger PL

Gene
2008 vol. 419 (1–2) pp. 75–81

Human Alu element retrotransposition induced by genotoxic stress
Hagan C, Sheffield R, Rudin CM

Nat Genet
2003 vol. 35 (3) pp. 219–20

The human LINE-1 retrotransposon creates DNA double-strand breaks
Gasiòr S, Wakeman TP, Xu B, Deininger PL

J Mol Biol
2006 vol. 357 (6) pp. 1383–93

LINE-1 retrotransposition in human neuroblastoma cells is affected by oxidative stress
Cingi C, Mancarella P, Del Re B

Cell Tissue Res
2011 vol. 341 (3) pp. 381–91
Fig. 1. Aging theories converge on accumulated DNA damage. Exogenous factors, such as UV irradiation, caloric excess, alterations in the IGF/mTOR pathways, and oxidative stress can alter the cellular balance between DNA damage and repair. Similarly, endogenous pathways such as telomere regulation and genetic defects in DNA repair can lead to cellular senescence and premature aging. These effects are of added importance when they alter stem cell regenerative activity.
Figure 8. A summary of the biologically relevant L1-related mRNA products and their respective impact on the host genome. Transcription of the L1 locus results in the production of either the full-length mRNA (FL1mRNA), the splice ORF2 mRNA (SpORF2mRNA), or both. FL1mRNA protein products can mobilize L1, Alu, and SVA elements, while SpORF2mRNA only produces ORF2 protein and as a result can only assist Alu retrotransposition. Expression of either L1 mRNA can generate ORF2, which leads to introduction of DNA DSBs potentially resulting in xccumulation of mutations in the cellular genome.

Figure 3. Steps of the L1 integration process. The L1 endonuclease domain encoded by the ORF2 protein loosely recognizes a consensus 5'-TTTTAA-3' sequence (shown in green) in the genomic DNA and introduces a first-strand nick between the T and A nucleotides of the minus strand. The resulting free 3' end of the host DNA is proposed to base-pair with the poly(A) tail of the L1 mRNA (shown in red) and serves as a primer for the first-strand cDNA synthesis (shown in blue) by the L1 reverse transcriptase that uses L1 mRNA as the template. This process is known as a target-primed reverse transcription (TPT). Mechanistic details of the rest of the L1 integration process are not well defined yet. At some point during L1 integration, either L1 ORF2 or a cellular activity introduces a nick into the plus strand and the structure is resolved to utilize the 3' end as a primer for the second-strand DNA synthesis (shown in light blue) by an unknown polymerase activity. Finally, the two nicks in the cellular DNA are repaired to complete the L1 integration event.
Fig. 3. Cellular mechanisms limiting selfish retroelements in mammals. L1 transcription is suppressed by DNA methylation and can be interrupted by premature polyadenylation. An antisense promoter residing within the L1 promoter can generate antisense L1 transcripts and lead to transcription of neighboring 5' sequences. RNA interference can also regulate L1 post-transcriptionally via small RNAs facilitated by Argonaute and PIWI proteins. Small RNAs may in-turn direct DNA methylation.
A Role for Neuronal piRNAs in the Epigenetic Control of Memory-Related Synaptic Plasticity

Cell
2012 vol. 149 (3) pp. 693-707

![Image: Aplysia Piwi ORF]

**Piwi Proteins:**
Carrying piRNAs & 21-U RNAs

**Argonaute proteins:**
carrying miRNAs & siRNAs

Piwi IP, Ago IP

piR-1

miR-22c

**PIWI-GFP**

**CyT NUC**

Piwi

GAPDH

Histone H3
A Role for Neuronal piRNAs in the Epigenetic Control of Memory-Related Synaptic Plasticity

Aplysia CREB2 promoter region

-800 -600 -400 -200 +1

CRE TATA ATG

Methylation Specific Primers (MSP) for CREB2

Distal Promoter Proximal Promoter

5HT

untreated 5HT RG108

CREB2 CREB1

% Methylation

untreated 5HT RG108 + 5HT

CpG Site

Piwi/piRNA complex binds the CREB2 nascent transcript:

CREB2 DNA

DNMT ?

Piwi

CREB2 mRNA
Activation of transposable elements during aging and neuronal decline in Drosophila

Li W, Razak I, Chatterjee N, Grüninger S, Krug L, Theodorou D, Dubnau J

Cordaux @ Batzer, Nature Reviews genetics, 10: 691-703, 2009

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**Figure a**

- Bar graph showing relative fold change for non-posable transposons in different aging stages (2-4 d, -14 d, -21 d, -28 d)
- WT 2-4 d vs WT 13 d, WT 23 d, WT 34 d
- ENV vs WT 23 d, WT 34 d

**Figure b**

- Images of tissue samples at different time points (2-4 d, 13 d, 23 d, 34 d)
- WT and ENV conditions

**Figure d**

- Diagram showing localization of gypsy-TRAP and Ovo binding site
- 2-4 d and ~28 d

**Figure e**

- Diagram showing localization of gypsy-TRAP and Ovo binding site
- 2-4 d and ~28 d

**Figure c**

- Diagram showing mutated gypsy-TRAP and Ovo binding site
- 2-4 d and ~28 d
Activation of transposable elements during aging and neuronal decline in Drosophila

24 h memory after 10 spaced training sessions

Performance Index

Percent survival

Days after eclosion