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lncRNA: a new danger for genome integrity

Anna Shmakova^{1,2} and Yegor Vassetzky^{1,2}*

¹CNRS, UMR 9018, Université Paris-Saclay, Institut Gustave Roussy, 94800 Villejuif, France;

²Koltzov Institute of Developmental Biology, 119334 Moscow, Russia;

*Corresponding author: yegor.vassetzky@cnr.fr

Summary

Many factors affect the genesis of chromosomal aberrations in cells. In this issue of the International Journal of Cancer, Demin et al. describe a long non-coding RNA CASTL (chromosomal aberrations stimulating lncRNA) that facilitates *CCDC6-RET* fusion (inv(10)(q11;q21))¹. Expression of CASTL1 is cell-type specific and can account for the appearance of *CCDC6-RET* fusion only in specific cell types.

Chromosomal rearrangements result from DNA breaks and erroneous DNA repair; their appearance is a risk factor for oncogenic cell transformation². Common threats for chromosomal rearrangements originate from the cellular machinery itself, which comprises DNA-damaging cellular activities (replication stress, reactive oxygen species), programmed DNA-cutting enzymes (e.g., recombination-activating gene (RAG) 1/2 complex or activation-induced deaminase (AID) in B cells indispensable for proper antibody production), specific genome architecture and stochastic DNA movements that allow DNA breaks clustering, and, finally, error-prone DNA repair activities². Another player in the genesis of chromosomal rearrangements could be microhomology in DNA of the partners involved in a chromosomal translocation, inversion or deletion³.

These factors render the cell intrinsically vulnerable to spontaneous chromosomal rearrangements. Recently, an unexpected novel contributor to this vulnerability was revealed. In this issue of the International Journal of Cancer, Demin et al. describe how a long non-coding RNA (lncRNA) ENSG00000269945 facilitates *CCDC6-RET* fusion (inv(10)(q11;q21))¹, a rearrangement encountered in thyroid and lung cancers and leading to a constitutive activation of the RET oncogenic tyrosine kinase⁴. The lncRNA located on chromosome 14 contains sequences that are homologous to *CCD6* and *RET* intronic regions, thus potentially providing an illegitimate repair template for chromosome 10. Upon stimulation of DNA damage, the presence of this lncRNA increased the formation of the *CCDC6-RET* fusion and chimeric oncogene expression in human thyroid cells, which warrants the terminology proposed by the authors for this lncRNA: chromosomal aberrations stimulating lncRNA 1 (CASTL1) (**Figure 1**). There could soon be more CASTLs found in the human genome.

It was previously proposed that RNAs might indeed act as a repair template for DNA double strand breaks repair *via* homologous recombination (HR) both in *cis* (RNA derived from the same locus) and in *trans* (RNA derived from distant parts of the genome)⁵. Further discovery and study of CASTLs should reveal their mechanisms of action. Do they facilitate

chromosomal rearrangements by "hacking" the accurate HR repair with a wrongful template? What ensures the proximity of RNA template to a DNA double strand break? Are they acting throughout the cell cycle or their action is limited to a particular cell cycle phase? What could be the influence of secondary structures of lncRNAs and the presence of repetitive elements within them on the DNA repair? By answering these questions, we should expand our understanding of RNA-templated DNA repair and its contribution to chromosomal rearrangements.

Furthermore, an important clue comes from the fact that the expression lncRNAs is cell- and tissue-specific. It has long been questioned why different chromosomal aberrations occur in different cells⁶. It is plausible that lncRNAs, expressed in a particular cell type, might contribute to the appearance of cell-specific chromosomal rearrangements between different loci *via* homologous regions. By analyzing previously published transcriptomes, Demin et al. demonstrated that *CASTL1* was expressed in normal thyroid tissue and in papillary thyroid carcinoma with *CCDC6-RET* inversion¹.

To conclude, Demin et al. describe an intriguing mechanism whereby the *CASTL1* lncRNA is involved in the formation of an oncogenic *CCDC6-RET* fusion through its homology to the *CCDC6* and *RET* intronic loci. Upon DNA damage in these loci, lncRNA *CASTL1* presumably serves as a micro-template for DNA repair, increasing the chances for gene fusion. It is currently unknown whether other lncRNAs with comparable activities exist in the human genome and if so, what could be their evolutionary role. In particular, why the genome encodes self-hacking lncRNAs remains to be elucidated.

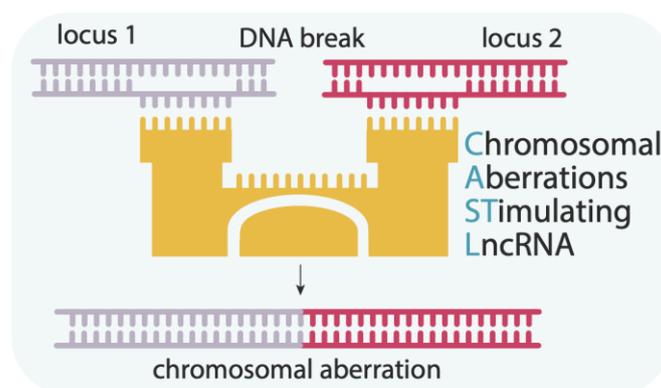


Figure 1. Chromosomal aberrations stimulating lncRNAs (CASTL) that contain sequences homologous to loci participating in chromosomal rearrangements.

Conflict of interests

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