[Frontiers In Bioscience, Landmark, 23, 1680-1686, March 1, 2018]

LINE-1 activity and regulation in cancer

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1. ABSTRACT

LINE-1 retrotransposons are ubiquitous genetic elements interspersed within the primary nuclear genome of modern day humans. Although shorter LINE-1-derived sequences occupy nearly one-in-five nucleotides of our genome, we are just beginning to appreciate the link between these important genetic elements and cancer, perhaps the most well-studied major degenerative disorder affecting humanity today. Herein, I summarize empirical observations linking LINE-1 to tumorigenesis. The work is organized into three major parts. First, I provide an overview of LINE-1 activity in cancer; highlighting major features of LINE-1 life-cycle such as: promoter methylation, transcription, translation, and retrotransposition. Second, I discuss three genetic pathways - epigenetic regulation, interferon signaling, and genome integrity – as they relate to LINE-1 regulation in cancer. Finally, I review most recent body of work linking LINE-1 as not only a diagnostic cancer biomarker, but also a potential therapeutic target.

2. INTRODUCTION

Causal relationships between cancer-related phenotypes and underlying genotype have traditionally been studied using both genetic engineering and epidemiological studies. Because there are likely a couple of hundred retrotransposition-competent active LINE-1 retrotransposons in our genome (1; 2) systematic inactivation of LINE-1 by gene knockout experiments have not been attempted to date. Given this limitation, epidemiologic studies do show a possible putative role of LINE-1 in cancer; a recent review on the topic finds that there is some evidence linking LINE-1 expression to tumorigenesis in several major human cancer types (3; 4). Of note, for an authoritative recent review on mobile DNA in various diseases, not just cancer, the readership is referred to (5).

To date, 1,057 articles focusing on LINE-1 retrotransposons and cancer are available on Pubmed archive. Of those, I identified and manually curated 35 articles focusing on experimental evidence examining some aspect of LINE-1 biology in cancer. Because of widespread availability of bisulfite-treated DNA-based assays in clinical research, vast majority of published reports are studies focusing on LINE-1 promoter hypomethylation as a proxy biomarker for genome-wide DNA hypomethylation, which is in itself a major hallmark of cancer. Of note, LINE-1 promoter-based studies have recently been reviewed in detail here (6). To arrive at a short list of 35 articles, I asked the following three questions: “Is the body of work contributing to mechanistic insight rather than simply reporting LINE-1 as a cancer biomarker?”, “What are the genes that likely modulate LINE-1 activation in cancer?”, and “Is there any evidence that LINE-1 targeting provides putative therapeutic benefit?”. Small portion, or 9 out of 35 articles, link LINE-1 expression in cancer to a potpourri collection of unique empirical observations, such as: micronuclei formation (7), LINE-1

as pre-diagnostic biomarker within circulating tumor cells/tumor DNA (8; 9; 10), gene expression profiles linked to LINE-1 expression (11), putative mechanism of LINE-1-mediated cellular transformation (12; 13), as well as induction of apoptosis and proliferation following LINE-1 expression in cancer (14; 15). To my mind, these nine studies represent preliminary discovery-based work that may prove to be of interest in the future.

3. ON LINE-1 TRANSCRIPTIONAL ACTIVATION IN CANCER

Recent seminal work by Scott *et al.*, 2016, discovered and documented the actual mechanism of how LINE-1 retrotransposon transcriptional activation can drive, at least in part, colorectal carcinoma (16). Studying only the second reported case of *APC* inactivation by LINE-1 retrotransposition, the authors revealed that LINE-1 insertion in one *APC* allele complements traditional single nucleotide variant-mediated inactivation of the other allele of *APC*. Specifically, one allele was inactivated by introduction of unequivocally deleterious premature stop codon, resulting in premature termination at p.R1450*; whereas the other allele was inactivated by LINE-1 mediated somatic retrotransposition of one APC allele by LINE-1 insertion event some 160 bp. By comparing the unique singleton mutation patterns of 295 sequence variants in full-length LINE-1 retrotransposons to that of the LINE-1 insert, the authors identified candidate LINE-1 retrotransposon source, which is located at genome position, chr 17:18776467, of the Hg19 Human Genome assembly. Another important body of work is by Phillippe *et al.*, 2016, identified that only very selected LINE-1 retrotransposons, unique to each individual, contribute to transcriptional activation and subsequently to the bulk of LINE-1 protein expression (17). As high-throughput technology, specifically PacBio-based DNA sequencers, are more widely used in cancer research, we will begin to understand more clearly just when and how LINE-1 transcriptional activation occurs in cancer.

4. ON LINE-1 ENCODED PROTEINS IN CANCER

Work on LINE-1 encoded proteins expression in cancer has largely been based on ORF1p profiling in many human cancer types. Nearly half of all cancers in human support LINE-1 ORF1p expression, which presents pre-diagnostic and/or diagnostic utility in clinical practice today (18). More interestingly, there is evidence that ORF2p encoded reverse transcriptase activity plays a necessary role in TMPRSS2 and ETV1 gene fusion (19), and growth of prostate cancer (19). Finally, there is also evidence that ORF1p expression induces hTERT in tumor cells (20).

5. ON LINE-1 RETROTRANSPOSITION IN CANCER

Despite panoply of intronic and intergenic LINE-1 retrotranspositions in several visceral cancers - including pancreatic ductal adenocarcinoma, colorectal carcinoma, esophageal carcinoma, and prostatic carcinoma – there is limited evidence for LINE-1 retrotransposition causing abbarent gene regulation (21; 22; 23; 24). The single example of unequivocal deleterious LINE-1 retrotransposition in cancer has been aforementioned report by Scott *et al.*, 2015 (16), whereby the authors identified that one APC allele was inactivated by traditional single nucleotide mutation and the other allele was mutated by LINE-1 insertion; providing evidence for the classic two-hit hypothesis for mutating APC gene.

6. ON LINE-1-RELATED GENE REGULATORY NETWORKS

The subgroup of 20 identified research articles collectively identify 18 unique genes whose expression is empirically linked to LINE-1 expression in cancer. The gene symbols representing the genes in question are as follows: *AID, APOBEC3D, APOBEC3G, DNMT1, DNMT3B, ERCC4, ETS1, IFNA1R, IFNB1, IL-6, PIWILINE-1, RAD21, RB, RNASEL, SIRT6, TERT, TP53*, and *UHRF1*. To better organize the discussion, I performed a biological pathway analysis using a free online database termed Reactome. The interactive server identified that 9 out of 18 genes belong into two groups of distinct biological pathways. The pathways identified pathways are as follows: (i) epigenetic regulation pathway (*DNMT1, DNMT3b, UHRF1*, and *ETS1*); and (ii) interferon signaling pathway (*IFNA1R, IFNB1, RB, TERT,* and *IL-6*) (Table 1). Remaining 8 genes were determined to belong to the genome integrity pathway.

6.1. ON LINE-1-related epigenetic regulation pathway

There is compelling empirical evidence that genome-wide LINE-1 promoter methylation is dependent on molecular pathway that entails *MUC1, DNMT1*, and *DNMT3B* genes (25). Specifically, Li *et al.*, 2015, performed both loss-of-function experiments (by MUC1 shRNA) and gain-of-function experiments (by vector expressing MUC1) to observe that MUC1 is transcriptional activator of both DNMT1 and DNMT3B promoters. In turn, MUC1 expression also causes genome-wide LINE-1 promoter hypomethylation in cultured cancer cells. Nakamura *et al.*, 2016, reported that UHRF1 overexpression led to genome-wide LINE-1 promoter hypomethylation, as well as that, conversely, siRNA UHRF1 knockdown increased the global LINE-1 promoter DNA methylation (26).

Table 1. Biological processes related to L1 retrotransposons

Epigenetic Regulation
• DNMT1
• DNMT3B
• UHRF1
• ETS1
Interferon Signaling
• IFNA1R
• IFNB1
• RB
• TERT
• IL-6
Genome Integrity
• AID
• APOBEC3D
• APOBEC3G
• ERCC4
• PIWIL1
• RAD21
• RNASEL
• SIRT6
• TP53

Li *et al.*, 2014, found out that ectopic LINE-1 ORF1p overexpression caused increased RNA expression of ETS1 related genes as well as promoted cell proliferation and anchor-independent growth of LoVo cancer cell line (27). The same group showed that LINE-1 siRNA caused decreased RNA expression of ETS1 related genes as well as reduced the proliferation and anchor-independent growth ability of LoVo cancer cell line. Taken together, there is empirical evidence that genes involved in epigenetic regulation pathway also regulate LINE-1 retrotransposons.

6.2. ON LINE-1-relazzted interferon signaling pathway

Aschacher *et al.*, 2016, observed that LINE-1 knockdown decreases TERT function as measured by both telomere dysfunction foci and telomerase activity (20). Conversely, LINE-1 overexpression increased telomerase activity. Yu *et al.*, 2015, discovered that IFNB1 treatment of cancer cell lines inhibits LINE-1 retrotransposition (28). In addition, knockdown of IFNA1R led to increase in LINE-1 retrotransposition. Separate work by Ishak *et al.*, 2016, shows that genetically engineered mice carrying F832A mutation in RB1 causes both genomewide upregulation of LINE-1 RNA in somatic tissues as well as increased susceptibility to leukemia (29). Taken together, the composite work by Aschacher *et al.*, Yu *et al.*, and Ishak *et al.*, is, to my mind, a collection of the most compelling empirical evidence to date that LINE-1 retrotransposon modify an important aspect of human tumorigenesis. Of note, Gasche *et al.*, 2011, identified that IL-6 treatment of cancer cell line induced genome-wide LINE-1 promoter hypomethylation (30).

6.3. ON LINE-1-related genome integrity pathway

The third group of genes associated with LINE-1 biology belong to genome integrity pathway, whose functions include DNA repair and innate cell immunity against viruses. A series of independent reports document the notion that some members of APOBEC ("apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like") cytidine deaminases regulate LINE-1 retrotransposition in somatic tissue. Specifically, Servant *et al.*, 2017, showed that ERCC4 limits LINE-1 retrotransposition, suggesting that other core components of the nucleotide excision repair (NER) pathway may also play a similar role (31). Liang *et al.*, 2016, also reported that ectopic expression on both APOBEC3 and APOBEC3DE limit LINE-1 retrotransposition (32). Koyama *et al.*, 2013, showed that APOBEC3G inhibit LINE-1 retrotransposition (33). Similarly, Metzner *et al.*, 2012, also showed that AID

inhibits LINE-1 retrotransposition (34). To conclude, multiple studies show that several cytidine deaminase enzyme isoforms regulate LINE-1 retrotransposition in cancer.

Several other genes involved in repair of DNA double-stranded breaks affect LINE-1 retrotransposition. Two studies support the idea that TP53 protein also limits LINE-1 retrotransposition. First, Haoudi *et al.*, 2004, proposed a dichotomous idea whereby LINE-1 retrotransposition in wild-type TP53 cancer cell line causes apoptosis, but not in cancer cell line carrying mutated TP53 allele (35). More recently, Wyulie *et al*, 2016, presented multiple lines of empirical evidence including gene complementation studies and genetic fish studies to support an assertion that TP53 restricts LINE-1 retrotransposition (36). Xu *et al.*, 2014, reported that Rad21 expression induces increase in LINE-1 retrotransposition, as well as that Rad21 knockdown by siRNA causes reduction in LINE-1 retronsposition (37). Van Meter *et al.*, 2014, discovered that expression of SIRT6 recruits KAP1 to LINE-1 promoters, thus inducing LINE-1 transcriptional silencing (38). In addition, the authors also observed that senescent cells harbor lower SIRT6 levels and comparably higher LINE-1 RNA levels, relative to young cells. Zhang *et al.*, 2014, examined the role of RNASEL on LINE-1 retrotransposition (39). Expression of wild type RNASEL, but not catalytically inactive protein, reduced many aspects of LINE-1 biology including LINE-1 RNA expression, ORF1p and ORF2p expression, and LINE-1 retrotransposition. Wang *et al.*, 2015, made an interesting observation that PIWILINE-1 protein level is decreased in melanoma cell line with metastatic potential (40). Importantly, overexpression of PIWILINE-1 caused LINE-1 promoter hypermethylation (41).

Taken together, biological pathways affecting epigenetic regulation, interferon signaling, and genome integrity play a role in regulating LINE-1 retrotransposon suppression in somatic tissues and abberations of some of these genes may, at least in part, be the underlying cause of LINE-1 activity in cancer.

7. ON LINE-1 AS PUTATIVE THERAPEUTIC TARGET IN CANCER

The greatest clinical utility/benefit of any biomarker, is not whether or not a given analyte solely provides diagnostic and/or prognostic information, but is knowing if it can be used as a therapeutic target. To broach that question, a hallmark preclinical studies by Sciamanna *et al.*, 2005 uncovered that pharmacologic LINE-1 inhibition by two reverse transcriptase inhibitors slows down the growth of malignant melanoma and prostatic carcinoma cells (19). Follow-up study by Carlini *et al.*, 2010 similarly demonstrated efficacy of reverse transcription inhibition of prostate cancer growth (42). Most importantly, a clinical trial showed that efavirenz provides therapeutic benefit by increasing progression free survival in a cohort of 53 patients with high-stage castration-resistant prostate cancer (43). The most recent review on the topic suggests that LINE-1 inhibition with reverse transcriptase inhibitors may not only slow down the progression of prostate cancer, but may also play a role in preventing the initiation of tumor growth (44).

8. ACKNOWLEDGEMENTS

The author (N.R.) gives kind regards and many thanks to the Department of Pathology, Immunology, and Laboratory Medicine at the University of Florida for their support during the preparation of this review article.

9.REFERENCES

1. B Brouha, J Schustak, RM Badge, S Lutz-Prigge, AH Farley, JV Moran, HH Kazazian Jr: Hot L1s account for the bulk of retrotransposition in the human population. *Proc Natl Acad Sci U S A* 100, 5280-5 (2003) DOI: 10.1073/pnas.0831042100

2. CR Beck, P Collier, C Macfarlane, M Malig, JM Kidd, EE Eichler, RM Badge, JV Moran: LINE-1 retrotransposition activity in human genomes. *Cell* 14, 1159-70 (2010) DOI: 10.1016/j.cell.2010.05.021

3. D Ardeljan, MS Taylor, DT Ting, K.H. Burns: The Human Long Interspersed Element-1 Retrotransposon: An Emerging Biomarker of Neoplasia. *Clin Chem* 63, 816-822 (2017) DOI: 10.1373/clinchem.2016.257444

4. N Rodic. Long interspersed element-1 (L1) Retrotransposons as Neoplastic Biomarkers, In: Human Retrotransposons in Health and Disease. Ed: G Cristofari, Cham, Switzerland (2017) ISBN 978-3-319-48344-3

5. HH Kazazian Jr, JV Moran: Mobile DNA in Health and Disease. *N Engl J Med* 377, 361-370 (2017) DOI: 10.1056/NEJMra1510092

6. Human retrotransposons in health and disease. Ed: G Cristofari, Cham, Switzerland (2017) ISBN 978-3-319-48344-3

7. YH Cho, HD Woo, Y Jang, V Porter, S Christensen, RF Hamilton Jr, HW Chung: The Association of LINE-1 Hypomethylation with Age and Centromere Positive Micronuclei

in Human Lymphocytes. *PloS one* 10, e0133909 (2015)
DOI: 10.1371/journal.pone.0133909

8. I Papasotiriou, K Pantopikou, P Apostolou: L1 retrotransposon expression in circulating tumor cells. *PloS one* 12, e0171466 (2017)
DOI: 10.1371/journal.pone.0171466

9. Y Nagai, E Sunami, Y Yamamoto, K Hata, S Okada, K Murono, K Yasuda, K Otani, T Nishikawa, T Tanaka, T Kiyomatsu, K Kawai, H Nozawa, S Ishihara, DS Hoon, T Watanabe: LINE-1 hypomethylation status of circulating cell-free DNA in plasma as a biomarker for colorectal cancer. *Oncotarget* 8, 11906-11916 (2017)
DOI: 10.18632/oncotarget.14439

10. IV Gainetdinov, KY Kapitskaya, EY Rykova, AA Ponomaryova, NV Cherdyntseva, VV Vlassov, PP Laktionov, and TL Azhikina: Hypomethylation of human-specific family of LINE-1 retrotransposons in circulating DNA of lung cancer patients. *Lung Cancer* 99, 127-30 (2016)
DOI: 10.1016/j.lungcan.2016.07.0059

11. R Patnala, SH Lee, JE Dahlstrom, S Ohms, L Chen, ST Dheen, D Rangasamy: Inhibition of LINE-1 retrotransposon-encoded reverse transcriptase modulates the expression of cell differentiation genes in breast cancer cells. *Breast Cancer Res Treat* 143, 239-53 (2014)
DOI: 10.1007/s10549-013-2812-7

12. P Bojang Jr, RA Roberts, MJ Anderton, KS Ramos: Reprogramming of the HepG2 genome by long interspersed nuclear element-1. *Mol Oncol* 7, 812-25 (2013)
DOI: 10.1016/j.molonc.2013.04.003

13. R Shukla, KR Upton, M Munoz-Lopez, DJ Gerhardt, ME Fisher, T Nguyen, PM Brennan, JK Baillie, A Collino, S Ghisletti, S Sinha, F Iannelli, E Radaelli, A Dos Santos, D Rapoud, C Guettier, D Samuel, G Natoli, P Carninci, FD Ciccarelli, JL Garcia-Perez, J Faivre, GJ Faulkner: Endogenous retrotransposition activates oncogenic pathways in hepatocellular carcinoma. *Cell* 153, 101-11 (2013)
DOI: 10.1016/j.cell.2013.02.032

14. F Feng, YY Lu, F Zhang, XD Gao, CF Zhang, A Meredith, ZX Xu, YT Yang, XJ Chang, H Wang, JH Qu, Z Zeng, JL Yang, CP Wang, YF Zhu, JJ Cui, YP Yang: Long interspersed nuclear element ORF-1 protein promotes proliferation and resistance to chemotherapy in hepatocellular carcinoma. *World J Gastroenterol*, 1068-78 19 (2013)
DOI: 10.3748/wjg.v19.i7.1068

15. SM Belgnaoui, RG Gosden, OJ Semmes, A Haoudi: Human LINE-1 retrotransposon induces DNA damage and apoptosis in cancer cells. *Cancer Cell Int* 6, 13 (2006)
DOI: 10.1186/1475-2867-6-13

16. EC Scott, EJ Gardner, A Masood, NT Chuang, PM Vertino, SE Devine: A hot L1 retrotransposon evades somatic repression and initiates human colorectal cancer. *Genome Res* 26, 745-55 (2016)
DOI: 10.1101/gr.201814.115

17. C Philippe, DB Vargas-Landin, AJ Doucet, D van Essen, J Vera-Otarola, M Kuciak, A Corbin, P Nigumann, G Cristofari: Activation of individual L1 retrotransposon instances is restricted to cell-type dependent permissive loci. *Elife* 5, (2016)
DOI: 10.7554/eLife.13926

18. N Rodic, R Sharma, R Sharma, J Zampella, L Dai, MS Taylor, RH Hruban, CA Iacobuzio-Donahue, A Maitra, MS Torbenson, M Goggins, M Shih Ie, AS Duffield, EA Montgomery, E Gabrielson, GJ Netto, TL Lotan, AM De Marzo, W Westra, ZA Binder, BA Orr, GL Gallia, CG Eberhart, JD Boeke, CR Harris, KH Burns: Long interspersed element-1 protein expression is a hallmark of many human cancers. *Am J Pathol* 184, 1280-6 (2014)
DOI: 10.1016/j.ajpath.2014.01.007

19. I Sciamanna, M Landriscina, C Pittoggi, M Quirino, C Mearelli, R Beraldi, E Mattei, A Serafino, A Cassano, P Sinibaldi-Vallebona, E Garaci, C Barone, C Spadafora: Inhibition of endogenous reverse transcriptase antagonizes human tumor growth. *Oncogene* 24, 3923-31 (2005)
DOI: 10.1038/sj.onc.1208562

20. T Aschacher, B Wolf, F Enzmann, P Kienzl, B Messner, S Sampl, M Svoboda, D Mechtcheriakova, K Holzmann, M Bergman: LINE-1 induces hTERT and ensures telomere maintenance in tumour cell lines. *Oncogene* 35, 94-104 (2016)
DOI: 10.1038/onc.2015.65

21. N Rodic, JP Steranka, A Makohon-Moore, A Moyer, P Shen, R Sharma, ZA Kohutek, CR Huang, D Ahn, P Mita, MS Taylor, NJ Barker,

RH Hruban, CA Iacobuzio-Donahue, JD Boeke, KH Burns: Retrotransposon insertions in the clonal evolution of pancreatic ductal adenocarcinoma. *Nat Med* 21, 1060-4 (2015) DOI: 10.1038/nm.3919

22. AD Ewing, A Gacita, LD Wood, F Ma, D Xing, MS Kim, SS Manda, G Abril, G Pereira, A Makohon-Moore, LH Looijenga, AJ Gillis, RH Hruban, RA Anders, KE Romans, A Pandey, CA Iacobuzio-Donahue, B Vogelstein, KW Kinzler, HH Kazazian Jr., S Solyom: Widespread somatic L1 retrotransposition occurs early during gastrointestinal cancer evolution. *Genome Res* 25, 1536-45 (2015) DOI: 10.1101/gr.196238.115

23. TT Doucet-O'Hare, N Rodic, R Sharma, I Darbari, G Abril, JA Choi, J Young Ahn, Y Cheng, RA Anders, KH Burns, SJ Meltzer, HH Kazazian Jr: LINE-1 expression and retrotransposition in Barrett's esophagus and esophageal carcinoma. *Proc Natl Acad Sci U S A* 112, E4894-900 (2015) DOI: 10.1073/pnas.1502474112

24. JMC Tubio, Y Li, YS Ju, I Martincorena, SL Cooke, M Tojo, G Gundem, CP Pipinikas, J Zamora, K Raine, A Menzies, P Roman-Garcia, A Fullam, M Gerstung, A Shlien, PS Tarpey, E Papaemmanuil, S Knappskog, P Van Loo, M Ramakrishna, HR Davies, J Marshall, DC Wedge, JW Teague, AP Butler, S Nik-Zainal, L Alexandrov, S Behjati, LR Yates, N Bolli, L Mudie, C Hardy, S Martin, S McLaren, S O'Meara, E Anderson, M Maddison, S Gamble, C Foster, AY Warren, H Whitaker, D Brewer, R Eeles, C Cooper, D Neal, AG Lynch, T Visakorpi, WB Isaacs, LV Veer, C Caldas, C Desmedt, C Sotiriou, S Aparicio, JA Foekens, JE Eyfjord, SR Lakhani, G Thomas, O Myklebost, PN Span, AL Borresen-Dale, AL Richardson, M Van de Vijver, A Vincent-Salomon, GG Van den Eynden, AM Flanagan, PA Futreal, SM Janes, GS Bova, MR Stratton, U McDermott, PJ Campbell, IBC Group, IBC Group, IPC Group: Mobile DNA in cancer. Extensive transduction of nonrepetitive DNA mediated by L1 retrotransposition in cancer genomes. *Science* 345, 1251343 (2014) DOI: 10.1126/science.1251343

25. H Rajabi, A Tagde, M Alam, A Bouillez, S Pitroda, Y Suzuki, D Kufe, DNA methylation by DNMT1 and DNMT3b methyltransferases is driven by the MUC1-C oncoprotein in human carcinoma cells. *Oncogene* 36, 6439-6445 (2016)

26. K Nakamura, Y Baba, K Kosumi, K Harada, H Shigaki, K Miyake, Y Kiyozumi, M Ohuchi, J Kurashige, T Ishimoto, M Iwatsuki, Y Sakamoto, N Yoshida, M Watanabe, M Nakao, H Baba: UHRF1 regulates global DNA hypomethylation and is associated with poor prognosis in esophageal squamous cell carcinoma. *Oncotarget* 7, 57821-57831 (2016) DOI: 10.18632/oncotarget.11067

27. MY Li, M Zhu, F Feng, FY Cai, KC Fan, H Jiang, ZQ Wang, EQ Linghu: Long interspersed nucleotide acid element-1 ORF-1 protein promotes proliferation and invasion of human colorectal cancer LoVo cells through enhancing ETS-1 activity. *Genet Mol Res* 13, 6981-94 (2014) DOI: 10.4238/2014.April.14.13

28. Q Yu, CJ Carbone, YV Katlinskaya, H Zheng, K Zheng, M Luo, PJ Wang, RA Greenberg, SY Fuchs: Type I interferon controls propagation of long interspersed element-1. *J Biol Chem* 290, 10191-9 (2015) DOI: 10.1074/jbc.M114.612374

29. CA Ishak, AE Marshall, DT Passos, C.R White, SJ Kim, MJ Cecchini, S Ferwati, WA MacDonald, CJ Howlett, ID Welch, SM Rubin, MR Mann, FA Dick: An RB-EZH2 Complex Mediates Silencing of Repetitive DNA Sequences. *Mol Cell* 64, 1074-1087 (2016) DOI: 10.1016/j.molcel.2016.10.021

30. JA Gasche, J Hoffmann, CR Boland, A Goel: Interleukin-6 promotes tumorigenesis by altering DNA methylation in oral cancer cells. *Int J Cancer* 129, 1053-63 (2011) DOI: 10.1002/ijc.25764

31. G Servant, VA Streva, RS Derbes, MI Wijetunge, M Neeland, TB White, VP Belancio, AM Roy-Engel, PL Deininger: The Nucleotide Excision Repair Pathway Limits L1 Retrotransposition. *Genetics* 205, 139-153 (2017) DOI: 10.1534/genetics.116.188680

32. W Liang, J Xu, W Yuan, X Song, J Zhang, W Wei, XF Yu, Y Yang: APOBEC3DE Inhibits LINE-1 Retrotransposition by Interacting with ORF1p and Influencing LINE Reverse Transcriptase Activity. *PloS one* 11, e0157220 (2016) DOI: 10.1371/journal.pone.0157220

33. T Koyama, JF Arias, Y Iwabu, M Yokoyama, H Fujita, H Sato, K Tokunaga: APOBEC3G oligomerization is associated

with the inhibition of both Alu and LINE-1 retrotransposition. *PloS one* 8, e84228 (2013)
DOI: 10.1371/journal.pone.0084228

34. M Metzner, HM Jack, M Wabl: LINE-1 retroelements complexed and inhibited by activation induced cytidine deaminase. *PloS one* 7, e49358 (2012)
DOI: 10.1371/journal.pone.0049358

35 A Haoudi, OJ Semmes, JM Mason, RE Cannon: Retrotransposition-Competent Human LINE-1 Induces Apoptosis in Cancer Cells With Intact p53. *J Biomed Biotechnol* 2004, 185-194 (2004)
DOI: 10.1155/S1110724304403131

36. A Wylie, AE Jones, A D'Brot, WJ Lu, P Kurtz, JV Moran, D Rakheja, KS Chen, RE Hammer, SA Comerford, JF Amatruda, JM: Abrams, p53 genes function to restrain mobile elements. *Genes Dev* 30, 64-77 (2016)
DOI: 10.1101/gad.266098.115

37. H Xu, Y Yan, S Deb, D Rangasamy, M Germann, J Malaterre, NC Eder, RL Ward, NJ Hawkins, RW Tothill, L Chen, NJ Mortensen, SB Fox, MJ McKay, RG Ramsay: Cohesin Rad21 mediates loss of heterozygosity and is upregulated via Wnt promoting transcriptional dysregulation in gastrointestinal tumors. *Cell Rep* 9, 1781-97 (2014)
DOI: 10.1016/j.celrep.2014.10.059

38. M Van Meter, M Kashyap, S Rezazadeh, AJ Geneva, TD Morello, A Seluanov, V Gorbunova: SIRT6 represses LINE1 retrotransposons by ribosylating KAP1 but this repression fails with stress and age. *Nat Commun* 5, 5011 (2014)
DOI: 10.1038/ncomms6011

39. A Zhang, B Dong, AJ Doucet, JB Moldovan, JV Moran, RH Silverman: RNase L restricts the mobility of engineered retrotransposons in cultured human cells. *Nucleic Acids Res* 42, 3803-20 (2014)
DOI: 10.1093/nar/gkt1308

40. X Wang, C Jiang, B Fu, R Zhu, F Diao, N Xu, Z Chen, W Tao, CJ Li: MILI, a PIWI family protein, inhibits melanoma cell migration through methylation of LINE1. *Biochem Biophys Res Commun* 457, 514-9 (2015)
DOI: 10.1016/j.bbrc.2015.01.007

41. HJ Ferreira, H Heyn, X Garcia del Muro, A Vidal, S Larriba, C Munoz, A Villanueva, M Esteller: Epigenetic loss of the PIWI/piRNA machinery in human testicular tumorigenesis. *Epigenetics* 9, 113-8 (2014)
DOI: 10.4161/epi.27237

42. F Carlini, B Ridolfi, A Molinari, C Parisi, G Bozzuto, L Toccacieli, G Formisano, D De Orsi, S Paradisi, OM Grober, M Ravo, A Weisz, R Arcieri, S Vella, S Gaudi: The reverse transcription inhibitor abacavir shows anticancer activity in prostate cancer cell lines. *PloS one* 5, e14221 (2010)
DOI: 10.1371/journal.pone.0014221

43. N Houede, M Pulido, L Mourey, F Joly, JM Ferrero, C Bellera, F Priou, C Lalet, A Laroche-Clary, MC Raffin, F Ichas, A Puech, PV Piazza: A phase II trial evaluating the efficacy and safety of efavirenz in metastatic castration-resistant prostate cancer. *Oncologist* 19, 1227-8 (2014)
DOI: 10.1634/theoncologist.2014-0345

44. N Houede, PV Piazza, P Pourquier: LINE-1 as a therapeutic target for castration-resistant prostate cancer. *Front Biosci* (Landmark Ed) 23, 1292-1309 (2018)
PMID: 28930600

Key Words: LINE-1 Retrotransposon, Cancer Biology, Experimental Evidence, Review

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