Uluslararası Fen Araştırmalarında Yenilikçi Yaklaşımlar Dergisi
International Journal of Innovative Approaches in Science Research 2018, Vol. 2 (1), 1-8
https://doi.org/10.29329/ijiasr.2018.132.1

Original article

Human Endogenous Retroviruses

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Abstract

Human Endogenous retroviruses (HERVs) occupy nearly 8% of human genome. They are thought to be remnants of retroviruses. These integrated elements have gag, pol and env coding regions. The genome order of 5 'LTR-gag-pro-pol-env-LTR 3' is completely conserved among known retroviruses and endogenous retroviruses. A complete LTRs consists of untranslated 5' (U5), repeat (R) and untranslated 3' (U3) regions. ERVs have the potential to proliferate within a genome. Due to the nonsense mutations, methylations and deletions, most families of HERV lost their coding regions and therefore could not produce functional proteins. Most of HERVs are structurally incomplete with deletions and insertions. Although human genome have many protective mechanisms, there are many transcriptionally active transposons and endogenous retroviruses in the human genome. Given their nature within the genome, HERVs have potential for genetic disorders, cancer, autoimmunity and neurological diseases. There are many studies investigating the association of HERVs with diseases. In this review, we give a short summary from a few of these studies.

Keywords: Human endogenous retroviruses, human diseases, HERV-K, HERV-E, HERV-W.

Received: 19 January 2018 * **Accepted**: 23 January 2018 * **DOI**: https://doi.org/10.29329/ijiasr.2018.132.1

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INTRODUCTION

Human Endogenous retroviruses (HERVs) occupy nearly 8% of human genome. They are thought to be remnants of retroviruses (Belshaw, 2004; Buzdin, 2007). These integrated elements have gag, pol (coding for reverse transcriptase and protease) and env (coding for transmembrane and surface proteins) coding regions. Due to the nonsense mutations, methylations and deletions, most families of HERV's lost their coding regions and therefore could not produce functional proteins. Despite this, there are several reports implicating HERV expression in cancer, neurological and autoimmune diseases. HERVs might be able to express proteins with pathological and physiological functions. Thus, expression and activation of HERVs draw great interest (Downey and Sullivan, 2015; Gonzalez–Cao et al., 2016; Volkman and Stetson, 2014).

HERV Biology

When a retrovirus integrates into a germline, it has the potential to become an endogenous retrovirus (ERV). When a retrovirus has endogenised it is subject to selection, mutation and genetic drift and can spread through the host population to fixation, or be eliminated from the population entirely. ERVs have the potential to proliferate within a genome, through reinfection, retrotransposition in cis and complementation in trans (Jern and Coffin, 2008). Genome structure of HERVs is similar to retroviruses. The genome order 5 'LTR-gag-pro-pol-env-LTR 3' is completely conserved among known retroviruses and endogenous retroviruses. A complete LTRs consists of untranslated 5' (U5), repeat (R) and untranslated 3' (U3) regions. Many transcription regulating elements including transcription initiating and terminating signals are located in LTR sequences. The LTR serves as enhancers (Suntsova et al., 2013), promoters (Buzdin et al., 2006), polyadenylation signals (Suntsova et al., 2015) and binding sites for several nuclear proteins (Schulman et al., 2010). These structures are comparatively frequent in the human genome and it is assumed that they influenced evolution of the primate genome via transposition, translocation and recombination (Paces et al., 2013).

The lack of a present nomenclature for ERV elements has caused confusion within the literature. Although various classification systems have been used, ERVs have been classified into groups. For example, some research groups described by molecular genetics means, others by primer binding site sequences and others by sequence similarity. Because of these various classification systems, different names have been used for the same ERV group (Mayer et al., 2011). In the past, HERVs separated from other endogenous retroviruses; but this approach was clearly incorrect as HERVs have also been detected in apes and Old World monkeys and in other mammalian species (Hayward et al., 2015; Jern et al., 2008; Mariani-Costantini et al., 1989). Therefore, Mayer et al (2011) reported that nomenclature of endogenous retroviruses should be as "ERV" because the term "HERV" represents humans only. However simplicity in referring to previous publications, researchers use the term 'HERV' to designate endogenous retroviruses originally found in humans (Mayer et al., 2011).

Function of HERVs

Because most of HERVs had lost their structural genes such as gag, env and RT with deletions and insertions of the human genome, they lost their movement ability and become inactive. However, some of them may remain functional. Transcription of these elements controlled by their LTR sequences. A complete LTR element contains primer binding site, transcription initiating and terminating signals (Jern et al., 2005). These elements are relatively frequent in the human genome, so it is presumed that they influenced the evolution of primate genome via transposition, translocation and recombination (Paces et al., 2013). Because of the ubiquity of transposons and endogenous retroviruses, host should have some defensive mechanisms in order to keep its own transcriptions under control. Mutations and methylations were proposed as such mechanisms. Higher organisms developed genomic hypermethylations of non-coding DNA to prevent unwanted transcription from retrotransposons (Blikstad et al., 2008; Stoye et al., 2001). Although human genome have many protective mechanisms, there are many transcriptionally active transposons and endogenous retroviruses in the human genome, still. For instance, HERV-K elements are known as the most active endogenous retroviruses in the human genome. Another function for HERVs is determining the resistance to viral infection. In mice, resistance to MLV infection is controlled by a gag-like protein encoded by HERV-L (Best et al., 1996; Griffiths, 2001). According to the other researchers, HERV-H is expressed in human embryonic stem cells and they are the primary mediators of cell fate reprogramming by overexpressing OCT3/4, SOX2, and KLF4 proteins (Buzdin et al., 2017; Ohniki et al., 2014). Hence, these data suggest that endogenous retroviruses may play an important role in shaping genomes and affecting specific transcription features.

Insertional Polymorphisms of HERVs

Insertion polymorphism of retroelements has attracted considerable attention because they could be used as molecular marker for human genetics studies. HERVs are also a potential source of genetic diversity in the human genome due to insertion polymorphism. There are many studies associated with HERV polymorphisms. One of these studies conducted by Guliyev et al. reported that HERV-H polymorphism ratios of subjects with different ethnic origins (Turkey, Azerbaijan, Indonesia, China and Somalia) are 0-86%. Another study conducted by Mamedov et al stated that new HERV-K insertion polymorphism was observed with a recent retrovirus insertion. Insertion polymorphism studies performed with the mammalian genomes have showed that plant specific retrotransposons are also located in the human genome and they could cause insertion polymorphisms. Elkina et al have showed BARE-1 and SIRE-1 plant retrotransposons are located in horse and sheep genomes. They also reported that the fragments of mobile elements in mammals are also found in the genomes of crop plants. Another plant specific retrotransposon study with the human genome conducted by Cakmak et al. In this study, Sukkula plant retrotransposon which was detected in the human genome caused 8-100% insertion polymorphism ratios.

HERVs in Health and Diseases

Given their nature within the genome, HERVs have potential for genetic disorders, cancer, autoimmunity and neurological diseases. On the other hand, there are few direct evidence to support this claim. There are many HERV elements are noise of defective elements. Thus, it is difficult to select active HERV elements (Griffiths et al., 2001). There are many studies investigating the association of HERVs with diseases. For instance, non-allelic homologous recombination between HERV elements on the Y chromosome causes deletion of the long arm of the human Y chromosome, which could result in male infertility (Blanco et al., 2002). Another example, HERV-W was first retroelement associated with multiple sclerosis (MS) (Perron et al., 1997). After many years, it was proved that HERV-W RNA and proteins have been ubiquitously found in active MS lesions (van Horssen et al., 2016). Furthermore, HERV-W positivity is directly correlated with rapid diagnosis of MS (Sotgiu et al., 2010). Morever, it is reported that HERV-W expression is increased bipolar disorders and schizophrenia (Kremer et al., 2017). Another disease that is related to HERV is HERV-K. Different reports indicated that HERV-K encoded proteins (gag, pol, env) are upregulated in Amyotrophic Lateral Sclerosis (ALS) brains as compared with control groups (Douville et al., 2011; Li et al., 2015). HERVs also may trigger autoimmune diseases. HERVs and autoimmune diseases association appeared by increased proviral transcript levels and finding anti-HERV protein antibodies from patient having autoimmune disorders (Bannert and Kurth, 2004). In systemic lupus erythematosus (SLE) HERV-E mRNA expression was higher in lupus CD4+ T cells when compared to the healthy controls (Suntsova et al., 2015). In patients with rheumatoid arthritis, there is a significant increase in IgG antibody against to HERV-K10 gag protein as compared to control group (Nelson et al., 2014). HERVs and its relationship with cancer is the most debated issue. A number of papers report lack of association with cancer and HERVs while others stated correlation between cancer and HERVs (Hurst and Magiorkinis, 2017). One of the common features of cancer is global hypomethylation of the genome. Hypomethylation was observed in HERV-W and the LINE-1 retroelements in ovarian cancers and hypomethylation was observed in HERV-K50 LTRs in melanomas and germ cell tumors (Hohn et al., 2013; Menendez et al., 2004; Stengel et al., 2010). Another cause of cancer is abnormal overexpression of HERV elements. A study conducted by Reis et al reported that overexpression of HERV-K was detected in prostate cancer. Thus, HERV-K encoded proteins are considered as possible biomarkers of malignancy for the patients with poor prognosis (Reis et al., 2013). In a study including patients with renal cell carcinoma and bone marrow transplantation reported that tumor regression could occurred due to a graft-versus-tumor effect. According to the same study, HERV-E encoded epitope was targeted by antitumor cytotoxic lymphocytes thus demonstrating the importance of anti-HERV immune response in the progression or regression of human diseases (Takahashi et al., 2008; Suntsova et al., 2015). According to the studies some of HERVs promote formation of the placenta. HERV-W env protein serves as a fusion protein called syncytin-1. This protein has critical role for formation of the syncytiotrophoblast. Another env

gene belonging to HERV-FRD encodes syncytin-2, which contributes to syncytiotrophoblast formation and has a role in immune tolerance of the foetus. Reduced expression of both syncytin-1 and -2 was associated higher risk of pre-eclampsia (Hurst and Magiorkinis, 2017; Lerat and Semon 2007; Yi et al., 2004). On the other hand, aberrant expression of syncytin-2 was associated with gestational diabetes (Denner, 2016). In brief, HERVs and its association with diseases is considerably complicated and remains still unclear.

Conclusion

Human endogenous retroviruses have drawn the attention of the researchers due to their effects on health and diseases. They could shape the human genome, could play molecular evolution and progression of many neurological, oncological and autoimmune diseases. Although all these effects of HERVs are known, many of them not could analysed yet.

REFERENCES

Bannert N, Kurth R, 2004, Retroelements and the human genome: new perspectives on an old relation, Proc Natl Acad Sci. 101, 14572–14579.

Belshaw R, Pereira V, Katzourakis A, Talbot G, Paces J, Burt, A, et al., 2004, Long-term reinfection of the human genome by endogenous retroviruses. Proc. Natl. Acad. Sci. 101, 4894–4899.

Best S, Le Tissier P, Towers G, Stoye JP, 1996, Positional cloning of the mouse retrovirus restriction gene Fv1, Nature, 382:826829.

Blanco P, Shlumukova M, Sargent CA, et al, 2002, Divergent outcomes of intra-chromosomal recombination on the human Y chromosome: male infertility and recurrent polymorphism, J Med Genet; 37:752–8.

Blikstad V, Benachenhou F, Sperber GO, Blomberg J, 2008, Evolution of human endogenous retroviral sequences: a conceptual account, Cellular and Molecular Life Sciences, 65:3348-65.

Buzdin A, 2007, Human-specific endogenous retroviruses, Scientific World Journal 7, 1848–1868.

Buzdin A, Kovalskaya-Alexandrova E, Gogvadze E, and Sverdlov E, 2006, At least 50% of human-specific HERV-K (HML-2) long terminal repeats serve in vivo as active promoters for host nonrepetitive DNA transcription, J. Virol. 80, 10752–10762.

Buzdin AA, Prassolov V, Garazha AV, 2017, Friends-Enemies: Endogenous retroviruses are major trascriptional regulators of human DNA, Front in Chem 5.

Cakmak B, Marakli S, Gözükirmizi N, 2017, Sukkula retrotransposon movements in the human genome, Biotechnology & Biotechnological Equipment 31, 900-905.

Denner, J, 2016, Expression and function of endogenous retroviruses in the placenta. APMIS Acta Pathol. Microbiol. Immunol. Scand, 124, 31–43.

Douville R, Liu J, Rothstein J, Nath A, 2011, Identification of active loci of a human endogenous retrovirus in neurons of patients with amyotrophic lateral sclerosis, Ann. Neurol. 69 (1), 577-587.

Downey R.F, Sullivan FJ, Wang-Johanning F, Ambs S, Giles FJ, Glynn SA, 2015, Human endogenous retrovirus K and cancer: Innocent bystander or tumorigenic accomplice? Int. J. Cancer 137, 1249–1257.

Elkina MA, Erkenov TA, Glazko VI, 2015, Mobile genetic elements as a tool for the analysis of genetic differentiation of varieties of cultivated plants and breeds of farm animals. IJRSR 6:5893-5900.

Gonzalez-Cao M, Iduma P, Karachaliou N, Santarpia M, Blanco J, Rosell R, 2016, Human endogenous retroviruses and cancer. Cancer Biol. Med. 13, 483–488.

Griffiths DJ, 2001, Endogenous retroviruses in the human genome sequence, Genome Biology 2 (6).

Guliev M, Yilmaz S, Sahin K, et al, 2013, Human endogenous retrovirus H (Herv-H) genome insertion variations in humans, Mol Med Rep. 7:1305-1309.

Hayward A, Cornwallis CK, Jern P, 2015, Pan-vertebrate comparative genomics unmasks retrovirus macroevolution. Proc Natl Acad Sci, 112:464–9.

Hohn O, Hanke K, Bannert N, 2013, HERV-K(HML-2), the best preserved family of HERVs: endogenization, expression, and implications in health and disease, Front Oncol 3:246.

Hurst TP, and Magiorkinis G, 2017, Epigenetic control of human endogenous retrovirus expression: Focus on Regulation of Long-Terminal Repeats (LTRs), Viruses 9, 130.

Jern P, Coffin JM, 2008, Effects of retroviruses on host genome function. Annu Rev Genet. 42:709–32.

Jern P, Sperber GO, Blomberg J, 2005, Definition and variation of human endogenous retrovirus. H Virology, 327:93-110.

Kremer D, Glanzman R, Traboulsee A, Nath A, Groc L, Horwitz M, Göttle P et al, 2017, Prehistoric enemies within: The contribution of human endogenous retroviruses to neurological diseases. Meeting report: "Second International Workshop on Human Endogenous Retroviruses and Disease. Mult Scler Relat Disord 15: 18-23.

Lenasi T, Contreras X, and Peterlin BM, 2010, Transcription, splicing and transport of retroviral RNA. In: BANNERT, N. & KURTH, R. (eds.) Retroviruses. Molecular Biology, Genomics and Pathogenesis. Norforlk: Caister Academic Press.

Lerat E, Semon M,2007, Influence of the transposable element neighborhood on human gene expression in normal and tumor tissue, Gene 396, pp.303–11.

Lettini AA, Guidoboni M, Fonsatti E, Anzalone L, Cortini E, Maio M et al, 2007, Epigenetic remodelling of DNA in cancer, Histology and Histopathology 22:1413-24.

Li M, Radvanyi LG, Yin B, Li J, Chivukula R, Lin K, Lu Y, et al, 2017, Down-regulation of human endogenous retrovirus type K (HERV-K) viral env RNA in pancreatic cancer cells decreases cell proliferation and tumor growth. AACR.

Mamedov I, Lebedev Y, Hunsmann G, Khusnutdinova E, and Sverdlova E, 2004, A rare event of insertion polymorphism of a HERV-K LTR in the human genome, Genomics 84: 596-599.

Mariani-Costantini R, Horn TM, Callahan R, 1989, Ancestry of a human endogenous retrovirus family. J Virol 63:4982–5.

Mayer J, Blomberg J, and Seal R, 2011, A revised nomenclature for transcribed human endogenous retroviral loci, Mobile DNA.

Menendez L, Benigno BB, McDonald JF,2004, L1 and HERV-W retrotransposons are hypomethylated in human ovarian carcinomas. Mol. Cancer 3, 12.

Nelson PN, Roden D, Nevill A, Freimanis GL, Trela M, Ejtehadi HD, Bowman S, Axford J, Veitch AM, Tugnet N, Rylance PB, 2014, Rheumatoid arthritis is associated with IgG antibodies to human endogenous retrovirus gag matrix: a potential pathogenic mechanism of disease? J Rheumatol 41(10): 1952–1960.

Ohnuki M, Tanabe K, Sutou K, Teramoto I, Sawamura Y, Narita M, et al, 2014, Dynamic regulation of human endogenous retroviruses mediates factor-induced reprogramming and differentiation potential, Proc. Natl. Acad. Sci 111, 12426–12431.

Paces J, Huang YT, Paces V, Ridl Y, and Chang CM, 2013, New insight into transcription of human endogenous retroviral elements, N Biotechnol 30 (3): 314-318.

Perron H, Garson JA, Bedin F, Beseme F, Paranhos-Baccala G, Komurian-Pradel F, Mallet F, Tuke PW, Voisset C, Blond JL, et al, 1997, molecular identification of a novel retrovirus repeatedly isolted from patients with multiple sclerosis, Proc Natl Acad Sci, 7583-7588.

Reis BS, Jungbluth AA, Frosina D, Holz M, Ritter E, Nakayama E, Ishida T, Obata Y, Carver B, Scher H, Scardino PT et al, 2013, Prostate cancer progression correlates with increased humoral immune response to a human endogenous retrovirus GAG protein, Clin Cancer Res 19(22):6112–6125.

Schumann GG, Gogvadze EV, Osanai-Futahashi M, Kuroki A, Münk C, Fujiwara H, et al, 2010, Unique functions of repetitive transcriptomes, Int. Rev. Cell Mol. Biol. 115–188.

Seal RL, Gordon SM, Lush MJ, Wright MW, Bruford EA, 2011, genenames.org: the HGNC resources in 2011. Nucleic Acids Res 39.

Sotgiu S, Mameli G, Serra C, Zarbo IR, Arru G, Dolei A, 2010, Multiple sclerosis-associated retrovirus and progressive disability of multiple sclerosis, Mult. Scler. 16, 1248-1251.

Stengel S, Fiebig U, Kurth R, Denner J, 2010, Regulation of human endogenous retrovirus-K expression in melanomas by CpG methylation. Genes. Chromosomes Cancer 49, 401–411.

Stoye JP, 2001, Endogenous retroviruses: still actie all these years? Current Biology 11: R914-6.

Suntsova M, Garazha A, Ivanova A, Kaminsky D, Zhavoronkov A, and Buzdin A, 2015, Molecular functions of human endogenous retroviruses in health and disease, Cell. Mol. Life Sci. 72, 3653–3675.

Suntsova M, Gogvadze EV, Salozhin S, Gaifullin N, Eroshkin F, Dmitriev SE, et al, 2013, Human-specific endogenous retroviral insert serves as an enhancer for the schizophrenia-linked gene PRODH. Proc. Natl. Acad. Sci 110, 19472–19477.

Takahashi Y, Harashima N, Kajigaya S, Yokoyama H, Cherkasova E, McCoy JP et al, 2008, Regression of human kidney cancer following allogeneic stem cell transplantation is associated with recognition of an HERV-E antigen by T cells, J Clin Investig 118(3):1099–1109.

Van Horssen J, van der Pol S, Nijland P, Amor S, Perron H, 2016, Human endogenous retrovirus W in brain lesions: rationale for targeted therapy in multiple sclerosis, Mult. Scler. Relat. Disord. 8, 11-18.

Volkman, HE, Stetson DB, 2014, The enemy within: Endogenous retroelements and autoimmune disease Nat. Immunol 15, 415–42.

Yi JM, Kim HM, Kim HS, 2004, Expression of the human endogenous retrovirus HERVW family in various human tissues and cancer cells. Journal of General Virology 85, pp.1203–10.

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