The involvement of human endogenous retroviruses K (HERV-K) in aging processes via induction of inflammation.

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Introduction

In 1952, Peter Medawar in his book titled "An unsolved problem of biology" began discussions on evolutionary implications in the theory of aging. He suggested the pressure of natural selection decreases after the reproductive period of an organism. Thus, evolution is directed into the fitness of young organisms than older organisms. Therefore, beyond a certain age, the evolutionary benefit of a longer lifespan would be insignificant (Medawar, 1952). However, until the recent times, an importance of endogenous retroviruses was not taken into account in the evolution of aging. Human endogenous viruses (HERV) comprises 8% of the genome (Lander et al., 2001). It is probable that the human genome was undergone numerous times of invasions of viruses during evolution. They invaded and endogenized through infection of germ-line cells gametes containing integrated proviruses. The symbiosis between the human genome and these DNA parasites has been a major contributing factor to genetic and transcriptional changes during hominid evolution (Blikstad et al., 2008; Wang et al., 2007). Natural selection drives exaptation of these viruses into the genome, and these elements acquired beneficial traits playing a high role in individual development through the domestication of a HERV gene for use by the organism (Patel et al., 2011). For example, syncytin is a product of the activity of human endogenous viruses W (HERV-W) aids in normal placental development during pregnancy (Mi et al., 2000). Almost all regulatory loci with pluripotency transcription factor-binding sites are located in LTR7/HERV-H, LTR5/HERV-K, and L1HS (human specific) that are distinct from other genomes (Glinsky, 2015). Moreover, ERVs are controlled in embryonic development by the action of TRIM28/KAP1 (Rowe et al., 2010). The TRIM28 complex is able to keep epigenetic marks and return the methylation state in the early mouse embryo (Lim and Knowles, 2015). Deletion of TRIM28 in these cells resulted in increased ERV expression (Fasching et al., 2015). KRAB-ZFPs are critical in suppressing endogenous retroviruses (ERVs) which then leads to the loss of pluripotency (Miles et al., 2017). Thus, ERVs are vital in individual development. In addition, ERVs participate in antiviral immunity (Aswad and Katzourakis, 2012).

However, the decreasing pressure of natural selection in the latter period of a life shows the “dark” side of endogenous viruses. HERV-K is reported to be transcriptionally active in inflammatory diseases including Rheumatoid Arthritis (RA) (Freimanis et al., 2010), Systemic Lupus Erythematosus (Krzysztalowska-Wawrzyniak et al., 2011), Schizophrenia (Frank et al., 2005), Amyotrophic Lateral Sclerosis (ALS) (Douville et al., 2011), and multiple types of cancers (Ruprecht et al., 2008), Also, some infectious pathogens enhance HERV-K expression, including Human Immunodeficiency Virus (HIV) infection (Contreras-Galindo et al., 2008; Gonzalez-Hernandez et al., 2012). Human endogenous retroviruses and other retrotransposons such as LINE and SINE may control gene expression through

non-coding RNAs and induce intrinsic stress stimuli prompting deterioration of the function of tissues and organs.

Long non-coding RNAs in the epigenetic regulation by human endogenous retroviruses

DNA methylation is one of the fundamental epigenetic mechanisms to regulate gene transcription (Klose and Bird, 2006). The CpG islands, that are rich in CpG-sites, are mostly located at the promoter of genes. In case of methylation of CpG islands, the transcription of the cognate genes will be blocked (Lister et al., 2009; Ziller et al., 2013). DNA methyltransferases (DNMTs) are critical enzymes in the establishment and preservation of methylation patterns (Bedi et al., 2014; Shen and Laird, 2013). The hypomethylation was identified during the pluripotency state of embryonic stem cells (ESCs) (Fouse et al., 2008; Meissner et al., 2008). In the absence of DNMTs, ESCs cannot initiate differentiation (Fouse et al., 2008; Jackson et al., 2004; Tsumura et al., 2006). Recent data show differential patterns of methylation in regions during cell differentiation that associated with the binding sites of transcription factors (Feldmann et al., 2013; Hogart et al., 2012; Ziller et al., 2013). Epigenetic regulation of gene expression is vital for the process of cell differentiation and normal development.

The expression of very long intergenic RNAs (vlincRNAs) may control pluripotency and tumorigenesis that are linked to long terminal repeats (LTR) of HERV (St Laurent et al., 2013). This demonstrates a role for HERV LTRs in regulating the expression of long non-coding RNAs. Thus, the LTRs are significantly important to control HERVs and human gene expression (St Laurent et al., 2013). Long non-coding RNAs (lncRNAs) are key regulators of gene expression at the epigenetic level. A significant part of lncRNAs have promoters of retroviral origin (Göke and Ng, 2016). LncRNAs control DNA methylation through direct physical interactions between lncRNAs and DNA methyltransferases (DNMTs) [32], (Law & Jacobsen, 2010). LncRNAs are able to regulate the organization of chromatin and gene expression on the transcriptional and post-transcriptional levels (Kung et al., 2013). For example, expression of the lncRNAs derived from HERV-H is detected during embryogenesis (Kelley and Rinn, 2012) and is required to maintain the stem cells state (Lu et al., 2014). Therefore, endogenous retroviruses may have a role as one of the main regulatory component in epigenetic regulation during individual development. A knockout of porcine endogenous retroviruses (PERV) leads to impaired growth that is treated with growth hormones (Yang et al., 2015).

Epigenetic regulation may also be directed through lncRNAs by other non-LTR retrotransposons such as LINE and SINE (Kelley and Rinn, 2012). The L1 family of LINEs has an ability to retrotranspose both in the germline and in somatic cells (Beck et al., 2010; Brouha et al., 2003; Kidd et al., 2010; Singer et al., 2010). L1 retrotransposons may induce genomic instability and mutagenesis in cancer through their transposition insertions (Iskow et al., 2010; Miki et al., 1992). It is potential that dysregulated L1 activity may explain the increase of somatic mutations linked to cancer and aging.

One of the most critical components of epigenetic regulation is the Polycomb Repressive Complex 2 (PRC2) that is essential for embryonic development and has the ability to bind numerous lncRNAs (Cifuentes-Rojas et al., 2014; Khalil et al., 2009; Zhao et al., 2010). LncRNAs might be involved in targeting PRC2 to specific gene control elements. LncRNAs can contribute to the DNA methylation as guiding molecules through interacting with DNMT enzymes (Zhao et al., 2016). LncRNAs also participate in the modification of chromatin states that changes gene expression (Campos and Reinberg, 2009).

It is notable that age-related DNA hypermethylation in bivalent chromatin domains is conserved across different tissues and cell types. These bivalent chromatin domains are a target for PRC2 molecules (Horvath et al., 2012; Rakyan et al., 2010; Teschendorff et al., 2010). Hypermethylation provided by PRC2 links lncRNAs and retrotransposons to the epigenetic clocks. For example, the methylation state of 193 CpG-sites, coupled with PRC2 and the bivalent chromatin, are positively correlated with age according to the epigenetic clock (Horvath, 2013). This epigenetic clock is based on the elastic net algorithm with the age correlation of the multi-tissue samples exceeding 0.95 (Horvath, 2013). This and other modern epigenetic clocks have demonstrated that the epigenetic biomarkers of aging fulfill the properties of molecular biomarkers of aging (Horvath and Raj, 2018). The epigenetic clocks also show the methylation state of a majority of CpG-sites demonstrate a weak correlation with age individually but their collective effect produces a composite multivariate biomarker that can accurately measure chronological age (Horvath, 2013). It is consistent with the idea that HERVs control gene expression through lncRNAs that can regulate clusters of genes simultaneously.

The epigenetic factors are crucial in the development and maintenance of differentiation. The epigenetic age of adult somatic cells can be reset to stem cells state by expressing Yamanaka factors (Horvath, 2013). Intriguingly, it is reported that partial reprogramming by expression of Oct4, Sox2, Klf4, and c-Myc (OSKM) improve cellular and physiological hallmarks of aging and extends the lifespan of mice with premature aging (Ocampo et al., 2016). It is probable that interactions between pluripotency factors and retrotransposons (Glinsky, 2015) coordinate and execute the epigenetic program that controls individual development.

The epigenetic clocks reveal several interesting facts. For example, female breast tissue is anomalously older than other parts of the body (Horvath, 2013; Sehl et al., 2017). Accelerated aging is identified in cancer tissues with a dramatic reversal of epigenetic age throughout cancer tissue dedifferentiation (Horvath, 2013, 2015). This is consistent with the fact that the epigenetic age resets to stem cell-like state by the effect of pluripotency factors (Horvath, 2013). Physical and cognitive fitness is also correlated with the epigenetic age (Breitling et al., 2016; Marioni et al., 2015a). Accelerated aging is also linked to neurodegenerative diseases in elderly individuals (Levine et al., 2015; Marioni et al., 2015a), Down syndrome (Horvath et al., 2015a), Parkinson disease (Horvath and Ritz, 2015), and Werner syndrome (Maierhofer et al., 2017). There are also evidences the offspring of semi-supercentenarians and centenarians have a lower epigenetic age than expected based on their chronological age (Horvath et al., 2015b). Thus, longevity is a heritable trait and this trait is controlled by endogenous retroviruses through the epigenetic mechanisms.

Chronic inflammation in the process of aging

Interestingly, accelerated aging is associated with chronic inflammation in age-associated diseases such as Parkinson disease (Tufekci et al., 2012), cancer (Karin, 2009; Meylan et al., 2009; Pikarsky et al., 2004; Staudt, 2010), and with premature aging in Werner syndrome (Davis and Kipling, 2006), but not with Hutchinson–Gilford progeria syndrome (Rosengardten et al., 2011). Apparently, in Hutchinson–Gilford syndrome, chronic inflammation is induced independently from the developmental program. Presumably, defective lamina proteins could not suppress properly endogenous retroviruses in the young organism.

Chronic inflammation is driven by the NF-κB proteins that are ubiquitously expressed and regulate the response to cellular and environmental stress (Hayden and Ghosh, 2008). Continuous activity of the inflammatory response system is deleterious to normal tissue function (Rodier and Campisi, 2011). Interestingly, inhibition of NF-κB in old tissue results in their rejuvenation (Adler et al., 2007).

Prolonged chronic inflammation is the main cause of tissue deterioration in aging organism. Expression of inflammatory markers and NF-κB activity increased in cells from older donors (Kriete et al., 2008). The NF-κB signaling pathway is implicated several aging phenotypes (Adler et al., 2007; Nasto et al., 2012; Zhang et al., 2013). The chronic inflammation is pervasive in aging tissues and is implicated in most age-related diseases.

The process of chronic inflammation is a significant risk factor for mortality in the elderly people (Franceschi et al., 2000). It is suggested that the organism of long-lived people, including centenarians, can slightly decrease chronic inflammation enhancing an anti-inflammatory response (Minciullo et al., 2016). Pro-inflammatory molecules are also effective predictors of age-related mortality (Howcroft et al., 2013; Varadhan et al., 2014). Identically, accelerated epigenetic aging is another important risk factor and predictor of mortality among the elderly people (Marioni et al., 2015b).

In addition, primate lentiviruses, including HIV, boost NF-κB activity to initiate viral transcription (Heusinger and Kirchhoff, 2017), leading to mild prolonged inflammation. The HIV infection also leads to accelerated aging detected by the epigenetic clock (Horvath and Levine, 2015).

In most cases, accelerated aging and aging itself is associated with increased chronic inflammation that cannot be a coincidence. Therefore, the epigenetic program launches inflammation in the latter part of an individual life that can also be initiated prematurely by extrinsic stress stimuli such as viruses, microbes, ionizing radiation, etc.

Chronic inflammation is critical in several signaling pathways that produce aging phenotypes. The NF-κB signaling pathway can induce senescence and SASP in melanoma cells (Ohanna et al., 2011). Up-regulation of NF-κB signaling pathway induces the senescence-associated secretory phenotype [SASP] of senescent cells (Freund et al., 2011). This may be explained that the mTOR pathway can determine senescence in p53-arrested cells (Korotchkina et al., 2010) through impairing autophagy that leads to the increase of misfolded proteins in senescent cells.

The NF-kB signaling pathway also contributes to rising levels of ROS in aging organism. NF-kB p65 subunit represses the Nrf2-antioxidant response element (ARE) pathway at the transcriptional level (Liu et al., 2008). In consequence, the inflammation and the increased NF-kB activity intensify ROS concentration produced in mitochondria.

Chronic inflammation also contributes to tumorigenic conditions in interaction with tumor suppressor p53. NF-κB and p53 are mutually antagonistic signaling pathways (Cooks et al., 2014) that are controlled by several molecular mechanisms (Ikeda et al., 2000; Xia et al., 2009). Additionally, both transcription factors compete for common cofactors (Wadgaonkar et al., 1999). Therefore, hyperactive NF-κB reduces the tumor suppressor activity of p53 leading to oncogene-mediated transformation (Gudkov et al., 2011), because p53 contributes to the maintenance of the differentiated state and restrain dedifferentiation (Molchadsky et al., 2010; Paskulin et al., 2012). Lower p53 levels improve reprogramming efficiency of somatic cells into induced pluripotent stem cells (Kawamura et al., 2009).

For example mutations in p53 enhance NF-κB activity promoting tumorigenesis and pluripotency factors, that suppressed by p53, are activated leading to activation embryonic-like properties (Cooks et al., 2014).

NF-κB transcriptional activity favor increased glucose uptake by suppressing of p53 that acts to reduce glucose uptake (Kawauchi et al., 2008). Therefore, metabolism is restructured by NF-kB to increase cell proliferation. TNF-α activates the PI3K/AKT/mTOR signaling pathway that impairs insulin signaling (Ozes et al., 2001). p53 inhibits glycolysis and favor mitochondrial oxidative phosphorylation linking to the tumor-associated 'Warburg effect' (Johnson and Perkins, 2012).

Involvement of HERV-K in the process of chronic inflammation

Most breast cancer cell lines and many breast tumor tissues exhibit significantly higher levels of HERV-K env transcription as compared to normal breast tissues (Wang-Johanning et al., 2001, 2003). This is also associated with accelerated aging detected in breast tissues (Horvath, 2013; Sehl et al., 2017) and inflammation in cancer, in general (Karin, 2009; Meylan et al., 2009; Pikarsky et al., 2004; Staudt, 2010). The expression of env transcripts is up-regulated in breast cancer cell lines due to estradiol treatment followed by progesterone (Golan et al., 2008; Ono et al., 1987) proposing the presence of functional hormone response elements in the HERV-K LTR. Several estrogen, androgen, and progesterone binding sites are predicted in the U3 region of the LTR (Golan et al., 2008; Hanke et al., 2013; Ono et al., 1987). Thereby, steroid hormones contribute to the regulation of HERV-K LTRs.

The up-regulation of HERV-K is induced by exogenous viruses such as Human Immunodeficiency Virus-1 (HIV-1), Human T-Lymphotrophic Virus-1 (HTLV-1), Herpes Simplex Virus-1 (HSV-1), and Epstein Barr Virus (EBV) (Armstrong et al., 1993; Cedeno-Laurent et al., 2011; Kwun et al., 2002) that are also implicated in accelerated aging and chronic inflammation.

The HERV-K family is evolutionary a young family of HERV relatively to other ERVs in the human genome (Mager and Medstrand, 2005). There is evidence of recent activity of HERV-K within the human genome (Marchi et al., 2014). HERV locus cannot now produce infectious virions (Kassiotis, 2014), but HERV-K reconstitution can drive the production of functional infectious viral particles (Dewannieux et al., 2006; Lee and Bieniasz, 2007). HERV-K proteins are recently identified in human blastocysts, indicating HERV-K expression is likely beneficial for human embryogenesis (Grow et al., 2015). HERV-K expression during embryogenesis induces an antiviral response, possibly protecting the embryo from exogenous viruses (Grow et al., 2015). However, there is also a positive correlation between HERVs and cancer. Isolation of mature HERV-K virions from primary cancer cells and cell lines reveals expected genomic viral RNA and proteins (Contreras-Galindo et al., 2008; Morgan and Brodsky, 2004). For instance, the accessory proteins of HERV-K, Rec, and Np9, have been associated with cancer incidences (Chen et al., 2013; Gonzalez-Hernandez et al., 2012; Singh et al., 2013). Possibly, embryonic HERV-K might suppress the activity of deleterious HERV-K during embryogenesis due to their high similarity of these viral transcripts. In somatic cells, embryonic HERV-K may be suppressed by hypermethylation of their promoters. DNMT inhibitors can reactivate this type of HERV-K. For example, DNMT inhibitor 5-Aza induces anti-viral response (Chiappinelli et al., 2015) to the HERV-K transcripts, implicated in cancer.

Intriguingly, the expression of certain HERVs is involved in immune suppression. For instance, placental syncytins (HERV-FRD and HERV-H) contribute to immunosuppression during

embryogenesis (Mangeney et al., 2007). In addition, the Env protein of HERV-K(HML2) elements is an antagonist of Tetherin that is a part of antiviral response pathway (Lemaître et al., 2014). Immunosuppression by HERVs could contribute to immune evasion by cancer cells, permitting tumor growth (Kassiotis, 2014). Thus, the consequences of HERV expression could include promotion of tumorigenesis by immune suppression. HERV Env proteins could also impair the immune response to exogenous pathogens and tumors. HERVs could have pathogenic potential through interaction with the immune response (Hurst and Magiorkinis, 2015).

In spite of the ability to evade a specific immune response, HERVs could trigger an innate immune response by producing viral particles that are similar the pathogen-associated molecular patterns (PAMPs) of exogenous viruses (Tang et al., 2012). The surface subunit of the Env protein (ENV-SU) of HERV-W stimulates the production of pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α (Rolland et al., 2006). HERV-K dUTPase proteins induce also the activation of NF-κB and pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) through Toll-like receptor 2 (TLR2) (Ariza and Williams, 2011; Saito et al., 2017). Both TLR4 and TNF-α receptor signaling can induce NF-κB, which could then bind to the response elements found in the HERV LTRs. This was demonstrated for HERV-W, wherein TNF-α signaling resulted in NF-κB binding to the promoter and the induction of HERV-W expression (Mameli et al., 2007). This all could lead to chronic activation of the innate immune response.

The pro-inflammatory transcription factor NF-κB can bind to the LTRs of HERV-K inducing expression of the provirus (Manghera and Douville, 2013). This establishes a positive-feedback loop creating a “vicious cycle”: HERV-K expression drives inflammation with increasing intensity. According to the Gompertz–Makeham law, the human death rate increases exponentially with age (Gompertz, 1825). This interaction between HERV-K and inflammation is consistent with Gompertz–Makeham law of mortality because the exponential rate of mortality must be based on a positive feedback loop prompting system instability and as a consequence – death. Although HERV-W are also involved in this positive-feedback loop, HERV-K could additionally be induced by sex hormones (estrogen, progesterone, testosterone) (Manghera and Douville, 2013). Thus, HERV-K transcription activity begins with rising level of sex hormones during puberty but this does not lead to chronic inflammation because sex hormones antagonize the NF-kB signaling pathway (McKay and Cidlowski, 1998). Since the end of a reproductive period, decreasing level of sex hormones opens a way to chronic inflammation and launches the positive-feedback loop mechanism between HERVs and pro-inflammatory factors. This conclusion is consistent with a data about significant changes with distinct patterns in the transcriptional levels of HERV-H, HERV-K, and HERV-W during the lifespan (Balestrieri et al., 2015). Median transcription level of HERV-K in childhood is negligible but dramatically boosts during puberty. The HERV-K transcription activity decreases in young adults, but then constantly rises with age. The HERV-W activity drops in young adults and surges in the middle-aged and slightly decreases in the elderly people (Balestrieri et al., 2015).

The HERV-K–inflammation loop is suppressed by sex hormones during the reproductive period. However, the decrease of sex hormones in the middle-aged leads to reestablishing of the HERV-K–inflammation loop and the inflammation increases HERV-W transcription. Probably, HERV-W serve in amplifying of inflammation process directed by HERV-K.

Conclusion

Analyzes of recent research in aging and cancer reveal that there is the epigenetic program that controls the regulation of gene expression during individual development. This system uses endogenous retroviruses and other retrotransposons as control elements that regulate gene expression through non-coding RNAs, particularly long non-coding RNAs (lncRNAs). During development, this epigenetic program triggers human endogenous retroviruses K (HERV-K) in puberty by sex hormones, but the antagonism of the pro-inflammatory NF-kB signaling pathway and sex hormones silences the positive-feedback loop between HERVs and chronic inflammation in young adults. However, this detrimental program steadily accelerates in organism according to the Gompertz–Makeham law leading to the exponential increase in mortality due to age-associated reasons. This leads to increasing chronic inflammation that has a deleterious effect on the organism and may cause a spontaneous transition of tissues to cancer state. Chronic extrinsic stress induces accelerated aging because the NF-kB protein complex with its antagonist p53 is the core of the stress-response system. Interactions between NF-kB and p53 produce age-associated effects such as genomic instability by retrotransposons, rising rates of ROS by suppressing the Nrf2 signaling pathway, and the “Warburg effect” by suppressing p53.

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