An analysis of the mechanism of aging: endogenous viral stimulus and the deleterious effect of chronic inflammation

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Background

A trivial logic suggests that aging is a product of damage induced by natural processes in the organism like reactive oxygen species (Harman, 1956) or random somatic DNA mutations leading to cell and tissue dysfunction (Failla, 1958; Szilard, 1959). These both opinions consider living organisms as if these are human-made mechanisms created once and then constantly being worn out during exploitation. Multi-cellular living organisms are effectively an unstoppable process of replacement, renewal and regeneration. Indeed, a causative relationship between damage and aging is not proved experimentally yet. The large size of the eukaryotic genome makes it difficult to assess the effect of DNA mutations on aging making yeasts as a suitable experimental model due to the well-characterized small yeast genome with significant conservation of proteins of the DNA repair pathway between yeast and higher eukaryotes (Bitterman et al., 2003). However, experiments on yeasts do not prove that DNA mutations cause aging (Kaya et al., 2015). Indeed, living organisms are open systems adjusting to keep homeostasis and aging cannot be explained as a process of “wear and tear” as it goes in inanimate closed systems suffering under the second law of thermodynamics. The internal system of repair becomes ineffective during the course of an individual life presumably due to an evolutionary purpose (Mitteldorf, 2010). Without a doubt, the cause of aging is located in the genome because aging rate and lifespan limit is highly specific for a particular species and may be fluctuated due to external environmental challenges or individual genome variability.

Transposons and evolution of aging

Limited lifespan may provide flexibility in the evolution of species but this statement was opposed by the current mainstream evolutionary theory that prefers individual selection as more significant for evolution. This statement based on an argument that natural selection is conducted only on protein-coding genes. In this case, it is not clear why evolution lets evolve genes that decrease the fitness of a single living being for benefits of the whole species. For instance, the protein-coding genes comprise merely 1.5% of the human genome. However, about half of the human genome is composed of transposable elements (transposons). Barbara McClintock believed transposons help to promote evolution and adaptations of the organism (McClintock, 1984). Contrary, others consider transposons are parasitic genetic elements using bodies as their carriers for limitless expansion (Doolittle and Sapienza, 1980; Orgel and Crick, 1980). Nowadays, we can see a multifaceted impact of transposons on the living organism and these may be both our friend and foes. Transposons increase a range of phenotypic variability facilitating the adaptation of genomes to their environment (Evsikov and Marín

de Evsikova, 2016). Also, transposons could induce the transition from unicellular to multi-cellular life in the past (Koonin, 2016) and cause reproductive isolation and speciation (Serrato-Capuchina and Matute, 2018). It reveals transposons as an important and influential driving force of evolution leading to discussions that transposons may increase the significance of higher levels of selection (Brunet and Doolittle, 2015). If it is true, transposon-driven evolution promotes fitness a whole species over an individual organism. It paradoxically merges two contrary opinions of beneficial and detrimental effects of transposons in the organism. We might consider transposons as engines of evolution that made us as we are but also made us aging.

Retrotransposons cause genome instability

Transposons are divided into two broad classes: DNA transposons and retrotransposons different in the mechanism of action. DNA transposons act as a “cut-and-paste” tool without making additional copies of these genetic elements. Retrotransposons act as a “copy-and-paste” tool using reverse transcriptase for producing additional copies of this type of transposons. This mechanism made retrotransposons the largest class in the human genome. For instance, the activity of retrotransposons increase with age in nearly every aging model and considered to promote genome instability during aging (Moskalev et al., 2013). This phenomenon is accompanied by a decrease in repressive heterochromatin with aging that suppresses the expression and mobility of retrotransposons (Moskalev et al., 2013; Wood and Helfand, 2013). High activity of retrotransposons and decrease of heterochromatin is also observed in cancer cells (De Cecco et al., 2013). Genome instability is driven mostly by L1 (LINE-1) retrotransposons by generating double-strand breaks (Belancio et al., 2010; Gasior et al., 2006). LINE transposons also drives SINE activation (Dewannieux et al., 2003). Transposons are a vital element in adaptation to various challenges of environment (Horváth et al., 2017) and any stress causes transposons activation, therefore increased mutation rate during aging may be a side effect of the stress response.

Lamina-associated domains are involved in normal and premature aging

Interestingly, the repressive heterochromatin is associated with peripheral areas of the nucleus and overlapped with lamina-associated domains (LADs). LADs are featured by gene scarcity and the repetitive genome. The borders of LADs are marked with the insulator protein CTCF, CpG islands, gene promoters and high expression of genes (Guelen et al., 2008). Also, the movement of these LADs away from the nuclear periphery is associated with the increase of gene expression (Peric-Hupkes et al., 2010). Nuclear lamina serves an anchor for LADs connected with repressive heterochromatin (Gibcus and Dekker, 2013). Thus, the detachment of LADs due to degradation of lamin proteins leads to massive derepression of retrotransposons. This mechanism explains how defects in lamin proteins cause premature aging due to mutation of the lamin-coding LMNA gene in Hutchinson-Gilford progeria syndrome. The same process occurs during of normal aging. For example, cell nuclei from old individuals acquire defects similar to those of Hutchinson-Gilford patient cells, including changes in histone modifications and increased DNA damage (Scaffidi and Misteli, 2006). Additionally, interactions with the nuclear lamina exhibit oscillating patterns regulating expression of circadian genes (Zhao et al., 2015).

Age-associated patterns in DNA and histone methylation

Loss of heterochromatin is also accompanied by the global loss of DNA methylation. Age-associated demethylation is correlated with a certain type of retrotransposons: Alu and HERV-K (Jintaridth and Mutirangura, 2010). Replicative senescence in human cells exhibits patterns of global DNA hypomethylation and local hypermethylation. Hypomethylation occurs preferentially in LADs. Hypermethylation arises in CpG islands including tumorigenic loci, associated with key developmental genes. Changes of hypermethylation in replicative senescence are similar to those in cancer (Cruickshanks et al., 2013). In contrast, patterns of hypomethylation are different for aging and cancer. Hypomethylation in H3K4me1 is observed preferentially in aging, while the loss of DNA methylation in cancer was mostly associated with H3K9me3 marks (Pérez et al., 2018). H3K4me1 is a mark of the chromatin remodeling complex BAF linked to the activity of p53 (Local et al., 2018). Therefore, normal p53 activity determines its antitumorigenic effect. Hypermethylated promoters are associated with Polycomb repressive complexes (Widschwendter et al., 2007) targeting bivalent chromatin (Rakyan et al., 2010). Inflammation induces expression of Jmjd3 demethylase due to the presence of inflammatory cytokines. Jmjd3 targets H3K27me3 histone and represses PcG target genes associated with the polycomb repressive complex (De Santa et al., 2007). Interestingly, the epigenetic clocks based on DNA methylation demonstrate paradoxically high correlation with chronological age (above 0.95) (Hannum et al., 2013; Horvath, 2013). Therefore, epigenetics is directly linked to aging processes. Epigenetic aging is also related to increased likelihood of cancer incidence through stabilizing stem cells features (Teschendorff et al., 2010). Moreover, epigenetic aging correlates with overall survival in several types of cancer (Lin and Wagner, 2015). Increased epigenetic age was associated with the increase of fatality and recurrence of cancer (Ren et al., 2018).

Oxidative stress and hypomethylation

Hypermethylation triggered by changes in signaling pathways, while hypomethylation looks like a result of stochastic processes (Marttila et al., 2015). The stochastic nature of global hypomethylation is likely a consequence of oxidative stress. Although there is no causal relationship between aging and oxidative stress triggered by reactive oxygen species (ROS) (Doonan et al., 2008; Stuart et al., 2014), ROS may have a role in cellular signaling and cause DNA hypomethylation (Afanas'ev, 2013). This mechanism can be explained through oxidation of 5-methylcytosine that leads to loss of markers of DNA methylation (Valinluck and Sowers, 2007). The increase of ROS during aging is presumably induced with chronic inflammation and innate immune response. Increased ROS production often is associated with mild hypoxia (Pialoux et al., 2009). Hypoxia is induced by the STAT3 signaling pathway (Niu et al., 2008) that is vital in immune system response including also the mTOR signaling (Saleiro and Platanias, 2015).

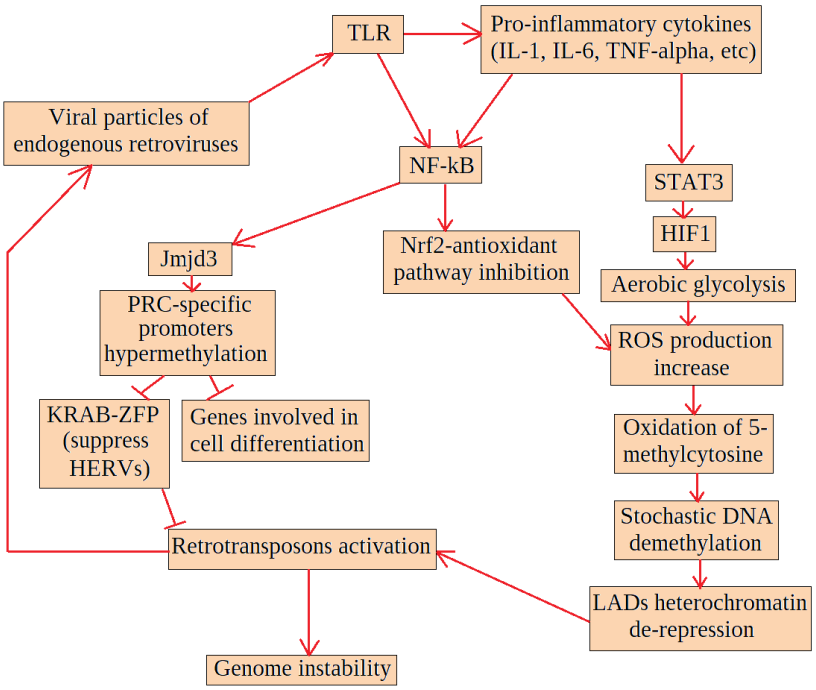

Figure 1. Interactions of signaling pathways mediated by antiviral response to endogenous retroviruses expression leads to genome instability, increased ROS production and epigenetic modification

Chronic inflammation, ROS, and epigenetics

The fact that increased ROS production is induced by inflammation and cause global hypomethylation with age is consistent with facts when accelerated epigenetic age is associated with activation pro-inflammatory and interferon pathways (Irvin et al., 2018; Levine et al., 2018). Moreover, patterns of methylation associated with mortality during aging reveal a genetic regulatory network focused on NF-kB (Jylhävä et al., 2016). Indeed, inhibition of NF-κB reduces oxidative stress and delayed cellular senescence leads to a suggestion that inflammation is considered as a culprit of senescence (Osorio et al., 2012; Salminen et al., 2008; Tilstra et al., 2012). NF-κB inhibits gonadotropin-releasing hormone (GnRH) in the hypothalamus (Zhang et al., 2013) reducing the production of sex hormones and triggering reproductive fading. Moreover, NF-κB p65 subunit represses the Nrf2-antioxidant response element (ARE) pathway (Liu et al., 2008). Thus, inflammation increases ROS production through suppression of anti-oxidant pathways and inducing hypoxia. Activation of NF-κB reduces the activity of p53 and increases the likelihood of cancer (Gudkov et al., 2011).

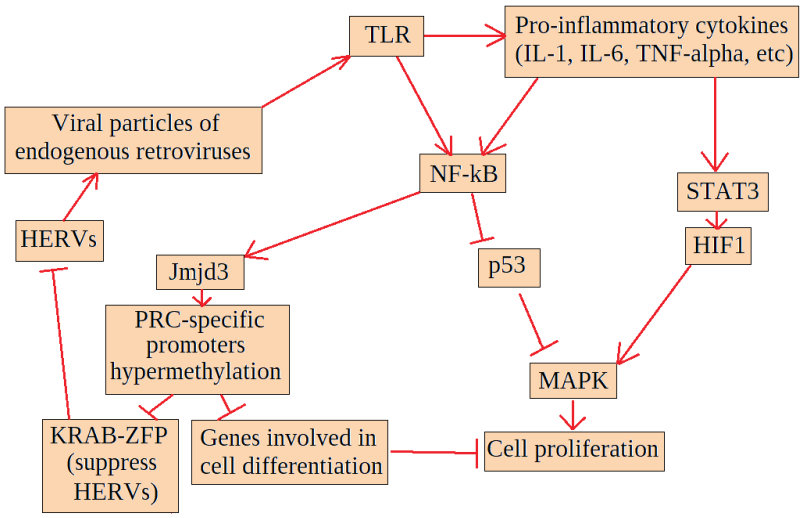

Figure 2. Endogenous retroviruses promotes NF-kB upregulation leads to excessive cell proliferation and tumorigenesis.

Autophagy and energy metabolism

Cellular senescence is determined by interactions of the p53 and mTOR signaling. The mTOR signaling pathway is vital to accumulate energy-storing substances that are necessary for intensive growth and cell proliferation. However, the p53 signaling pathway prevents cell dedifferentiation and proliferation leading to cell overload with redundant metabolites and impaired cell self-cleaning. Thus, the mTOR-induced autophagy inhibition promotes cellular senescence in p53-arrested cells (Korotchkina et al., 2010). Moreover, innate immune response induces PI3K-Akt-mTOR signaling pathway that is a major regulator of macrophages (Covarrubias et al., 2015). Therefore, the innate immune response is important in modulation the mTOR pathway. Also, mTOR activation during aging contributes to a lower induction of autophagy (Romero et al., 2016). Autophagy plays a major role in tackling cellular junk. Aspects of autophagy include lipid metabolism through lipophagy (Singh and Cuervo, 2012; Singh et al., 2009), removing dysfunctional mitochondria (Sarparanta et al., 2017) and also eliminating damaged portions of the endoplasmic reticulum (Bernales et al., 2007). The mTOR signaling pathway regulates many fundamental metabolic and physiological processes, including lipid metabolism. mTOR is a central regulator of lipid metabolism, regulating not only lipogenesis and lipolysis but also adipogenesis (Lamming and Sabatini, 2013). Pro-inflammatory cytokine TNF-alpha leads to increased insulin resistance (Hotamisligil, 1999), and induces mTOR (Ozes et al., 2001). Senescence-associated β-galactosidase (SA-β-gal)-stained cells is linked with mTOR activity (Sung et al., 2018). mTOR activation is mediated through TLR activation (Schmitz et al., 2008). For example, toll-like receptors 4 (TLR4) affects lipid uptake and foam cell formation through mTOR (Banerjee et al., 2018) and inflammation-induced foam cell formation results in atherosclerosis (Angelovich et al., 2015).

Extracellular matrix and stem cells

Chronic inflammation may also determine the remodeling of extracellular matrix and visible aging in the skin through the action of matrix metalloproteinases (MMPs). NF-kB activity up-regulates MMP-1,-3 and -9 (Bond et al., 2001). Matrix metalloproteinases cause extracellular matrix remodeling (Stamenkovic, 2003) through degeneration of its structural components mostly collagen. Extracellular matrix has fundamental importance in regulating epidermal stem cells maintenance, proper mobilization, and differentiation (Chermnykh et al., 2018). Extracellular matrix controls both embryonic and adult stem cell behavior (Ahmed and ffrench-Constant, 2016). Down-regulation of stem cell maintenance due to chronic inflammation leads to stem cells depletion (Rosengardten et al., 2011). Therefore, stem cells depletion during aging may be explained due to inflammation-mediated extracellular matrix remodeling through MMPs.

Inflammation-mediated degeneration

Chronic inflammation during aging also promotes catabolic processes leading to complex body degeneration. Pro-inflammatory cytokines TNF-alpha and IL-1 induce inflammation-mediated osteoporosis (Lacativa and Farias, 2010). Chronic inflammation causes frailty (Fulop et al., 2015). Sarcopenia also is associated with chronic inflammation through an inflammatory marker – C-reactive protein (Bano et al., 2017). Circulating levels of another pro-inflammatory cytokine IL-6 determines the decrease of muscle mass during cancer (Carson and Baltgalvis, 2010). Frailty, sarcopenia, and immunosenescence appear to share common inflammatory drivers (Wilson et al., 2017).

Chronic inflammation interactions with endogenous retroviruses

The effect of chronic inflammation induced by innate immune response explains epigenetic alterations, increased ROS production, mild hypoxia and genome instability due to retrotransposons derepression. Among retrotransposons, production of viral proteins by endogenous retroviruses provide a clue for the innate immune response system. Viral proteins can be detected by toll-like receptors (TLRs) that recognize pathogen-associated molecular patterns (PAMPs) leading to activation of the NF-κB and interferon pathways (Kawasaki and Kawai, 2014). In adult tissues, endogenous retroviruses are suppressed by KRAB-ZFP proteins (Hurst and Magiorkinis, 2017). Hypermethylation of a Cluster of KRAB-ZFP genes on Chromosome 19 in cancer (Lleras et al., 2011) reveals a role of endogenous retroviruses in cancer and aging because both have similar patterns of hypermethylation. For example, activation of HERV-K envelope protein is essential for tumorigenesis and metastasis of breast cancer cells (Zhou et al., 2016) due to stimulation of the innate immune system by endogenous viruses and therefore initiating the autoimmune response (Nexø et al., 2016). Transmembrane unit in the envelope of endogenous viruses also induces immunosuppression to evade the adaptive immune response promoting inability of adaptive immune system to suppress tumors (Morozov et al., 2013). HERV-K viral proteins may be biomarkers and/or tumor-associated antigens (Li et al., 2017). In contrary, the transcription of HERV-K was observed in normal human cell physiology (Schmitt et al., 2015). This collision may be explained through mutual antagonism between NF-kB and steroid hormones (McKay and Cidlowski, 1998). In a healthy organism, normal level of steroid hormones prevents inflammation induced by viral particles from endogenous viruses.

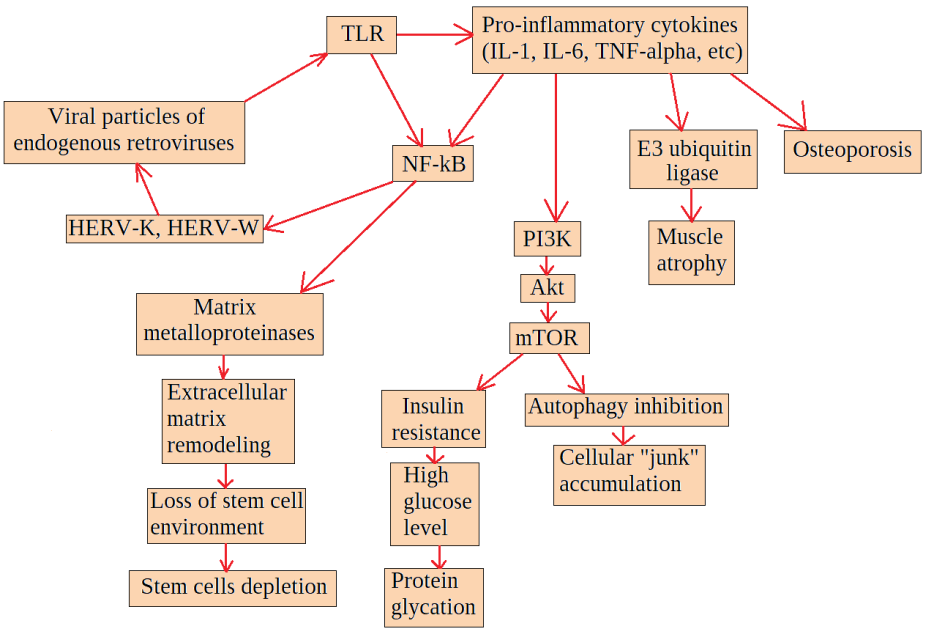

Figure 3. Endogenous retroviruses may provide senescent phenotype by inducing chronic inflammation

Dynamics of endogenous retroviruses and the endocrine system

Endogenous retroviruses induce the innate immune system and prolonged chronic inflammation (Hurst and Magiorkinis, 2015). Human endogenous retroviruses 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). Viral proteins stimulate the production of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-alpha) (Ariza and Williams, 2011; Rolland et al., 2006; Saito et al., 2017). These pro-inflammatory cytokines can induce NF-κB, which could then bind to the LTR regulatory elements of HERVs. This was exhibited for HERV-W (Mameli et al., 2007) and HERV-K (Manghera and Douville, 2013). This establishes a positive feedback loop between NF-kB and HERV-K and HERV-W expression that drives inflammation. HERV-K could additionally be induced by sex hormones (estrogen, progesterone, testosterone) (Manghera and Douville, 2013) linking HERV-K activity with the developmental program. The burst of sex hormones during maturation leads to inducing of HERV-K transcription activity. However, age-associated chronic inflammation is not developed immediately due to sex hormones which suppress the NF-kB signaling pathway (McKay and Cidlowski, 1998). The equilibrium between NF-kB and sex hormones prevents the deleterious effect of HERV-K because endogenous retroviruses lack lytic ability. Endogenous retroviruses are able to harm organism mostly through activation of innate immune response and then promoting chronic inflammation. It is demonstrated by the dynamics of the transcriptional levels of HERVs during the lifespan (Balestrieri et al., 2015). Median transcription level of HERV-K in childhood is negligible but dramatically elevates during puberty. The HERV-K transcription activity slightly decreases in young adults, but then constantly rises with age. The HERV-W activity drops in young adults and drastically surges in the middle-aged and slightly decreases in the elderly people (Balestrieri et al., 2015). Age-associated changes in the activity of HERVs explains why individual development is linked to aging

processes because growth retardation and late maturation lead to increased lifespan prompting an idea of the developmental origin of aging (de Magalhães, 2012). The rising activity of endogenous retroviruses cause chronic inflammation and suppresses sex hormones production through inflammation of hypothalamus (Zhang et al., 2013).

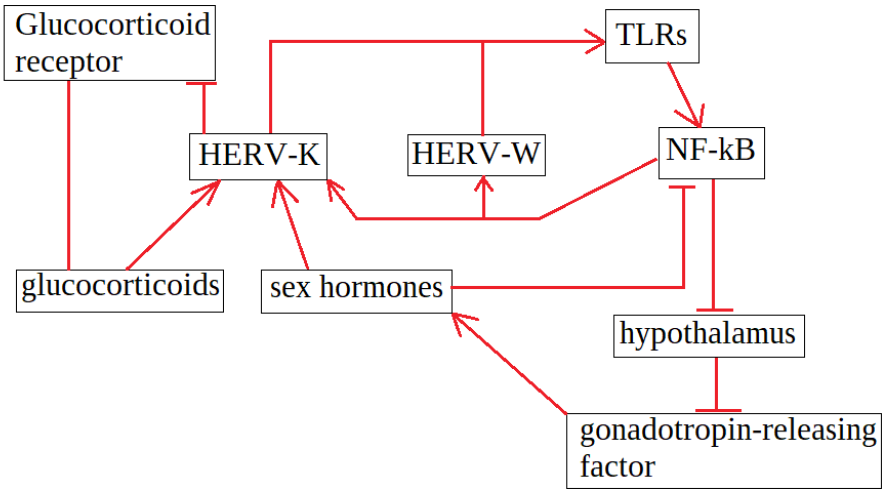

Figure 4. Mutual antagonism of pro-inflammatory pathways and sex hormones provides the delayed deleterious effect of endogenous retroviruses.

Conclusion

The detrimental program of aging is likely evolved during the transposon-driven evolution. Viral particles of endogenous retroviruses induce the innate immune response. This innate immune response is not accompanied by the adaptive immune response due to the ability of endogenous retroviruses to immune response evasion. The signaling pathways involved in innate immune response provide a clue how chronic inflammation induces senescence and age-associated diseases. Most aging-associated effects like DNA mutations and increased ROS production may be considered as attempts of adaptive systems of the organism to overcome intrinsic stress stimulus. However, the organism cannot overcome this stress stimulus because endogenous retroviruses are already part of the genome. Activation of endogenous retroviruses occurs during maturation but their deleterious effect is displayed only after some period of time when endogenous retroviruses are able to suppress sex hormone production through an impact on the endocrine system. Sex hormones suppress chronic inflammation in young adults and alterations in the endocrine system drive aging process. However, this program is very stable due to multiple copies of active endogenous retroviruses and cannot be completely broken without gene editing. The most active class of human endogenous retroviruses is HERV-K that has binding sites for NF-kB and sex hormones and HERV-K is considered to be the most probable culprit of aging.

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