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The effect of retrotransposons on aging and diseases

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ABSTRACT

Retrotransposons convert ribonucleic acid (RNA) into deoxyribonucleic acid (DNA) through the reverse transcription process using an RNA transposition intermediate. They are a type of genetic component that copy and paste themselves into different genomic locations. By reverse transcription and insertion into the genome (Class I: Retrotransposons), or through direct excision and movement of the element (Class II transposable elements: DNA transposons). When the studies on retrotransposons were examined, it was predicted that retrotransposons affect the aging process. They trigger inflammation. DNA damage causes inflammation, while inflammations cause DNA damage. In addition to aging, retrotransposons have a close relationship with diseases. Understanding the relationship between retrotransposon and diseases requires knowledge of long-interspersed nuclear elements, short-interspersed nuclear elements, Alu elements, and SVA elements. Silencing retrotransposons linked to a variety of diseases, such as cancer and brain disorders, can improve our health and lifespan. The secret to a longer-lasting and healthier life may lie in retrotransposons. P-element-induced wimpy testis (PIWI)-interacting RNA (piRNA) is the largest class of small non-coding RNA molecules expressed in animal cells. piRNA interacts with PIWI proteins to form RNA-protein complexes. These complexes are linked to epigenetic and post-transcriptional gene silencing of retrotransposons and other genetic elements in germline cells, in particular, spermatogenesis. In this review, the impacts of retrotransposons on aging and related diseases were discussed.

Keywords: Aging, alu elements, piRNA, PIWI protein, rasiRNA, retrotransposon.

Aging causes a progressive deterioration of physiological integrity, which increases the risk of death and decreases the functioning of a living being's body functions.[1] It is a universal process that involves the interaction of various mechanisms that have not yet been explained. Transposable elements (TEs) are suggested to play a role in aging.[2] Retrotransposons convert ribonucleic acid (RNA) from RNA to deoxyribonucleic acid (DNA) by the reverse transcription process. They are a type of genetic component that can copy and paste themselves into different locations in the genome.[3] By reverse transcription and insertion into the genome (Class 1: Retrotransposons) or through direct excision and movement of the element (Class 2 TE: DNA transposons).[4] Thirty-five percent of the DNA sequence of the human genome consists of retrotransposons. They are also divided into long terminal repeat (LTR) elements. Non-LTR retrotransposons consist of two main groups: long interspersed nuclear elements (LINEs), which encode proteins that need to be used for retrotransposition; and short interspersed nuclear elements (SINEs), which are short and noncoding RNAs that kidnap the LINE protein machinery.[5] Retrotransposons may be the necessary agent for evolution.[6] Transposon jumps are a very important evolutionary mechanism, since they have both effects that can radically change the phenotype, and they can change the size of the genome. It has very serious effects on genome size, especially in eukaryotic cells. Since a transposon can copy itself and attach both itself and its copy to different regions of DNA. In this way, it causes the genome to grow. If this change provides an advantage to a living being, it is also passed on to future generations. Thus, the genome sizes of living things change during the long evolutionary process. In addition, by comparing transposon jumps and their conservation in different species, a highly reliable evolutionary analysis can be performed, and the kinship of species with each other can be studied.[7] Long terminal repeat retrotransposons are Class 1 transposable elements with LTR surrounding an internal coding

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region. These elements are less abundant in mammals compared to other Class 1 transposable elements. About eight percent of human genomic DNA is made up of LTR retrotransposons. Some of the common examples of LTR retrotransposons are the Ty elements in yeast and the copia elements in Drosophila. The internal coding region and transposition mechanisms of LTR retrotransposons are very similar to a retroviral genome. They can synthesize structural proteins to form a virus-like particle, as well as encode the enzymes necessary for its mobilization. But most LTR retrotransposons lack the genes to synthesize a viral membrane. Thus, unlike retroviruses, which can form infectious virions and move horizontally from one cell to another, LTR retrotransposons are only allowed to move from one locus to another within the genome of a single cell. However, some LTR retroelements have been found to have an extra ORF in the same position as the env gene found in retrovirus genomes, for example, gypsy elements in Drosophila. These elements can encode three defining proteins, one of which resembles a retroviral membrane protein, resulting in an infectious form of the element.[8,9] Whether retrotransposons affect aging is a topic that has not been fully elucidated. The fact that retrotransposons, as genomic parasites, affect the aging process is an intriguing topic.[10] A study conducted on interventions that silenced retrotransposons extended life expectancy in Drosophila melanogaster, and it was observed that nucleoside reverse transcriptase inhibitors (NRTIs) treatments partially extended life expectancy. Flies carrying mutations that suppress retrotransposons have become advantageous from the length of life span.[11,12] In studies in mice treated with NRTIs, progeroid Sirt6-deficient mice doubled and the life of patient, mice have increased bone density, muscle increase in mass, bowel function, and an increase in exercise performance was observed. In other words, mice's quality of life has improved. The NTRIs treatment slowed progression in middle-aged and wild-type mice, implying that DNA methylation age is a particularly aging marker.[13] When we examine these studies, the retrotransposons causally support the aging process. Carrying out interventions that will counteract the activity of retrotransposons can increase life expectancy. Studies on long-lived animals provide us with important information about the mechanism of aging.[14,15] The naked mole-rat, an long-lived rodent, contains fewer retrotransposons than other rodent genomes. This finding indicates that a small number of retrotransposons can increase life expectancy.[16] However, bats, which have a long life span, have a large number of TE in their genome.[17] In fact, looking at the evolutionary process of bats is necessary since bats have evolved a dampened response to cytoplasmic DNA.[18] With this information, it is possible that there may not be a direct relationship between life expectancy and the abundance of transposons. By finding better ways to respond to retrotransposons and retrotransposon-induced inflammations, long-lived species may evolve in this way. Inflammation has emerged as an important factor in diseases that occur mainly due to aging. Cancer, cardiovascular diseases, and diabetes are examples of such diseases. As a distinctive feature of aging, chronic low-level stimulation of the immune system appears.[19]

RETROTRANSPOSON ACTIVATION AND DNA DAMAGE

Retrotransposons use RNA as a decoherent RNA transposition intermediate through the process of reverse transcription. As a result, it recycles RNA into DNA.[20] They strengthen themselves in a rapid process through reverse transcription. Retrotransposons are abundant in the eukaryotic genome. They act as genetic material; maize (49-78%)[21] and humans (42%).[22] Retrotransposons are found only in eukaryotes but have common features such as retroviruses and human immunodeficiency virus (HIV). An example of these common features is discontinuous reverse transcriptase-mediated non-chromosomal recombination.[23,24] DNA transposons play a major role in DNA damage. DNA transposons can become harmful by placing themselves in different genomic positions without copying themselves. This is known as horizontal gene transfer. Therefore, retrotransposons can be considered replicative, while DNA transposons are not. Due to their replicative structure, they can rapidly increase the eukaryotic genome size and survive permanently in eukaryotic genomes.[25,26] Retrotransposon activation causes DNA damage in Drosophila.[27-29] In mammals, retrotransposons promote DNA damage. Interferon signaling and inflammation are in a complex intertwined state.

They cause DNA damage, but DNA damage has also been shown to activate retrotransposon expression.[30] DNA damage is effective in cell aging, as well as causes inflammation. They also trigger innate immune sensors, at the same time, interferon mechanisms can rearrange retrotransposons.[31]

REPEAT-ASSOCIATED SMALL INTERFERING RNA TO SILENCE RETROTRANSPOSONS

Repeat-associated small interfering RNA (rasiRNA) is a class of small RNA involved in the RNA interference (RNAi) mechanism. The rasiRNA is one of the P-element-induced wimpy testis (PIWI)-interacting RNA (piRNA), which are small RNA molecules that interact with PIWI proteins.[32] PIWI proteins are composed of the Argonaute family. rasiRNAs are involved in establishing and maintaining the structure of heterochromatin, controlling copies that come out of repeat sequences, and silencing transposons and retrotransposons.[33,34] Along with microRNA (miRNA), rasiRNA is involved in translational repression and mRNA cleavage. It regulates chromatin structure and transcriptional silencing. In Drosophila, rasiRNA-related mutations in PIWI proteins cause infertility and loss of germ cells in both males and females. Transposon repression is not affected by the loss of Dicer in germ cells, which is the target of the rasiRNA pathway.[35] Similar to miRNA and small interfering RNA (siRNA), the rasiRNA silencing pathway has been evolutionarily conserved and is homology-dependent.[36] If the rasiRNA pathway is not present, germline cells may undergo retrotransposition, which is perceived as DNA damage, and the cell may signal apoptosis.[37] rasiRNA is the key to the regulatory mechanism of many organisms as part of the RNA interference pathway.[38]

PIWI PROTEINS AND PIWI-INTERACTING RNA IN GENOME INTEGRITY

PIWI proteins and piRNAs are found in a wide range of living things ranging from sponges to eukaryotes it is preserved and expressed in the organs that make up the gametes, which are reproductive cells.[39] Drosophila PIWI genes, the prototype of PIWI proteins, as a class of essential genes in germline development it is defined.[40] Decreased or absent PIWI gene expression correlates with an increased expression of transposons. Transposons have the potential to cause detrimental effects on their hosts.[41] Derepression of transposons, in all of the PIWI mutant ovaries, is observed. While Aub and Ago3 cleave the target transposon transcripts in the cytoplasm, PIWI regulates target transposons in the nucleus at transcriptional levels.[42] The Drosophila piRNA pathway also stimulates transposon activity to ensure telomere continuity. Transfer of a set of transposons to chromosomal endings, unlike many eukaryotes, Drosophila maintains the continuity of its chromosomes. Therefore, with defects in the piRNA pathway the expression of telomere-specific piRNAs decreases, and the telomere protection complex decreases. It can lead to a breakdown of its connection. Meanwhile, piRNA pathway defects in somatic tissues do not affect telomere structure and transposon expression.[43,44] Three mouse-expressed PIWI proteins are MIWI, MIWI2, and MILI. All of these three PIWI proteins are expressed at different stages during spermatogenesis, but only MILI, albeit very slightly, is expressed in female germ cells. Mutations in mouse PIWI genes cause male germ; it affects the female line but does not affect the female germ line. Damage to MILI or MIWI2 has long interspersed core elements and LTR which leads to activation.[45] Mouse PIWI proteins bind to piRNAs expressed in two phases: Pre-pachytene piRNAs and pachytene piRNAs. Pre-pachytene piRNAs are linked to MILI and MIWI2 in the gonocyte stage and transposon originates from the elements. Pachytene piRNAs are located in various regions of the genome originate from piRNA genome clusters and bind to MILI and MIWI2.[46,47] The functions of mouse PIWI proteins are not only posttranscriptional gene silencing by breaking transposon transcripts, but also directly on transposon regions CpG also provides transcriptional silencing by DNA methylation. The MILI and MIWI2 genes have defects in their activity, DNA methylation, and silencing mechanisms in the male germ line. These findings show that piRNAs de novo DNA in silencing target transposons shows that methylation is used.[48,49]

TRANSPOSONS AND RELATED DISEASES

Retrotransposons play an effective role in neurodegenerative disorders due to aging.[50] Macular degeneration occurs due to age. If an increase in Alu RNA level occurs, epithelial cells activate retinal pigmented NLRP3 inflammation. This event causes cytotoxicity and degeneration.[51] The Alu RNA underwent reverse transcription in the cytoplasm. As a result, it was found to activate complementary DNA (cDNA) and cyclic GMP–AMP synthase-stimulator of interferon genes (cGAS-STING) signaling.[52] Treatment with NRTIs was performed to alleviate Type 1 interferon (IFN-I) and inflammatory responses following the events.[52,53]

Endogenous retroviruses act as a retrotransposon when transferring their inherited genetic information to DNA. Endogenous retroviruses transmit their genetic information to the next generation.[54] For this reason, it is known that retrotransposons and retroviruses have common features. When retroviral DNA is integrated with the genome of the host, they affect the eukaryotic genomes, transforming them into endogenous retroviruses. The influence of endogenous retroviruses on eukaryotic genomes has caused the evolution of retrotransposons and the role played by retrotransposons in diseases to become a curious topic in biology. The vast majority of retrotransposons have common features with endogenous retroviruses, which can detect and fuse the host's genome into the host's genome. However, there is a decisive difference between retroviruses and retrotransposons regulated by env gene traffic. If there is no retroviral, the env gene determines that there is a retrotransposon. if the gene is retroviral, it can transform from a retrotransposon to a retrovirus. They differ according to the gene sequences in the content of sequences in the 'pol' genes. The env genes, on the other hand, are found in LTR retrotransposons types Ty1-copia (Pseudoviridae), Ty3-gypsy (Metaviridae), and BEL/Pao.[54,55] Retroviruses can move decently between cells. The host synthesizes glycoproteins, which are necessary for retroviruses. The LTR retrotransposons, on the other hand, can only transport themselves to the genome of the same cell.[56] Retroviruses and LTR transposons are found in the genomes of many vertebrates. An endogenous retrovirus or LTR retrotransposons have the same function and the same genomic locations, even if they function in different species. In these results, the similarity of their role in evolution or their role in diseases is revealed.[57]

The LINE-1 (L1) retrotransposons make up a large part of the human genome. The genes that encode for LINE-1 usually have their transcription inhibited by methyl groups that are attached to the DNA via PIWI proteins and DNA methyltransferases. The L1 retrotransposition can lead to human disease. This is because they can attach themselves to or near the genes. They can disrupt the structure of the copied gene or genes. In this case, it causes a mutation. LINE-1s can only be retrotransposed to form different chromosome structures, which in some cases can cause genetic differences.[58] The L1 insertions activate the oncogenes of some cancer-related genes and have been associated with this cause of cancer by reducing the number of tumor suppressor genes. As a result, tumor formation was observed.[59,60]

Depending on the SINEs, they cause too many human diseases.[61] if it is added near the exon or directly into it, SINEs will cause incorrect insertion. As a result of this incorrect addition, they may be in the coding zone or have the ability to change the reading frame. They cause the disease phenotype in humans and other animals.[62]

In addition, as a result of the insertion of Alu elements into the human genome, they are associated with colon cancer, dent diseases, breast cancer, cystic fibrosis, neurofibromatosis, hemophilia, leukemia, and many other diseases such as them.[63] Alu elements affect gene expression. They have established that they have a functional, i.e. working, promoter region for the steroid and hormone receptors.[64,65] The Alu element acts as a methylation site, contributing up to about 30% of the methylation sites in the human genome. The main reason for this is the abundance of CpG dinucleotides contained in Alu elements.[66] Alu elements are known as a common source of mutations in humans. These mutations are little noticeable and are limited to the non-intron coding regions of the pre-mRNA.[67] Alu insertions are sometimes destructive and there

is a possibility that they are inherited, causing the disorder. But the presence of a specific allele does not mean that a person carrying this allele will get the disease. Alu-mediated recombination caused hereditary nonpolyposis colorectal cancer.[68]

Retrotransposons can potentially cause diseases using various mechanisms.[69] They are the inserts that cause many known diseases. They inactivate the function and structure of the gene through splicing mutagenesis or aberrant splicing. The addition of LINE-1 to an exon or an intronic addition inserted into it causes nonsense-mediated RNA degradation. This distortion is caused by a frameshift mutation.[70-73] Depending on the insertion site, the retrotransposon can cause an alternative C-terminus of a protein. In this event, it can change the function, and structure of a gene and cause disease. The introduction of the SINE-VNTR-Alu (SVA) element into the fukutin (FKTN) gene which causes Fukuyama muscular dystrophy is a good example.[74,75] The addition of the FKTN gene mRNA with the SVA alternative splicing located in the 3'-UTR caused an incorrect protein synthesis. This protein is a protein that is incorrectly localized from the golgi to the endoplasmic reticulum.[75] LINE-1-mediated insertions are known to cause diseases. Deleting target sites affects an important mechanism that causes diseases.[76,77] Target site deletions that cause significant mutations have been identified in retrotransposons. These target site deletions LINE-1,[78] Alu,[79] and SVA[80] are also effective. Non-allelic homologous recombination (NAHR) is frequently observed for Alu elements. This is probably due to the high number of copies found. It causes structural variations that can cause genetic diseases. deletions are produced as a result of the incorrect pairing of two retrotransposon sequences on the same strand, usually on homologous chromosomes. However, decoupling between retrotransposon sequences that are inverted relative to each other can cause inversion.[81]

In conclusion, retrotransposons have been found to be preserved in the genes of eukaryotes. Thanks to its ability to convert RNA into DNA, it has contributed to evolution as genetic material and led to various mutations. Many studies have shown that there are close interactions between the mechanisms of aging and disease and retrotransposons. To understand the mechanisms of aging, which are still unknown, we need to understand retrotransposons.

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