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Wędrowski Mateusz, Waśniowski Paweł, Wędrowska Ewelina, Golińska Joanna, Piskorska Elżbieta, Zukow Walery. Mobile genetic elements – mechanism and consequences of transposition. Journal of Education, Health and Sport. 2017;7(12):412-428. eISSN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.1161264

http://ojs.ukw.edu.pl/index.php/johs/article/view/5223

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26.01.2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7
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The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 01.12.2017. Revised: 15.12.2017. Accepted: 31.12.2017.

Mobile genetic elements – mechanism and consequences of transposition

Mateusz Wędrowski[1,2], Paweł Waśniowski[2], Ewelina Wędrowska[3], Joanna Golińska[3], Elżbieta Piskorska[4], Walery Zukow[5],

[1]Department of Positron Emission Tomography and Molecular Diagnostics, Nicolaus Copernicus University Collegium Medicum, Bydgoszcz, Poland

[2]Nuclear Medicine Department, Oncology Centre, Bydgoszcz, Poland

[3]Department of Gene Therapy, Faculty of Medicine, Nicolaus Copernicus University Collegium Medicum, Bydgoszcz, Poland

[4]Department of Pathobiochemistry and Clinical Chemistry, Nicolaus Copernicus University Collegium Medicum, Bydgoszcz, Poland

[5]Faculty of Earth Sciences, Nicolaus Copernicus University, Torun, Poland

Corresponding author:

Ewelina Wędrowska

Zakład Genoterapii Collegium Medicum UMK

85-094 Bydgoszcz, ul. M. Skłodowskiej-Curie 9

tel. +48 517-545-893

e-mail: ewelina.wedrowska@gmail.com

Abstract

Retrotransposons represent a significant part of the genome in eukaryote organisms. With DNA transposons, they belong to mobile genetic elements. There are two classes of transposons, DNA transposons and retrotransposons. Retrotransposons have three genes in their structure (gag, pol, env), responsible for the activation and encoding of structural proteins and envelope proteins. There is a group of retroelements without LTR (non-LTR). This group consists LINE (Long Interspersed Nuclear Elements) and SINE (Short Interspersed Nuclear Elements) sequences. LINE sequences represent 20% of human genetic material. Sequences of retrotransposons can move within the genome of a particular organism, occasionally subjected to replication as a result of enzyme activity, i.e. reverse transcriptase. The process of retro transposition is imperfect. These processes often cause mutation (most often: insertion, deletion), genetic instability, they contribute to the development of diseases on the genetic basis, including cancer. Retrotransposons are also used to analyze genetic variation as genetic markers.

Key words: retrotransposons, retro transposition, transposons, mobile genetic elements

Introduction

Mobile genetic elements (MGEs) or differently transposable elements, also called "jumping genes" are sequences of genetic material that are able to move from one place to another within the genome. In prokaryotes, they can move, for example, from a plasmid to a chromosome or vice versa, and in eukaryotic from one part of a chromosome to another or from one chromosome to another. They are present in almost all organisms, including humans, where they constitute about 50% of the genome [1,2]. MGEs were discovered by Barbara McClintock in the 1940s, who identified two new regions in the corn genome: Ds (dissociator) and Ac (activator) located on chromosome 9. McClintock discovered that both regions Ds and Ac , have the ability to transpose, contributing to the modification of gene expression, e.g. by insertions into their sequence or their vicinity. The results of these studies were confirmed only in the 1970s and it was concluded that "jumping genes" are present not only in maize, but almost in all living organisms and constitute a natural way to create genetic variability [1,2,3,4,5].

Purpose of work

The aim of this paper is presentation of chosen information about mobile genetic elements activity and the mechanism of retrotransposition.

Short description of knowledge

To mobile genetic elements we can include RNA and DNA transposons. *Transposable DNA* is a DNA segment capable of transitioning to new sites in the genome, usually in "cut-and-paste" mode. This process involves direct excision of the DNA sequence and then introducing it to a different place in the genome. To carry out this process, a transposase coding gene is necessary - an enzyme that recognizes short, inverted repeats of nucleotide sequences at the ends of moving elements. While cutting at a particular location loci, the enzyme produces sticky ends. Furthermore, in the transposition process DNA polymerase is important, as it has the ability to reproduce genetic material. To the structural elements of the transposon DNA we can include inverted terminal reps (TIR) and TSD (target site duplication). They are subject to transposition processes, as a result of which they are able to change their position within the genetic material [4,5,6,7].

Transposone RNA is characterized by the fact that they replicate through RNA. They are not cut, they remain in a given place in the genome. Retrotransposon is transcribed and on the matrix of the RNA thus formed, the reverse transcriptase enzyme synthesizes a DNA copy which can then be integrated into the genome. It is a class of highly differentiated moving elements, above all because the reverse transcriptase has no polymerase properties, namely it cannot check whether an open reading frame (ORF) is read correctly. As a result, a number of substitutions and deletions of bases are found during DNA synthesis on the RNA matrix [4,5,6,7,8,9]. Retroelements are divided on the basis of structure into two main groups: retrotransposons containing LTR (long terminal repeat) sequences and those that do not contain them (non-LTR) [7,8,10,11,12,13].

Retroelements LTR

The LTR sequences are characterized by the presence of promoters, enhancer, regulatory sequences, U3 and U5 and R fragments. The 5 'end of the LTR sequence is the site of tRNA

attachment [13]. The 3 'end has a PPT (polypurine tract) region in its structure. It is characterized by the presence of polyadenyl signals. They are important in the reverse transcription process [14, 15, 16, 17].

LTR retroelements include: retrotransposons, exogenous retroviruses, endogenous retroviruses and solitary LTR (so-called solo-LTR) [8,10,14].

Retrotransposons are a group of high-resolution LTR elements. It is a group of transposons, having in their structure genes: *gag, pol, env.* These genes encode both enzymatic and structural proteins. Two groups of retrotransposons were distinguished: Ty1-copia and Ty3-gypsy [13,18]. The Ty1-copia group includes retrotransposons lacking the *env* gene, so they do not restore infectious virus particles. Ty3-gypsy, on the other hand, are distinguished by the same set of genes as endogenous retroviruses. Retrotransposons are formed as a result of recombination between endogenous retroviruses, simultaneously leading to the loss of the env gene [19].

Exogen retroviruses are characterized by the presence of regulatory sequences and the *gag, pol and env* genes that encode the envelope proteins of the virus enabling its spread [20]. They have the ability to infect all cells except the sexual cells [21].

Endogenous retroviruses (ERVs) are considered to be remnants of exogenous retroviruses (the effect of evolutionary mechanisms) [21,22,23]. Their common feature is the presence of three structural genes between the LTR sequences [8]. These elements are inherited according to Mendel's laws and passed down from generation to generation [14]. Examples of endogenous retroviruses are: JRSV (Jagsiekte sheep retrovirus) - sheep retrovirus [24], RSV (Rous sarcoma virus) - Rous sarcoma virus [8], MMTV (mouse mammary tumor virus) - mouse breast virus [8], FeLV (feline leukemia virus) - T4 leukemia virus of cats [8], ALV (avian leukemia virus) - avian leukemia virus [8], PERV (porcine endogenous retrovirus) - an endogenous porcine virus [8]. Endogenous retroviruses that are present in the human genome are called human endogenous retroviruses (HERVs) [25].

Solo-LTR arise as a result of homologous recombination leading to the loss of sequences flanked by LTR. Often there are 10-1000 times more than the original sequences from which they

were made [6,7,25].

Retroelements non- LTR

Non-LTR structures do not have long LTR repeats, and the transposition process takes place using reverse transcriptase (RT). The non-LTR group includes retro lines (LINE) (Long Interspersed Nuclear Elements) and SINE (Short Interspersed Nuclear Elements) [5,6,7,25,26].

LINE are autonomic elements, characterized by the presence of the gene *pol* coding their own RT [5,19,20,25,27]. They have a length of 5 to 10 kbp, have two main reading frames (open reading frame), one of them encodes a protein that specifically binds L1 RNA, while the other encodes reverse transcriptase and endonuclease enabling reverse transcription [27]. These are retroelements potentially dangerous because they are easily transposed and are associated with the occurrence of different mutations, and most often accumulate in places rich in AT pairs with low transcription activity. They constitute about 20% of the genome, and the LINE-1 (L1) elements occur in about 100,000 copies [20,25,27].

SINEs are non-autonomous RT non-coding sequences. They are characterized by the presence of a promoter for RNA polymerase III. The SINE sequences are derived from three RNA genes, i.e. 7SL, 5S and tRNA. They differ from other mobile genetic elements because they do not have open reading frames. SINE for transposition use enzymes coded by other retroelements [28]. Most often they integrate in places of DNA rich in GC pairs with high transcriptional activity. Depending on the population, they have additional sequences (in the case of primates - Alu, in rodents - B1) [4,26,27]. Alu elements can cause a number of different mutations, including the deletion is about 0.3% of disorders, resulting in genetic diseases including some breast cancer, Huntington's disease, agammaglobulinemia, haemophilia (blood coagulation factor IX gene) and adenosine deaminase deficiency [23,25,29].

Mechanisms of action of mobile genetic elements

Prokaryotic DNA transposons

There are three types of transposons in prokaryotes. They are characterized by the presence of IS insertion sequences with a length from 800 to 1200 base pairs. The transposase gene is a necessary element of IS that is responsible for the transposition process [6]. Depending

on the transposition mechanism, replication and conservative transposition are distinguished.

Replication transposition is a two-stage process. In the first stage, a transitional product called cointegrate is created, at the same time with the participation of replication forks a DNA molecule is reconstructed, thanks to which this sequence does not disappear from the initial location, but also appears in a new place [30]. The transitional product binds to itself the primary DNA sequence (donor DNA), the target site for transposition (acceptor DNA) and two copies of the transposon. Under the influence of the separation of the cointegrate, two molecules of the transposon are formed. One of them is similar to the original structure, while the other one becomes the target (acceptor) particle with the transposon on. In the second stage, one thread of the transposon is cut and inserted into a new place [31]. This process requires the presence of enzyme complexes, i.e. a complex of transposase and resolvases. In the first stage, the action shows a transposase that occurs at terminal sites of inverted repeats. Recognized regions are sequences rich in AT rules. However, in the second stage of replication transposition, the presence of resolvase is necessary, which separates the progeny replicon in the transposition process and distinguishes the proper distribution of chromosomes during homologous recombination [32].

Conservative transposition occurs via DNA. In contrast to replication transposition, it does not create duplicate fragments. The mechanism of this process is comparable to the "cut-and-paste" method and consists in the complete excision and joining of fragments in a new place while maintaining the same nucleotides. A pre-cut donor molecule is inserted into the acceptor molecule. In this process, the presence of a transposase is required that cuts the transposon from the donor DNA molecule and punctures the DNA along the target sequence [31].

Eukaryotic DNA transposons

Eukaryotic DNA transposons are genetic elements of various lengths. Each transposon is distinguished by the presence of the transposase gene (transposase) and the terminal repeating TIR (terminal inverted repeat) [6]. Such DNA transposons are called domains. For the first time, Ac / Dc sequences as moving elements have been identified in the maize genome. Ac elements are structures with a simple structure. They contain TIR sequences as well as sequences responsible for transposase coding. In the case of Dc elements, we can distinguish a different

structure, they are described as defective moving elements characterized by the lack of the transposase gene. The Dc elements contain in their structure only TIR sequences [6]. Transposition in eukaryotes takes place by means of a conservative mechanism. The main role in this process is transposase, which task is to recognize the TIR sequence. At the site of the transposon, a free space is created, which, by the effective operation of the DNA repair system, is filled. A large part of eukaryotic transposons leads to the formation of tandem repeats, called "footprints" (these are transposon defects after unsymmetrical cutting at the target site), specific for different types of transposons [6,25,33].

Retrotransposition

Retrotransposition is the process of duplicating certain elements of DNA and integrating them into other genomic sites. At the same time, it is a process in which more retrotransposons are produced with the participation of mRNA. The process consists of several stages:

1. Transcription - consists in the synthesis of RNA on a template DNA using RNA polymerase II. This process takes place mainly in the cell nucleus.
2. Transcription - consists in the synthesis of RNA on a template DNA using RNA polymerase II. This process takes place mainly in the cell nucleus.
3. Reverse transcription - transcription of genetic information from RNA to DNA using reverse transcriptase.
4. Degradation of RNA by RNAse H.
5. Synthesis of a complementary DNA strand.
6. Connecting retroelements with the genome [34].

The process of retrotransposition is influenced by biotic and abiotic factors. Retrotransposons are able to be mutated, they can cause many genetic diseases [35,36].

The effects of transposition and retrotransposition

Depending on the type and presence in the genetic material, moving elements can have various effects, e.g. insertion of the element into the gene coding region, can lead to inhibition of gene expression or cause its malfunction, insertion in the 5 'gene control area can block the transcription process, in turn, the excised elements often cause cracks in the chromosome and the

formation of chromosomal aberrations. Due to their properties, mobile genetic elements play an important role in shaping biodiversity and give pace of evolution. They can participate in the regulation of the expression of certain genes, DNA repair and genomic stabilization. It was found that mobile genetic elements are also responsible for the increase in the size of the genome [25,37].

Genomic markers associated with the presence of mobile genetic elements

In molecular genetics and biology, markers of various types are used for scientific research. There are genetic markers, morphological markers and the most commonly used molecular markers. An ideal marker should be characterized by a wide range of variability (polymorphism), high specificity and high incidence in the population. It should be detected in a relatively simple manner and at a low cost [38,39,40,41]. Retrotransposons are classified as molecular markers. They belong to genome elements that have become convenient tools for analyzing genetic variation [40,41].

Techniques used to analyze genetic variation

There are many techniques by which we can study differences in genomic sequences using DNA markers. Such techniques are, among others, RFLP, RAPD, AFLP, SSR and VNTR [42].

RFLP (Restriction Fragment Length Polymorphism) - a technique based on the analysis of the length of restriction fragments in DNA. It is one of the main methods for the recognition of DNA markers [38]. It consists in creating a certain spectrum of DNA fragments, most often resulting from digestion with restriction enzymes that recognize specific sites [43,44]. This method has found application, among others in gene mapping and research on related populations [45,46].

AFLP (Amplified Fragment Length Polymorphism) - this method involves the identification of a large number of markers in the short term. In this technique, a small amount of starting material is sufficient. AFLP deals with the detection of the presence of specific restriction fragments. This technique uses two types of restriction enzymes. One of them is characterized by a higher one and the second is a lower cutting frequency [39]. The AFLP method is used to

identify breeding varieties, research on genetic variation and gene expression studies [38].

SSR (Simple Sequence Repeat) - SSR markers are also called microsatellite markers. Microsatellar DNA is a fragment with a length of 1 to 4 nucleotides [38]. These markers are characterized by a wide range of polymorphism, application in genetic mapping and determining the level of heterozygosity [47].

VNTR (Variable Number of Tandem Repeats) - this is a kind of mini-satellite DNA polymorphism. VNTR markers have a variable number of tandem repetitions. This method is distinguished by the presence of a 11-60 base pair motives [48]. These motives are characterized by a large diversity in terms of length, which depends relatively on the number of repetitions of the original motif. The VNTR polymorphism at a given loci is detected by digesting DNA with restriction enzymes. The subsequent stages of polymorphism analysis are carried out using probes complementary to the mini-satellite DNA. VNTR markers have found applications in medico-judicial tests and in establishing paternity [48].

Methods using retrotransposons as genetic markers

REMAP (Retrotransposon-Microsatellite Amplified Polymorphism) - consists in increasing the amount of DNA fragments between LTR elements and microsatellite sequences. The technique was developed based on BARE-1 transposons in barley. The REMAP method allows the identification of polymorphisms of DNA molecules using a specific primer for the LTR sequences of a given retrotransposon and a microsatellite primer located at the 3 'or 5' ends. The high polymorphism of REMAP markers limits their application to intraspecific levels [34,49,50].

S-SAP (Sequence-Specific Amplified Polymorphism) - this is a method that uses the polymorphism of the length of fragments located between the retrotransposon and the restriction site. It is a technique that is derived from AFLP. During conductig examination, the DNA molecule is digested with two restriction enzymes. The first stage of PCR allows to limit the amount of products and amplify fragments of DNA molecules. However, the next stage of PCR involves increasing the number of fragments between the adapter molecule and the LTR of retrotransposons. The use of a primer with no selective nucleotides is possible when the number

of copies of retotransposon in the genetic material is small. The separation of PCR products takes place on polyacrylamide gels. The S-SAP method gained the greatest recognition for the identification of retrotransposons [49,50].

IRAP (Inter Retrotransposon Amplified Polymorphism) - applicable to BARE-1 retrotransposons. The method allows the analysis of genomic regions contained between two LTRs and the duplication of sequences between retrotransposons of the same families. This technique requires the presence of three combinations of primers: between the left and right LTR, between the two left LTRs and between the two right LTRs. The IRAP method is related to the PCR process, while the separation of reaction products takes place on agarose gels [50,51].

RBIP (Retrotransposon-Based Insertion Polymorphism) **-** is a technique that allows detection of retrotransposon insertion at a specific locus. This method is characterized by the presence of primers complementary to the sequences surrounding the locus. There are three primers: two complementary to the surrounding sequences (f1, f2) and one specific primer for the retrotransposon sequence (t). If during the tests carried out, retroelements are inserted in a specific loci, the amplification process takes place between the starters t and f1. In the event that the retrotransposon insertion is not noticed, the section between primers f1 and f2 will be duplicated. The RBIP technique is a derivative of SSR (Simple Sequence Repeat) [50,52].

The contribution of mobile genetic elements to the development of hereditary based diseases and neoplastic ones

Nearly 100 cases of genetic diseases are directly related to insertions (de novo) of retrotransposons. Over 60 of them are associated with the activity of the Alu sequence, and 30 with the activity of the L1 element [53,54]. Especially frequently in the above-mentioned context there are alterations - rearrangements in the DNA, consisting in changing the sequence of purine and pyrimidine bases in the gene - within the X chromosome. Modifications of this kind may significantly influence the expression level of some genes [55]. The Alu sequence may be the cause of diseases such as: A and B type haemophilia, Menkes disease, adrenoleukodystrophy, Denta's disease, Bruton agammaglobulinemia. On the other hand, the most dangerous disorders associated with the L1 element include: Duchenne's myotonic dystrophy, chronic granulomatous diseases and choroideremie [56]. There may also be uneven homologous recombinations between

the resulting copies of retrotransposons leading to deletions or insertions. Changes of this kind were detected in such disease entities as: Ehlers syndrome - Dansol, Tay - Sachs disease, thrombophilia [55].

The Alu, L1 or SVA sequences are present not only in the X chromosome but also in other parts of the genome. The activity of Alu elements was also demonstrated within the chromosomes: 1, 2, 3, 5, 6, 7, 8, 10, 11, 12, 13, 16 and 17, while the L1 sequence within 3, 5, 8, 9, 11 and 17. In the case of SVA sequences, these are chromosomes: 1, 6, 9, 11 [54,57].

Genetic instability is one of the main causes of neoplastic diseases development. Structural changes associated with genetic instability can lead to chromosomal aberrations, resulting in the development of neoplastic diseases. Among the cancers associated with the above genetic instability are: breast cancer, myeloid leukemia, ovarian cancer, colorectal cancer, lung cancer, Edwing sarcoma, desmoid tumor and diffuse gastric cancer [56,58,59,60].

What is more, the number of specific sites of the activity of mobile genetic elements in the human genome is significant. In the case of L1 and Alu elements, insertions related to the TPRT mechanism (Target-Primed-Reverse Transcription) can be observed in the regions of such genes as: APC (for colorectal cancer), BRCA1 / BRCA2 (in the case of breast / ovarian cancer) or MLVI (in the case of leukemia). In turn non-allelic recombination involving Alu elements may lead to deletions in the CHEK genome region (in the case of prostate cancer) and CDH1 (in the case of diffuse gastric cancer) [27,60].

The first described disease, the occurrence of which is associated with the activity of Alu-type elements is the Alstrom syndrome. It is a genetic disease about the autosomal recessive inheritance. The cause of this disease is a mutation in the ALMS1 gene at the 2p13 locus. Symptoms of this disease may include hearing loss, vision and obesity [61]. Another disease is pulmonary arterial hypernesis (PAH). This disease is caused by a mutation in the BMPR2 gene. In the early stage, the disease is manifested primarily by chronic fatigue and respiratory problems [62]. It has also recently been considered that the Alu sequence is responsible for the deletion causing the disease WS4 (Waardenburg syndrome type IV). It is a rare genetic disease, described as a syndrome of congenital malformations associated with deletion of the SOX10 gene [63].

It has been proved that the activity of mobile genetic elements is influenced by external factors and a significant part of intracellular processes. External factors include the benzopyrene group. These are aromatic hydrocarbons, strongly carcinogenic, formed during combustion of coal and appear in tobacco smoke due to incomplete combustion [64]. Benzopireins that activate retrotransposons are able to enter the human body by ingesting smoked foods. The chemical compounds described above have been identified as a risk factor in colorectal cancer, breast or lung cancer [27]. The activity of retrotransposons is also affected by oxidative stress and the release of reactive oxygen species. By causing DNA damage and greater instability of genetic material. The presence of free radicals in the cell may cause hypomethylation of various regions in a given genome [65]. For the first time, hypo- methylation of the L1 sequence was discovered in colon cancer (in the case of insertion in the APC gene). After further analysis, the hypomethylation of LINE elements with other forms of cancer was also associated. Decrease of hypermethylation level LINE-1 was observed in cases of colon, liver, breast, esophagus and melanoma [66, 67].

Summation

It seemed that the discovered genome is a stable structure. Published studies indicate that genetic material is subject to many changes and modifications. From the previous considerations, it follows that mobile elements have become tools of evolution. MGEs are found in the genomes of all living organisms, constituting an important element of eukaryotic cells.

Their presence in the genome is not indifferent. Depending on the insertion site, they can influence the organization, evolution of the genome, or the expression of cellular genes. Thus, they are elements simultaneously involved in beneficial and unfavorable processes for the body. In evolutionary processes, they are responsible for the duplication of genetic material, gene shuffling and the creation of new regulatory systems. An important role is played by these elements in cellular processes. Some transposons lose the ability to insert further copies in the genome. Certainly, disturbances in the regulation of MGE activity lead to side effects for the body. The result of mutations may be disturbances in the number and / or structure of chromosomes, which determines the formation of genetic diseases.

Due to their properties, mobile genetic elements have found wide application in molecular

biology and immunology.

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