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Review

Non-Coding RNAs and Cancer

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ABSTRACT

Non-coding RNAs (ncRNAs) are actively transcribed by regions of the mammalian transcriptome that do not encode proteins. ncRNAs are divided into several groups, the most studied members microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) are identified as important key players in the regulation of gene expression, and they are involved in various cellular processes and disease pathogenesis, including cancer. In recent years, increasing experimental evidence have shown that ncRNAs functions of great importance for cancer mechanisms since they are deeply associated with the oncogenes and tumor suppressor networks. Thus, ncRNAs are identified as potential diagnostic biomarkers and therapeutic targets for cancer diagnosis, prognosis and therapies. In this review, it is aimed to summarize the functional roles of ncRNAs on cancer mechanisms and highlight the promising applications of ncRNAs for cancer treatment.

Keywords: Cancer mechanism, cancer therapy, circRNA, gene expression regulation, lncRNA, miRNA, ncRNA, oncogene, tumor suppressors

Cancer is a group of diseases in which normal cells begin to divide in an uncontrolled way, gaining successive genetic and epigenetic changes, resulting in the development and expansion of malignancies.[1] Protein-coding gene regions play an important role in the process and transformation of cancer, as we have known for many years, but newly emerging evidence points to ncRNAs (non-coding RNAs). For decades, most cancer researchers have been studied on protein-coding genes, but the sequencing of the human genome indicates that only 2% of the entire human genome codifies proteins and many scientists believed that the remaining 98% regions are non-functional and called as ''junk''.[1] However, scientists are now focusing more on the vast majority of the human genome, which consists of non protein-coding sequences where more carcinogenesis takes place instead of coding regions. Although, the non protein-coding genes which the successive genetic and epigenetic alterations occur and do not encode proteins, they are actively transcribed into some unique RNA molecules called ncRNAs that have very significant roles in the regulation of several cellular processes such as chromatin organization, transcriptional and post-transcriptional regulation and signal transduction.[2,3]

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ncRNAs can be transcribed by RNA polymerases such as RNA PolI, RNA PolII, or RNA PolIII depending on ncRNA types, but mostly RNA PolII plays a role in this transcription process, and also the expression mechanisms of ncRNAs are generated by canonical promoter elements and transcription factors.[2] Besides, ncRNAs have very common properties with messenger RNAs (mRNAs) such as consisting of poly A tail at the 3′ end and having a cap structure at 5′ end.[2]

There are several members of ncRNAs which are important for regulation of gene expression and function. However, to date, the exact number of ncRNAs within the human genome and functions and mechanisms of most ncRNA species still remains unknown.[4] ncRNAs can be roughly classified by their transcript size such as small ncRNAs, if they are generally shorter than 200 nucleotides in length, intermediate ncRNAs (60-300 nucleotides),

and lncRNAs (long non-coding RNAs), if they are longer than 200 nucleotides in length.[5] Small ncRNAs include miRNAs that are highly conserved and most extensively studied ncRNA species which mediates post-transcriptional RNA silencing, small interfering RNAs (siRNAs), PIWI-interacting RNAs (piRNAs) which regulates chromatin modifications and repression of transposons, and more recently discovered ncRNA species called transcription initiation RNAs (tiRNAs).[2,3,5] Another important class of ncRNAs that is most studied in cancer mechanisms is lncRNAs which are found in even greater numbers than protein-coding genes in the human genome. They are lack of conservation and translational activity, and can be classified into several subclasses based on their transcription position and directions, such as intergenic lncRNAs which are located between two protein-coding genes, intronic lncRNAs which are transcribed from introns of protein-coding genes, sense-overlapping lncRNAs which are overlap with part of a protein coding genes in the sense RNA strand direction, antisense lncRNAs which arise from the protein coding gene's antisense RNA strand, processed lncRNAs which is lack of open reading frames (ORFs), bidirectional lncRNAs subclasses which are transcribed from the same promoter of a protein-coding gene but in the reverse direction and recently discovered circRNAs.[3,4,6]

Although ncRNAs still have functions and characteristics that are waiting to be discovered, it is apparently clear in the light of known facts that ncRNAs are of crucial functional importance for the development and progression of cancer. In this review, we will focus on the various ncRNA species, especially miRNAs and lncRNAs which are considered to be very effective in cancer mechanisms based on the most recent genetic studies and discuss their significant functions in the cancer onset and progression. We also highlight ncRNA-based potential applications for diagnosis, prognosis and treatment of cancer.

ncRNAs AND CANCER

ncRNAs, mainly miRNAs and their functions in cellular mechanisms, are of great importance as the epigenetic and genetic alterations are a common hallmark in human diseases, especially in their association with cancer.[2] However, miRNAs and their link to cancer is a small part of a bigger complexity, and the other main classes of ncRNAs such as the heterogenous group of lncRNAs and recent circRNAs are also known to play an important role in the contribution to the development of many diseases, notably cancer.[2]

miRNAs

MiRNAs are one of the most widely studied small ncRNAs species which are approximately 19-25 nucleotides in length. They play an important role in the regulation of various cellular processes such as cell growth, differentiation, stress tolerance, energy metabolism, and immune response.[7] miRNAs are known as oncogenes (tumor suppressors), thus they are involved in the development and progression of cancer by the regulation of proliferation, apoptosis, metastasis, and angiogenesis.[7,8] miRNAs are single stranded RNA molecules (ssRNAs) which are produced from characteristic endogenous hairpin transcripts and functional in RNA silencing and post-transcriptional regulation of gene expression.[9,10] Entire human genome consists of about 1-4% of miRNAs and their number is nearly 300.[6] The first miRNAs were first identified in the gene lin-4 of Caenorhabditis elegans, in 1993.[11] Researchers found that this gene does not codify for proteins, but it is transcribed into 22 nucleotides in length RNA molecules and is involved in the development of this nematode by regulation of the expression of the lin-14 protein, in the 3' untranslated region (UTR) of the mRNA.[11,12] Another newly discovered miRNA was in the gene let-7 of C. elegans in 2000, and is involved in the negative regulation of the expression of the lin-41 protein by unique RNA-RNA interactions within the 3' UTRs of mRNA genes.[11] So far, miRNAs are identified in several organisms such as worm, fly, and mammalian genomes.[12] According to this knowledge, scientists have concluded that some miRNAs are highly conserved across species.[12]

miRNAs are accepted as one of the greatest gene regulators, and they have a very significant role in the regulation of other RNAs, especially mRNAs by base pairing.[6,7,13] This regulation is called negative regulation, and the partially complementary sequences of the miRNAs with the target mRNAs are generally in the 3' untranslated region (UTR) through translational repression and exonucleolytic mRNA degradation.[7,9] In the mammalian genome, the majority of the miRNAs are located in the intronic genomic regions of protein coding or non-protein coding gene sequences, thus their host gene transcripts can be used as carriers.[9] Some miRNAs might be located

in the intergenic regions, therefore they have a unique and independent transcriptional regulatory mechanisms.[9]

miRNA BIOGENESIS AND REGULATION MECHANISM

In the human genome, there is a prior mechanism for miRNA-mediated gene repression called mRNA degradation.[7] These primary miRNAs (pri-miRNAs) are longer primary transcripts about 22 nucleotides in length and can contain many hairpin structures called as polycistronic miRNA clusters.[14] The transcription of miRNAs mainly mediated by RNA PolII in the canonical processing pathway from miRNA genes.[7,9] However, RNA PolIII might be involved in the transcription process of some miRNAs called pre-miRNAs.[14] The biogenesis of miRNAs and the regulation of target gene expression mechanism initially begin with the transcription of miRNAs into pri-miRNAs with the help of RNA PolII, in the nucleus.[7] The pri-miRNAs are recognized and cleaved by the RNA-binding protein DGCR8 and the RNase III enzyme Drosha, which known as microprocessor complex, into a pre-miRNAs that are about 70 nucleotides in length.[7,14] Then, Exp5/Ran-GTP complex transport the pre-miRNAs from nucleus to cytoplasm and the pre-miRNAs are processed into miRNA-miRNA duplex by the Dicer/TRBP/PACT.[7,11] After the mi-RNA duplex is unwound into single strands with the help of helicase, the single strand is combined with the RNA-induced silencing complex (RISC) and turned into a mature miRNA.[7] Finally, miRNA-induced silencing complex (miRISC) is bound to the target mRNAs through 3'UTR, preventing its translation which means they can regulate their target genes.[7,12]

miRNAs IN CANCER

Cancer is a very complex process involving which normal cells gain genetic and epigenetic alterations that cause abnormal cell growth (proliferation) and with the potential to invade and spread throughout the other body parts (metastasis).[9] There are some genes which are involved in this cancer development and progression processes called oncogenes and tumor suppressors.[9] Recent studies suggest that miRNAs can regulate these cellular processes, and play an important role in cancer.[12] Over the past years, most of the miRNAs have been found to be very effective in the regulation of several types of human cancer and the majority of miRNA genes are located in the cancer-associated genomic regions.[9,15] miRNAs have been implicated to promote to oncogenesis and tumor suppression, since they are classified as oncogenes (miR-155 and miR-17-92 cluster) (oncomirs) and tumor suppressors (miR-15a and miR-16-1).[9,16] Oncogenic miRNAs are significantly overexpressed in cancer and lead to the development of tumors by negative regulation, resulting in cell differentiation or apoptosis.[16]

The miR-17-92 cluster of miRNAs are consist of miRNAs 17, 18a, 19a, 20a, 19b-1 and 92a-1 at 13q31 region of chromosome and widely overexpressed in mainly lung cancer and lymphoma.[16] The MYC oncogenes are activated by chromosomal translation (overexpressed) in the human B cell line P493-6.[16] The tumor suppressor miR-17-92 genes of miRNAs decrease the expression of E2F1 through their tumor suppressor activity, and inhibit the MYC-mediated cellular proliferation through tumor protein p53 pathway.[16,17] However, the same members of miRNAs miR-17-92 genes associate with MYC and induce apoptosis, acting as oncogenes.[16] The same miRNA clusters might be play different roles in separate pathways due to the unique miRNA-mRNA interactions, which means that the miRNAs can target many mRNAs and mRNAs can be targeted by several miRNAs according to different cell types and the gene expression patterns.[16] For instance, the dysregulation mechanism of tumor suppressor miRNAs which was firstly identified in B cell-chronic lymphocytic leukemia (CLL), lead to loss or downregulation of miR-15a and miR-16-1 genes at the 13q14 chromosomal region.[11,12,16] When these miR-15a and miR-16-1 genes combine with the anti-apoptotic gene BCL2 , result in the inducing of apoptosis.[16] However, the human embryonic kidney 293 cells normally express the miR-15a, miR-16-1 and BCL2 genes, and there is no cellular reaction like apoptosis.[16] Hence, it is possible that the loss of miR-15a and miR-16-1 genes can cause over expression of BCL2 in B cell-CLL and lead to B cell malignancies; in contrast, the over-expression of miR-15a and miR-16-1 genes can lead to decreased expression of a tumor suppressor in a different cell and result in apoptosis.[16]

The firstly studied miRNA in a mouse model was miR-155.[17] miR-155 is encoded through the 241-262 nucleotides of non-protein coding BIC gene and significantly over expressed in several

types of cancer such as breast, lung, colon and hematopoietic cancers, acting as oncogenes.[17] Studies in the transgenic mouse model show that the over expression of miR-155 genes in early B-cells are involved in pre-leukemic expansion of the pre-B-cell proliferation and finally lead to B cell malignancy.[16,17] Also, in human breast cancers, miR-155 is up-regulated by mutant p53 gene which plays a tumor promoting role, resulting in tumor cell invasion.[16,17] MiR-155 genes are widely over expressed in cancers, therefore they are very attractive for the therapeutic targets.[17]

As we mentioned earlier, the let-7 genes that are identified in Caenorhabditis elegans, associated with cancer. In the human genome, there are 12 let-7 homologous genes that originate into 8 clusters.[12] Recent studies show that these let-7 gene clusters are involved in many types of cancers such as breast, lung, urothelial and cervical, which perform as a tumor suppressor.[12] In human lung cancer, let-7 genes are down regulated and a few clusters of this family are lost in some malignancies, hence these miRNAs can be involved in growth suppression and might be used as therapeutic targets.[12]

lncRNAs

lncRNAs are the most studied ncRNA groups in cancer mechanisms which containing different RNA molecules that are longer than 200 nucleotides in length and have no protein coding potential.[18] According to recent research, the human genome codifies 15,000 distinct lncRNAs.[18]

lncRNAs are transcribed by RNA Pol II, 3′ polyadenylated, 5′ capped and have exon-exon splicing connections like mRNAs.[18,19] In 1989, the first mammalian lncRNA H19 was discovered, and followed by the discovery of lncRNA Xist which plays a key role in X chromosome inactivation in mammals.[18,19]

The naming of these non-coding transcripts with various functions has developed over time as the number of them has grown.[18] Some sources refer to these non-coding transcripts as long intergenic non-coding RNAs (lincRNAs), while others do not include the intergenic term and merely refer to them as lncRNAs.[18] The term "intergenic" refers to the identification of these transcripts in genome regions that lack protein-coding genes.[18] These regions correspond to regions of our genomes that were previously known as "junk DNA".[18] As a result of all genome RNA sequencing studies, these regions have been shown to encode RNA transcripts.[18] According to some sources, lncRNAs are roughly divided into several subclasses based on various features such as their location on protein-coding genes, impact on DNA sequences, mechanism of function and targeting mechanism.[18,19] These are lincRNAs which are RNAs located between two protein-coding genes; intronic lncRNAs that are copied from introns of protein-coding genes; overlapping lncRNAs that have a coding gene inside an intron on the same strand; antisense lncRNAs that are copied from the reverse of the protein-coding thread; processed lncRNAs that are lack of an ORF and bidirectional lncRNAs are subclasses of RNAs that are transcribed in the opposite direction from the promoter of s protein-coding gene.[18]

lncRNAs are present throughout the cytoplasm, but are especially abundant in the chromatin sections of the nucleus.[18] lncRNAs play various roles in the nucleus and cytoplasm.[20] They serve as competing endogenous RNAs (ceRNAs) in the cytoplasm, acting as molecular sponges for miRNAs, and inhibiting translation by targeting mRNAs.[20] In the nucleus, lncRNAs function as chromatin remodeling and transcription guides, as well as regulating transcription factors (TFs) and TF-associated factors, and pre-mRNA splicing and miRNA processing are also regulated.[20] They can also be found in a variety of intracellular compartments, for example mitochondria is another location for some lncRNAs that are encoded by nuclear DNA.[18] RMRP (RNA component of mitochondrial RNA processing endoribonuclease) is a lncRNA which is encoded in the nucleus and transported to the mitochondria by RNA-binding proteins, has been found to play a key role in mitochondrial DNA replication and RNA processing.[18]

lncRNAs have been found in a wide range of organisms, including mammals, plants, yeast, prokaryotes, and even viruses.[19] As compared to well-studied RNAs such as mRNAs and miRNAs, lncRNAs are poorly conserved across organisms.[19] However, according to evolutionary studies, exons of lncRNA are more conserved than repeat sequences, but they are less conserved than those of protein-coding genes.[18] In contrast to promoters, exons and introns, different regions of lncRNA genes are the most conserved regions of the genome.[18] Furthermore, lncRNAs are generally low expressed,

they appear to be transcriptional noise.[19] Despite this, recent studies show that lncRNAs play an important role in a number of important biological processes such as transcription, splicing, translation, protein localization, cellular structure integrity, imprinting, cell cycle, apoptosis, stem cell pluripotency, reprogramming, and heat shock response.[19] Thus, lncRNAs have been proposed to play a crucial role in the initiation of a number of various human diseases and development of cancer acting as oncogenes or tumor suppressors throughout the regulation of metastasis, cell death inhibition and affecting DNA damage response, and they have been related to tumorigenesis in particular.[19,20]

lncRNAs IN CANCER

lncRNAs play a critical role in the development and progression of cancer.[21] The human genome includes a significant number of lncRNAs that are involved in cancer-related biological processes.[18] Therefore, lncRNA mutations, dysregulation, or irregular expression are thought to be linked to cancer.[18] Epigenetic and genomic modifications have a big impact on lncRNA expression in tumors.[21] As a result, these lncRNAs have the ability to regulate both protein-coding and non-coding genes, as well as interact with known cancer genes.[21] lncRNAs have a variety of functions, including oncogenes, tumor suppressors, and therapeutic potential.[21] The main cause of these variations is thought to be their complex structures and ability to participate in multicomponent complexes.[21] lncRNAs, which differ in gene expression depending upon tissue or cell type, have been shown to play both tumor suppressor and oncogenic roles in different cancers such as lung cancer, colorectal cancer, liver cancer, glioblastoma, breast cancer, and leukemia.[20-22]

Firstly discovered mammalian lncRNA H19 was identified as a mutated tumor suppressor gene, and according to some research it has been shown to have irregular expression in a number of cancers.[21] H19 gene is activated in lung, cervical, esophagus, bladder, and breast tumors.[21] In bladder and hepatocellular cancers, highly expression of H19 promotes cell proliferation and development.[21,22] The X-inactive specific transcript (XIST) was one of the earliest discovered mammalian lncRNAs which have a role in gene expression regulation and X-chromosome inactivation.[23] Overexpression of the XIST lncRNA has been dysregulated in several types of cancers and related to tumor malignancies.[21,22] XIST has been shown to inhibit KLN2 expression in non-small cell lung cancers.[21] However, according to some studies, XIST lncRNA can be acted as an oncogene and induces miR-140/mIR-124 expression from microRNAs and induces gene expression, thus it has a crucial function in the cellular processes, regulating cell cycle via miR-140/miR-124 inducing progression of pancreatic carcinoma.[21]

lncRNA ANRIL is an antisense lncRNA in the INK4 locus, which acting as oncogene in mediation of transcriptional silencing by chromatin modifications and affects tumorigenesis in diverse cancer types such as prostate cancer.[21-25] In patients with high levels of ANRIL expression in osteosarcoma (OS) which is the most common type of cancer, tumor size was also found to be increased.[21] Hence, in patients having shorter survival times, there is a link between high ANRIL expression and a poor prognosis in patients with OS (bone tumor).[21] Furthermore, multiple studies have shown that increasing the lncRNA ANRIL promotes the development of nasopharyngeal carcinoma resulting in tumor formation.[21]

HOX antisense intergenic RNA (HOTAIR) is a well-studied oncogenic lncRNA linked to several types of cancer such as breast cancer, lung cancer and gastric cancer.[18,21] HOTAIR lncRNAs play a functional role in cell proliferation and invasion due to their overexpression, promote cancer metastasis and tumor progression by inducing epigenetic changes in cancer cells.[20,24,25] For instance, HOTAIR competes with the protein BRCA1 in breast cancer, and miRNAs Mir7 and Mir-34a have been found to regulate the level of HOTAIR expression, which interacting via mir-141 and mir-34a resulting in promoting cancer growth.[21] In breast and gastric cancer, overexpression of the HOTAIR genes promote cancer cells to invade and spread other body parts.[21] Additionally, HOTAIR upregulation causes poor prognosis in breast, liver, colorectal, gastrointestinal, and pancreatic cancers.[24] However, HOTAIR downregulation stimulates the cell cycle to stop in the G0/G1 phase, resulting in a major reduction in cell proliferation, mygrassion and metastasis in endometrial cancer.[21] Therefore, HOTAIR may be a key player in the development of endometrial cancer.[21]

Another important cancer-related lncRNA is urothelial carcinoma associated 1 (UCA1) which is act as an oncogene and linked to several types

of cancer, affecting mRNA stabilization.[21,23] UCA1 has a role in the stabilization of CDKN2A-p16 mRNA by reduction of heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1).[23] Depending on UCA1 overexpression, this lncRNA has been linked to cancer development, progression and metastasis, and observed in bladder carcinoma, tongue squamous cell carcinoma, ovarian cancer, and melanoma.[21,23] Besides, according to some research, another type of lncRNA GAS5 has a different impact on cancer cells. GAS5 influences the miR-32-5p/PTEN axis, inhibiting cancer cells from growing and spreading to other tissues, acting as a tumor regulator.[21] For instance, overexpression of GAS5 can prevent colorectal cancer HT-29 cells from invading, migrating, and proliferating.[21] However, overexpression in pancreatic tissues can cause the development of pancreatic carcinoma, it is caused by the fact that the same lncRNAs might have different functions according to several cell types or pathways.[21]

ncRNAs AND CANCER TREATMENT

ncRNAs are functional RNA molecules that do not code for proteins and play an important role in gene expression regulation and are involved in several cellular processes and disease pathogenesis, cancer in particular.[26] Since ncRNAs are intimately linked to oncogenes and tumor suppressor networks, growing experimental evidence has revealed that their roles are critical for cancer mechanisms in recent years.[26] Thus, ncRNAs have been identified as potential diagnostic biomarkers and therapeutic targets in the diagnosis, prognosis, and treatment of cancer.[26,27]

Since deregulated ncRNA expression is seen across a wide range of cancers, ncRNAs are useful molecular biomarkers.[27] miRNA and lncRNA classes include significant examples.[27]

miRNAs have unique characteristics that make them ideal tumor markers, such as their stability, ease of detection, and association with proven clinicopathological prognostic parameters, in addition to their tissue specificity.[28] Because of miRNAs exceptional resilience in visceral tissue, researchers set out to see whether they could be maintained, detected, and quantified in the bloodstream and other bodily fluids such as urine, saliva, and sputum.[28] In recent years, growing evidence has emerged to support the use of miRNAs as non-invasive, responsive biomarkers of disease states, especially breast, lung, pancreas, ovarian, and prostate cancers.[28] For instance, several miRNAs have been found to play a significant role in lung cancer initiation, development, and prognosis.[28] Most transcripts in the let-7 family have been shown to be under-expressed in tumors, which is consistent with its established tumor suppressor function.[28] Reduced let-7 levels have also been linked to a better prognosis in lung cancer patients, regardless of stage of disease.[28] Recent studies have shown that many miRNAs reflect the signatures of the primary lung tumor, accurately distinguishing cancer cases from controls, indicating that this non-invasive blood-based miRNA analysis may be used as a possible screening method for lung cancer early detection and treatment.[28]

Since the majority of lncRNAs are highly tissue and cell-type specific, they may be highly effective targets for systemic cancer treatment.[29] Dysregulated lncRNA expression is closely linked to the development of different tumors and can be identified reasonably effectively in the body fluids of patients with a variety of cancer types.[30] In terms of their function in the development of malignant cancer, lncRNAs are categorized as either oncogenic or tumor suppressive, depending on whether they are upregulated or downregulated when compared to normal tissues from healthy people.[30] Cancer-related lncRNAs such as HOTAIR, H19 and UCA1, expressed differently in various cancers, represent promising cancer biomarkers for detection in bodily fluids of patients.[30] For instance, HOTAIR was found to be highly expressed in saliva samples from patients with oral squamous cell carcinoma.[30] Since metastatic patients have higher levels of HOTAIR expression, this lncRNA is a good candidate for diagnosing metastatic oral cancer.[30] Additionally, the lncRNA UCA1 has been identified as a possible bladder cancer biomarker.[30] It has a strong potential for discriminating between bladder cancer and other cancer forms or diseases of the urinary system due to its relatively high overall specificity.[30]

Conclusion

Recent research on non-coding RNA genes has shown that, in addition to protein-coding genes, our genome may contain a large number of non-coding RNA genes. These findings demonstrate that ncRNAs have significant roles that go beyond gene expression regulation to epigenetic pathways and signal transmission. The discovery of mostly studied ncRNA class miRNAs, added a new dimension of

gene expression regulation. Proliferation, apoptosis, metastasis, and angiogenesis are only a few of the functions of miRNAs in cancer onset and progression. As a result, miRNAs are likely to be discovered acting as tumor suppressors or oncogenes. Since miRNA expression is related to a variety of cancers, miRNAs can be used as an important tool for cancer diagnosis, prognosis and treatment. Another well-studied ncRNA class lncRNAs are also expressed in a variety of cancers and play a significant role in disease pathogenesis, cancer in particular. By interacting with a gene's promoter or enhancer region to modulate gene expression, lncRNAs may act as either a tumor suppressor or an oncogene. Thus, like miRNAs and protein-coding genes, lncRNAs can also be used as biological markers to predict prognosis and therapeutic agent for treatment of cancer. However, more research is required to fully understand the function of ncRNAs in cancer diagnosis, prognosis, and treatment.

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