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The role of LINE-1 transposon plays in cancer: Development, treatment

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Abstract. LINE-1 accounts for about more than 15% of the genetic composition in human body, and LINE-1 is the single type of transposon which has the ability of self-initiated transposition. LINE-1 can be inserted into new gene sites through reverse transcription and transposition, leading to genomic instability. Therefore, the body has strict restrictions on not only replication but also transposition, and almost no presence of LINE-1 can be found in casual somatic cells. However, LINE-1 has widespread expression in the vast majority of tumor or cancer tissues, and there is also a lot of evidence indicating that the expression and transposition of LINE-1 are closely related to the emergence and growth of tumors. Expression of LINE-1 is different in tumor cells can serve as a marker for early diagnosis of tumors and an important indicator for evaluating the prognosis of tumor treatment. At the same time, LINE-1 has a potential if being a target for tumor treatment is also expected to be evaluated and validated. This article introduces the operational mechanism and clinical application of LINE-1 in clinical practice, with the aim of providing some reference for the diagnosis and treatment of tumors in clinical practice.

Keywords: LINE-1 transposon, cancer, hypomethylation, tumor.

1. Introduction

Cancer is a malignant tumor originating from epithelial tissue, characterized by uncontrolled cell proliferation. Cancer cells can quickly spread from one part to other parts of the body, causing severe illnesses that are difficult to control. Therefore, cancer is a key source of human death worldwide. According to the World Health Organization, about 10 million (about one sixth) mortality rate were consequences of cancer in 2020, posing a tremendous threat to human health. Thus, controlling the occurrence and spread of cancer has also become a major concern, and early detection and treatment are still the optimal means. However, in order to address more cancers, some new methods should be used. This article will elaborate on the relationship and possible practical uses of LINE-1, providing idea for the production and cure of cancer, with aim of providing more possibilities for the later use of LINE-1 in cancer treatment.

1.1. Types of LINE-1 transposons

Transposons are a kind of mobile DNA fragments in the genome, which can move from one position to another freely. The discovery of transposons has broken the traditional idea that genetic materials are

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arranged in a linear fixed way on chromosomes, and has far-reaching significance for the development of genetics and molecular biology.

Transposons are mainly divided into 2 branches, type I transposons and type II transposons. Type I transposon, also known as reverse transposon, uses RNA as the medium to transpose, belonging to the "copy-and-paste" type. Each transposon can add one copy, which is rich in plant genome. Type II transposons, also known as DNA transposons, use DNA as a medium to transpose, belonging to the "cut - paste" type.

There's one specific type of transposon strongly related to cancers, LINE-1 transposon. LINE-1 is one of the most important repeat sequences in human body, and is the only transposon in the human genome that can autonomously transpose. It works by copy and paste LINE-1 and its reverse transcriptase can act on the transposition process of other non-autonomous reverse transcriptional transposons. LINE-1 participates in the DNA sequence generated by transposition, which occupies approximately 30% of genetic material in human beings.

1.2. Mechanism of LINE-1 transposons

LINE-1 transposition is carried out in the way of "copy paste". First, it starts RNA polymerase II, and then it binds to the 5 ′ UTR forward promoter region, and regulates the transcription of LINE-1 mRNA with no deletion in sequences. After the completion of transcription, the mRNA was transposed into the cytoplasm and translated into ORF1P and ORF2P. These two proteins preferentially form ribonucleoprotein particles (RNP) with LINE-1 mRNA in a cis-binding manner. Then the RNP enters the nucleus, and the ORF2P plays the role of endonuclease, recognizing the specific sequence on the genomic DNA (AATTTT) and cutting a DNA strand at the site; Then in RNP region, ORF2P uses 3 '-OH at the fracture to reverse transcribe LINE-1 message RNA as a template, so the base pairing of LINE-1 DNA gene and LINE-1 mRNA are complementary. After that, RNP continued to cut and reverse transcribe on another DNA strand, and filled the resulting gap to complete transposition [1]. So far, the specific details and relevant mechanisms of this process still need to be further studied.

2. How does LINE-1 related to cancer

2.1. Hypomethylation of LINE-1

Methylation is one of the most critical ways of LINE-1 manipulation among other types of modes. LINE-1 transposon is highly expressed in almost all human tumor cells due to its demethylation, and the highly expressed LINE-1 can promote cell proliferation, such as lung cancer cell A549, breast cancer cell MCF-7, liver cancer cell HepG2, but it is silent in normal tissue cells. Liu et al. have shown that LINE-1 may cause great damage to the genome due to its activation and expression, such as mutation, gene instability, and its specific function still need further study.

The hypomethylation of LINE-1 is not a rarely happened epigenetic phenomenon, which has a certain impact on the occurrence of cancer. Under normal conditions, Line-1 is highly methylated. However, some studies have shown that in epithelial cancer, colorectal cancer, gastric cancer and other cancers, LINE-1 shows obvious hypothyroidism glycosylation [3]. The reduction of LINE-1 methylation leads to the increase in LINE-1 reverse transcriptional activity, affects the normal function of cells, and increases the risk of cancer.

2.2. Relationship between LINE-1 and different types of cancer

2.2.1. Esophageal squamous cell carcinoma and LINE-1 transposon. Hoshimoto et al. believed that the hypomethylation of LINE-1 could be a primitive biomarker of esophageal squamous cell carcinoma [3]. The hypomethylation level of LINE-1 in early esophageal squamous cell carcinoma is closely related to the depth of cell invasion.

In addition, Zhu et al. showed that the methylation level of LINE-1 is highly correlated to the expression level of CDK mRNA and CDK protein in esophageal squamous cell carcinoma [4]. The

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epigenetic change of LINE-1 is accompanied by the activation of the expression of multidrug resistance gene MDR1, resulting in the abnormal function of its expression product P-glycoprotein, the reduction of cell resistance, and the increase of the possibility of tumor cell mutation.

2.2.2. Nephroblastoma and LINE-1 transposon. Hypomethylation can shorten telomere length by promoting LINE-1 transcription through DNA damage or other ways. The nephroblastoma cell line was treated with 5-deoxycytidine, a hypomethylated drug, and it is proved that telomeres are no much longer than before, accompanied with reduction in LINE-1 methylation in experimental group. These results show that the methylation of LINE-1 is common in nephroblastoma, and the hypomethylation of LINE-1 is one of the reasons for the shortening of telomere length.

2.2.3. Hepatocellular carcinoma and LINE-1 transposon. In the report of HARADA et al., the expression of cyclin-dependent kinase CDK6 was significantly increased in hepatocellular carcinoma with hypomethylation of LINE-1, which indicated that the risk of hepatocellular carcinoma is increased due to the hypomethylation of LINE-1 by regulating the cell cycle [6]. Zhu et al. believes that the hypomethylation of LINE-1 in hepatocellular carcinoma affects the total survival and disease-free survival of the prognosis of hepatocellular carcinoma by affecting activation of the oncogene c-MET, which is correspond to the progression of hepatocellular carcinoma [4].

In addition, some studies have shown that ORF1 protein on LINE-1 can promote the mitosis and growth of HepG2 cells and lower the cytotoxicity of chemotherapy drugs. Moreover, the new LINE-1 retrotransposon can inhibit the tumor mutant protein (MCC) of colorectal cancer and activate the tumor suppressor ST18 in hepatocellular carcinoma. In conclusion, the hypomethylation of LINE-1 has a great potential to be a biomarker for the diagnosis and prognosis of hepatocellular carcinoma.

3. Therapeutic application of LINE-1 in cancer

3.1. LINE-1 reverse transcriptase as tumor therapeutic target

Early evidence showed that LINE-1 RNA and its encoded protein could not be detected in normal somatic cell, but there were signs of high levels of reverse transcriptase activity in many tumor cells. Although high-level expression and transposition of LINE-1 have been found in many tumor tissues, it is generally believed that the tumor provided appropriate conditions for LINE-1 transposition in the early stage, but it cannot be determined whether LINE-1 transposition is the "cause" or "consequence" of the tumor.

Subsequent studies found that when using reverse transcriptase inhibitors or targeting LINE-1 siRNA to reduce LINE-1 reverse transcriptase activity, it can reduce the proliferation of various tumor cells, promote their differentiation and reconstruct the normal transcriptome profile of cells. In addition, other studies have shown that the expression of LINE-1 is down-regulated by RNA intervention, and it can significantly reduce the tumorigenic potential of human cancer cells in nude mice. The regions where LINE-1 is located in the genome are highly methylated, and the demethylation phenomenon of LINE-1 is very common in tumor tissue. In clinical tumor samples, the demethylation phenomenon of LINE-1 is often accompanied by an increase in LINE-1 RNA and its encoded protein. Therefore, the expression level of LINE-1 reverse transcriptase can also be indirectly reflected by determining the methylation of LINE-1 in tumor tissue.

In the treatment of tumors, endogenous reverse transcriptase is a potential target for the treatment of tumor proliferation. According to existing data, it can be seen that reverse transcriptase inhibitors can exert effects on various tumor cells. Therefore, targeting reverse transcriptase is very in line with the principle proposed by scholars such as Hanahan et al. that "the design of anticancer drugs should prioritize targeting common targets of multiple cancers" [7]. Recently, a phase II clinical trial has been conducted on the reverse transcriptase inhibitor in patients with metastatic prostate cancer. Due to the fact that its dosage is set based on the antiviral (HIV-1) dosage, the lower dosage affects its clinical efficacy. Subsequent clinical trials are expected to conduct with relatively high does [8].

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3.2. LINE-1 as a biomarker for tumor prognosis

The main evidence which supports the feasibility of LINE-1 as a biological marker for prognosis is that the presence of LINE-1 methylation state. In various cancers with poor prognosis, it has been demonstrated that hypomethylation of the LINE-1 promoter is significantly correlated with those cases. A study collected clinical and pathological data from 643 patients with colorectal cancer, illustrating a significant connection between LINE-1 hypomethylation and colorectal cancer specific death. Patients with colorectal cancer have a 30% decrease in methylation levels and 2.37 times increase in risk of death. Patients were assigned into four groups according to their degree of methylation (≥ 75%, 60%~75%, 45%~60%, and<45%). Patients with LINE-1 methylation levels below 45% had a 5-fold significant risk for death than those with LINE-1 methylation levels above 75% [9]. Later, similar results also shown in cases of hepatocellular carcinoma, esophageal cancer, bladder cancer and lung cancer. The methylation status of the LINE-1 promoter has the potential of profoundly affect the proliferation, differentiation, and invasion of tumor cells, and may become an independent prognostic indicator for tumors [10].

Also, overexpression of ORF1p in multiple types of cancer has become one of the biomarkers for cancer, and ORF2p has been shown to affect the occurrence and development of cancer. These two important pieces of evidence support the potential of ORF1p and ORF2p as biomarkers for tumor prognosis evaluation. A study on the relationship between LINE-1 and the prognosis of breast cancer showed that the expression of ORF1p in the nucleus shows strong relationship to breast cancer prognosis. Compared with breast cancer patients with ORF1p mostly located in cytoplasm, patients with ORF1p located in the nucleus had higher local recurrence rate and distal metastasis rate, and their disease-free survival rate and overall survival rate were relatively low [10]. Similarly, the nuclear localization of ORF2p also has prognostic value. Some studies have found that in ductal carcinoma in situ of the breast, ORF2p and ORF1p are both situated in the cytoplasm. The presence of ORF1p and ORF2p were verified that they not only exist in nucleus, but also cytoplasm of infiltrating ductal carcinoma with higher degree of deterioration, and patients with high levels of ORF1p and ORF2p expression in the nucleus had significantly higher lymph node metastasis rates than patients with relatively obvious expression of ORF1p and ORF2p in the cytoplasm. Patients with high degrees of ORF1p and ORF2p expression in the nucleus also had shorter survival times, so this may be due to the high expression and localization of ORF1p and ORF2p in the nucleus, which increases the reverse transcriptional transposition of LINE-1 and thus increases genomic instability.

4. Conclusion

More and more evidence showed a close correlation between the expression of LINE-1 and the occurrence and development of tumors. Looking for diagnostic, prognostic, and therapeutic methods for cancer from the perspective of LINE-1 has become a new direction. For example, ORF1p and ORF2p can serve as biomarkers for cancer diagnosis. LINE-1 promoter in cancer tissue is expected to become an independent prognostic indicator for cancer due to the methylation status, and ORF2p is gradually showing potential as a therapeutic target. Some reverse transcriptase inhibitors have shown hope for treating cancer in clinical trials. Despite existing evidence is still limited.

However, the specific mechanism underlying the relationship between the expression of LINE-1 and the emergence and expansion of tumors remains unclear. The experiments supporting LINE-1 as a cancer treatment target mainly focus on the cellular level, and clinical trial information is still very limited. At the same time, the potential use of LINE-1 for cancer treatment has not yet been explored, such as whether the expression of LINE-1 is correlated with tumor resistance during chemotherapy, radiotherapy, and immunotherapy. If it can be proven that chemotherapy, radiotherapy, or immunotherapy promote the abnormal activation of LINE-1 in tumors, causing gene mutations and ultimately leading to the formation of tumor resistance, LINE-1 can help clinical doctors provide more information A more effective treatment plan.

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