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REVIEW ARTICLE

Recurrent Fusion Genes in Leukemia: An Attractive Target for Diagnosis and Treatment

Yuhui Wang[1], Nan Wu[1], Duo Liu[1,2] and Yan Jin[1,*]

[1]*Laboratory of Medical Genetics, Harbin Medical University, Harbin, Heilongjiang, P.R. China;* [2]*Department of Pharmacy, Harbin Medical University Cancer Hospital, Harbin, Heilongjiang, P.R. China*

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Abstract: ***Introduction*:** Since the first fusion gene was discovered decades ago, a considerable number of fusion genes have been detected in leukemia. The majority of them are generated through chromosomal rearrangement or abnormal transcription. With the development of techniques, high-throughput sequencing method makes it possible to detect fusion genes systematically in multiple human cancers. Owing to their biological significance and tumor-specific expression, some of the fusion genes are attractive diagnostic tools and therapeutic targets. Tyrosine kinase inhibitors (TKI) targeting BCR-ABL1 fusions have been widely used to treat CML. The combination of ATRA and ATO targeting PML-RARA fusions has proven to be effective in acute promyelocytic leukemia (APL). Moreover, therapy with high dose cytarabine (HDAC) has significantly improved the prognosis of core binding factor (CBF) acute myeloid leukemia (AML) patients. Therefore, studies on fusion genes may benefit patients with leukemia by providing more diagnostic markers and therapies in the future. ***Conclusion*:** The presented review focuses on the history of fusion genes, mechanisms of formation, and treatments against specific fusion genes in leukemia.

Keywords: Fusion genes, Recurrent, Leukemia, AML, Treatment, Target.

1. INTRODUCTION

Chromosomal abnormalities are closely related to the pathogenesis of malignant hematological disorders. Many of chromosomal abnormalities lead to the formation of fusion genes, which are essential during tumorigenesis and tumor development. The progress in new methods allows us to discover more fusion genes in solid cancers. However, it has been demonstrated that the vast majority of fusion genes occur in hematological malignancies. In addition, a portion of the fusions arise recurrently in a specific subtype of leukemia, which shows potential clinical value.

1.1. Discovery and Formation of Fusion Genes

1.1.1. Discovery of Fusion Genes

In 1960, an extended chromosome 9 and a shortened chromosome 22 were discovered in chronic myeloid leukemia (CML), forming a smaller chromosome 22, which was named the Philadelphia chromosome (Ph chromosome) [1]. Then in 1973, a few years after the introduction of chromosome banding techniques, Rowley further confirmed that a Ph chromosome was generated from the translocation between chromosomes 9 and 22 [2]. Afterwards, Grosveld and his colleagues identified that the translocation involved *ABL* on the distal end of the q-arms of chromosome 9 and the gene breakpoint on the breakpoint cluster region (BCR) of chromosome 22 in 1982 [3]. Later, E. Shtivelman found that the translocation led to a chimeric *BCR-ABL1* transcript, which encoded a continuously activated form of the ABL kinase, resulting in inhibited apoptosis and promoted proliferation [4]. During the same period, some other fusion genes had also been found in B cell lymphomas, including *IGH–MYC*, *IGL–MYC* and *IGK–MYC*. They cause the disease by altering cell cycle, apoptosis, adhesion and metabolism [5].

1.2. Formation of Fusion Genes

Various fusion genes can lead to cancers, so it is extremely necessary to comprehend their causes. Fusion genes are mainly generated from chromosomal rearrangements and abnormal transcription, but the former one is much more common.

Translocations, deletions, tandem duplications, and inversions (Fig. **1**) are four basic forms of chromosomal rearrangement [6]. Translocations cause the switch of genetic materials among different chromosomes. These chromosomal abnormalities usually come in two kinds: one is non-reciprocal, in which minor DNA fragments translocate to novel locuses without any reciprocal product; the other is reciprocal, involving the swapping of the arms of the chromosomes and generating two translocated products. Lots of fusion genes are generated through translocation,

*Address correspondence to this author at the 157 Baojian Road, Nangang District, Harbin 150081, People's Republic of China; Tel: 86–451-86674798; Fax: 86–451-86674798; E-mail: jinyan@ems.hrbmu.edu.cn

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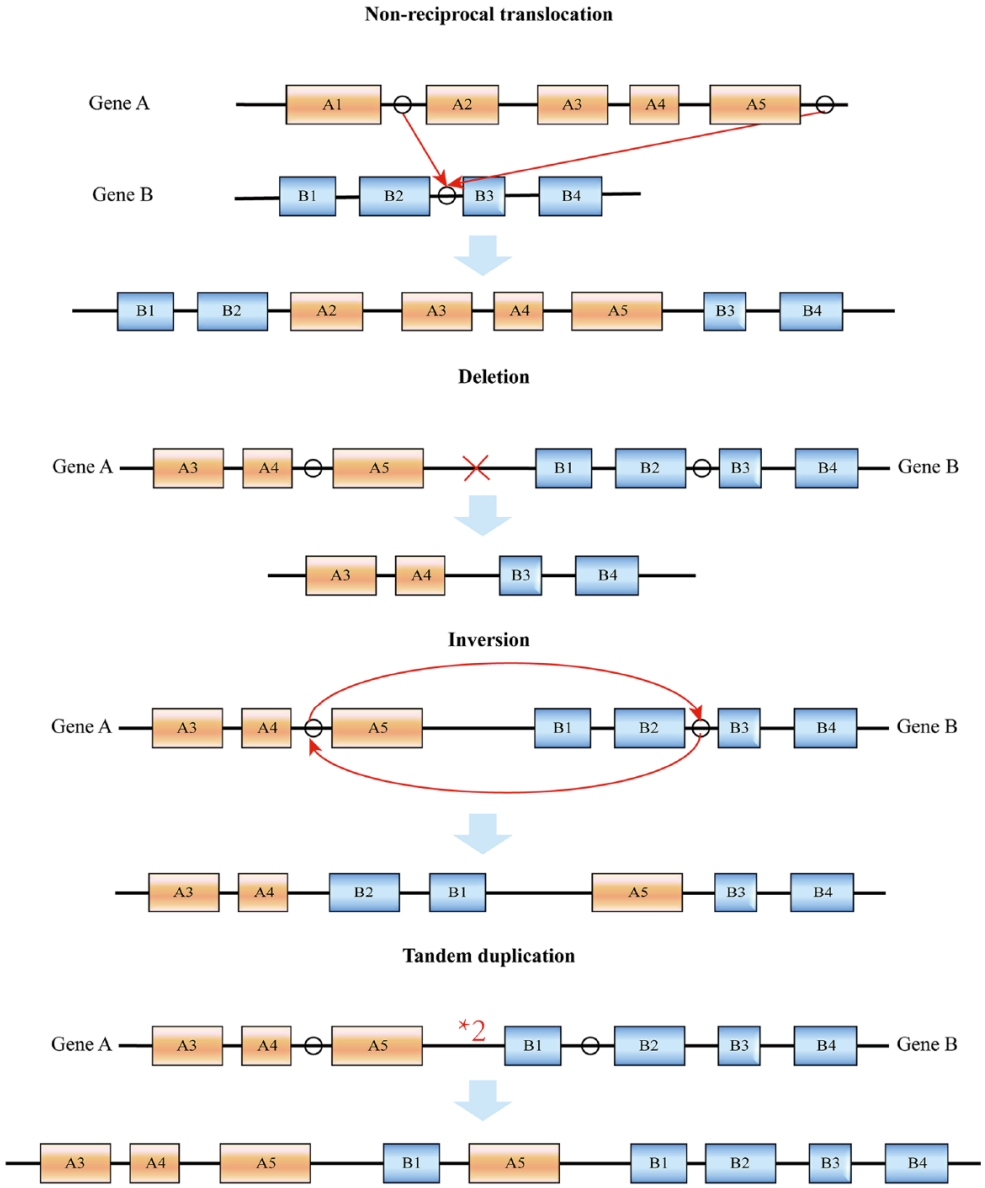

Fig. (1). The formation of fusion genes through chromosomal rearrangement. A and B indicate involved genes and boxes signify introns or exons. Circles indicate genomic breakpoints. Red lines and arrows indicate the way rearrangement occurred. The big blue arrows indicate the resulting fusion genes. (*For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper.*)

such as *IGH-MYC* fusions in Burkitt lymphoma [5a], *RUNX1-RUNX1T1* fusions in acute myeloid leukemia (AML) [7], and *BCR-ABL1* fusions in CML [3]. Sometimes a fusion gene is caused by deletion, which only involves one chromosome. In this situation, a DNA fragment between two genes is missing. For example, in prostate cancer, the *TMPRSS2-ERG* fusion genes are generated from interstitial deletion of chromosome 21q22 [8]. In addition to the above two mechanisms, fusion genes can also arise *via* tandem duplications or inversions. For instance, the *FGFR3-TACC3* fusion genes in glioblastoma result from tandem duplication on 4p16.3 [9]. The *CBFB-MYH11* fusions are formed by inversion on chromosome 16, which are presented in the M4E0 subtype of AML [10].

Fusion genes can also arise *via* transcription-induced chimeras, which is unrelated to chromosomal rearrangements. There are two mechanisms of transcription-induced chimeras: trans-splicing and read-through. Trans-splicing is a result of the fusion between two separate pre-mRNAs, which are spliced to give rise to a single mRNA molecule. Read-through refers to a chimeric transcript which is made of two neighboring genes by a splicing event. For example, the *PPP1R1B-STARD3* chimeric RNA results from the fusion between *PPP1R1B* in the upstream and *STARD3* in the downstream, with exon 7 of *PPP1R1B* and exon 1 of *STARD3* removed by splicing [11].

2. RESEARCH METHODS OF FUSION GENES

Historically, the exploration of chimeric genes started with the observation on chromosomal rearrangement *via* chromosome banding analysis (karyotyping). The next step to learn more about the rearrangement is fluorescence *in situ* hybridization (FISH), utilizing probes which span the chromosomal breakpoints, so that it can locate the breakpoints

accurately. This method uses gradually diminishing probes, like YAC, BAC, PAC and Fosmid, to find the chromosomal breakpoints by hybridizing with the abnormal metaphase chromosomes. Further, in order to locate the breakpoints more accurately and find out the genes relevant to chromosomal rearrangement, molecular cloning techniques (Southern blot and PCR) are usually used. Although these classic research methods are slightly complicated to perform, they are considered to be highly reliable and useful, and they have been applied to the identification of fusion genes in a variety of cancers [12].

Recently, the development of second-generation sequencing technique has provided a novel approach to detect fusion genes in cancer [13]. This method has much more advantages. First, it enables genome-wide identification of new fusion genes at an unparalleled level of resolution [14]. Second, it makes it possible to identify the structure and transcriptional level of fusion genes. Third, it does not need prior cell culturing, like chromosome banding analysis does, thus saving time. Although it is expensive at present, with the continuous progress in technology, the cost of this new approach will eventually decrease. At that time, it will be widely used and identify more fusion genes in cancer.

3. FUSION GENES IN LEUKEMIA AND TREATMENT OF RECURRENT FUSION GENES

Nowadays, fusion genes are relatively easier to be identified with the development of technology, from Sanger sequencing to high-throughput sequencing. This promotes the discovery of fusion genes in malignant hematological disorders and solid cancers, providing great convenience to diagnosis and treatment of cancers. Currently, fusion genes are widely used in the diagnosis and treatment of leukemia.

3.1. Fusion Genes in Leukemia

Leukemia is a kind of malignant neoplasm that developed from the hematopoietic system. It is mainly divided into AML, acute lymphocytic leukemia (ALL), CML and chronic lymphocytic leukemia (CLL).

CML is a clonal hematopoietic stem cell disorder characterized by the cytogenetic hallmark of Ph chromosome [1]. At the molecular level, the (9;22)(q34;q11) translocation fuses the 5' region of *BCR* to the 3' region of *ABL1* [3]. *BCR-ABL1* encodes a chimeric protein, which is presented in more than 95% of CML patients and plays a major part in its diagnosis and treatment. It also exists in ALL, but the incidence is only 20%, far lower than that in CML [15].

There are some other fusion genes in ALL besides *BCR-ABL1*, one of which is the *ETV6-RUNX1* fusion. The *Runt-related transcription factor1* (*RUNX1*, also known as *AML1*, *CBFA2* and *EVI-1)* gene, located in chromosome 21q22, is relatively conserved in evolution. The protein encoded by *RUNX1* plays a crucial role in cell lineage differentiation during development. The *Ets variant 6* (*ETV6*) gene codes for a transcription factor, which belongs to the E-twenty-six (ETS) family. These two genes form the *ETV6-RUNX1* fusion resulting from t(12;21)(p13;q22), which is common in pediatric B-cell ALL, occur in 20-25% of cases [16]. Another recurrent translocation in pediatric B-cell ALL is t(1;19)(q23;p13), for an overall incidence of about 5% [17]. The (1;19)(q23;p13) translocation leads to the formation of *TCF3-PBX1* chimeric gene. The *TCF3* gene at 19p13.3 codes for a helix-loop-helix protein and the *PBX1* gene at 1q23 codes for a homebox gene product. The protein generated by *TCF3-PBX1* shows oncogenic function as a transcriptional activator. It was related to poor outcome in the past, but modern intensive chemotherapy seems to overcome adverse prognostic impact.

In AML patients, t(15;17)(q22;q12), inv(16)(p13;q22) or t(16;16)(p13;q22), t(8;21)(q22;q22) and t(9;11)(p22;q23) are the most commonly identified chromosomal abnormalities. The (8;21)(q22;q22) translocation results in the fusion between *RUNX1* and *RUNX1T1* (also known as *ETO*). The breakpoints involved in the fusion gene occurred in exons 5 and 6 of the *RUNX1* gene and in exons 1 and 2 of *RUNX1T1*. The RUNX1 transcription factor is important for hematopoiesis, and transformation by RUNX1-RUNX1T1 probably results from transcriptional inhibition of normal RUNX1 target genes. This fusion was found in approximately 10% of AML patients [7]. While t(16;16)(p13;q22) or inv(16)(p13;q22) contributes to the generation of *CBFB-MYH11* fusion. *MYH11* encodes a smooth muscle myosin heavy chain [18]. The protein encoded by *CBFB* forms a heterodimeric transcription factor with CBFA, the gene product of *RUNX1*. Whereas the heterodimeric complexes were interfered by the formation of CBFB-MYH11 chimeric protein, resulting in poorly differentiated hematopoietic cells. The (15;17)(q22;q12) and (9;11)(p22;q23) translocations cause the generation of *PML-RARA* and *KMT2A-MLLT3*, respectively. More recurrent fusion genes in leukemia are listed in Table **1**.

3.2. Treatment Against Recurrent Fusion Genes in Leukemia

3.2.1. BCR-ABL

Allogeneic hematopoietic stem cell transplantation (HSCT) was once a major therapy for CML [32]. It could prolong the survival time and even cure the disease, especially when the transplantation was carried out in chronic phase [33]. However, a large portion of patients were not suitable for this treatment, due to shortage of right donors or old age. The *BCR-ABL1* fusion gene, observed in most CML cases, encodes an active protein tyrosine kinase (PTK) which affects various cellular activities, such as enhanced proliferation and decreased apoptosis [34]. This makes PTK an ideal target for drugs. Imatinib, also known as Gleevec, was the first tyrosine kinase inhibitor (TKI) used in clinical tests. It has activity against ABL1 kinase, BCR-ABL1, Steel factor receptor (c-KIT) kinases, *etc*. Imatinib blocks the ATP binding pocket of ABL1 kinase domain, preventing the activation of phosphorylated protein, eventually resulting in the apoptosis of BCR-ABL1 positive cells [35]. The subsequent second generation drugs include bosutinib, nilotinib and dasatinib. Lately, ponatinib has emerged as the third generation drug [36]. Since the advent of TKIs, HSCT is now recommended as second line or even third line therapy for CML patients, restricted to those who have failed multiple TKIs, or whom with very advanced disease [36, 37].

Although imatinib is extremely successful in treating CML, there are still 40% of the cases experiencing resistance

Table 1. Fusion genes in leukemia.

Disease	Fusion Gene	Chromosomal Aberration	Frequency (%)
Acute myeloid leukemia (AML)	RUNX1- RUNX1T1	t(8;21)(q22;q22) [7]	10
	CBFB-MYH11	inv(16)(p13;q22) [19]	
		t(16;16)(p13;q22) [19]	5-10
	KMT2A-MLLT3	t(9;11)(p22;q23) [20]	2-5
	RPN1-MECOM	t(3;3)(q21;q26)	
		inv(3)(q21;q26)	1.4-1.6
	DEK-NUP214	t(6;9)(p22;q34) [21]	1
	PVT1-MECOM	t(3;8)(q26;q24) [22]	<1
	RUNX1-MECOM	t(3;21)(q26;q22)	0.14
Acute promyelocytic leukemia (APL)	PML-RARA	t(15;17)(q22;q12) [23]	90
	ZBTB16-RARA	t(11;17)(q23;q21) [24]	<1
Acute lymphocytic leukemia (ALL)	ETV6-RUNX1	t(12;21)(p13;q22) [16]	20-25
	BCR-ABL1	t(9;22)(q34;q11) [15]	20
	TCF3-PBX1	t(1;19)(q23;p13) [17]	5
	KMT2A-AFF1	t(4;11)(q21;q23) [25]	2-5
	PICALM-MLLT10	t(10;11)(p13;q21) [26]	<1
	IGH-CEBPA	t(14;19)(q32;q13) [27]	<1
	TCF3-HLF	t(17;19)(q22;p13) [28]	<1
	TRA-MYC	t(8;14)(q24;q11) [29]	0.5-1.3
Chronic myeloid leukemia (CML)	BCR-ABL1	t(9;22)(q34;q11)	95
Chronic lymphocytic leukemia (CLL)	IGK-BCL3	t(2;19)(p12;q13) [30]	——
	IGH-BCL3	t(14;19)(q32;q13) [30]	
	BCL3-IGL	t(19;22)(q13;q11) [30]	
	CXCR4-MAML2	t(2;11)(q22.1;q21) [31]	

or intolerance. The main cause of this is the mutations occurring in the *BCR-ABL1* kinase domain, which interfere binding with the drug. Therefore, the second-generation TKIs were developed to target majority of imatinib resistant mutations. Clinical studies revealed that patients treated with dasatinib [38] or nilotinib [39] had fewer mutations than patients treated with imatinib. Moreover, the second-generation TKIs showed faster and deeper molecular response and had greater efficacy against CML compared with first-generation TKIs [40]. However, the presence of some notable mutations like T315I also confers resistance to nilotinib and dasatinib. Emerging data indicate that the third-generation TKI, ponatibib, may overcome resistance against all common single mutants, including T315I [41]. A latest study demonstrated that ponatinib is more effective for patients with multiple mutations (except for T315I) than first- or second-generation TIKs. However, patients with multiple mutations containing T315I showed inferior responses overall compared to patients with T315I mutation only [42]. This suggests that new drugs are still needed for the treatment.

3.2.2. PML-RARA

Acute promyelocytic leukemia (APL) is a subtype of AML, accounting for about 10-15% of the total cases. The disease is identified by typical translocation t(15;17)(q22;q12), which contributes to the production of *PML-RARA* chimeric transcript [23], being present in more than 90% APL patients. In normal condition, promyelocytic leukemia (PML) takes part in growth suppression, while the retinoic acid receptor α (RARA) protein is involved in the promyelocyte differentiation process [43]. After the fusion between PML and RARA, the original functions are affected, leading to abnormal differentiation and growth of cells. In the past, APL was regarded as a highly lethal type of leukemia. After the revolutionary use of all-trans retinoic acid (ATRA) in 1985, the treatment for APL changed significantly [44], hence a large number of patients achieved complete remission, but about 50% of which relapsed in two years [45]. Since the early 1990s, arsenic trioxide (ATO) had been reported to treat both relapsed and newly diagnosed APL patients [46]. In clinic, ATRA and ATO combination therapy is widely used, causing apoptosis of APL cells and significantly improving the prognosis. Currently, the complete remission rates and cure rates in APL cases are 90% and 80%, respectively. The prognosis of this subtype of AML is thought to be the best in adult, compared with other subtypes [47].

However, a recent clinical study found that some of the APL patients were not sensitive to ATRA or other routine chemotherapy, because of the formation of a new *GTF2I-RARA* fusion gene. The N-terminal of GTF2I-RARA fusion can recruit corepressors, which would no longer separate when treated with ATRA, resulting in resistance to drug [48]. This suggests that we should treat patients individually even in the same subtype of disease.

3.2.3. RUNX1-RUNX1T1 and CBFB-MYH11

The t(8;21)(q22;q22) and inv(16)(p13;q22), leading to the production of *RUNX1-RUNX1T1* and *CBFB-MYH11* chimeric gene, both contain subunits of core binging factor (CBF) at the molecular level and share similarities in response to therapy. Therefore, they are always combined into one category, the CBF-AML. In 1998, Bloomfield *et al.* showed that high-dose cytarabine (HDAC) intensification could improve outcome in cases diagnosed as CBF-AML, but not in those with other karyotypic abnormalities [49]. It was later demonstrated that the risk of relapse was reduced by multiple courses of HDAC, but the overall survival was not significantly increased [50]. Patients with CBF-AML usually have a relatively good outcome, for overall survival rates of 60-70% in adults and 80% in children [51]. However, the expression of CD56 and the activation of *c-KIT* mutations have been correlated to greater risk of recurrence and shorter survival. The *c-KIT* mutations were found in 20-25% of t(8;21)(q22;q22) and in about 30% of inv(16)(p13;q22) patients [52]. Therefore, novel therapies should be used for patients with *c-KIT* mutations.

CONCLUSION AND PERSPECTIVE

Fusion genes are crucial in the diagnosis and treatment of leukemia. It is now clear that some of the fusion genes are characteristic in leukemia, so they can serve as important indicators of disease diagnosis. At the same time, fusion genes also have guiding significance for clinical treatment of leukemia. They can be used as targets for molecular treatment in combination with other drugs, greatly improving the therapeutic effect. The introduction of TKIs has extremely improved outcomes in CML patients. The resistance mechanisms of TKIs are well studied and more potent drugs are needed, especially for patients with BCR-ABL1 multiple mutations containing T315I. As more TKIs are emerging, it is also important to standardize the sequence and dose when using them. Targeted therapies are also commonly used in AML. Further studies of functional and molecular characteristics of the fusion proteins are still needed to improve the treatment.

With the increasing popularity of second-generation sequencing, we may find more iconic fusion genes by sequencing and obtaining more targets for molecular diagnosis and treatment. After that, the disease can be classified in a more detailed way. By detecting the expression of iconic fusion gene, we can treat patients individually with drugs target to these fusion genes. In this way, the cure rate of leukemia will be improved effectively.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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