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Genomic Activities of Mixed Lineage Leukemia Proteins

Senol D*

Genetics and Bioengineering Department, International Burch University, Bosnia and Herzegovina

Opinion

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***Corresponding author:** Senol Dogan, Genetics and Bioengineering Department, International Burch University, Sarajevo, Bosnia and Herzegovina, Tel: +38762801777; Email: senol1dogan3@gmail.com

Abstract

MLL is one of the most aggressive leukemias which mostly targets pediatric patients. Genetic rearrangement of the 11q23 location is the main reason for this type of acute leukemia. MLL gene and its fusion proteins have produced a core complex which leads to abnormal hematopoesis. Although many clinical and lab studies have been done to show the prominent role of MLL in leukemogenesis since its discovery in 1992, large-scale genomic data seems to be the most effective way to analyse the hematologic malignancies extensively. Gene expression, methylation, mutation, RNA-seq, and SNP arrays have updated the understanding of the transformation oncohematologic disorder mechanism. As a result of the genomic data analysis, new biomarkers may have been detected as therapy target genes and used for personalized medicine. The genomics-bioinformatics studies and novel technical advances provide some precious knowledge to discover novel therapeutic strategies and better treatment outcomes in the future.

Keywords: Mixed Lineage Leukemia; Cytogenetics; Fusion Proteins

Abbreviations: MLL: Mixed Lineage Leukemia; TREs: Trithorax Response Elements

MLL (Mixed Lineage Leukemia)

MLL is represented by KMT2 lysine (K)-specific methyltransferase 2A gene which consists of 90.156 bases and encodes histone-lysine N-methyltransferase protein [1]. The gene which was firstly defined in 1970 from an ALL patient and named MLL (mixed-lineage leukemia) is located in the 11q23 chromosome. Since the location is very sensitive and active for chromosomal translocation, it is observed in both myelogenous and lymphoblastic lineages of leukemia [2]. The gene is responsible for transmitting the memory of active genes to daughter cells through interactions with Trithorax Response Elements (TREs) which regulates gene expression of hematopoiesis as an encoding a transcriptional coactivator [3]. The Trithorax and Polycomb families keep the right genes on or off. While TREs keep the genes active, Polycomb proteins generally bind to the heterochromatin structure to freeze the genes in a repressed state [4]. MLL is directly or indirectly responsible for regulating the expression of target genes, epigenetic regulation of transcription, embryonic development, and hematopoiesis [5].

MLL Leukemia

MLL gene is a frequently repeated translocation target that shows distinguished genomic-clinical characteristics, and it is often correlated with poor prognosis, very low overall survival in 70% of infants with leukemia, and not

effective target treatment. The gene and its associated fusion proteins regulates hematopoietic development by altering epigenetic profiles which deregulate transcription activity globally. The target therapeutic chemicals disrupt the MLL fusion protein super complex and inhibit the growth of MLL-associated leukemic and show differences between adults and children [6]. Since MLL type leukemia is very aggressive and 90% of the time it is observed in infant aged < 1 year old, (2-5%) children-it is hardly ever observed in older patients (aged 60 and up) [7]. The infant or age-group around 1 year old (70% of ALL and 35%-50% AML) involve 11q23 translocation [8]. While the five-year survival rate among older patients is 30%, a pediatric patient varies between 40% to 65% [9]. Since MLL patients present very bad prognostic factor, they are diagnosed with high-risk protocols and a very poor outcome [10]. Although cytogenetics often diagnose the leukemia type, risk stratification, and therapeutic implications, genomic analysis of leukemia subtypes is needed to guide clinicians and hematologists for predicting the risk of treatment and developing novel and targeted therapies [11].

MLL Re-arrangements

Chromosomal rearrangement is one of the major causes of genetic diseases or abnormalities. E2A/PBX1, BCR/ABL, ETV6, RUNX1, and MLL chromosomal rearrangements are the mostly observed examples in leukemia. The rearrangements do not only change transcriptional profile and cellular pathways, such as cell cycle, apoptosis, cell differentiation and tumor suppression, but also affect prognosis and therapy methods [12]. While other rearrangements need additional hits to cause a problem, MLL type rearrangement is enough itself to stimulate a leukemic transformation. The main MLL type rearrangements are (4;11), t(6;11), t(9;11), t(11;19) which are clustered within a 9-kb BamHI genomic region and 5-kb region and diagnosis, overall survival rate and therapy methods are arranged depending on the type rearrangements. For example, while t(6;11)(q27;q23) and t(10;11)(p12;q23) are correlated with a poor prognosis, t(9;11)(p22;q23) type survival rate is significantly longer than others [13,14].

Fusion Proteins and Their Functions

MLL protein is cleaved by Taspase 1 enzyme into MLL-N and MLL-C terminals which consist of 2718 a.a and 1250 a.a respectively but it is generally fused with at least four main proteins, around 100 different MLL fusion proteins detection [15]. The MLL-protein complex regulates gene expression by modifying chromatin structure during early development, hematopoiesis process, methylation and acetylation of histone protein. The complex is suspected to form and transform hematopoietic cells into leukemia cells successively [16]. Here are the fusion proteins and their functions:

- MOF protein loosens up chromatin by histone charge neutralization [17].
- WDR5 protein recognizes the histone H3 lysine 4 methyl-mark and ensures the progression of histone modification [18].
- AT-hook is a DNA binding domain [19].
- CxxC motif recognizes unmethylated CpG dinucleotides [20-22]. PHD is transcriptional co-activators [23].
- SET is histone methyltransferase active site [24].

MLL Protein and Its Complex Formation

The two MLL parts come together after being delivered to the nucleus, including 8 functional domains Ala/Gyl/Ser-rich, Poly/Gly, three AT-hooks, Zinc finger CXXC type, three zinc fingers PHD type, Bromodomain, FYR N-term, MLL-C part has 5 functional domains TAD, FYRC-term, SET, 4post SET and S-adenosyl-L-methionine binding sites [25]. The complex regulates 3 main chromatin modifications; acetylation, methylation and nucleosome remodeling. Those epigenetic modifications affect transcription factors acccession to the active genes and direct RNA synthesis.

MLL Breaking Point

MLL breakpoint occurs within a 4kb region exon8 to exon12 which is the most sensitive part among MLL introns and exons. The core breakpoint is a very fragile fragment and important pioneer to rearrangement with mostly correlated infant acute and therapy-related leukemia [26,27]. Since it is abnormally expected to occur in a gene coding region, the oncogenic gene fusion is produced by broken of both DNA strands which are most frequently observed within an intron. Thus, an exclusive work and mysterious promoter was identified within intron11, the border of exon12 [28]. It has already been understood that to poisomerase II consensus sequence locates within exon12, which is the target of etoposide application. This suggests that etopside stimulation of the cleavage is expressed at the distal site of the enzyme binding consensus sequence [29-32].

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