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Review

Chromosomal translocations involving the *MLL* gene: Molecular mechanisms

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ABSTRACT

A wide array of recurrent, non-random chromosomal translocations are associated with hematologic malignancies; experimental models have clearly demonstrated that many of these translocations are causal events during malignant transformation. Translocations involving the *MLL* gene are among the most common of these non-random translocations. Leukemias with *MLL* translocations have been the topic of intense interest because of the unusual, biphenotypic immunophenotype of these leukemias, because of the unique clinical presentation of some *MLL* translocations (infant leukemia and therapy-related leukemia), and because of the large number of different chromosomal loci that partner with *MLL* in these translocations. This review is focused on the potential mechanisms that lead to *MLL* translocations, and will discuss aberrant VDJ recombination, *Alu*-mediated recombination, non-homologous end joining, as well as the effect of DNA topoisomerase II poisons and chromatin structure.

Contents

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1. Introduction

The study of recurrent, non-random chromosomal translocations has proven to be a rich source of insights into the biology of hematologic malignancies [1,2]. A number of themes concerning these chromosomal translocations has become apparent over the past decades [3]. For instance, particular translocations are associated with particular subtypes of leukemia; the t(15;17) is exclusively associated with acute promyelocytic leukemia (APL) [4], and the t(1;19) is associated only with pre-B cell acute lymphoblastic leukemia (ALL) [5]. Additionally, each gene involved in chromosomal translocations has a preferred partner, with perhaps two to four additional, infrequent partners. For instance, *E2A* is typically fused to *PBX1* but less frequently to *HLF* [6], and *RARA* is most commonly involved in translocations with *PML*, but can also be fused to *PLZF* or *NPM* [4]. Chromosomal translocations involving the *MLL* (for Mixed Lineage Leukemia, also called *ALL-1*, *HRX*, and *Htrx*) locus on chromosome 11 band q23 provide exceptions to these two aforementioned generalizations. *MLL* translocations are associated with a wide array of hematologic malignancy, including acute myelogenous leukemia (AML), T-cell ALL, B lineage ALL, myelodysplastic syndrome (MDS), lymphoblastic lymphoma, and Burkitt's lymphoma [7–9]. In addition, *MLL* has been labeled a "promiscuous" oncogene since over 60 partner genes or regions have been identified [9].

The *MLL* gene was initially cloned by virtue of its involvement in t(4;11), t(11;19), and t(9;11) translocations [7,9]. The *MLL* genomic structure consists of 36 exons distributed over 100 kb, and produces a 12 kb mRNA that encodes a 3968 aa protein with an estimated molecular weight of 430 kD [7]. The *MLL* protein is widely expressed in the developing embryo, and is expressed at lower levels in most adult tissues. The predicted amino acid sequence of *MLL* indicates that it is homologous to the trithorax gene of *D. melanogaster*. Recent experiments have indicated that *MLL* is normally processed *via* a cytoplasmic cleavage event into a 320 kD amino terminus (*MLL*-N), and a 180 kD carboxy terminus fragment [7]. A number of protein motifs/domains have been identified in the primary structure of *MLL*, including AT hooks, a DNA methyltransferase domain, PHD domains, a transactivation domain, and a SET domain. Several lines of evidence indicate that one important function of *MLL* is in the maintenance of *HOX* gene expression during embryonic development. Loss of *MLL* function in flies leads to homeotic transformation, and deletion of *MLL* in mice leads to embryonic lethality and homeotic transformation [7]. Biochemical analysis of *MLL* suggests that it normally functions as a transcription regulator, and expression of *MLL* fusion proteins has been shown to be leukemogenic in mice. A detailed discussion of these aspects is beyond the scope of this review, which will focus on mechanisms that lead to *MLL* translocations; the reader is referred to several excellent reviews for an overview of these aspects [7,9,10].

2. Clinical observations

2.1. Clinical overview

MLL translocations are among the most common translocations in hematologic maliganacy. Approximately 3–10% of patients with AML have *MLL* translocations, and 8–10% of patients with B-lineage ALL have *MLL* translocations [7,9]. Patients with AML and *MLL* translocation have an intermediate prognosis compared to all cases of AML, whereas patients with B-lineage ALL and *MLL* translocations tend to have a poor prognosis. In contrast, although *MLL* translocations are relatively rarely associated with T-ALL, these patients tend to have a very good prognosis [11]. Two distinct forms of acute leukemia are associated with *MLL* translocations and will be discussed in more detail below. *MLL* translocations are exceedingly common in infants with AML and ALL, and have been identified in up to 80% of all infant acute leukemia cases [12]. In addition, *MLL* translocations are seen in approximately 25% of patients with therapy-related leukemias, particularly those associated with the use of chemotherapeutic agents that target DNA topoisomerase II (topo II) [13].

2.2. Infant leukemia

Current models of malignant transformation suggest that multiple pathways, including those governing cell growth, differentiation, death, and responsiveness to external signals need to be disrupted in order to generate any malignancy [14]. It has been suggested that myeloid leukemias require at least two collaborating mutations, one that impairs blood cell differentiation, and a complementary one that leads to increased proliferation and/or decreased apoptosis [15]. Support for this conceptual framework comes both from clinical observations (patients with APL often have *PML-RARA* fusions, which impair differentiation, and *FLT3* mutations, which lead to increased proliferation), as well as murine bone marrow transduction/transplantation experiments, in which bone marrow cells transduced with both *BCR-ABL* (which leads to increased proliferation) and *NUP98-HOXA9* (which impairs differentiation) were leukemic, whereas cells transduced with only *BCR-ABL* were not [15]. Further support for this framework comes from the observation that many leukemic fusions can be detected in hematopoietic cells from healthy individuals. For instance, *AML1-ETO* fusions can be detected in long term survivors who are presumably cured of their disease, and *TEL-AML1* fusions can be detected in cord blood from healthy newborns [16]. Moreover, "knock-in" mice that express