Available online at www.sciencedirect.com
SCIENCE DIRECT
Molecular Genetics and Metabolism 88 (2006) 216–224
Molecular Genetics and Metabolism
www.elsevier.com/locate/ymgme

Minireview

Molecular targets and the treatment of myeloid leukemia

A. Ikeda [a], D.B. Shankar [a], M. Watanabe [e], F. Tamanoi [e], T.B. Moore [a], K.M. Sakamoto [a,b,c,d,*]

[a] *Division of Hematology/Oncology, Department of Pediatrics, Gwynne Hazen Cherry Memorial Laboratories, and Mattel Children's Hospital, Jonsson Comprehensive Cancer Center, USA*
[b] *Department of Pathology and Laboratory Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095-1752, USA*
[c] *Molecular Biology Institute, UCLA, Los Angeles, CA 90095, USA*
[d] *Division of Biology, California Institute of Technology, Pasadena, CA 91125, USA*
[e] *Department of Microbiology, Immunology and Molecular Genetics, UCLA, Los Angeles, CA 90095, USA*

Received 18 November 2005; received in revised form 16 March 2006; accepted 16 March 2006
Available online 5 May 2006

Abstract

Leukemia is a multistep process involving accumulation of genetic alterations over time. These genetic mutations destroy the delicate balance between cell proliferation, differentiation, and apoptosis. Traditional approaches to treatment of leukemia involve chemotherapy, radiation, and bone marrow transplantation. In recent years, specific targeted therapies have been developed for the treatment of leukemia. The success of treatment of acute promyelocytic leukemia with All Trans Retinoic Acid (ATRA) and CML with imatinib have lead to increased efforts to identify targets that can be inhibited by small molecules for treatment of hematological malignancies. In this review, we describe the current advances in the development of targeted therapy in acute myeloid leukemia.

Keywords: Targeted therapy; Chromosomal translocations; Apoptosis; Cell cycle; Small molecule inhibitors

Introduction

Leukemia is the most common form of cancer diagnosed in children. Acute leukemias represent a group of diseases that include both myeloid (AML) and lymphoid hematologic malignancies (ALL). Leukemia arises from the clonal expansion of aberrant progenitor cells that show increased proliferation and failure to differentiate, resulting in accumulation of "blasts." ALL is the most common type of acute leukemia in children and the overall survival has been reported to be as high as 80 percent. Availability of molecular markers to predict prognosis will help in determining treatment options to maximize survival and minimize toxicity in the future. Children with acute myeloid leukemia (AML) have less than 60% overall survival despite aggressive chemotherapy and bone marrow transplantation. Similarly only one third of the adult patients (18–60 years) diagnosed with AML can be cured [1]. Disease free survival in adults is uncommon and the relapse rate is high.

For several decades, acute leukemias have been characterized on the basis of morphology, special stains, cytogenetics, and cell surface markers. However, recent studies on molecular characterization of specific cytogenetic defects in acute leukemias have provided new avenues for targeted therapy.

Molecular mechanisms

Human leukemia, like all cancers, result from multiple mutations that lead to abnormalities in the expression or function of gene products that affect the delicate balance between proliferation, differentiation, and apoptosis. Leukemias are characterized by acquisition of recurring genetic aberrations and chromosomal translocations [2]. Important insights into the pathogenesis of this disease have been obtained by cloning translocation breakpoints. Chromosomal aberrations identified in acute myeloid leukemias

* Corresponding author. Fax: +1 310 206 8089.
E-mail addresses: kms@ucla.edu, ksakamoto@mednet.ucla.edu (K.M. Sakamoto).

1096-7192/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.ymgme.2006.03.011

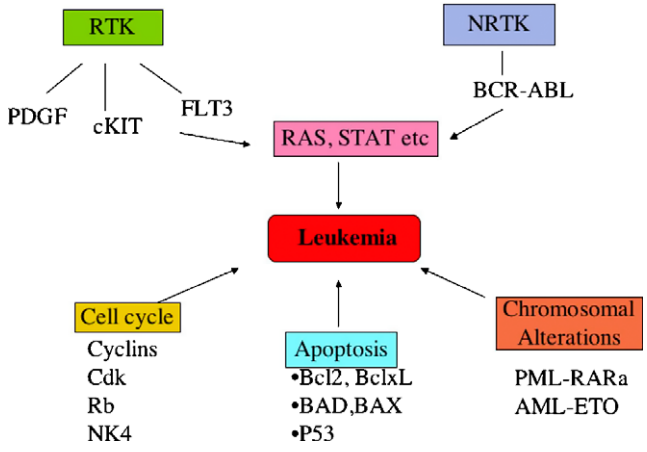

Fig. 1. Molecular targets for treatment of acute leukemias. Schematic representation of targets for small molecule inhibitors in leukemia. RTK: receptor tyrosine kinases, NRTK: non-receptor tyrosine kinases.

include loss of function mutations in transcription factors that are required for normal hematopoietic development. However, these mutations are often not sufficient to cause leukemia and appear to be one hit in the multistep pathway. Amplification is another mechanism whereby cancer, especially leukemia, develops [3,4]. Recent studies indicate that activating mutations that confer proliferative and survival signals to the progenitor cells cooperate with loss of function mutations in the transcription factors that lead to uncontrolled proliferation and impaired differentiation [5]. One example is the presence of mutations in hematopoietic tyrosine kinases such as c-KIT, FLT-3, and signaling molecules including N-RAS and K-RAS.

Understanding the genes that are involved in the pathogenesis of leukemias has paved the way for new treatment modalities that target specific gene products implicated in cancer. Targeted therapies for hematological malignancies have come to the forefront of treatment options for leukemia patients. The classic examples are All Trans Retinoic Acid (ATRA) for treating acute promyelocytic leukemia (APL) and Imatinib Mesylate (Gleevec) that targets the BCR-ABL oncogene in CML [6–8]. In this review, we will discuss the various types of molecular mechanisms involved in leukemias that are targets for small molecule inhibitors (Fig. 1).

Chromosomal translocations

A number of chromosomal translocations have been described for AML and MDS [9]. These translocations result in the fusion of genes that result in a new gene product that have abnormal functions and in addition have the capacity to inhibit the wildtype gene product. Interestingly most translocations described in AML involve transcription factors and the transcriptional machinery [10] (Table 1). Translocations can be broadly grouped into Hox family members, ETS family members, Core binding factors, and other transcriptional regulatory proteins. Chromosomal rearrangements result in abnormal proliferation, lack of differentiation, and disruption of apoptosis thereby giving the leukemia cells an advantage

Table 1
Chromosomal translocations in acute myeloid leukemia

Translocation	Fusion gene	Reference
t(3;21)(q26;q22)	AML1/MDS1/EVI1	[79]
t(8;21)(q22;q22)	AML1/ETO	[80]
t(16;21)(q24;q22)	AML1/MTG16	[80]
Inv 16(p11;q22)	CBFβ/MYH11	[81]
t(2:11)(9q31;p15)	NUP98/HOXD13	[82]
t(7;11)(p15;p15)	NUP98/HOXA9	[83]
t(3;12)(q26;p13)	TEL/MDS1/EVI1	[84]
t(5;12)(q33;p13)	TEL/PDGFRβ	[85]
t(15;17)(q22;q21)	PML/RARα	[86]
t(11;17)(q13;q21)	PLZF/RARα	[11]
t(5;17)(q35;q21)	NPM/RARα	[87]
Int del 17(q11;q21)	Stat5b/RARα	[88]
t(4;11)(q21;q23)	MLL/AF4	[89]
t(9;11)(p22;p23)	MLL-AF9	[90]
t(11;16)(q23;q13.3)	MLL/CBP	[91]
t(11;20)(p15;q11)	NUP98/TOP1	[92]
Inv11(p15;q22)	NUP98/DDX10	[93]
t(8;16)	MOZ/CBP	[94]

to expand abnormally [9,10]. Many of these translocations have been the primary focus for the development of targeted therapies. The most common translocations in APL is the fusion of the retinoic acid receptor-α chain to the PML gene (PML-RARα) or to the promyelocytic leukemia zinc finger protein (PLZF/RARα) [11]. The use of the retinoic acid receptor ligand, ATRA, for differentiation therapy is a classic example for targeted therapy. Overall survival of up to 80% had been achieved in APL patients treated with ATRA with minimal complications, including significant bleeding [12,13]. In the PML-RARα cells ATRA induces the dissociation of the nuclear co-repressors and restores the transactivation potential and promotes differentiation of the cells Fig. 2. Transgenic mice specifically expressing the PML-RARα protein in the myeloid cells develop APL. These mice respond to treatment with ATRA [14]. The PLZF-RARα on the other

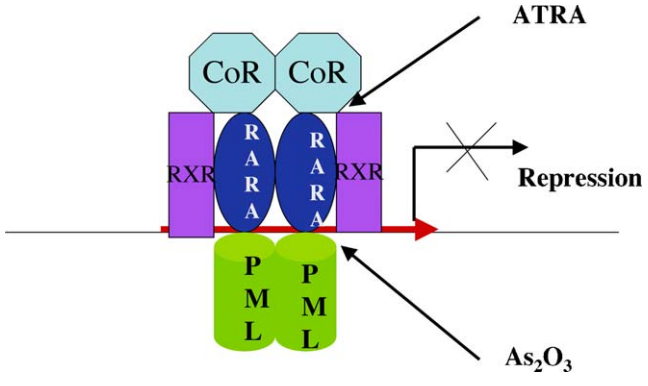

Fig. 2. Transcriptional Repression by PML-RARα in APL and effect of ATRA and Arsenic Trioxide. In the absence of Retinoic acid (RA), RARα and RXR heterodimers recruit corepressors (CoR), which mediates transcriptional repression. In the presence of RA, the CoR is released leading to transcriptional activation. In APL, the PML-RARα fusion protein binds to the RARα target genes and recruits CORs, leading to transcriptional repression and inhibition of myeloid differentiation. ATRA acts on the RARα and releases the CoR resulting in transcriptional activation and induction of differentiation. Arsenic trioxide acts on PML and causes partial differentiation of APL cells and apoptosis.