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Targeting Novel Signaling Pathways for Resistant Acute Myeloid Leukemia

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Abstract

Acute myeloid leukemia (AML) is a hematologic malignancy that is the most common type of acute leukemia diagnosed in adults and the second most common type in children. The overall survival is poor and treatment is associated with significant complications and even death. In addition, a significant number of patients will not respond to therapy or relapse. In this review, several new signaling proteins aberrantly regulated in AML are described, including CREB, Triad1, Bcl-2 family members, Stat3, and mTOR/MEK. Identifying more effective and less toxic agents will provide novel approaches to treat AML.

Keywords

acute myeloid leukemia; signaling pathways; novel therapies; resistance

Introduction

Acute Myeloid Leukemia (AML) is a hematologic malignancy that originates in hematopoietic stem and myeloid progenitor cells (1-3). AML is the most common type of

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acute leukemia diagnosed in adults and the second most common leukemia in children. Despite intensive chemotherapy and stem cell transplantation, the overall survival is less than 30% for adults and 60% for children (3). In addition, the treatment for AML results in significant morbidity and late effects, including secondary malignancies or graft vs. host disease after stem cell transplant. The major challenge in finding a cure for AML is the development of resistant disease and subsequent relapse. Current advances in technology include genomic sequencing, epigenetic and phenotypic characterization, and identification of novel signaling pathways. Current efforts in improving AML therapy focus on inhibiting proteins that promote drug resistance and survival of AML initiating cells. Here, we review select signaling molecules and pathways including CREB, Triad1, Bcl-2 family members, Stat3, and mTOR/MEK that are aberrantly regulated in AML and potential targets for therapy in patients with resistant disease.

CREB

Cyclic AMP Response Element Binding Protein (CREB) is a leucine zipper transcription factor that is critical for cell proliferation, survival and differentiation (4). CREB can act as an activator or repressor to regulate genes that control cell cycle, metabolism, and apoptosis in diverse cell types (5, 6). CREB-dependent signaling is important for gluconeogenesis, memory, neuronal plasticity, and hippocampal development. Upstream kinases that activate CREB include MAP kinase, RSK, adenylate cyclase, and CAMKIV (4, 7). A critical phosphorylation site in CREB identified in leukemia cells is serine 133, through MAP kinase/RSK activation (4-6). CREB phosphorylation leads to interaction with the histone acetyltransferase, CREB Binding Protein (CBP) and induction of specific CREB target genes (5, 6).

CREB is overexpressed in acute leukemia cells from the majority of patients with both AML and acute lymphocytic leukemia (8, 9). The expression of CREB was identified primarily at the protein level but in certain AML samples, also at the mRNA level (10, 11). Expression of CREB protein in leukemia cells from AML patients was associated with decreased event-free survival and increased risk of relapse (5). Overexpression of CREB in AML cell lines resulted in increased cell proliferation and growth in the absence of cytokines (5). Lentiviral transduction of CREB in primary hematopoietic cells results in increased myeloid progenitors and colony formation (5). Transgenic mice expressing CREB in myeloid progenitors leads to a myeloproliferative syndrome after approximately 1 year, but not AML, suggesting additional cooperating oncogenes required for full transformation (5). Retroviral insertional mutagenesis led to the finding that the proto-oncogene Sox4 cooperates with CREB towards leukemogenesis (12). In addition, Sox4 and CREB are both highly expressed in AML cells from a significant number of patients with the disease (12).

Another interesting mechanism of CREB regulation is by microRNA34b (miR34b) (13, 14). In AML cells, the promoter of miR34b is highly methylated leading to increased AML cell proliferation. Mir34b is a negative regulator of CREB expression and binds directly to the 3’ UTR of CREB mRNA. Mir34b is upregulated in cells from patients with JMML and MPN/MDS, but downregulated in AML cells. These data suggest that CREB is critical for full transformation to AML (13).

Since CREB is overexpressed in leukemia cells from the majority of AML patients and is associated with a worse prognosis, CREB might be a potential target for therapy. Knockdown of CREB using shRNA lentiviral constructs significantly inhibited the growth of AML cells (15, 16). This appears to be in part due to inhibition of expression of cell cycle genes, such as cyclins A and D. Furthermore, *in vivo* knockdown of CREB in an aggressive model of BCR/ABL-driven leukemia resulted in a statistically significant increase in median survival (16). Transduction of CREB shRNA in normal hematopoietic stem cells did not affect long-term engraftment, although there were transient effects on short-term engraftment and myelopoiesis (16). Therefore, CREB is critical for AML cells but is not required for normal hematopoietic stem cell activity. Taken together, these results suggest that CREB and CREB-dependent pathways are potential avenues for drug development for treatment of AML. Small molecule inhibitors of CREB are currently under development (17).

Triad1

The *ARIH2* gene encodes Triad1; an E3 ubiquitin ligase that is expressed in bone marrow progenitor cells and increases in expression during granulopoiesis (18). Interaction of Triad1 with Ubc7 or Ubc13 (E2 ligases) results in K48 or K63 linked ubiquitin chains, respectively (19, 20). K48-linked chains lead to proteasomal or lysosomal degradation, and K63 only the latter. Consistent with this, Triad1 participates in lysosomal degradation of EGF-R and GH-R in epithelial cells, but may also facilitate proteasomal degradation of Mdm2 in multiple cell types (21, 22). Therefore, Triad1-inhibition results in recycling and sustained signaling by these growth factor receptors, and enhances degradation of Mdm2 substrates such as p53. Furthermore, Triad1 inhibits Mdm2 and Mdm2 degrades p53. Increased Triad1 stabilizes p53 by impairing Mdm2 activity, which is anti-oncogenic. Inhibition of Triad1 stabilizes Mdm2 resulting in increased p53 degradation, which would facilitate cell survival along with stabilization of growth factor receptors. Triad1 also associates with cullin proteins (23). The significance of this interaction is unknown, but suggests that Triad1 may broadly effect protein-ubiquitination by regulating cullin ligases.

A number of laboratories found that engineered overexpression of Triad1 in bone marrow progenitor cells decreases colony formation and impairs cytokine stimulated proliferation (18, 21, 24). The mechanism for this is unknown and no hematopoietic specific Triad1 substrates have been identified. Disruption of the *ARIH2* gene in mice is embryonic lethal due to hepatocyte apoptosis at ~E16 (25). Despite this, E16 fetal liver-hematopoietic cells are normal in colony forming assays and repopulate hematopoiesis in irradiated wild type mice (25). However, recipients of Triad1$^{-/-}$ hematopoietic cells die rapidly of an inflammatory process that involves dendritic cell activation (25).

Clinical correlative studies suggest that Triad1 may function as a leukemia suppressor. For example, *ARIH2* is located on chromosome 3p21 and deletion of this region is reported in AML and blast crisis CML (26-28). And, examination of publically available databases defines a specific decrease in Triad1 mRNA in AML with chromosomal translocations involving the *MLL1*- gene (11q23-AML), *MYST4/CREBB* gene translocation, and *FLT3* internal tandem duplication (ITD) (29). The first two are associated with increased

expression of a set of homeodomain transcription factors that includes HoxB4, B4, A7-11 and Meis1 (30, 31). And, incidence of *ITD-FLT3* mutation is increased in Hox-overexpressing-AML (29). Additionally, a set of twins were reported both of whom had the same *MLL1*-gene translocation, but leukemia only developed in the twin who also had a deletion of 3p21 (28).

Functional studies of bone marrow progenitor cells also support a role for Triad1 as a leukemia suppressor. HoxA10 activates *ARIH2* gene transcription during myelopoiesis in a tyrosine phosphorylation dependent manner (24). HoxA10 is a substrate for Shp2 protein tyrosine phosphatase, and HoxA10-induced Triad1 expression is blocked by constitutive activation of Shp2 (24,32-35). Engineered overexpression of HoxA10 in bone marrow progenitor cells increases cytokine induced proliferation *in vitro*, and results in a myeloproliferative neoplasm with neutrophilia *in vivo* (35-38). However, effects of HoxA10-overexpression are paradoxically antagonized by the increase in Triad1 expression that is observed in these cells (24). This suggests the possibility that Triad1 antagonizes generally pro-proliferative effects of Hox proteins via ubiquitin-mediated degradation of proteins that are involved in hematopoietic stem and progenitor cell expansion.

The myeloproliferative neoplasm that develops in mice with HoxA10-overexpressing bone marrow progresses to AML with time (35, 36). This latency suggests that additional mutations are required for induction of AML. Such mutations may include events that silence leukemia suppressors, such as Triad1. Perhaps in support of this hypothesis, AML develops rapidly in mice transplanted with bone marrow that is co-overexpressing HoxA10 plus a constitutively active form of Shp2 (35). Both Shp2 activation and increased *HOX* expression are associated with *FLT3* internal tandem duplication in human AML (19, 39, 40).

ITD-FLT3 mutation and increased *HOX* expression are associated with drug resistance and poor outcomes in AML Defining relevant substrates for Triad1 in leukemic progenitor cells may suggest novel molecular therapeutic targets to address this problem.

Targeting MLL leukemias with BH3-mimetics and survival signaling inhibitors

Rearrangements of the mixed lineage leukemia (*MLL*) gene on chromosome 11q23 occurs in up to 10% of acute myelogenous leukemia (AML), and is generally associated with a relatively unfavorable prognosis (41). Consequently, this AML sub-type may represent a prototype of intrinsically resistant AML. The *MLL* rearrangement is associated with multiple translocation partners, most frequently *AF9* in AML (42), which result in a variety of genetic and epigenetic aberrations culminating in increased cell survival (43). Over the last decade, rational and highly specific therapeutic strategies targeting MLL leukemias have focused on disrupting *MLL* fusion partners and enzymes implicated in leukemogenesis. These targets have included menin, the histone methyltransferase DOT1L, the transcriptional elongation factor p-TEFb, and bromodomain proteins (e.g. BRD4), among others (42).

Resistance to therapy of AML in general, and *MLL* leukemias in particular, may also stem from aberrant expression of Bcl-2 family proteins (44). This consideration has prompted interest in BH3-mimetics, such as the Bcl-2/Bcl-xL antagonist ABT-737 and the Bcl-2-selective antagonist ABT-199 as therapeutic candidates in AML (45, 46). BH3-mimetics mimic the actions of BH3-only pro-apoptotic proteins such as Bim and effectively neutralize the pro-survival functions of anti-apoptotic multi-domain Bcl-2 family members. Past efforts have highlighted the value of BH3-profiling in predicting whether a particular tumor type may or may not be susceptible to such BH3-mimetics (47). Interestingly, *MLL* leukemias have very recently been shown to be extremely sensitive to ABT-199, suggesting that these cells are highly dependent upon Bcl-2 functions for their survival (48).

While the use of such BH3-mimetics in combination with standard chemotherapy to overcome resistance in *MLL* or other forms of AML represents a logical strategy, an alternative approach involves disrupting survival signaling pathways, including the MAPK and PI3K/AKT/mTOR pathways, with the goal of further enhancing BH3-mimetic anti-leukemic potency. For example, activation of the MEK1/2/ERK1/2 pathway regulates the abundance of the pro-apoptotic molecule Bim by phosphorylating it and promoting its proteasomal degradation (49). Indeed, MEK1/2 inhibitors have been shown to interact synergistically with ABT-737 in AML cells, in part by diminishing the expression of the anti-apoptotic protein Mcl-1 (50). Similarly, activity of the PI3K/AKT/mTOR pathway is known to be important for AML cell survival (51) as well as maintenance of expression of Mcl-1 through a GSK-dependent pathway (52). Notably, PI3K inhibitors have recently been reported to increase the anti-leukemic activity of ABT-737 in diverse AML cell types, including those exhibiting *MLL* rearrangements (e.g. MV4-11) (53). Given the intrinsic sensitivity of *MLL* leukemias to BH3-mimetics, such dual targeting may be highly appropriate in this setting. Collectively, these findings raise the possibility that in addition to targeting proteins directly implicated in *MLL*-related leukemogenesis (e.g. menin, DOT1L etc.), a strategy combining clinically relevant BH3-mimetics with PI3K or MEK1/2 inhibitors could prove to be particularly effective against this intrinsically resistant form of AML.

Targeting MAPK and mTOR pathways in AML

Recent studies have shown that AML relapse is associated with the gain of additional mutations and clonal evolution, due to the cytotoxic chemotherapy that patients receive and survival of preleukemic clones (54-57). Thus, the need for novel and effective therapies for AML remains a high clinical priority. This is particularly true for selective targeted therapeutic approaches that can be combined with chemotherapy.

Several mutations lead to constitutive activation of signals that promote expansion and survival of the leukemic clones (58, 59). Among them, the mitogen-activated protein kinase (MAPK) and mammalian target of rapamycin (mTOR) pathways play prominent roles (60-63). MAPK pathways include at least four major signaling cascades: extracellular signal-related kinases (ERK) 1 and 2, c-JUN N-terminal kinase (JNK) 1, 2, and 3, p38 MAPK, and ERK5 (63). Extensive studies from many groups have shown that molecular or pharmacological targeting of MAPK signaling cascades, alone or in combination with other

drugs, results in enhanced anti-leukemic responses in AML (64, 65). Work from our laboratory has shown that the downstream effector of MAPK pathways, Mnk kinases, may be attractive targets for the treatment of AML (66, 67). Specifically molecular or pharmacological targeting of Mnk kinases promotes anti-leukemic responses in pre-clinical AML models (66, 67).

mTOR can form two distinct multiprotein complexes: mTOR complex 1 (mTORC1) and 2 (mTORC2) (60, 61). Although the complexes include mTOR as their central common element, they have different purposes and functions (60, 61). Activation of mTORC1 complexes controls mRNA translation of oncogenic proteins, cell cycle progression, autophagy, and cellular growth and metabolism (60, 61), while mTORC2 complexes regulate cellular metabolism, and promotes malignant cell survival (60, 61). Inhibition of mTORC1 pathways using rapamycin or other rapalogs alone or in combination with other anti-leukemic agents, including chemotherapeutic regimens, have shown potent anti-leukemic properties *in vitro* and *in vivo* (reviewed in 68). Recent studies have also raised the possibility that catalytic mTOR inhibitors alone or in combination with other chemotherapeutic agents may induce more potent anti-leukemic effects than single- or combined-rapamycin treatment (69-71). This is important as such agents inhibit both mTORC1 and mTORC2 complexes and, potentially, other mTOR complexes that may exist but have not been yet identified. Other studies have also described potent anti-leukemic properties of dual PI3K-mTORC1/2 inhibitors, such as NVP-BGT226 (72) and NVP-BEZ235 (73), in AML.

One approach that may result in more potent anti-leukemic effects includes co-targeting negative feedback regulatory cascades that may be activated during AML treatment of cells with chemotherapy, or selective targeted therapy (67, 68, 75). The combination of MAPK signaling inhibitors and mTORC1/2 inhibitors is such an example (76-78). In fact, the combination of the catalytic mTOR inhibitor AZD8055 with the MEK inhibitor selumetinib was shown to exert synergistic proapoptotic effects in AML cells (78). Altogether, there is accumulating evidence supporting the development of future clinical trials combining such agents for the treatment of AML.

Targeting STAT3 in myeloid malignancies

Activation of JAK/STAT signaling is a hallmark of the myeloproliferative neoplasms (MPNs). Mutations in *JAK2*, *MPL*, and *CALR*, which account for the vast majority of MPN cases, all result in increased STAT activation and subsequent cytokine hypersensitivity or independence (79, 80). The identification of the V617F activating allele of *JAK2* in primary myelofibrosis (PMF) led to rapid clinical development of JAK inhibitors, with the hope that such drugs would be analogous to imatinib in CML. Unfortunately, despite providing important clinical benefits and a survival advantage (81, 82), the only FDA approved JAK inhibitor, ruxolitinib, does not cure PMF (83). In addition, recent studies have found that myelofibrosis cells develop JAK inhibitor resistance (84) as well as have an intrinsic resistance (85), which in both cases, allows for continued STAT3/5 phosphorylation.

Activating *JAK2* mutations are less commonly seen in other myeloid malignancies, with one large study reporting an incidence of 3% in de novo AML (86). Despite this low incidence of *JAK* mutations, an intriguing report demonstrated that STAT3 activation is common in de novo AML (87). Moreover, several studies have revealed that other oncogenic events can drive enhanced STAT phosphorylation. For example, the t(8;21) fusion has been shown to enhance the JAK/STAT pathway (88). FLT3 ITD also leads to enhanced JAK/STAT signaling (89). The knowledge that the JAK/STAT pathway is activated in many cases of AML, and data from pre-clinical studies that have shown an anti-tumor effect for JAK inhibitors (for example, see ref 88), have led to initiation of clinical trials of JAK inhibitors in AML. However, in a Phase 2 study, ruxolitinib only showed modest anti-leukemia activity as a single agent, with 3 significant responses in a study of 18 post-MPN AML patients (90).

Although there has been a focus on the upstream kinase JAK2 as a target for therapy, many studies suggest that directly targeting STAT3 may be effective. Indeed, several types of STAT inhibitors are under development as cancer therapies (91). For example, the small molecule STAT3 inhibitor C188-9 induced apoptosis in multiple AML cell lines and primary cells (92). A different STAT3 inhibitor, OPB-31121, inhibited STAT3 and STAT5 phosphorylation and had strong anti-growth effect on human leukemia cells, including those with FLT3-ITD or JAK2 V617F (93). Targeting STAT3 may also be key in treatment of chemotherapy resistant AML. A recent study revealed that feedback activation of STAT3 in cancer cells facilitated drug resistance in tumors with activation of a variety of kinases, including EGFR, MET and KRAS (94). Thus, combining STAT3 inhibitor with other targeted therapies or conventional chemotherapy may be effective in combating refractory and relapsed AML.

In conclusion, although advances have been made in the treatment of certain types of cancer due to development of targeted therapies, patients with AML continue to receive intensive chemotherapy and stem cell transplantation. These approaches result in significant toxicities and long-term complications. The primary challenge in finding a cure for AML, is the development of resistance following chemotherapy. The identification and characterization of signaling molecules discussed in this review provide potentially novel targets for drug development to treat AML patients in the future.

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Research Highlights

Standard treatment for AML is associated with significant toxicities and late effects.

Characterization of signaling pathways aberrantly regulated in AML cells could lead to identification of novel targets for therapy.

CREB is a transcription factor that is overexpressed in AML cells and is required for proliferation and survival, suggesting that inhibiting this protein is a novel approach to treat AML.

Triad1 is an E3 ubiquitin ligase and leukemia suppressor that is decreased in AML with MLL1 gene rearrangements, MYST4/CREBB gene translocations, and FLT3 internal tandem duplications.

BH3-mimetics in combination with chemotherapy overcomes resistance in AML cells.

Downstream effectors of MAPK pathways, Mnk kinases, may be attractive targets for treatment of AML.

Stat3 activation is common in newly diagnosed AML and small molecules to inhibit STAT3 induce apoptosis in AML cells.