From mRNA Metabolism to Cancer Therapy: Chronic Myelogenous Leukemia Shows the Way

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Abstract Altered mRNA metabolism is a feature of many cancers including blast crisis chronic myelogenous leukemia. Indeed, loss of function of many tumor suppressors regulating cell proliferation, survival, and differentiation results from aberrant mRNA processing, nuclear export, and/or translation. Here, we summarize the effects of increased BCR/ABL oncogenic activity on the expression and function of RNA binding proteins (e.g., FUS, hnRNP A1, hnRNP E2, hnRNP K, and La/SSB) with posttranscriptional and translational regulatory activities and their importance for the phenotype of BCR/ABL-transformed hematopoietic progenitors. We also provide evidence that these studies not only advance our understanding on the molecular mechanisms contributing to tumor/leukemia emergence, maintenance, and/or progression but they also serve for the identification of novel molecular targets useful for the development of alternative therapies for imatinib-resistant and blast crisis chronic myelogenous leukemia and, perhaps, for other cancers characterized by similar alterations in the mRNA metabolism.

Background

Chronic myelogenous leukemia and altered mRNA metabolism. Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder of the pluripotent hematopoietic stem cell clinically characterized by the accumulation of myeloid precursors in peripheral blood, bone marrow, and extramedullary sites. These cells retain the ability to differentiate but show enhanced survival and decreased susceptibility to drug-induced apoptosis. As a result, CML in its stable phase [chronic phase CML (CML-CP)] is clinically diagnosed from the marked neutrophilia. If untreated, CML progresses into the rapidly fatal blast crisis CML (CML-BC), which is characterized by enhanced proliferation, increased survival, genomic instability, and suppression of differentiation of myeloid or lymphoid progenitors (1, 2).

The Philadelphia chromosome (Ph1) translocation t(9;22)(q34;q11), the main feature and the sole cytogenetic alteration observed in CML-CP, carries the *BCR/ABL1* oncogene (2). Instead, additional molecular and chromosomal abnormalities are often detected in CML-BC, which frequently lead to inactivation of tumor suppressor genes (e.g., p53; ref. 2). Although the pathogenic effects of most CML-BC secondary changes are still poorly understood, the phenotype of CML-BC progenitors seems to depend on the cooperation of BCR/ABL with genes dysregulated during disease progression (2).

Expression of the p210 BCR/ABL oncoprotein is responsible for inducing and sustaining the leukemic phenotype through its deregulated tyrosine kinase activity. This is essential for recruitment and induction of signaling pathways leading to cytokine-independent proliferation, resistance to apoptosis, and impaired differentiation of BCR/ABL-expressing myeloid and lymphoid progenitors (2, 3). By contrast, the molecular mechanisms responsible for transition to CML-BC remain poorly understood, although a reasonable assumption is that the unrestrained activity of BCR/ABL in hematopoietic stem/progenitor cells is the primary determinant of disease progression. Indeed, BCR/ABL expression increases during disease progression (4–6). Thus, blastic transformation may arise as a consequence of the unrestrained activity of BCR/ABL and the inactivation of genes with tumor suppressor activity (2). In this scenario, the cytogenetic and molecular changes observed in CML-BC might also be caused by the reported ability of BCR/ABL oncoprotein to increase genomic instability (7, 8).

Altered mRNA metabolism seems to play a pivotal role in CML-BC because processing, export, and translation of specific mRNAs that control the survival and differentiation of myeloid progenitors are aberrantly regulated by increased BCR/ABL expression through the activity of specific mRNA binding proteins (refs. 9–14; Fig. 1). Furthermore, there is also evidence that BCR/ABL globally affects the efficiency of the basal mRNA translation machinery by regulating the mammalian target of rapamycin and S6 kinase pathways and the function of the translation factors eukaryotic translation initiation factor 4E and eukaryotic initiation factor 4E-binding protein 1 and (15, 16). In BCR/ABL-transformed cells, inhibition of BCR/ABL kinase activity by imatinib not only alters at the posttranslational level the activity of many signal transducers

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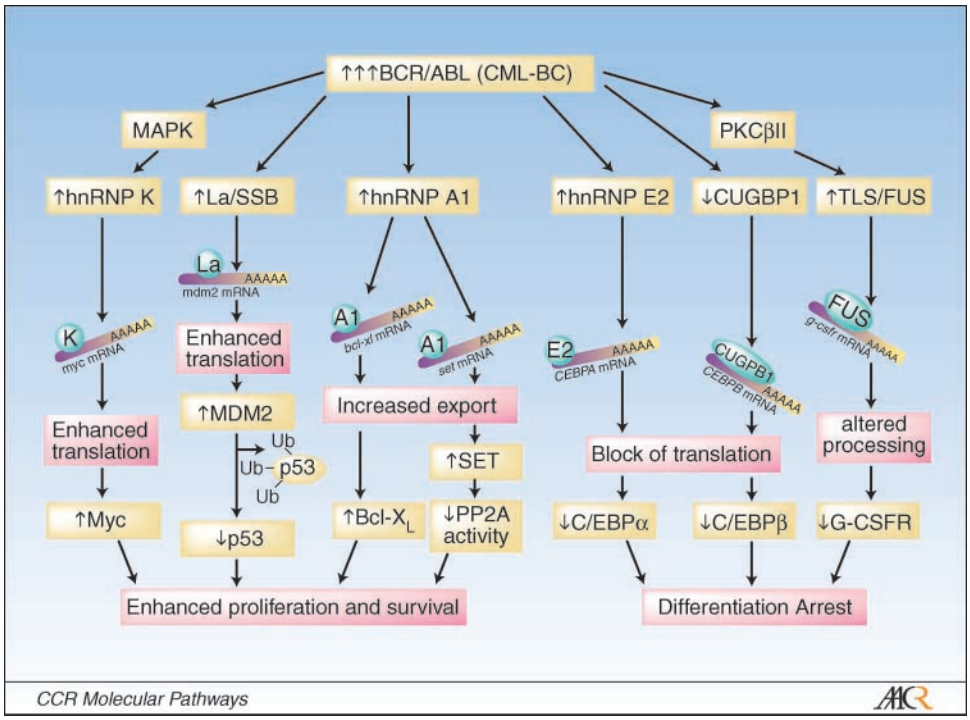

Fig. 1. Altered RNA binding protein expression in CML-BC. Schematic representation of the BCR/ABL-induced and RNA binding protein – mediated pathways affecting proliferation survival and differentiation of CML-BC progenitors. MAPK, mitogen-activated protein kinase; PKCβII, protein kinase CβII.

or induces changes in gene transcription but also modifies the polysome loading and, therefore, the translation rate of several mRNAs that encode proteins involved in the regulation of cell proliferation, survival, and differentiation (16).

RNA binding proteins: pathways to blastic transformation. RNA binding proteins play an essential role in RNA metabolism because they regulate the mRNA fate from the active site of transcription to that of translation (17). In fact, nuclear RNA binding proteins, involved in the regulation of transcription, interact with the nascent pre-mRNA when genes are actively transcribed by RNA polymerase II. Following synthesis, other RNA binding proteins prepare the pre-mRNA for cytoplasmic export, which requires the activity of ribonucleoprotein capable of nucleocytoplasmic shuttling. In this initial journey, the mRNA becomes 5′-capped and polyadenylated and undergoes splicing. Once exported into the cytoplasm, the mature mRNA is transported to the translational machinery where, on association with ribosomes, it is decoded and used several times as a template for protein synthesis. During the entire process, the mRNA is not naked but different RNA binding proteins take turn and bind to regulatory elements or are involved in the maintenance of a specific mRNA secondary structure (17). Thus, whereas some RNA binding proteins are general regulators of mRNA transcription, processing, nuclear export, stability, and translation, others bind mRNA in a sequence-specific manner and determine whether and how a specific mRNA will end its journey (18, 19). It is conceivable that altered expression of this category of RNA binding proteins has a profound effect on cell cycle progression, survival, and differentiation. Indeed, enhanced expression of various RNA binding proteins that bind mRNA in a sequence-specific manner is among the changes in gene expression found in primary mononuclear marrow cells from CML-BC patients and in BCR/ABL-transformed murine myeloid progenitors. Enhanced expression of specific RNA binding proteins correlates with the levels of BCR/ABL and is sensitive to treatment with the Abl kinase inhibitor imatinib mesylate (16, 20). Different molecular mechanisms are responsible for such an increase and may involve the activation of a cascade of phosphorylation events leading to either enhanced gene transcription [e.g., heterogeneous nuclear ribonucleoprotein K (HNRPK)] or increased protein stability (e.g., TLS/FUS, hnRNP A1, hnRNP E2, and La/SSB; refs. 10–14, 21). Increased expression of these RNA binding proteins correlates with enhanced activity, which may be regulated by different BCR/ABL-activated pathways (e.g., phosphatidylinositol 3-kinase/Akt, extracellular signal–regulated kinases, and protein kinase C). Conversely, expression of the RNA binding protein CUGBP1 inversely correlates with BCR/ABL activity and diminishes in CML-BC compared with CML-CP and normal bone marrow progenitors (9).

HNRPK and MYC. In BCR/ABL-expressing myeloid and lymphoid cell lines and in primary CML-BC but not CML-CP progenitor cells, *HNRPK* transcription and mRNA stability are enhanced by mitogen-activated protein kinase/extracellular signal–regulated kinase 1/2 ($MARK^{ERK1/2}$) in a BCR/ABL dose-dependent manner (11). Expression of HNRPK is required for BCR/ABL leukemogenesis; in fact, HNRPK down-modulation impairs cytokine-independent clonogenicity and leukemogenesis of BCR/ABL^{+} cells (11). These effects mostly depend on decreased levels of MYC, an oncogene essential for BCR/ABL leukemogenesis (22) and whose expression is transcriptionally and translationally controlled by HNRPK (23, 24). Whereas HNRPK transcriptional regulation is dispensable for BCR/ABL oncogenic potential, its mitogen-activated protein kinase–dependent translational-regulatory activity is required *in vitro* and *in vivo* for BCR/ABL leukemogenic potential (11). In fact, HNRPK binds to the internal ribosome entry site element of *MYC* mRNA and enhances its translation in a

BCR/ABL- and mitogen-activated protein kinase–dependent manner (11). This data is consistent with MYC protein but not mRNA overexpression detected in most of CML-BC progenitors (11, 25).

La/SSB and MDM2. The RNA binding protein La/SSB controls RNA metabolism at different levels: it binds and protects newly RNA polymerase III–transcribed RNAs, regulates the processing of 5′ and 3′ ends of pre-tRNA precursors, functions as RNA chaperone, and controls translation of specific mRNAs (26). Expression of La is markedly increased by BCR/ABL and correlated with that of MDM2 (14). La is more abundant in CML-BC than CML-CP patient cells and its levels seem to correlate with BCR/ABL levels and activity (14). Interestingly, La is a bona fide positive regulator of *mdm2* translation because (*a*) it recognizes a specific conserved sequence in the intercistronic region of *mdm2* mRNA that is required for efficient MDM2 expression; (*b*) a dominant-negative La inhibits *mdm2* mRNA translation in BCR/ABL$^+$ cells; (*c*) La down-regulation leads to a marked decrease in MDM2 levels; and (*d*) overexpression of wild-type La increases MDM2 expression (14). That La-mediated effect on MDM2 expression is functionally relevant for BCR/ABL leukemogenesis is indicated by the changes in susceptibility of BCR/ABL-expressing cells to p53-dependent drug-induced apoptosis (14). Inactivating mutations of the *p53* gene are rarely found in CML-CP but are relatively common in CML-BC (27), suggesting that loss of function of p53 plays an important role in disease progression. Indeed, loss of wild-type p53 potentiates the leukemia-inducing effects of BCR/ABL (28, 29). Because genetic inactivation of p53 is detected in ~25% of CML-BC patients (27), the La-dependent MDM2 overexpression may represent a mechanism whereby BCR/ABL functionally inactivates p53 in CML-BC patients with a wild-type *p53* gene. Thus, the La-dependent stimulation of MDM2 translation is not only relevant for survival of CML-BC progenitors but may also contribute to disease progression through functional inactivation of the p53 tumor suppressor.

hnRNP E2 and CCAAT/enhancer binding protein α. The main feature of CML-BC is the inability of myeloid progenitors to undergo terminal differentiation. This is primarily dependent on inhibition of CCAAT/enhancer binding protein α (C/EBPα; ref. 13), a transcription factor essential for granulocytic differentiation (30). In BCR/ABL-expressing myeloid progenitor cells, loss of C/EBPα depends on the BCR/ABL-induced activity of the RNA binding protein hnRNP E2, a poly(rC)-binding protein that, like hnRNP K, controls the translation of specific mRNAs (20, 31). In fact, hnRNP E2, on interaction with the 5′ untranslated region of *CEBPA* mRNA, inhibits *CEBPA* translation (13). As a result, C/EBPα protein but not mRNA expression is down-modulated in primary bone marrow cells from CML-BC patients and inversely correlates with BCR/ABL levels (13). Accordingly, hnRNP E2 expression inversely correlated with that of C/EBPα (32) because hnRNP E2 levels were abundant in CML-BC but undetectable in CML-CP mononuclear marrow cells. The importance of loss of C/EBPα as a central mechanism leading to differentiation arrest of CML myeloid blasts is supported by reports that (*a*) ectopic C/EBPα expression induces maturation of differentiation-arrested BCR/ABL-expressing myeloid precursors (13); (*b*) a blast crisis–like process emerges in mice transplanted with BCR/ABL-transduced *c/ebpα*-null but not heterozygous or wild-type fetal liver cells (33); and (*c*) genetic or functional inactivation of C/EBPα is a common event in differentiation-arrested acute myeloid leukemia blasts (34).

CUGBP1 and C/EBPβ. C/EBPβ is another transcription regulator that controls myeloid maturation and a functional equivalent of C/EBPα based on its ability to restore granulocytic differentiation in C/EBPα-null mice (35). In BCR/ABL-expressing cells, imatinib treatment shifts c/ebpβ mRNA onto polysomes. The effect of imatinib is mediated by the activity of the RNA binding protein CUGBP1 that binds a CUG-repeat region located between the first and the third AUG of c/ebpβ mRNA and enhances its translation (9, 36). Like C/EBPα, expression of C/EBPβ is repressed in primary CML-BC progenitors (9), suggesting that loss of C/EBPα and C/EBPβ activity contributes to differentiation arrest and aggressive behavior of CML-BC cells. Accordingly, levels of CUGBP1 are higher in normal and CML-CP CD34$^+$ cells than in CD34$^+$ CML-BC progenitors (9). Ectopic expression or inducible activation of C/EBPβ inhibits proliferation and promotes granulocytic maturation of differentiation-arrested BCR/ABL$^+$ cells through a mechanism that depends on C/EBPβ transcriptional activity (9). Thus, complete loss of C/EBPs activity might be necessary to disrupt the differentiation potential of CML-BC progenitors.

FUS and the granulocyte colony-stimulating factor receptor. FUS, also known as TLS, is another nucleocytoplasmic shuttling hnRNP protein that contributes to block of differentiation of BCR/ABL$^+$ myeloid progenitors by altering the expression of cytokine receptors (12). FUS is expressed at high levels in hematopoietic and nonhematopoietic tissues and is involved in pre-mRNA processing and nucleocytoplasmic shuttling, as well as in the regulation of basal transcription. FUS expression and DNA binding activity are induced by BCR/ABL in hematopoietic cells (12) through a protein kinase CβII–mediated mechanism that, by increasing FUS protein stability, prevents FUS proteasome degradation (21). Knockdown of FUS expression in differentiation-arrested BCR/ABL$^+$ myeloid cells rescues, in part, granulocytic differentiation by restoring expression of the C/EBPα-regulated granulocyte colony-stimulating factor receptor (G-CSFR) and modestly impairs tumorigenesis (12). By contrast, ectopic FUS expression delays G-CSFR up-regulation induced by G-CSF treatment (12). Because FUS binds *in vitro* to a segment of *G-CSFR* mRNA (12), these data suggest that FUS binds to the *G-CSFR* pre-mRNA in the nucleus and interferes with its processing or export to the cytoplasm.

hnRNP A1 and the SET/protein phosphatase 2A interplay. hnRNP A1 is a nucleocytoplasmic shuttling protein that binds the nascent pre-mRNA in a sequence-specific manner and regulates splice site selection, exon skipping or inclusion, nuclear export of mature mRNA, mRNA turnover, and translation (37). As a consequence of enhanced protein stability, hnRNP A1 expression is induced by p210 BCR/ABL in a dose- and kinase-dependent manner (10, 32). In fact, hnRNP A1 levels are higher in CML-BC than CML-CP progenitors (10, 32). The use of a nucleus-localized dominant negative mutant hnRNP A1 deficient in shuttling activity indicates that the mRNA export activity of hnRNP A1 is required for cytokine-independent proliferation, survival, and tumorigenesis of acute phase CML blasts and BCR/ABL-expressing myeloid progenitor

cell lines (10). Thus, hnRNP A1 controls the nuclear export of mRNAs encoding factors important for the leukemic phenotype of CML-BC progenitors. Indeed, the antiapoptotic factor BCL-X_L and SET, the physiologic inhibitor of protein phosphatase 2A (PP2A), are among the cytoplasmic mRNAs whose export and translation are a consequence of hnRNP A1 shuttling activity (10, 32). SET expression is induced by high BCR/ABL activity and increases during CML disease progression (32). Interestingly, enhanced SET levels lead to inactivation of the tumor suppressor PP2A in CML-BC $CD34^+$ progenitors (32). In these cells, PP2A loss-of-function accounts for increased and sustained BCR/ABL activity in CML-BC progenitors (32). In fact, molecular or pharmacologic reactivation of PP2A phosphatase activity inhibits BCR/ABL activity and triggers BCR/ABL proteasome degradation through a mechanism that requires the activity of the SHP1 tyrosine phosphatase (32). As a result of rescue of PP2A activity, imatinib-sensitive and imatinib-resistant (T315I included) BCR/ABL^+ lines and CML-BC patient cells cease to proliferate and undergo apoptosis (32). Furthermore, impaired clonogenicity of CML-BC patient cells and decreased *in vivo* BCR/ABL-driven leukemogenesis are observed on treatment with PP2A-activating drugs (e.g., forskolin, 1,9-dideoxy forskolin, and FTY720) used at pharmacologic doses that do not exert toxic effect in rodents and/or humans (32).[1] Interestingly, SET-dependent inactivation of PP2A may also occur through the activity of another ribonucleoprotein, hnRNP A2. In fact, hnRNP A2 cooperates with SET in the inhibition of PP2A (38). In agreement, we found hnRNP A2/B1 overexpressed in human $CD34^+$ progenitors ectopically expressing p210 BCR/ABL,[2] suggesting the possible involvement of hnRNP A2/B1 in blastic transformation of CML.

Clinical-Translational Advances

Increased BCR/ABL activity, as observed in CML-BC, induces pathways that drive myeloid progenitors toward a phenotype typical of the acute leukemia blasts. A likely mechanism involves the control of mRNA metabolism via the altered expression and/or function of specific RNA binding proteins. Here, we gave a few important examples of how an oncogenic protein (i.e., BCR/ABL) controls at posttranscriptional level the expression of factors essential for the establishment and/or maintenance of a phenotype (enhanced proliferation, increased survival, and arrested differentiation) characteristic of cancer cells (e.g., CML-BC; Fig. 1). Some of the changes in gene expression brought about by modulating the levels of translation-regulating proteins have a profound effect on the phenotype of BCR/ABL-transformed cells. For example, the block of differentiation associated with down-regulation of C/EBPα protein levels, the increased survival associated with MDM2-dependent inhibition of the p53 proapoptotic effects, and the loss of PP2A phosphatase activity, which allows BCR/ABL to increase and sustain high levels of tyrosine kinase activity, are essential features of the highly malignant cell clones of CML-BC. It seems likely that aberrant regulation of mRNA processing/export/translation in tumor cells is not limited to BCR/ABL leukemogenesis but involves other activated tyrosine kinases. It is also plausible that, in addition to mdm2, c/ebpα, c/ebpβ, SET, and MYC mRNA, there are many more targets for posttranscriptional/translational regulation, which may be identified by the isolation via ribonomics of specific mRNA subsets associated with the various RNA binding proteins whose expression/function is aberrant in tumor cells. An obvious question raised by the recent discoveries in the emerging field of altered mRNA metabolism in cancer is whether the interaction of RNA binding proteins with the 5′ and 3′ untranslated regions of specific mRNAs can provide targets for therapeutic intervention. For example, we may envision several strategies whereby disruption of the hnRNP E2/*CEBPα* mRNA 5′ untranslated region interaction may lead to activation of endogenous E2/CEBPα expression, which, in turn, may promote differentiation and/or suppress proliferation of tumor cells. Such strategies may take advantage of the rapidly growing field of nanotechnology for developing novel tools that, for example, directly target the RNA binding protein itself (antisense, RNA interference, and microRNAs) or the RNA binding protein/mRNA interaction (small molecules which may prevent or disrupt the interaction). Alternatively, we can envision therapies that affect the function of a specific RNA binding protein by targeting its upstream regulator or that directly rescue the expression and/or activity of a specific RNA binding protein target. For example, we have evidence that the differentiation inhibitory effects of hnRNP E2 are dependent on the BCR/ABL-induced mitogen-activated protein kinase phosphorylation of four different hnRNP E2 sites that control protein stability. For example, treatment with clinically relevant mitogen-activated protein kinase/extracellular signal–regulated kinase kinase-1 inhibitors restores granulocytic maturation of BCR/ABL-expressing myeloid progenitors through down-regulation of hnRNP E2 and restoration of C/EBPα expression.[3] In fact, the lack of long-term response of CML-BC patients to kinase inhibitor monotherapy (imatinib, nilotinib, or dasatinib; refs. 39–41) underscores the importance of therapies that target multiple oncogenic pathways. Thus, a "differentiation therapy" aimed at restoring C/EBPα expression and a BCR/ABL kinase inhibitor treatment might synergize and improve prognosis of CML-BC patients. Similarly, the discovery of the BCR/ABL-hnRNP A1-SET-PP2A interplay not only unravels the importance of the PP2A tumor suppressor in the biology of Ph1 leukemias but also strongly indicates the use of PP2A-activating drugs (42) as an alternative therapeutic approach for CML-BC and other cancers characterized by functional loss of PP2A activity. Indeed, PP2A activator monotherapy can efficiently suppress p210 and p190 BCR/ABL leukemogenesis in mouse models of imatinib/dasatinib-sensitive and imatinib/dasatinib-resistant CML-BC and Ph1(+) acute lymphoblastic leukemia (32).[1]

Based on the discoveries of the past few years, it is safe to predict that new observations will be made in the field of mRNA metabolism in cancer cells and that some of them will reveal new targets for therapeutic intervention.

[1] Neviani, et al., 2006, submitted for publication.
[2] Unpublished observation.
[3] Chang and Perrotti, 2006, submitted for publication.

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