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Mini Review

The roles of DNA epigenetics and clinical significance in Chronic Myeloid Leukemia: a review

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Abstract: Chronic Myeloid Leukemia (CML) is a myeloproliferative disorder characterized by the genetic translocation t(9;22) (q^{34};$q^{11.2}$) encoding for the *BCR-ABL* fusion oncogene. Growing body of evidence suggests that epigenetic abnormalities are involved in tyrosine kinase resistance in CML, leading to leukemic clone escape and disease propagation. The significant of therapeutic role in chronic myeloid leukemia (CML) depends on both genetic and epigenetic mechanisms. This article focused on the CML and epigenetic and clinical significance. An electronic search of peer-reviewed articles was systematically performed to obtain the relevant literature with the CINAHL, cancer, Google scholar, self-experience and PubMed databases. The keywords included leukemia, cancer, illness, epigenetic. The inclusion criteria for the reviews were that the documents were original quantitative research and published in English. Articles that were not directly relevant to the present objective were excluded. Current progress in molecular biology and bioinformatics offer novel promising experiments namely as next generation sequencing for new development in epigenetic figures characterization and more understanding of the epigenetic mechanisms to be successfully utilized for personalized CML therapy in the next coming years.

Key words: Epigenetics; CML; Cancer; Mechanisms; MiRNAs.

Introduction

Abnormal epigenetic error together with gene mutations and chromosomal aberration are involved in leukemias development and regulation.

MiRNAs are a family of short, noncoding RNAs that take part in the post-transcriptional regulation of gene expression. Their influence on the proteome and cellular events is extensive; it is estimated that miRNAs regulate around 60% of the transcriptome and play key roles in cellular processes like proliferation, differentiation, development, cell fate determination, and apoptosis (1). The human genome contains-2000 distinct mature miRNAs. It is known that the transcription of miRNA genes can be regulated by epigenetic factors or transcription factors. Recent studies indicate that Drosha-mediated pri-miRNA processing may be altered in cancer cells, which may explain the lack of correlation between pri-miRNA and mature miRNA expression levels (2) miRNA expression is in search process that reflects changes in the physiological situation on the cellular level.

The efficacy of therapeutic modalities in chronic myeloid leukemia (CML) depends on both genetic and epigenetic mechanisms. Settings event at the levels of gene regulation by transcription factors and microRNAs are discussed in the context of CML pathogenesis and therapeutic modalities.

DNA Methylation in CML

The methylation of CpG islands is an active enzymatic and transcription-inhibiting control mechanism that balances the levels of gene expression that is frequently dysregulated in hematological malignancies. large number of genes (mostly tumor suppressors) are inactivated by Deacetylation of CpG islands mainly in the promoter regions while some genes (such as oncogenes) are Acetylate.

Methylation of additional genes was later associated with progression of CML and potential resistance to TKI treatment. *TFAP2A* (transcription factor AP-2 alpha) and *EBF2* (early B-cell factor 2), were found to be more methylated in blast crisis (BC) compared to CP in the study of 55 CP CML and 8 BC CML samples (3) autophagy related 16-like 2 gene *ATG16L2* was methylated in 69 % of CML patients. Patients with methylated *ATG16L2* had a lower probability of achieving a major molecular response (MMR) at 12 or 18 months compa-

red with the unmethylated cases at baseline (3)

DNA Methylation Inhibitors (DNMTi) in CML

Several drugs, especially demethylating agents, targeting DNA methyl transferase1, are being utilized in AML and MDS (4) and are strongly considered also in CML. DNMTi are 5-azacitidine and 5-aza-2´-deoxycitidine (decitabine). Important factors are incorporated into both DNA and RNA during replication or transcription, respectively, and inhibit effects of DNA methyltransferase (DNMT) (5)

miRNAs regulated by BCR-ABL1 MiRNAs are thought to be significant to the molecular level and development of chronic myeloid leukemia and exhibit great potential as drug targets and biomarkers. Upregulates the expression of oncogenic miRNAs; for example, miR-17-92 cluster of oncomirs, which facilitate tumor progression and on the other hand it simultaneously downregulates the expression of tumor suppressor miRNAs like *miR-203* and *miR-328* thereby blocking differentiation of the myeloid cells. miR-17- 92, also known as 'oncomiR-1' polycistron is among the best-studied miRNA clusters.

As a result of Bcr-Abl kinase activity, a negative growth factor, *CCN3* is downregulated. CCN3 confers growth regulation in CML cells by causing growth inhibition and regaining sensitivity to the induction of apoptosis; this gene also shows a reciprocal relationship of expression with BCR-ABL1. *miR-130a*, *miR-130b*, *miR-148a*, *miR-212* and *miR-425-5p* were significantly reduced on BCR-ABL1 knockdown. *MiR-130a* has been implicated in platelet differentiation and is highly expressed in hematopoietic stem cells, while its expression reduces during differentiation and maturation. *miR-130b* downregulates the expression of tumor protein 53–induced nuclear protein 1 (*TP53INP1*), a key protein required for the induction of cell cycle arrest and apoptosis. *PI3K/AKT* signaling pathway has been shown to be modulated by BCR-ABL1, while *miR-21* targets different negative regulators of the PI3K/AKT pathway in different cell types.

miRNAs epigenetically modified in CML Methylated microRNAs show tissue-specific or tumor-specific pattern of methylation. Tumor suppressor miRNAs are expected to be hypomethylated in normal cells but hypermethylated in cancer cells. Epigenetic inactivation of *miR-129-2* and *miR-124-1* is particularly interesting in hematological malignancies. *miR-129-2* is a tumor suppressive microRNA frequently methylated in lymphoid but not myeloid malignancies. Loss of *miR-129* expression by *miR-129-2* methylation, leading to upregulation of oncogenes including cyclindependent kinase 6 (CDK6) has been shown in solid cancers. Recently, *miR-124-1* has been shown to be hypermethylated in multiple cancers. *MiR-203* is one of the most extensively studied microRNAs that can be epigenetically inactivated in CML. Recently, hypermethylation of *hsa-miR-203* has been reported in CML and hepatocellular carcinoma, conferring proliferative advantage in tumor cells.

Micro RNAs in CML

Based on bioinformatics predictions, it is expected that more than a half of gene products in the human genome may be regulated by microRNAs, with each microRNA capable of regulating hundreds of genes (6)

Important hallmarks of CML is a decreased expression of *miR-150* (in comparison to healthy individuals) in bone marrow-derived mononuclear cells (MNC) and CD34+ cells (7) and in MNC (8) and total leukocytes of PB (9) at CML diagnosis.

The amount of *miR-146a* was found to be significantly decreased at CML diagnosis (7-9). Was shown that *miR-146a* expression was normalized after imatinib treatment (8,9). Significantly decreased expression of *miR-10a* was reported in MNC and CD34+ cells in CML patients at diagnosis in comparison to healthy controls (7).

MiR-17-92 is a polycistronic cluster of six microRNAs with their increased expression levels in CD34+ cells of CML patients at diagnosis. The expression levels of pri-miR-17-92 were found increased in CD34+ cells at the CML diagnosis and blast crisis (10)

miR-451 expression level found in total leukocytes of PB at diagnosis. *miR-451* level may Its upside down with the BCR-ABL transcript level in some CML patients (11).

Function of miRNAs Regulated by BCR-ABL Two Essential groups of miRNAs may play a significant role in the CML pathogenesis: miRNAs that are downregulated by BCR-ABL and miRNAs that are upregulated by BCR-ABL. Several miRNAs are regulated by BCR-ABL in the Ph+ cell lines: Pri-miR-17-92 transcription is directly regulated by c- MYC and also by BCR-ABL (12). The inhibition of c- MYC using anti-c-MYC specific shRNA together with imatinib treatment induced the highest reduction in the amount of pri-miR-17-92 in K562 cells. *MiR-130a* is inductor by BCR-ABL in K562 cells .After the BCR-ABL silencing in K562, the levels of *miR-130a* and *miR-130b* significantly decreased. The expression of miR-150 significantly increased following the inhibition of the *BCR-ABL* activity by imatinib treatment in the Ph+ cell line MOLM7 (9). The *MYB* is a proved target gene of *miR-150* and represents a transcription factor for the proliferation and survival of normal and leukemic blasts.

the reduction of *miR-150* might contribute to the upregulation of c-MYB. Moreover, an observed significant inverse correlation of *miR-150* and *MYB* and with BCR-ABL expressions. and a significant correlation of MYB with the BCR-ABL transcript levels support the above mentioned conclusions (9)

The differentiation arrest in the myeloid blastic phase of CML depends on the BCR-ABL-MAPK induced activity of hnRNP E2. The induced activity of hnRNP E2 in CML blast crisis silences miR-328.the pro-apoptotic effect is arrested through the PIM1 overexpression. In association with the described BCR-ABL-MAPK-hnRNP E2-*miR-328* pathway, rediscovered a novel function for microRNA – a decoy activity hnRNP E2 suppresses the translation and synthesis of the transcription factor CCAAT/enhancer binding protein (C/EBP), alpha (CEBPA, that is essential for myeloid differentiation) through the C-rich element in 5'UTR mRNA of CEBPA.

The *MiR-328* interacts outside its "seed sequence" with hnRNP E2 with a higher affinity than between hnRNP E2 and mRNA CEBPA. The interaction between *miR-328* and hnRNP E2 enables the translation of CEBPA, thus a myeloid differentiation is induced.

miRNAs and MAPK signaling pathway in CML

It is well known that the MAPK pathway is an important downstream signaling cascade in several types of cancer MAPK signaling cascade is a highly conserved component and plays a central role in CML. In CML, auto-phosphorylation of tyrosine 177 on *BCR-ABL* fusion protein provides a docking site for the adapter molecule, growth factor receptor-bound protein 2 (GRB-2) (13).

Other two adapter molecules, Src homology 2 domain containing (SHC), and CRKL, can also activate RAS. Both acts as substrates for *BCR-ABL* (14,15). Activated RAS prompts the kinase activity of RAF. Activated RAF in turn initiates a signaling cascade through the serine–threonine kinases MEK1/MEK2 and ERK (MAPK), which eventually leads to the activation of gene transcription (16).

miRNAs may regulate the expression of proteins at different levels by binding with the complementary sequence of 3' untranslated region of the target mRNAs, thereby controlling the signal transduction processes (17). Several miRNAs play significant role in the MAPK signaling pathway and among them, the following *miR-203, miR-196b, miR-29b, miR-30a, miR-138, miR-155, miR-19a, miR-17, miR-126, miR-128, miR-221, miR-15a, miR-188-5p* and *miR-181a* (Fig 1).

miRNAs and cascades of MAPK signaling

A number of miRNAs regulate the expression of BCR-ABL, of which, *miR-203* has been extensively studied. *miR-203* is located intergenically on human chromosome 14 ($14q^{32.33}$) (18) and has been identified as a skin-specific miRNA. *miR-203* reduces ABL1 and BCR-ABL1 fusion protein levels in an ABL1-dependent manner. A recent study of combined treatment effects of *miR-203* and imatinib (small molecule kinase inhibitor) on imatinib-resistant cell lines demonstrated that *miR-203* can serve as a novel target for CML treatment (19).

miRNA-196b is a vertebrate-specific miRNA, which appears to be expressed from intergenic regions in *Homobox* (*HOX)* gene clusters in many vertebrate species (20). Three *miR-196* genes have been found so far i.e., *miR-196a-1*, *miR- 196a-2* and *miR-196b* (21). In humans, the gene for *miR-196b* is located in a highly evolutionarily conserved region between *HOXA9* and *HOXA10* genes, on chromosome 7 ($7p^{15.2}$) (22) study demonstrated that low level of expression of the tumor-suppressor, *miR-196b* can cause up-regulation of BCR-ABL1 expression which leads to the development of CML.

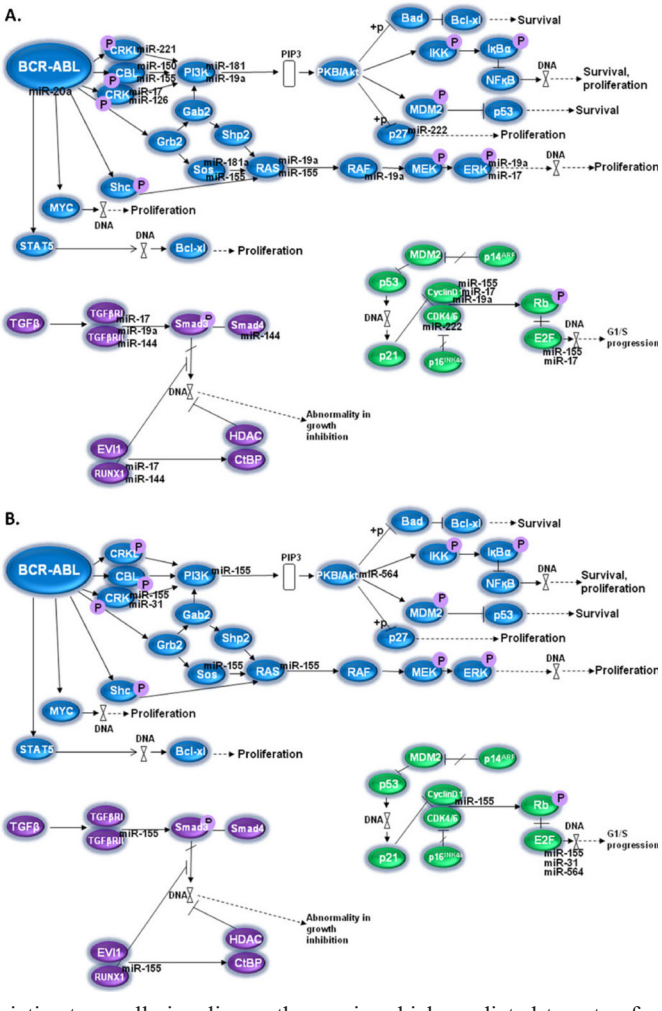

Figure 1. Scheme of CML hematopoietic stem cell signaling pathways in which predicted targets of microRNAs associated with CML are involved.

Furthermore, the study reported that a decline in the expression of *miRNA-196b*, in the cells overexpressing it, can restore BCR-ABL1 protein levels, enhance cell multiplication, and impeded the synthesis (S) phase of the cell cycle.

down-regulation of *BCR-ABL1* gene by small interfering (si) RNAs reduced the BCR-ABL1 protein levels an obstructed proliferation. The *miR-30a*, generated from an intronic transcriptional unit, is located on human chromosome 6 ($6q^{13}$) and belongs to *miR-30* family (23,24). overexpression of the *miR-30a* in K562 cells (human immortalized myelogenous leukemia line) decreases the BCR-ABL1 protein levels, reduces cell proliferation and arrests the cells between G1 and S phase of the cell cycle.

The *miR-29* is a family of small RNA molecule in the shape of a stem-loop or hairpin. The genes coding for the precursors of *miR-29b-1* and *miR-29b-2* are located on chromosome 7 ($7q^{32.3}$) (25) and chromosome 1 (Ch1 $q^{32.2}$). A recent study utilizing luciferase reporter assay demonstrated that *miR-29b* considerably reduces the activity of a luciferase reporter containing ABL1-3'UTR.

The microarray studies of miRNAs downregulated in CML blast crisis revealed that *miR-29b* expression was significantly lower in CML patient samples as compared with normal volunteers (26). The *miR-138* family was first detected in humans (*Homo sapiens*) (27). It was observed that pre-miR-138-2 is cleaved to its mature form by Dicer in nucleus and is exported to cytoplasm only in distinct cells. In particular, the *miR-138-1* and *miR-138-2* gene is located on chromosome 3 ($3p^{21.32}$) and chromosome 16 ($16q^{13}$), respectively (28). The expression of miR- 138 is triggered by treatment of imatinib which enhances the activity of GATA-binding factor 1(GATA1) and promotes its binding to *miR-138* promoter. this expression of *miR-138* is repressed by *BCR-ABL*. *miR-138*, by the advantage of a BCR-ABL/GATA1/*miR-138* integrated circuitry, acts as a tumor suppressor miRNA involved in the pathogenesis of CML and its clinical response to imatinib. overexpression of *miR-138* leads to the down regulation of *BCR-ABL* suggesting that there is negative regulatory loop between *miR-138* and *BCR-ABL* (29)

CRK family proteins

The CRK family is known to comprise of five members namely, v-CRK, CRKI, CRKII, CRKIII and CRK-like protein (CRKL) (30). The cellular homolog of v-CRK were found to have an SH2 domain and either one (for CRKI) or two (for CRKII) SH3 domains (31). CRKIII is predicted to encode a protein which have truncated C-terminal SH3 domain (32) CRK proteins are prevalent phosphorylation substrates for the *BCR-ABL* fusion oncogene and are found in more than 95% of CML. CRKL is a key tyrosine-phosphorylated protein present in neutrophils of CML patient (33). miRNAs play an essential role in regulating CRK and CRKL. *miR-126* is located within the 7th intron of the *EGFL7* gene, residing on human chromosome 9 ($9q^{34.3}$) (34). While, *miR-17* is positioned on chromosome 13 ($13q^{31.3}$) and belongs to the *miR-17-92* cluster (35). *miR-126* in humans is expressed only in endothelial cells, throughout capillaries as well as larger blood vessels (36). Recently, a study demonstrated that both, *miR-126* and *miR-17* were up-regulated in blast crisis (BC) samples of CML patients. *miR-221* is a tiny RNA molecule whose gene is located on the X chromosome (Xp11.3) (37). Recent study showed that the *miR-221* level was up-regulated in BC samples of CML patients (38). Research have demonstrated that *miR-221* have an important role in the regulation of apoptosis by directly affecting the pro-apoptotic molecule, p53 upregulated modulator of apoptosis (PUMA), *in vitro.*

SOS proteins

SOS locus to a address of genes that were prime identified in *Drosophila melanogaster* as a important gene product downstream of protein-tyrosine kinase in the RAS/ MAP kinase pathway (39,40), that *miR-155* is a significant target of *SOS1* gene. The miRNA is functioning from an exon of a noncoding RNA pretranscribed from the B-cell Integration Cluster (BIC), identified intergenically on locus 21 ($21q^{21.3}$).

miR-155 is currently downregulated in K562 cells, in chronic myeloid leukemia cell lines, and in patients with chronic myeloid leukemia as compared to non-chronic myeloid leukemia cellular type and blood specimen from healthy person, *miRNA-181a* (*miR-181a*), one of the copious miRNAs conserved among vertebrates, is differentially overexpressed in a different type of leukemias.

The *miR-181a-1* and *miR-181b-1* are joint together and present on chromosome 1, *miR- 181a-2* and *miR-181b-2* are present together and located on chromosome 9 (41). Indicating that downregulation of miR-181a might act as a great role in leukemogenesis.

RAF1 protein

RAF1 is a significant target for molecular therapies and target-based therapies which are widely considered to be the key point of cancer occurrence. As discussed in current genetic knowledge, *miR-19a* is located on human chromosome 13 and subclass of the *miR-19* family of *miR-17-92 locus*. More recently demonstrated that the expression pattern of *miR-19a* was reported up-regulated in chronic myeloid leukemia patients (42).

MAPK/ERK protein

MAPKs gene is eukaryotic protein Ser/Thr kinases, which is encoded by *MAPK1* locus and activated by an upstream activator, RAF, in the MAPK signaling pathway. Some miRNAs act as significant role in MAPK1 synthesis, of which, *miR-17* and *miR-19a* can straight forward regulate the MAPK1. *miR-17* and *miR-19a* are as subclass to *miR-17* and *miR-19* miRNA protein, respectively and are members of highly conserved *miR-17-92* cluster in genome of vertebrates (43). Both of these miRNAs are expressed on human chromosome 13 ($13q^{31.3}$). The 17-92 miRNA clusters is recognized as an important chronic myeloid leukemia target oncogene. Usually miR- *17-92* cluster can detect dysregulated in solid tumors and hematopoietic. A study also reported that *miR-17* is expressed from the 3' arm of the hair-

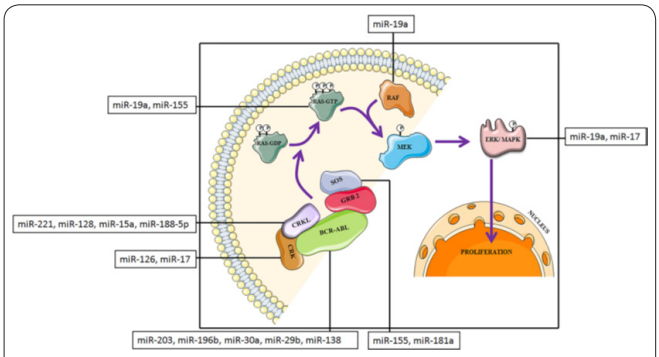

Figure 2. Schematic representation of MAPK protein cascade downstream of BCR-ABL transformed cells with miRNAs that target MAPK signaling pathway components.

pin precursor in human epithelial carcinoma cell line (HeLa) cells (44).

The manual PCR analysis has demonstrated that the levels of *miR-17* and *miR-19a* are up-regulated in chronic myeloid leukemia patients as compared to non- chronic myeloid leukemia patients (45). Another study dealing with miRNA expression in chronic myeloid leukemia demonstrated abnormal expression of the *miR-17* and *miR-19a* in chronic myeloid leukemia CD34+ cells (Fig 2) (46,47).

Conclusions

Methylation of additional genes and MicroRNAs unlike their small size make a significant role in the regulation of gene expression at the post-transcriptional level and are small non-coding molecules. The founding of miRNAs and Methylation is one of the top scientific discovery in current genetic era and has revolutionized breakthrough cell biology and medical epigenetic and sciences. We can emphasis that the ability of miRNAs to control different cellular function in various tissues at multiple levels makes them one of the most competent therapeutic agents in modern medicine. miRNAs can target or be a target for BCRABL1 fusion gene, have a potential use in TKIs treatment or be epigenetically modified. Downregulation of two specific miRNAs families that directly target BCRABL1 gene, *miR-29*, and miR-30, has been well characterized in the context of CML, with specific molecular mechanisms that these tumor suppressor miRNAs play role in. If confirmed using larger datasets, these miRNAs are promising biomarker candidates for prognosis and monitoring drug response. Conflicting reports on *miR-424* and *miR-17-92* clusters indicate that the deregulation of miRNAs can be inconsistent in CML patients. Down-regulation of specific miRNAs, for example, *miR-150* and the *miR-29a/b* cluster, has been well characterized in the context of CML, with specific molecular mechanisms. If confirmed using larger datasets, these miRNAs are promising biomarker candidates for patient prognosis and the development of drug resistance. mi RNAs, that can act as oncogenes or tumor suppressor genes in CML, contribute to the pathogenesis, disease progression, and response to therapy of CML and resistance to TKIs. The potential of using these small RNAs as therapeutic targets opens up new opportunities for leukemia therapy by either inhibiting or augmenting their activity. Moreover, with miRNA-based therapeutics entering early phase human clinical trials, hope for a novel class of effective anticancer agents may be realized. However, more fundamental understanding of miRNA regulated signal transduction pathways and methylation is needed to address more study into the mechanism of chronic myeloid leukemia that can help to develop novel miRNA/anti-miRNA-based therapy in the coming future.

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Conflict of interest

All the authors declare no conflict of interest included in the study.

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