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IDENTIFICATION OF KNOWN AND NOVEL MIRNAS IN CHRONIC MYELOGENOUS LEUKEMIA (CML) STEM CELLS AND NAÏVE HEMATOPOIETIC STEM CELLS

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ABSTRACT

Chronic myelogenous leukemia (CML) is a chronic myeloproliferative illness with an incidence of 1-2 cases per 100,000 people and an estimated 6,000 new patients diagnosed each year.This work identifies both known and new miRNAs in naïve hematopoietic stem cells and chronic myeloid leukemia (CML) stem cells using IonTorrent Next-Generation Sequencing (NGS) technology. Using miRNA profiling, significant differences in miRNA expression were found; certain miRNAs linked with epigenetic regulation and promoter methylation. The function of differently expressed miRNAs in drug resistance mechanisms was investigated using both functional assays and quantitative RT-PCR. Apart from giving fresh understanding of the epigenetic terrain of CML, the results imply possible therapeutic targets to fight drug resistance in CML stem cells. This work clarifies miRNA-mediated control in chronic myeloid leukemia (CML) and emphasizes the relevance of epigenetic elements in therapy of this disease.

INTRODUCTION

An example of a neoplastic condition is leukemia, which can affect cells in the bone marrow or the blood. An aberrant increase of immature blood cells known as "blasts" is one of the defining characteristics of this condition. The absence of proper maturation is a fundamental flaw that is present in leukemic cells, particularly in the acute stages of the disease. As a result of the fact that these immature cells continue to bear the potential for additional multiplication, their lifespan has the potential to be significantly extended. Indeed, a significant number of leukemic cells have the potential to be considered immortal. The leukemic cells may have a prolonged total and reproductive life, and they are likely to accumulate in the tissues. This may be a key component in the pathophysiology of the disease, since it may be one of the factors that brings about the sickness. Immature cells that are constantly growing are unable to carry out the duties that are normally performed by regular blood cells, and these cells compete with normal blood cells for nutritional resources and space. In the long run, this results in the elimination of normal cells, which in turn produces an imbalance in the regular process of hematopoiesis. These alterations are followed by a decrease in the quantity of erythrocytes and platelets in the blood, which leads to anemia as well as an increased risk of infection and bleeding. Headaches, joint or bone pains, and painful swellings are some of the symptoms that can be caused by the accumulation of neoplastic cells in other organ systems, which can occur when the cells leave the bone marrow and go to other organ systems.

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Classification of Leukemia

Acute and chronic types of leukemia can be distinguished from one another according to the nature of the course of the illness. There are unique patterns that can be observed in the clinical presentation of chronic and acute variants. In contrast to acute leukemias, which manifest themselves almost immediately, chronic leukemias are illnesses that progress gradually over time. A substantial number of immature cells, also known as blasts, that are unable to perform their functions correctly are present in acute leukemia. The illness progresses swiftly as a result of the rapid multiplication of these blast cells. According to Rabbitts T. H. (1991), one of the characteristics of chronic leukemia is that the growth of blast cells is slower than that

of acute leukemia. Leukemic blasts in chronic leukemia, in contrast to those in acute leukemia, exhibit varying degrees of maturation, and some of these cells even function normally. In the event that it is not treated, acute leukemia can turn fatal within a few weeks to several months, but people with chronic leukemia can live without therapy for a number of years.

Both myeloid and lymphoid series of cells, as well as their progenitors, have the potential to give birth to leukemia cancer. As stated by Bunn HF and Aster JC (2011), leukemia of lymphoid series is referred to as lymphoid, lymphocytic, or lymphoblastic leukemia. On the other hand, leukemia of myeloid series is referred to as myeloid or myelogenous leukemia. There are four primary forms of leukemia, each of which is distinguished by the cell lineage from which it originates and the ways in which the disease proceeds. The following are the types of leukemia that are classified as acute lymphoblastic leukemia, acute myelogenous leukemia, chronic lymphoblastic leukemia, and chronic myelogenous leukemia.

WHAT IS CML?

Leukemia is a kind of blood cancer that mostly affects white blood cells, which are among the cells that make up your blood. CML is a kind of leukaemia that develops steadily over time. Chronic myeloma can be diagnosed in three phases, with the majority of patients being diagnosed in the early (chronic) phase. Granulocytes, which are mature white blood cells that are completely functional, are produced in excessive quantities by your body during this period. It is possible for treatment to bring the amount of blood cells under control; but, if the disease is not treated, it can advance to a more severe type of chronic myelogenous leukemia known as blast phase, in which the white blood cells do not mature as they should. The accelerated phase is a period of time that may occur between the chronic phase and the blast phase. During this time, your condition may become more difficult to treat, and there may be a small number of immature cells in your blood. These cells are not completely functional.

Disease Overview

Chronic myeloid leukemia (CML) is a kind of leukemia that develops slowly and mostly affects a group of blood cells that are collectively referred to as myeloid cells. When a person is in good health, their myeloid stem cells, also known as the "starter cells" in their bone marrow, grow into myeloid blasts. These myeloid blasts eventually mature into adult red blood cells, platelets, and certain types of white blood cells known as granulocytes and monocytes. Your body is always in need of new blood cells, and it typically produces the appropriate quantity of these cells. However, if you have chronic myeloid leukemia (CML), this mechanism is disrupted, and your body creates an excessive amount of myeloid blasts and granulocytes. These cells cause the bone marrow to become overcrowded, which means that there is not enough space for the production of other blood cells that are essential. In addition, some blasts are able to penetrate the circulation; but, since they have not yet grown to their full potential, they are unable to effectively combat infection. The signs and symptoms of chronic myelogenous leukemia are caused by both of these factors.

The human malignancy known as chronic myeloid leukemia (CML) has been the subject of the greatest research and investigation of any kind of leukemia. From a pathogenetic standpoint, is a clonal genesis of myeloproliferative hematopoietic stem cell illness that affects the population of myeloid, erythroid, and megakaryocyte cells (Fialkow et al., 1977). It is one of the genetic diseases that is best understood from the perspective of its cytogenetic abnormalities and the molecular mechanisms involved. The exchange of genetic material between chromosome 9 and 22 results in a shortened "Philadelphia chromosome," which is known to be a major landmark in understanding the intricate biology of chronic myelogenous leukemia (CML). A translocation that causes the "BCR-ABL" oncoprotein to reveal strong and constitutive tyrosine kinase activity (Quintas et al., 2009; Nowell and Hungerford, 1960; Kantarjian et al., 2006; Salesses et al., 2002) stimulates several downstream intracellular signaling networks that are responsible for the pathogenesis and progression of chronic myelogenous leukemia.

Incidence Rate & Clinical Symptoms

The global illness was responsible for around 15 to 20 percent of all instances of leukemia, with an annual incidence of 1-1.6 cases per 100,000 individuals per year (Hoglund et al., 2016; Rohbracher., 2013; Cortes., 2004; Hoglund et al., 2013). However, the median age at diagnosis is substantially lower, averaging between 38 and 41 years in many nations, namely in Southern and Eastern Europe, Asia, Africa, and Latin America. In western populations, the median age at diagnosis is between 55 and 65 yearsyears. The illness is seen in both males and females, with a ratio of 1.3:1 indicating that males are somewhat more likely to be affected than females. According to the hospital cancer-based registry of the year 2015, chronic myelogenous leukemia (CML) accounted for 25-30% of all leukemia cases that were recorded at the Gujarat cancer & research institute, which is a regional cancer center in Western India (Siegal et al., 2012; Cortes., 2004; Mendizabal et al., 2013).

According to Hehlamann et al. (1993), around forty percent of patients diagnosed with chronic myeloid leukemia are asymptomatic at the time of diagnosis, and the diagnosis is suspected due to an inadvertent increase in aberrant blood counts. Fatigue, anorexia, and a loss of weight are the usual symptoms that are present at the time of presentation. Patients frequently had stomach discomfort as a result of large splenomegaly, which is present in as many as fifty percent of the patients (Sachhi et al., 1999). This discomfort was a typical concern during regular physical examinations and diagnostic procedures.

Manifestations and Staging

In the United States, around fifty percent of people who have been diagnosed with chronic myelogenous leukemia are asymptomatic. During a regular physical examination or blood test, the diagnosis of chronic myelogenous leukemia (CML) is frequently made. CML may be broken down into three distinct phases: the blast phase (BP), the accelerated phase (AP), and the regular phase (CP). CML-CP is observed in the majority of patients (90–95%). When present, the most common signs and symptoms of chronic myelogenous leukemia with chronic splenomegaly are caused by anemia and splenomegaly. Symptoms such as weariness, weight loss, malaise, easy satiety, and soreness or fullness in the left upper quadrant are included in this category. Rare manifestations include bleeding (which is associated with a low platelet count and/or platelet dysfunction), thrombosis (which is associated with thrombocytosis and/or marked leukocytosis), gouty arthritis (which is caused

by elevated uric acid levels), priapism (which is typically associated with marked leukocytosis or thrombocytosis), retinal hemorrhages, and upper gastrointestinal ulceration and bleeding (which is caused by elevated histamine levels due to basophilia). Leukostatic symptoms, which include dyspnea, sleepiness, loss of coordination, and disorientation, are not commonly observed in patients with cerebral palsy (CP), even when white blood cell (WBC) counts above 100 × 109/L. These symptoms are caused by leukemic cells sludging in the veins of the pulmonary or cerebral regions. In twenty to forty percent of instances, splenomegaly is the most accurate physical symptom that can be identified. A lower percentage of people (less than 10%) have hepatomegaly. Infiltration of the skin or other tissues, as well as lymphadenopathy, are extremely uncommon. In the event that they are present, they choose Ph-negative CML or AP or BP for CML. CML transformation is associated with an increased risk of experiencing symptoms such as fever, headaches, bone pain, arthralgias, and pain from splenic infarction. The majority of individuals develop AP before developing BP, while twenty percent of people get BP without any AP warning indications. CML-AP may thus be a stealthy form of the disease or appear with progressive anemia, splenomegaly, and organ infiltration. On the other hand, CML-BP manifests as an acute form of leukemia (myeloid in sixty percent of cases, lymphoid in thirty percent, megakaryocytic or undifferentiated in ten percent) with escalating manifestations of constitutional symptoms, bleeding, fever, and infections.

LITERATURE REVIEW

Yuan-Xue Jing, Yihong Chai, Xiaohong Sun, Xiaofeng He, Shi-Long Xue, Ya-Ming Xi, and Xiao-Ling Ma (2023) Systematic network pharmacological methodologies were used to study PCB2's effect on chronic myeloid leukemia (CML). First, the pharmacological database and analytic platform (TCMSP and Pharmmapper) predicted PCB2 target genes. Meanwhile, GeneCards and DisGene were used to identify CML target genes. Pooled data were used to look for common target genes. Entering the intersecting genes into the String website created a protein-protein interaction (PPI) network. KEGG pathway studies and Gene Ontology (GO) functional annotations were also performed. Molecular docking was also used to confirm PCB2's probable binding conformations with prospective targets. Finally, K562 cells were used for MTT and RT-PCR experiments to confirm the network pharmacology research. CML interacted with 186 of 229 PCB2 target genes. Several oncogenes and signaling pathways were linked to PCB2's pharmacological effects on chronic myelogenous leukemia. The network analysis predicted the top 10 core targets: AKT1, EGFR, ESR1, CASP3, SRC, VEGFA, HIF1A, ERBB2, MTOR, and IGF1. Molecular docking showed that hydrogen bonding is the main contact force between PCB2 binding sites. Molecular docking showed that three target proteins had the highest PCB2 binding probability. These proteins were VEGFA (-5.5 kcal/mol), SRC (-5.1), and EGFR (-4.6). VEGFA and HIF1A mRNA expression in K562 cells decreased significantly after 24 hours of PCB2 therapy. The mechanism of PCB2's anti-chronic myeloid leukemia effect was discovered using molecular docking and network pharmacology.

Jialu Ma, Nathan Pettit, John R. Talburt, Shanzhi Wang, Sherman M. Weissman, and Mary Qu Yang (2022) A single-cell RNA sequencing profile of chronic myeloid leukemia (CML) stem cells was merged with network analysis in order to decode the causes of various TKI responses. This information might be used for the prediction of treatment response and could lead to the development of novel techniques for the monitoring and prevention of drug resistance.

Jurgec et al. (2022) used meta-analysis and modern statistics to compare the global transcriptome profiles of AML and CML at the molecular and cellular levels. They identified novel genes and biological pathways connected to AML and CML. Their work improved our understanding of myeloid leukemia and identified new treatment targets and biomarkers for progression, control, and effectiveness.Background: Hematological malignancies like AML and CML are characterized by leukemic myeloid cell harmful clonal expansion. New molecular diagnostics and pharmacological targets were needed since AML and CML's genetic heterogeneity hampers diagnosis and prognosis. Careful analysis of NCBI GEO transcriptome data based on RNA-seq from five studies showed differentially expressed genes (DEGs) between AML and CML. A complete literature study and functional gene ontology (GO) enrichment analysis were performed on the top 100 DEGs to uncover new AML and CML-related genes and biological processes. The studies identified LINC01554, PTMAP12, LOC644936, RPS27AP20, and FAM133CP as novel AML/CML risk genes. GO enrichment analysis related DEGs to pre-RNA splicing, the cellular endomembrane system, reactive oxygen species and glycoprotein metabolism, neutrophil movement, and the antimicrobial immune response. The study found novel biomarkers and biological processes connected to AML and CML, suggesting that more research is needed to determine their potential as molecular targets for myeloid leukemia therapy.

Karanpreet Bhatia, Vedant Sandhu, Mei Hsuan Wong, P. Iyer, and Shruti Bhatt (2024) reviewed the current state of genetic and functional therapeutic biomarkers used to treat acute myeloid leukemia (AML). They then went on to address the limitations of these methods, looked into future efforts to enhance precision medicine's application, and finally, presented a summary of these methods.

Kazem Mousavizadeh (2022), Mohammad Keramatipour (2022), Shahrbano Rostami (2022), Mohammad Vaezi (2022), Kaveh Kavousi (2022), Amin Talebi (2022), Marjan Yaghmaie (2022), Bahram Chahardouli (2022), and Golnaz-Ensieh Kazemi-sefat (2022) Several common and rare important findings in myeloid blast crisis chronic myeloma (MBC-CML) were discovered with the use of integrated genome sequencing. All gene classes implicated in the leukemogenesis model were found in these results. To conduct integrated genomic sequencing, the researchers obtained peripheral blood samples from three patients with chronic myeloid leukemia who were going through a myeloid blast crisis. They employed Whole Exome Sequencing (WES), Chromosome-seq, and RNA sequencing approaches. Using an internal filtering procedure, we evaluated significant alterations in genes connected to cancer. We employed established variant interpretation criteria to decipher PAFs and PIFs, which stand for potentially actionable and potentially important discoveries, respectively.

In another study, Zafar Iqbal, Muhammad Absar, Tanveer Akhtar, Aamer Aleem, Abid Jameel, Sulman Basit, Anhar Ullah, Sibtain Afzal, Khushnooda Ramzan, Mahmood Rasool, Sajjad Karim, Zeenat Mirza, Mudassar Iqbal, Maryam AlMajed, ButhinahAlShehab, Sarah AlMukhaylid, Nouf AlMutairi, Nawaf Alanazi, Muhammad Farooq Sabar, Muhammad Arshad, Muhammad Asif, Masood A. Shammas,

and Amer Mahmood (2021) conducted a study to identify novel biomarkers of CML progression by employing whole exome sequencing (WES). Patients with chronic phase CML (CP-CML) were used as controls, whereas participants of the WES were patients with accelerated phase (AP-) or blast crisis (BC-) chronic myelogenous leukemia. Using Illumina platforms, clustering and sequencing were executed following DNA library preparation and exome enrichment. We conducted statistical analysis using the R package and SAS/STAT software version 9.4 to discover mutations shared by all AP-/BC-CML patients. The mutations were confirmed using Sanger sequencing and I-Tasser for protein structure modeling. The last step was to create mutants and observe them using PyMOL.

Objective of the study

1. To identify both known and novel miRNAs in naïve hematopoietic stem cells and CML stem cells 2.
2. To use the ion torrent next generation platform to identify sequenced based mirna profiling.

Research method

MiRNA profiling using Ion Torrent Next-Generation Sequencing (NGS) technology helped to find both known and new miRNAs. The study materials consisted in drug-resistant in vitro models of chronic myeloid leukemia stem cells and naive hematopoietic stem cells. MiRNA libraries were made ready for sequencing after all RNA—including tiny RNAs—was extracted. Differentially expressed miRNAs were found using bioinformatics analysis; confirmation came from functional tests and quantitative RT-PCR.

Analysis

There is evidence that epigenetic dysregulation is one of the variables that contribute to the acceleration of the genesis and development of chronic myelogenous leukemia (CML) sickness. A significant factor in the development and progression of chronic myelogenous leukemia (CML) with promoter methylation is the deregulation of microRNAs (miRNAs). As a result of Next-Generation Sequencing, a more comprehensive examination of both known and newly discovered miRNAs has been permitted. In order to identify a potential epigenetic regulator of drug resistance in chronic myelogenous leukemia stem cells, mi-RNA profiling was conducted utilizing the IonTorrent next generation sequencing technology (Life Technologies) on drug resistant in-vitro CML stem cell models and naïve hematopoietic stem cells. It was decided to combine the total RNA of the drug resistance model with that of duplicates that had the same concentrations. Consequently, the sequencing process was carried out only on two samples, one consisting of cells that were resistant to the medication, and the other consisting of naïve hematopoietic stem cells. The subsequent phase, which came after the library was constructed, was to get the template ready. The torrent software suit (TSS) plug-in was used in order to exclude polyclonal and PCR duplication sequences from the datasets. Additionally, adaptor trimming was performed on the raw sequencing reads with this software. In order to be ready for the subsequent analysis, a BAM alignment file was produced, and reads were mapped to the human genome 19 reference (hg19). In order to determine the optimal cut-off for read length, it was first necessary to map the distribution of read lengths over both samples simultaneously. It was shown that the distribution was normal in hematopoietic samples that had never been exposed to any hazardous compounds. The peak of the distribution occurred at 22 nucleotides, which is the typical length of mature miRNAs. On the other hand, CML-resistant samples were found to have short RNAs with a frequency of 18 nucleotides, which indicates that these organisms have just a minor degree of degradation. In order to calibrate the resistance sample, a cut-off length of 14 nanometers was used. For this reason, reads having a length that was more than 14 nucleotides were used in order to carry out further research. The essential statistics used by these various datasets are shown in the table that may be seen below.

Table 1. Basic Statistics of Sequencing Samples

Samples	Total number of Reads	Total number of reads (>14nt)
Resistance CMLcell	11,519,605	11,478,412
Naïve hematopoietic Stem cells	13,271,190	13,114,123

Following the elimination of adaptor sequences from naïve hematopoietic stem cells and poor quality readings from resistant CML stem cells, respectively, a total of 4728961 and 5145393 reads remained. In order to remove any trace amounts of ncRNA contamination from the high-quality measurements that were mapped to the Rfam database, we used the BLASTn algorithm. There were 699738 reads obtained from the mapping method for the resistive sample, whereas there were 734567 reads obtained from the hematopoietic sample. Both miRbase and tag2mirRNA were used in order to identify conserved miRNAs in the extra reads that were obtained, and tag2mirRNA was utilized in order to identify new miRNAs in the unmapped reads. An overview of the fundamental statistics of the readings that were obtained after each filter is shown in the tables that follow. It was identified via the use of miRNA mapping what their fold change expression was.

Table 2. Basic Statistics of Samples after Quality Check Using Prinseq and Cut adapt

Samples	Number of Reads	Number of bases	Mean read length
Resistance CML cell	4728961	111096036	16.5
Naïve hematopoietic Stem cells	5145393	292,365,999	20

Table 3. Basic Statistics of Samples After restraining Small RNAs using Rfam database

Samples	Number of Reads	Number of mapped reads	Number of unmapped reads
Resistance CML cell	4728961	699738	4029223
Naïve hematopoietic Stem cells	5145393	734567	4410826

Table 4. Basic Statistics of Samples mapping on miRbase

Samples	Number of Reads	Number of mapped reads	Number of unmapped reads
Resistance CML cell	4029223	288556	3740667
Naïve hematopoietic Stem cells	4410826	305,561	4,105,265

Table 5. Uniq Tag Count for Novel miRNA Prediction

Samples	Number of Reads	Number of Uniq tag count
Resistance CML cell	3740667	1,526,70
Naïve hematopoietic Stem cells	4,105,265	1,70,690

Identification of Known and Novel miRNA s in CML stem cells and Naïve Hematopoietic Stem Cells

Based on the findings of the extensive bioinformatics research, it has been shown that resistant CML stem cells and naïve hematopoietic stem cells exhibit distinct amounts of 357 microRNAs. Among the 76 microRNAs that were expressed in resistant cells, 181 microRNAs were discovered in hematopoietic stem cells. Additionally, 100 different miRNAs were discovered in both sources of the sample. Only sixty of the one hundred common miRNAs that were found in both sets of samples had expression levels that were substantially different between the two groups.

```
Total 357 miRNAs Identified
   ├── Total 76 miRNAs Identified in Resistant Cells
   │       └── Total 36 miRNAs Show Significant Expression
   ├── Total 181 miRNAs Identified in HSCs
   │       └── Total 48 miRNAs Show Significant Expression
   └── Total 100 miRNAs Identified in Both
           └── Total 60 miRNAs Show Significant Expression
```

Figure 1. Total Number of miRNAs Expressed in Resistance CML Stem Cells and Naïve Hematopoietic Stem Cells

The data presented in Figure 1 demonstrates that 27 out of 60 microRNAs are expressed improperly in CML stem cells that are resistant to imatinib. Additionally, Figure 3 demonstrates that 25 miRNAs are expressed in a variable manner across different kinds of cancer. On the other hand, the expression of just eight microRNAs is shared by the two samples combined. Of the 27 miRNAs, 5 miRNAs expression are found to be significantly up regulated (miR-92a-3p, miR-574-3p, miR-17-5p, miR-103a-3p, miR- 181a-5p), whereas, 22 miRNAs (miR-128-3p, miR-132-3p, miR-451a, miR-451a, miR-24- 3p, miR-25-3p, miR-22-3p, miR-143-3p, miR-26a-5p, miR-21-5p, miR-126-3p, miR-27a-3p, miR-17-3p, miR-27b-3p, miR-582-5p, miR-151a-5p, miR-26b-5p, miR-199a-3p, miR-18a- 5p, miR-199b-3p, miR-101-3p) are found to be significantly down regulated in CML resistance cell than hematopoietic stem cells (Figure 2).

It has been shown via research that resistant CML stem cells are the only ones that display a considerable overexpression of 36 miRNAs for the first time. Hematopoietic stem cells have not been discovered to express these microRNAs, according to the findings.

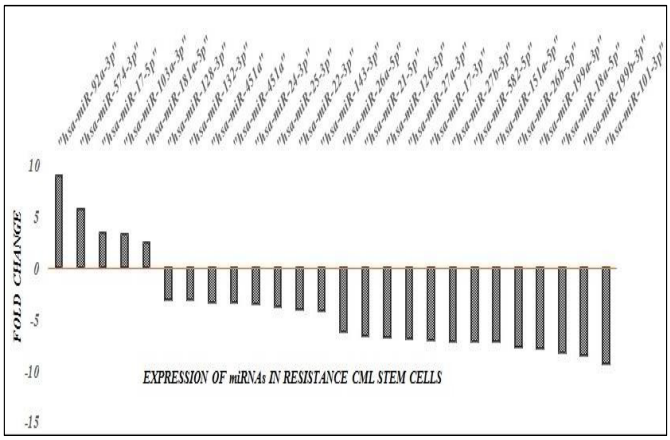

Figure 2. Differential Expression of miRNAs in Resistant CML Stem Cells

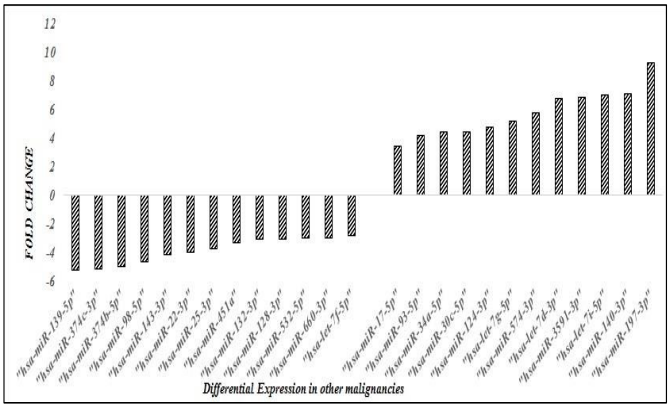

Figure 3. Differential Expression of miRNAs in Different malignancies

Out of 36 miRNAs, 32 miRNAs (miR-223-3p, miR-342-3p, miR- 326, -miR-23a-3p, miR-195-5p, miR-193a-5p, miR-652-3p, miR-150-5p, miR-142-3p, miR-125a-5p, miR-21-3p, miR-200b-5p, miR-99b-5p, miR-339-5p, miR-146b-3p, miR-532-3p, miR-1260b, miR-1976, miR-5585-3p, miR-489-3p, miR-320a, miR-99b-3p, miR-125b-5p,miR-205-5p, miR-500a-5p, miR-206, miR-455-5p, miR-92b-3p, miR-29c-5p, miR-142-5p, miR-500a-3p, and miR-96-5p) have been previously reported in different malignancies, whereas, 4 miRNAs (miR-506-5p, miR-877-3p, miR-1226-3p and miR-1301-3p) arereported in this study are significantly up regulated in CML resistance clone than naïve HSCs and not reported so far either in CML or in other cancers.

The purpose of this study was to discover genes and signaling pathways that may be implicated in CML resistance. To do this, we used three databases (mirBase, miRanda, and TargetScan) to evaluate the projected targets of four miRNAs that were expressed in a distinct manner. There is a possibility that the overall number of false positives is wholly arbitrary due to the fact that various databases include a variety of methods. Through the process of intersecting the results, it was possible to identify the genes that were consistently predicted by all three databases. The genes that are often predicted by all three databases are shown in the table that follows at this point.

On the basis of their roles, we classified the anticipated human target genes into three distinct groups: biological processes, molecular functions, and cellular components.

Table 6. List of Commonly Predicted Genes by three different databases for each miRNAs		
Sr.No	**miRNAs**	**List of genes**
	miR-506-5p	SLC38A4, C5orf30, HOXB13, B3GNT2, ATE1, SLC6A1, WNK1, GPD2, HMGN3, ZMYM2, PTDSS1, SLC6A15, MYO5A, S100A7A, RNF10, EPB41, TAOkBC-L7A, METTL8, WFDC13, OR2L13, PAN3, MAN1A2, IL20, SLC48A1, AIG1, KIAA2022, IL36B, ITK, GSG1L,GPR137C, RBM41.
2.	mir-877-3p	PMEPA1, PRKG2, NEK9, STAG2, RBM41, KCMF1, BRCC3, TBL1XR1, LMOD2, RBFOX2, NPM3, ZNF254, ATP2B4, ZNF430, SLTM, SEL1L, HRG, GRPEL2, FA-M107A, SSTR3, METTL6, JDP2, SLCO1A2, ATP6V1A, EIF4A3, WDR43, VEG-FRAD54L2, SLC39A14, PLXDC1, TRIM39, STMN1, KIAA2022, TMEM207 , C19orf82, ANTXR2, GLI2, ADAMTS15, DLC1, RPTNKLK15, CAMK2G, DTD1, SQLE, DNAJB14, LMO7, RPL36A, HNRNPH2, UBXN7, LEPREL2, CCNJL , OSBP, AQR, PATE1 TSPAN1, ZFP91, SRCIN1, FKBP15, BRD8, B3GNT2, TMEM110, CELF5 ABCB1, SNTA1, KIAA1644, CLIC5, PRRX1, ZNF629, KIAA0141, GPBP1, DIO1, FZD1, CTDSP2, GOLPH3, GLIPR1, C6orf106, FZD10, PDLIM5, NGFR, ARNT2, RPL36A, AK2, SNX13, TOP1, TRAK2, TBC1D9B, LRPPRC, PANK2, GSK3B, RNF10, XRCC6, TFG, GPD2, AKT2, ERO1LB, ZBTB18, SET, EXPH5, TTL, SUMO1, WDR1, HIPK1, SLC48A1, ADAMTS1, WDR4, ITPR2, ATXN1, RPS6KB1, WNK1, HMGB1, SETD5, PBX1, KIAA1429, PIGS, DNMT1, ANP32E, LCOR, UTP18, PRDM1, HN1L, XPO4, F2R, CDK11A, AAMP, APPL1, NGFRAP1, ARNT, ANK2, CDC42EP1, NRAS, DDX31, SLC38A1, SUPT16H, EP-B41L3, TTLL4, GSG1, EPB41, TWIST2, RPS27, SOCS7, ELF5, CYP2C18, CD-C42BPG,VEGFB, COX7B, DCAF16, TMEM98
3.	mir-1301-3p	TP6V1A, DBP, CYBRD1, HAUS4 SEL1LUTP14C, EIF5A, PAN3, GLI2, FAM72C, RORA, UTP18, SSFA2, PIGS, CELA3B, FTSJ3, ATP2B4, COMMD3, DDX31, VAMP7, CFHR5, IKZF2, EXPH5, ATXN10, TULP3, XPO4, NXT1, EDIL3 , RPS6KB1, SSR3, LONRF1, MAN1A2 GRPEL2, PRDM16, MYO5A, SLC16A1, ZNF430, SLC16A12, LCOR, KCMF1, XRCC6, EIF2AK1, OIP5, RGL2, ITPR2, APPL1, LARP4, VSTM2L, SPRR2A, SPRR2D, DHRS12, EIF5AL1, TBL1XR1, FGF2, SFT2D2, STMN1, SGPL1, SLC38A1, GPR137C, TFEC, ZBTB18, WDR13, DCAF16, CORT, APITD1-CORT, TUSC2, PAQR3, RPS27L
4.	miR-1226-3p	VASH1,APPL1,KIAA1644, NAA50,HRK, NUP153, ABCA12, ZMYM2,AAMP,N-RAS, RPS6KB1,TBC1D9B,ABCG4,IGF2R, TFEC, AKR1C4, ATXN-7L3,COPG1,SLC6A17,HIPK1, PTDSS1, TUSC2, PRRX1, ATXN1L, EI-F5A2,ADRB1,CDC42,ABCG1, CLIC5,OSBPL3,ERO1LB,TNFAIP8,FZD2,APIP, ZNF254,TMEM229B, GRPEL2, PBX1, SSR3, C6orf106, SFT2D2, HN1, ATXN-7L3B, CTDSP2, GOLPH3L,TSPAN14, JAK2, SSFA2, ZNF227,TMEM110, AIG1, PLXDC1,C15orf38-AP3S2, SRCIN1, SNX13, WDR5, ABL2,AP3S2, SOCS7, GLIPR1, FGF2, NEK9, SSU72, TWIST2,SLC39A14,SGPL1,DHRS12, OSBP2, LYRM5, DNAJB14, TMEM98, ITFG2,

CONCLUSION

The study effectively found both new and known miRNAs linked with naïve hematopoietic stem cells and chronic myelogenous leukemia (CML) stem cells, therefore emphasizing their function in treatment resistance and disease development. Differential expression analysis revealed important miRNAs presumably involved in epigenetic control; some of these were linked to promoter methylation and treatment resistance. These results clarify the molecular pathways of CML and also point to possible targets for therapy approaches meant to overcome drug resistance in CML stem cells. Improved functional validation of certain miRNAs could offer fresh approaches for therapy.

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