

Downregulation of *Bcr-Abl* oncogene in Chronic Myeloid Leukemia by microRNAs**Priyanka Singh¹, Sonu Kumar Gupta¹, Villayat Ali¹ And Malkhey Verma^{1*}**¹*Department of Biochemistry and Microbial Sciences, Central University of Punjab, Bhatinda, India*

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Abstract

The well-known myeloproliferative malignancy, chronic myeloid leukemia (CML), causes due to the formation of short and modified Philadelphia chromosome having the *Bcr-Abl* oncogene. Many therapeutic approaches have been made for the treatment of CML, the best one was the development of Tyrosine Kinase Inhibitors (TKIs), mainly Imatinib. But after the development of mutation against Imatinib, researchers moved towards RNA interference (RNAi) of BCR-ABL mRNA via microRNAs. In this review, we identified 105 miRNAs by Target Scan, miRbase and miRMAP, which target the proteins of CML signaling pathway. These are selected on the basis of their constitutive activation in the *Bcr-Abl* positive cell lines. Targeting these proteins by miRNAs might effectively enhance chemotherapy-induced cytotoxicity in CML cells. Out of these 105 miRNAs, 21 were found to commonly effective against those proteins. These 21 microRNAs may or may not have been studied in CML cases, but have been studied in other solid or myeloid tumors. This review might be helpful in extending the studies regarding regulation of CML signaling proteins by miRNAs.

Keywords: Chronic Myeloid Leukemia (CML), MicroRNAs (miRNAs), Target Scan, miRbase, miRMAP**Introduction**

Long-lasting myeloid blood cancer, chronic myeloid leukemia (CML), happens due to the translocation between the long arms of chromosomes 9 (ch9) and 22 (ch22). This abnormal chromosome which formed after translocation was first observed by Peter C. Nowel and David A. Hungerford at Fox Chase Cancer Centre, Philadelphia, USA, because of this it is also termed as the Philadelphia (Ph) chromosome [1]. The chromosome translocation is found in 95-96% of CML cases [2]. This chromosome is unusually short and has a fused gene called *Bcr-Abl* oncogene. This gene code for a protein BCR-ABL, a tyrosine kinase signaling protein that is “always on,” causing the cell to divide uncontrollably [3].

The protein also activates several intracellular signaling pathways after enhancing the expression of growth proteins such as interleukin-3 or granulocyte colony-stimulating factor by binding to their receptors [4], and affects the DNA double-strand break repair process which leads drug resistance after therapy [5].

There are three clinical phases of CML: an initial chronic phase (during which the disease process is easily controlled), a transitional accelerated phase, and blast crisis phase. In Western countries, 90% of CML patients are diagnosed in the chronic phase. The therapies for treatment and management of CML includes Tyrosine Kinase Inhibitors (TKIs), Protein Translation Inhibitors, Myelosuppressive agents, Leukapheresis, Interferon-alfa (INF- α), Transplantation and Splenectomy. Among all the therapies the highly recommended one is TKIs therapy. Imatinib, a kind of TKI, blocks ATP binding on the *Abl* part of the fused oncogene *Bcr-Abl*, as a result, the constitutive tyrosine kinase activity responsible for the development of CML get exaggerated [6]. But, afterward, the Imatinib resistance was observed in the CML patients due to the inability of the Imatinib to tackle the *Bcr-Abl* over expression. The Imatinib

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resistance may be BCR-ABL independent and BCR-ABL dependent. The BCR-ABL independent mechanism is due to high *Bcr-Abl* kinase levels [7,8], while the BCR-ABL dependent mechanisms include Abl kinase mutations like T315I (threonine to isoleucine missense at position 315) [6]. The independent resistance mechanism depends on the intercellular concentration of this drug. In this mechanism, the cells either activate various signaling pathways or overexpress multidrug resistance proteins, such as P-glycoprotein (MDR-1), which controls the drug's entry and exit in the cell [9,10].

In order to eradicate Imatinib resistance, multiple strategies have been proposed at the protein level as well as the transcript level [6]. In October 2012, to cope up with the TKIs resistance, the US Food and Drug Administration (FDA) approved Omacetaxine as a protein translation inhibitor that is specified for chronic or accelerated phases of CML patients. Another myelosuppressive agents/therapy used for CML treatment comprises Hydroxyurea (Hydrea), a deoxynucleotide synthesis inhibitor; Busulfan, an alkylating agent; Leukapheresis, a method to decrease WBC count in the leukemic patients by using a cell separator; INF- α along with Imatinib; bone marrow transplantation (BMT) and splenectomy. But, due to the failure of the above-mentioned therapies somewhere, scientists moved towards RNA interference (RNAi) via small naturally occurring RNA molecules called microRNAs (miRNAs/ miRs).

MicroRNAs (miRNAs) are endogenous non-coding RNAs of 19–25 nucleotides in length which regulate gene expression. Lin-4 and let-7 were the first two microRNAs that isolated from *Caenorhabditis elegans* [11,12,13]. Since then, a list of microRNAs has been discovered and the investigations of their functions are going on. The miRNAs get transcribed in the nucleus by polymerase II into pri-miRNAs and later get transported into the cytoplasm in the form of pre-miRNA. In the cytoplasm, pre-miRNA is cleaved by Dicer (RNase III endonuclease) to produce RNA duplex of 19-23 nucleotides. The RNA duplex consists of two strands, one is guide strand, which gets integrated into miRISC, while the other strand, the anti-guide or passenger strand, get degraded by the RISC. The guide strand binds to the complementary nucleotide sequence on the strand and causes mRNA degradation.

In this review, we have tried to discuss the monitoring role of miRNAs in the signaling pathways of CML. For this, we have highlighted the miRNA mediated regulation of different proteins involved in signaling, such as STAT5A/B, Shc, Grb2, Ras, Gab2, CRKL, CRK, CBL, as well as PI3K. The knowledge about the expression pattern and regulative role of miRNAs in monitoring the components of CML signaling pathways might help to design the approaches needed to combat CML.

MicroRNA and CML Signaling Pathways

CML comprises an incredibly complex network of signaling cascade mechanism. The hybrid protein BCR-ABL having tyrosine kinase characteristics and transforming ability, which activates the downstream signal transduction pathways involved in CML (Fig. 1) [14].

In *Bcr-Abl* oncogene, *c-Abl* acts as the catalytic domain while the *Bcr* acts as the interacting site for various substrates, and so after enhancement of the 'biological portfolio', BCR-ABL activates various signaling pathways.

JAK2-STAT5 was one of the primary pathways that are being constitutively activated by BCR-ABL [15,16]. The C-terminus of BCR-ABL binds to JAK2 physically and cause its phosphorylation; after activation, JAK2 itself enhances the downstream molecules including STAT3 and STAT5. BCR-ABL also activates STAT5 directly and thus independent of JAK2 [17]. STAT5 activation has been shown to be correlated with the activation of anti-apoptotic protein Bcl-xL, and finally develop drug resistance by activation of Rad51 [5]. BCR-ABL directly stimulates the tyrosine-phosphorylation and STAT5 dimerization, the STAT5 dimer then translocated into the nucleus and binds to DNA and endorses activation of downstream target genes [18]. The study proved that the STAT5 overexpression leads to the TKI-resistant phenotype while STAT3 and STAT1 have no effect [19]. The mRNA expression of STAT5A and STAT5B (two homologous STAT5 gene products) found to be increased at advanced CML stage.

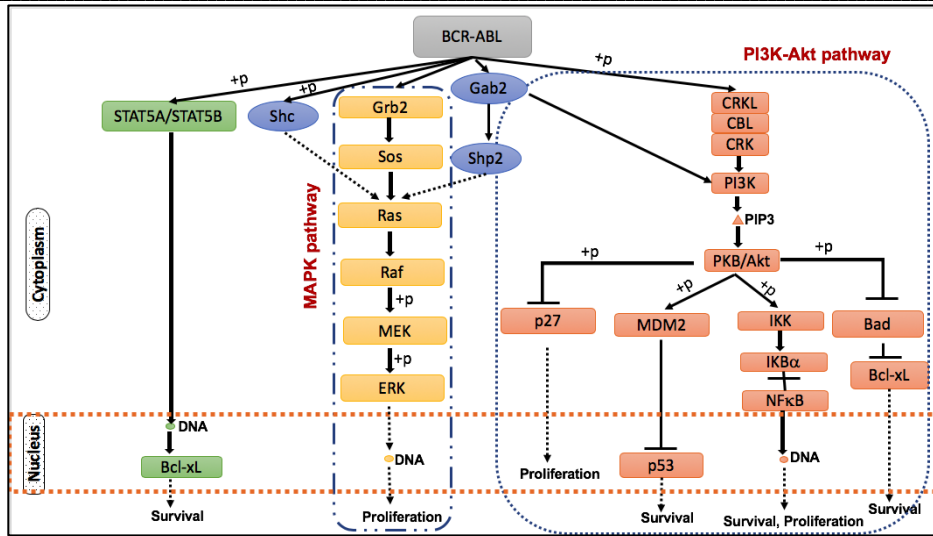


Fig. 1 Signaling cascade in Chronic Myeloid Leukemia Hematopoietic Stem Cell

The mammalian Shc gene codes for adaptor proteins, which stimulates the cytoplasmic transduction of mitogenic stimuli from RTKs Ras [20]. Shc proteins get phosphorylated by Receptor Tyrosine Kinases (RTKs) after ligand stimulation [20]; and then interacts with the SH2 domain of Grb2 and acts as an alternative docking site for the Grb2/Sos complex [21-23]. The reports suggest that the Shc/Grb2/Sos complex is involved in Ras stimulation. Shc proteins are found to be constitutively tyrosine-phosphorylated in cancer that causes continuous activation of oncogenes with TK activity [24,25]. Shc polypeptides are found to be good substrates of the BCR-ABL kinase activity, and the constitutive phosphorylation of Shc found to be express in the *Bcr-Abl* expressing cells [26,27]. MAPK pathway is the main and well known downstream signaling cascade in various cancers and other cellular processes [28]. This signaling cascade also plays a pivotal role in Ph⁺ cells and is necessary for the transcription of proliferating and anti-apoptotic genes [29]. In Ph⁺ cells, the autophosphorylation of tyrosine 177 on BCR-ABL fusion protein provides the binding site for growth factor receptor-bound protein 2 (Grb2). Subsequently, Grb2 binds to the SOS protein, which stabilizes RAS (GTPase) in its active form. Activated RAS provokes the kinase activity of RAF, which later on initiates a signaling pathway via the kinases MEK1/MEK2 and ERK (MAPK), finally begins the activation of gene transcription [30].

One critical signal transducer of BCR-ABL is Gab2. Through many interaction motifs, Gab2 proteins link growth factor and cytokine receptors to downstream effectors such as the Shp2/Ras/ERK, PI3K/AKT/mTOR and JAK/STAT pathways [31]. The

Grb2 acts as the connecting link between BCR-ABL and Gab2, by binding to the SH2 domain of the *Bcr* and SH3 domain of Gab2 [32,33]. Gab2 is also involved in oncogenic signaling as it gets express in multiple solid tumors and also in acute myeloid leukemia (AML) [31]. Gab2 get silenced by the shRNAs, that inhibit proliferation and colony formation of CD34⁺ cells in CML patients [34], and this supports that human CML might be dependent on the BCR-ABL-driven Gab2 signaling and may be Gab2 signaling directs the TKI sensitivity of CML cells.

Similar to previously discussed networks, PI3K/Akt also play an important role in cell cycle progression, differentiation, transcription, translation and finally apoptosis [35,36]. BCR-ABL along with PI3K, CBL, CRK, and CRKL form multimeric complexes and that lead to the activation of PI3K pathway [37]. Later, AKT a serine-threonine kinase activates the anti-apoptotic signaling by binding and phosphorylating the pro-apoptotic protein, Bad. After that, Bad becomes inactive because it is trapped by cytoplasmic 14-3-3 proteins and no longer free to bind anti-apoptotic proteins [38].

The study on the regulation by microRNAs in cancer has increased unexpectedly over the last 10 years. Similar to diabetes, cancer is also found to be the common disease for today's world; at least one-third of the population is suffering from cancer. Despite progress in the treatment of cancer, most people with advanced cancer get eventually die. So, the need of new treatments for cancer lead to the discovery of miRNAs and siRNAs, that approved as the new tool for the diagnosis and treatment of cancer. A total of

38,589 mature miRNAs have been registered in the miRBase (as of March 2018), which were recognized from humans, primates, rodents, birds, fish, worms, flies, and viruses. The miRNAs sequences are found to be highly conserved across species. The first link between miRNA and cancer was recognized when the gene locations of miR-15 and miR-16 found to be deleted on chromosome 13 in the Chronic

Lymphocytic Leukemia (CLL), so both these miRNAs recognized as the tumor suppressors [39]. Several miRNAs (having the sites of 8-mer, 7mer-m8 and 7mer-A1), which play a significant role in the signaling pathway of CML identified with the help of tools such as Target Scan (target predicting tool), miRBase (alignment tool) and miRMAP (secondary structures determining tool) (Fig. 2) (Table 1) (Fig. 3).

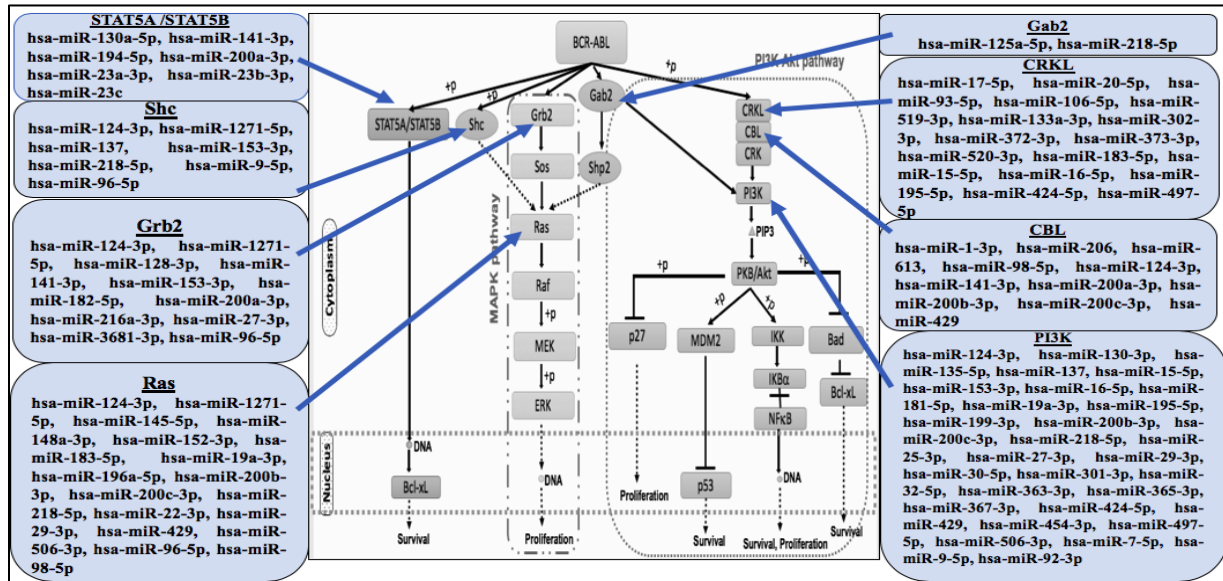


Fig. 2 miRNAs that target the components of CML signaling pathways

Table1: Different Human miRNAs (hsa-miRs), which target the genes of CML pathways, alongwith their accession no., mature sequence, chromosomal location and gene location

miRNAs	Accession no.	Mature sequence (5' → 3')	Chromosomal Location	Gene Location (Exon/Intron/UTR)	Target gene
miR-130a-5p	MIMAT0004593	gcucuuuacacauugucuaacu	chr 11	Intergenic	STAT5A / STAT5B
miR-141-3p	MIMAT0000432	uaacacugucuguaaagaugg	chr 12	Intergenic	
miR-194-5p	MIMAT0000460	uguaacagcaacucacauugugga	chr 1	Intron-12/-1	
miR-200a-3p	MIMAT0000682	uaacacugucuguaacgaugu	chr 1	Intergenic	
miR-23a-3p	MIMAT0000078	aucacauugccagggaauuucc	chr 19	Intergenic	
miR-23b-3p	MIMAT0000418	aucacauugccagggaauaccac	chr 9	Intron+14/+6/+15/+5/+4	
miR-23c	MIMAT0018000	aucacauugccagugauuacc	chr X	----	
miR-124-3p	MIMAT0000422	uaaggcacgcgugaaugccaa	chr 8	Intergenic	Shc
miR-1271-5p	MIMAT0005796	cuuggcaccuagcaagcacuca	chr 5	----	
miR-137	MIMAT0000429	uuauugcuuaagaaucgcguag	chr 1	Intergenic	
miR-153-3p	MIMAT0000439	uugcauagucacaaaagugauc	chr 2	Intergenic	
miR-218-5p	MIMAT0000275	uugugcuugaucuaaccaugu	chr 4	Intron+14/+15	
miR-9-5p	MIMAT0000441	ucuuugguuaucucgugauaga	chr 1	Intron +1/+2	
miR-96-5p	MIMAT0000095	uuuggcacuagcacauuuuugcu	chr 7	Intergenic	

miR-124-3p	MIMAT0000422	uaaggcacgcgguaaugccaa	chr 8	Intergenic	Grb2
miR-1271-5p	MIMAT0005796	cuuggcaccuagcaagcacuca	chr 5	----	
miR-128-3p	MIMAT0000424	ucacagugaaccggucucuuu	chr 2	Intron+15/+18	
miR-141-3p	MIMAT0000432	uaacacugucugguaaagaugg	chr 12	Intergenic	
miR-153-3p	MIMAT0000439	uugcauagucacaaaagugauc	chr 2	Intergenic	
miR-182-5p	MIMAT0000259	uuuggcauugguagaacucacacu	chr 7	Intergenic	
miR-200a-3p	MIMAT0000682	uaacacugucugguaacgaugu	chr 1	Intergenic	
miR-216a-3p	MIMAT0022844	ucacaguggucucugggauuau	chr 2	Intergenic	
miR-27a-3p	MIMAT0000084	uucacaguggcuaaguuccgc	chr 19	Intergenic	
miR-27b-3p	MIMAT0000419	uucacaguggcuaaguucugc	chr 9	Intron+14/+6/+15/+5/+4	
miR-3681-3p	MIMAT0018109	acacagugcucauccacuacu	chr 2	----	Ras
miR-96-5p	MIMAT0000095	uuuggcacuagcacauuuuugcu	chr 7	Intergenic	
miR-124-3p	MIMAT0000422	uaaggcacgcgguaaugccaa	chr 8	Intergenic	
miR-1271-5p	MIMAT0005796	cuuggcaccuagcaagcacuca	chr 5	----	
miR-145-5p	MIMAT0000437	guccaguuuuccaggaaucccu	chr 5	Intergenic	
miR-148a-3p	MIMAT0000243	ucagugcacuacagaacuugu	chr 7	Intergenic	
miR-152-3p	MIMAT0000438	ucagugcaugacagaacuugg	chr 17	Intron +2/+1	
miR-183-5p	MIMAT0000261	uauggcacugguagaauucacu	chr 7	Intergenic	
miR-19a-3p	MIMAT0000073	ugugcaaaucuaugcaaacuga	chr 13	3UTR+2	
				Intron +2/+3	
miR-196a-5p	MIMAT0000226	uagguaguuucauguuguuggg	chr 17	Intergenic	
miR-200b-3p	MIMAT0000318	uaauacugccugguaaugauga	chr 1	Intergenic	
hsa-miR-200c-3p	MIMAT0000617	uaauacugccggguaaugaugga	chr 12	Intergenic	
miR-218-5p	MIMAT0000275	uugugcuugaucuaaccaugu	chr 4	Intron +14/+15	
miR-22-3p	MIMAT0000077	aagcugccaguugaagaacugu	chr 17	3UTR+3/+2	
				Exon+3	
miR-29a-3p	MIMAT0000086	uagcaccaucugaaaucgguaa	chr 7	Intergenic	
miR-429	MIMAT0001536	uaauacugucugguaaaaccgu	chr 1	Intergenic	
miR-506-3p	MIMAT0002878	uaaggcacccuucugaguaga	chr X	Intergenic	
miR-96-5p	MIMAT0000095	uuuggcacuagcacauuuuugcu	chr 7	Intergenic	
miR-98-5p	MIMAT0000096	ugagguaguagauguuuuuuu	chr X	Intron +59/+60/+61/+34	
miR-125a-5p	MIMAT0000443	ucccugagaccuuuaaccuguga	chr 19	Intergenic	Gab2
miR-218-5p	MIMAT0000275	uugugcuugaucuaaccaugu	chr 4	Intron +14/+15	
miR-17-5p	MIMAT0000070	caaagugcuuacagugcagguag	chr 13	3UTR+2	CRKL
				Intron +2/+3	
miR-20a-5p	MIMAT0000075	uaaagugcuuauagucagguag	chr 13	3UTR+2	
				Intron +2/+3	
miR-93-5p	MIMAT0000093	caaagugcuguucgugcagguag	chr 7	Intron +13/+8	
miR-106a-5p	MIMAT0000103	aaaagugcuuacagugcagguag	chr X	Intergenic	
miR-519a-3p	MIMAT0002869	aaagugcauccuuuagagugu	chr 19	Intergenic	
miR-133a-3p	MIMAT0000427	uuuggucccuucaaccagcug	chr 18	Intron-12/+3	
miR-302a-3p	MIMAT0000684	uaagugcuuccauguuuugguga	chr 4	Intron-10/-11	
miR-372-3p	MIMAT0000724	aaagugcugcgacauuugagcgu	chr 19	Intergenic	
miR-373-3p	MIMAT0000726	gaagugcuucgauuuuggggugu	chr 19	Intergenic	

miR-520a-3p	MIMAT0002834	aaagugcuuccuuuggacugu	chr 19	Intergenic	
miR-183-5p	MIMAT0000261	uauggcacugguagaaucacu	chr 7	Intergenic	
miR-15a-5p	MIMAT0000068	uagcagcacauaaugguuugug	chr 13	Intron+3/+4/+5	
				Exon+3/+4	
miR-16-5p	MIMAT0000069	uagcagcacguaaaauuggcg	chr 13	Intron+3/+4/+5	
miR-195-5p	MIMAT0000461	uagcagcacagaaauuuggc	chr 17	Intron+1	
miR-424-5p	MIMAT0001341	cagcagcaaucauguuuugaa	chr X	Exon+1	
miR-497-5p	MIMAT0002820	cagcagcacacugguuuugu	chr 17	Intron+1	CBL
miR-1-3p	MIMAT0000416	uggaauguaaagaaguau	chr 18	----	
miR-206	MIMAT0000462	uggaauguaaggaugugugg	chr 6	Intergenic	
miR-613	MIMAT0003281	aggaauguuccuucuuugcc	chr 12	Intron+2/+1	
miR-98-5p	MIMAT0000096	ugagguaguaaguuguuu	chr X	Intron +59/+60/+61/+ 34	
miR-124-3p	MIMAT0000422	uaaggcacgcgugaugccaa	chr 8	Intergenic	
miR-141-3p	MIMAT0000432	uaacacugucugguaaagaugg	chr 12	Intergenic	
miR-200a-3p	MIMAT0000682	uaacacugucugguaacgaugu	chr 1	Intergenic	
miR-200b-3p	MIMAT0000318	uaauacugccugguaaugauga	chr 1	Intergenic	
miR-200c-3p	MIMAT0000617	uaauacugccgguaaugaugga	chr 12	Intergenic	
miR-429	MIMAT0001536	uaauacugucugguaaaaccgu	chr 1	Intergenic	
miR-124-3p	MIMAT0000422	uaaggcacgcgugaugccaa	chr 8	Intergenic	
miR-130a-3p	MIMAT0000425	cagugcaauguuaaaaggcau	chr 11	Intergenic	
miR-135a-5p	MIMAT0000428	uauggcuuuuuauuccuauguga	chr 3	Intergenic	
miR-124-3p	MIMAT0000422	uaaggcacgcgugaugccaa	chr 8	Intergenic	
miR-130-3p	MIMAT0000425	cagugcaauguuaaaaggcau	chr 11	Intergenic	
miR-135a-5p	MIMAT0000428	uauggcuuuuuauuccuauguga	chr 3	Intergenic	
miR-137	MIMAT0000429	uuauugcuuaagaauacgcuag	chr 1	Intergenic	
miR-15a-5p	MIMAT0000068	uagcagcacauaaugguuugug	chr 13	Intron+3/+4/+5 Exon+3/+4	
miR-153-3p	MIMAT0000439	uugcauagucacaaaagugauc	chr 2	Intergenic	
miR-16-5p	MIMAT0000069	uagcagcacguaaaauuggcg	chr 13	Intron+3/+4/+5	

miR-181a-5p	MIMAT0000256	aacauucaacgcugucggugagu	chr 9	Intron-2/+1	PI3K
miR-19a-3p	MIMAT0000073	ugugcaaaucuaugcaaacuga	chr 13	3UTR+2 Intron+3/+2	
miR-195-5p	MIMAT0000461	uagcagcacagaaauuuggc	chr 17	Intron+1	
miR-199-3p	MIMAT0000232	acaguagucugcacauugguua	chr 19	Intron-14/-15/-16	
miR-200b-3p	MIMAT0000318	uaauacugccugguauugauga	chr 1	Intergenic	
miR-200c-3p	MIMAT0000617	uaauacugccgguaauaugga	chr 12	Intergenic	
miR-218-5p	MIMAT0000275	uugugcuugaucuaaccaugu	chr 4	Intron+14/+15	
miR-25-3p	MIMAT0000081	cauugcacuugucucggucuga	chr 7	Intron+13/+8	
miR-27a-3p	MIMAT0000084	uucacaguggcuaaguuccgc	chr 19	Intergenic	
miR-29a-3p	MIMAT0000086	uagcaccaucugaaaucgguaa	chr 7	Intergenic	
miR-30-5p	MIMAT0000087	uguaaacaucucgacuggaag	chr 6	Intron+3	
miR-301-3p	MIMAT0000688	cagugcaauaguauugucaaagc	chr 17	Intron+1/-1	
miR-32-5p	MIMAT0000090	uaaugcacauuacuaaguugca	chr 9	Intron+12/+13/+14	
miR-363-3p	MIMAT0000707	aauugcacgguaucacucugua	chr X	Intergenic	
miR-365a-3p	MIMAT0000710	uaaugcccuuaaaaauccuuau	chr 16	Intergenic	
miR-367-3p	MIMAT0000719	aauugcacuuuagcaaugguga	chr 4	Intron-10/-11	
miR-424-5p	MIMAT0001341	cagcagcaauucauguuuugaa	chr X	Exon+1	
miR-429	MIMAT0001536	uaauacugucugguaaaaccgu	chr 1	Intergenic	
miR-454-3p	MIMAT0003885	uagugcaauauugcuauaggggu	chr 17	Intron+1/-1	
miR-497-5p	MIMAT0002820	cagcagcacacugguuuugu	chr 17	Intron+1	
miR-506-3p	MIMAT0002878	uaaggcacccuucugaguaga	chr X	Intergenic	
miR-7-5p	MIMAT0000252	uggaagacuaguuuuuguugu u	chr 9	Intergenic	
miR-9-5p	MIMAT0000441	ucuuugguuaucuaugcuguauga	chr 1	----	
miR-92a-3p	MIMAT0000092	uaaugcacuuguccggccugu	chr 13	3UTR+2 Intron+3/+2	

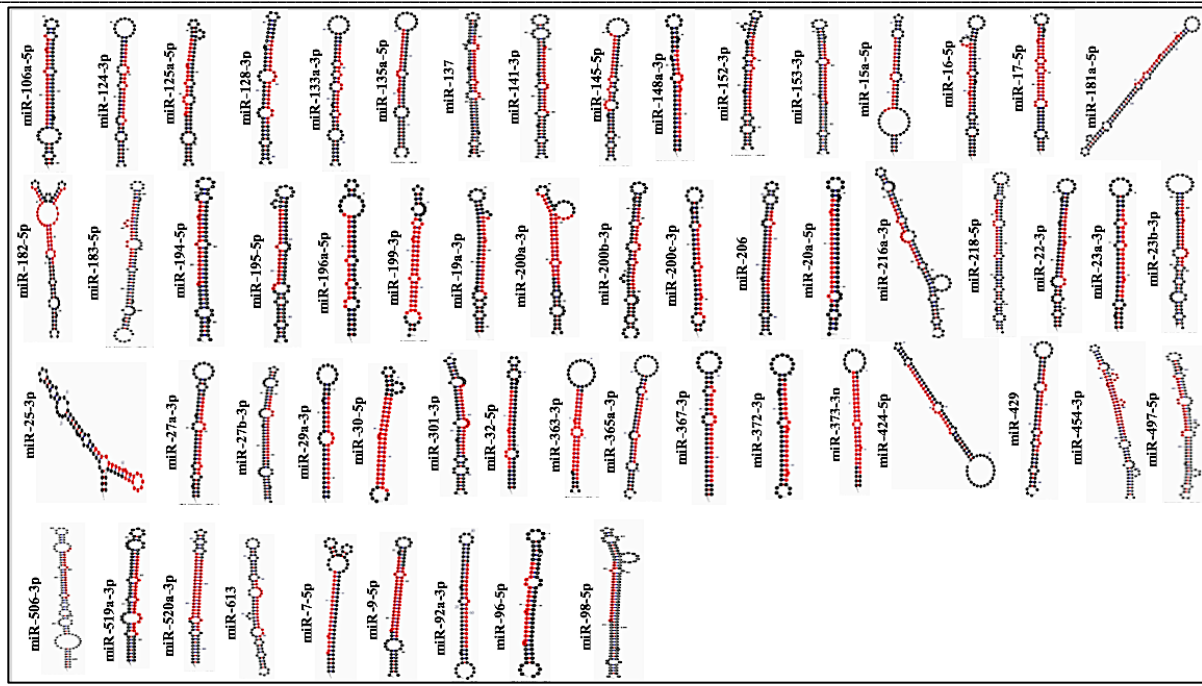


Fig. 3 Secondary structures of miRNAs that target the components of CML signaling pathways

(Note: The red colour segment in the structure represents the mature sequence)

Few miRNAs (21 out of 105) which are found to be common, includes hsa-miR-124-3p, hsa-miR-1271-5p, hsa-miR-137, hsa-miR-141-3p, hsa-miR-15a-5p, hsa-miR-153-3p, hsa-miR-16-5p, hsa-miR-183-5p, hsa-miR-195-5p, hsa-miR-19a-3p, hsa-miR-200, hsa-miR-218-5p, hsa-miR-27-3p, hsa-miR-29-3p, hsa-miR-424-5p, hsa-miR-429, hsa-miR-497-5p, hsa-miR-506-3p, hsa-miR-9-5p, hsa-miR-96-5p and hsa-miR-98-5p (Table 1). The reports on the function of these miRNAs in CML have not been found generally, but the role of them in other cancers has been reported. These miRNAs may possess oncogenic or tumor suppressive characteristics.

MiR-124 is found to act as the tumor suppressor in glioma, medulloblastoma, oral squamous cell carcinomas and hepatocellular carcinoma (HCC) [40-43]. The miR-124 was also reported to affect the invasive and metastatic potential of breast cancer [44]. MiR-124 also downregulates the pancreatic cancer progression after binding to 3'UTR of Rac1, which proved as the tumor promoter in pancreatic cancer [45].

Using bioinformatics, miR-1271 was predicted to target the FOXQ1, a transcription factor that plays a significant role in growth, aging, metabolism, and cancer [46,47]. Several findings proved different expression patterns of miR-1271. It gets upregulated in

head and neck tumor cells [48] downregulated in hepatocellular cancer [49], and gastric cancer cell lines [50]. This miRNA also affects the PI3K-Akt pathway in the Non-small cell lung cancer (NSCLC) cell lines, by acting against mTOR. Akt gets phosphorylated by mTOR and carry out the PI3K-Akt pathway of the cell signaling. miR-1271 was found to affect the translation of mTOR only without causing the degradation of mTOR mRNA [51].

A negative correlation was found between the paxillin (*Pxn*) gene and miR-137 in the Colorectal cancer (CRC) [52]. The *Pxn* codes for a focal adhesion molecule, that forms link between the extracellular matrix (ECM) and actin cytoskeleton [53]. Similar to miR-1271, the expression of miR-137 also vary according to cancer. Downregulation of miR-137 has also been observed in oral cancer cells [54], glioblastoma cell lines [52], while it gets upregulated in squamous cell carcinoma of the tongue [55]. In the cell cycle, this miRNA affects the cyclin D1-CDK4/CDK6 complex, by targeting CDK6, as a result, in cell cycle the G1/S transition gets halted [56].

MiR-141 found to act as an antagonist in the Ovarian Cancer. OC is a lethal disease in women, which occur mainly due to Epithelial-mesenchymal transition (EMT). During this transition, make the cells to gain

the capacity of migration and invasion. Overexpression of miR-141 in the OC cell line SKOV3 significantly inhibit the cell proliferation by affecting the EMT [57]. miR-141 is found to inhibit the proliferation of melanoma cells [58], and gastric cancer cells [59]. miR-141 also get downregulated in the renal cell carcinoma (RCC) in comparison with the normal kidney. miR-141 inhibit ZFH1B, a transcriptional repressor of E-cadherin, and thus suppress the EMT transition in RCC [60].

MicroRNAs-15 and -16 belong to a common predecessor family. Both act as an antagonist on the downstream target of the p53 signaling pathway. Upregulation of miR-15/16 block cell cycle and also accomplish caspase-3 dependent apoptosis. Involuntary expression of miR-15/16 led the low expression of RPS6KB1 mRNA and thus affect the mTOR pathway [61]. miR-15/miR-16 is found to be removed in more than 65% of Chronic Lymphocytic Leukemia (CLL) cell lines which suggest the suppressive role of miR-15 in this cancer [39]. These miRNAs target the antiapoptotic protein Bcl2, which get overexpressed in most of the nondividing B cells of CLL [62]. miR-15a/16-1 target the genes involving in the “cell cycle”, in both a leukemic cell model and in primary CLLs, and categorizes a signature of common genes whose suppressing characterizes the miR-15a/16-1-stimulated phenotype in CLL [63]. The miR-16 upregulation decreases Cyclin D1 and BCL2 at mRNA and protein levels in MCF-7 cell line (breast cancer cell line). It also affects cell proliferation and provokes apoptosis in MCF-7 cells [64].

High-throughput method recognized miR-153 as an oncogene in the prostate cancers. miR-153 inhibits the expression of PTEN (a tumor suppressor gene); and as a result, enhances the G1/S transition [65]. miR-153 also found to act as the tumor suppressor. It was reported that miR-153 reduce EMT transition and hence destroy tumor cells in gastric cancer and breast cancer; and suppress metastasis in human non-small-cell lung cancer [66-68]. miR-153 also promote cisplatin-mediated apoptosis in breast cancer cell lines by suppressing Homologous to the E6-associated protein carboxyl terminus domain containing 3 (HECTD3) expression [69]. miR-153-3p was found to inhibit metastasis in the Oral cavity squamous cell carcinoma (OSCC) by targeting Nrf2. Nrf2 protein gets constitutively upregulated in the tumor under oxidative stress. The miR-153-3p/Nrf2 interaction might be considered as a potential therapeutic target in OSCC [70].

The expression of miR-183 gets over-express or under-express depending on the types of cancer. MiR-183 have been found to be upregulated in leukemia, hepatic and colorectal cancer [71-74], and downregulated in lung cancer [75]. miR-183 binds to 3'UTR of VIL2/Ezrin a member of the ezrin/radixin/moesin (ERM) family of proteins that controls cytoskeletal-membrane interactions and cell signaling [76]. Ezrin is a membrane cytoskeleton crosslinker and controls the actin during adhesion and motility in breast cancer cells [77]. Hence it is reported that miR-183 diminishes migration in breast cancer cells.

The miR-195-5p have been studied in several cancer cell lines as the tumor suppressor. miR-195-5p was identified to inhibit the glucose uptake in the bladder cancer T24 cells by directly targeting the glucose transporter member 3 (GLUT3) [78]. miR-195-5p is also involved in the suppression of human prostate cancer (PCa). The miR-195 target the ribosomal protein S6 kinase, 70 kDa, polypeptide 1 (RPS6KB1) gene in PCa and reduce the cell invasion and migration and also enhance the apoptosis [79]. miR-195-5p regulate the PHD finger protein 19 (PHF19) in the Hepatocellular carcinoma (HCC) [80]. PHF19, a component of polycomb repressive complex 2 (PRC2), promote the hepatoma cell migration, invasion, and proliferation; also regulate the growth of xenograft tumors [81].

MiR-19a-3p regulate the 5-Lipoxygenase (5-LO), the key enzyme in leukotriene biosynthesis [82]. Leukotrienes are mediators of the innate immune system and inflammatory processes, and they might also be involved in cancer development. miRNA-19a/b acts as an oncogene in oral cancer and it negatively regulates SOCS3 by JAK-STAT pathway [83].

MiR-200a induce apoptosis in the renal cell carcinoma by directly targeting SIRT1 [84,85]. SIRT1 has been shown to deacetylate and thereby deactivate the p53 protein. The regulatory relationship between miR-200c and Heme oxygenase-1 (HO-1) determined in Renal cell carcinoma (RCC). miR-200c might sensitize RCC cells to Sorafenib and Imatinib to hinder cell proliferation by targeting HO-1 [85]. HO-1 is a heme degrading enzyme; and acts as the anti-inflammatory and anti-apoptotic protein, due to which it may lead to cancer. HO-1 was found to express in lung cancer [86], and it was recently reported that HO-1 nuclear localization was involved in imatinib resistance in chronic myeloid leukemia cells [87], indicating the increased significance of HO-1 in cancer biology. Chen et al., found the low expression of miR-200a in

hepatocellular carcinoma cells, and it might inhibit the metastasis in the hepatocellular carcinoma cells by targeting FOX2 [88]. Ovarian cancer is found to be the most lethal among gynecological tumors, and it is due to its metastatic behavior. The metastasis occurs in cancer cells due to the EMT. The miR-200 family induce the mesenchymal to epithelial transition (MET), therefore, miR-200 family members found to be effective against metastasis [89].

MiR-218 is found to be Lamin targeting miRNA. In the mammalian cells, Lamin, the protein of nuclear lamina is of two types: Lamin A (Lamin A and C, which are all products of alternative splicing from the LMNA gene) and Lamin B (Lamin B1 and B2, which are encoded by two separate genes, LMNB1 and LMNB2, respectively) [90]. These proteins provide shape and stability to the nucleus; and also control protein complexes involved in replication, transcription and nuclear positioning. Lamin A is often found to be low expressed in breast, ovarian, colon and gastric cancers [91-93], while Lamin B1 is overexpressed in liver, pancreas and prostate cancers [94-96]. Breast cancer emerged as the most commonly diagnosed life-threatening cancer in women, especially the Triple-negative breast cancer (TNBC). But the treatment of TNBC remains challenging, so the miRNAs have emerged as a potential tool for the diagnosis and treatment of breast cancer. miR-218 is downregulated in TNBC samples and it directly targets the Lamin B1, so the report revealed that miR-218 has a tumor suppressive activity in breast cancer [97].

MiRNA-27a-3p found to act against Yes-associated protein-1(YAP1) in oral squamous cell carcinoma (OSCC) patients and OSCC cell lines [98]. YAP1 act as the co-activator for TEAD transcription factor, which activate cell growth genes and anti-apoptotic genes. Increased expression of miR-27a-3p also inhibit the EMT related molecules in OSCC cell lines, including Snail and Twist; and hence manipulate the metastasis through the EMT inhibition. miR-27a also get downregulated in cervical cancer by obstructing TGF- β RI expression and TGF- β signaling. miR-27a is also found to act as antitumor in colorectal cancer [99,100], oral squamous carcinoma [54], and esophageal carcinoma [101]. miR-27a was also found to act as an oncogene in many tumors by regulating cell proliferation, metastasis and drug resistance [102-104]. The role of miR-27a in human colon cancer was found to be as the key regulator of lymph angiogenesis and it functions via the TGF- β -SMAD4 signaling pathway. TGF- β /SMAD4 signaling pathway regulates the signal transduction from cell membrane to nucleus

and controls a wide series of cellular activities, as well as cancer progression and metastasis [105]. These findings indicated the key roles of miR-27a in tumorigenesis and metastasis in human colon cancer and implicated miR-27a as a potential target for the development of new anticancer therapies [106].

MiR-29a/b/c is considered as tumor suppressive in head and neck squamous cell carcinoma (HNSCC), where it targets the Lysyl oxidase-like 2 (LOXL2), and thus affect the metastasis in this carcinoma [107]. LOXL2 gene encodes for an extracellular copper-dependent amine oxidase that catalyzes the initial stage in the formation of crosslinks between collagen and elastin, and this cause remodeling in ECM and enhances the cellular metastasis [108]. A study reported the role of miR-29a/b/c in EMT also after interacting with the transcription factor Snail1, which further repressed E-cadherin [109]. miR-29 act against anti-apoptotic protein Mcl-1in bile duct epithelial cancer [110]; low expression of miR-29 found in breast cancer patients [111]; the downregulation of miR-29 is associated with metastasis and so this miRNA can be used as the biomarker for tumor advancement [112].

MiR-424-5p act as both tumor suppressor and oncogene depending upon the tissues. The downregulation of miR-424-5p was found in hepatocellular carcinoma [113], cervical cancer [114], esophageal squamous cell carcinoma [115], compared to the upregulation in pancreatic cancer [116]. In Epithelial Ovarian Cancer (EOC), miR-424-5p arrest G1/S transition in cell cycle by targeting CCNE1, which code for cyclin that bind to CDK2 and cause cell cycle progression [117]. miR-424 acts as the oncogene in non-small cell lung cancer (NSCLC) by enhancing cell migration and invasion after targeting Tumor Necrosis Factor Alpha-Induced Protein 1(TNFAIP1) [118].

Like other miRNAs, mir-429 perform as both oncogenic and tumor suppressive. It gets over expressed in endometrial carcinoma [119], and colorectal cancer [120]; while low expressed in osteosarcoma [121], renal cell carcinoma [122] and cervical cancer [123]. In the case of bladder cancer, the behavior of miR-429 is controversial. This considered having a tumor suppressive role based on the earlier report in which miR-429 was found to inhibit the EMT by restoring the expression of E-cadherin in bladder cancer [124], while in another report miR-429 enhance bladder cancer by targeting CDKN2B [125]. Mir-429 is also showing the oncogenic effect in prostate cancer by targeting p27kip1 [126]. p27kip1 regulate cell cycle

after interacting with cyclins or cyclin/CDK complexes to inhibit their kinase activities that normally promote G1/S phase progression [127,128].

The tumor suppressive role of miR-497-5p along with miR-195-5p and miR-455-3p found in melanoma A375 cells by targeting hTERT, which encode for the catalytic subunit of telomerase [129]. Its expression is involved in the process of cell immortalization and cancer tumorigenesis, growth, migration, invasion, and prognostic evaluation, although the underlying mechanism remains unclear [130]. MiR-497-5p acts as the negative regulator for SMAD3 and affect the TGF β signaling pathway and finally lead to the G0/G1 arrest [131]. MiR-497-5p has been reported to suppress the tumor cell proliferation and metastasis in prostate cancer, hepatocellular carcinoma, and non-small cell lung cancer (NSCLC) tissues [132-135].

MiR-506-3p repress the activity of long non-coding RNA (lncRNA) NEAT1, which is found to play a crucial role in Pancreatic cancer (PC) [136]. Long non-coding RNAs consist of 200 nucleotides and play an important role in tumorigenesis. miR-506 is considerably downregulated in many cancers and act as a tumor suppressor by targeting oncogenes like N-Ras, PIM3, SPHK1, ROCK1, and ETS-1, hence regulate cell proliferation, apoptosis, metastasis and drug resistance [137]. In cervical cancer, miR-506 acts as an anti-proliferative agent by directly targeting the Gli3 transcription factor of the hedgehog pathway [138].

MiR-9 (miR-9-5p and miR-9-3p) get overexpressed in tumors in comparison to the normal breast tissues (NBTs), but both miR-9-5p and miR-9-3p found to differentially expressed in the breast cancer subgroups as identified by the expression of estrogen receptor (ER) and progesterone receptor (PgR) [139]. In Human Papilloma Virus (HPV)-positive cancer, miR-9 along with HPV E6 oncoprotein increase cell migration by downregulating follistatin-like 1 (FSTL1) and Activate Leukocyte Cell Adhesion Molecule (ALCAM) mRNAs [140].

The role of miR-96-5p is found suspicious in the case of hepatocellular carcinoma (HCC) because according to a data it suppresses apoptosis in hepatocellular carcinoma (HCC) by inhibiting caspase 9, an important protein for mitochondria regulated apoptosis [141], while another study reveals its metastatic role along with miR-182-5p in HCC by targeting 5'-UTR and 3'-UTR of three key Insulin Growth Factor (IGF) axis genes, namely IGF-1R, IGF Binding Protein-3 (IGFBP-3) and IGF-II transcripts [142]. In TNBC,

highly aggressive form of breast cancer miR-96 including miR-557, and miR-3182 inhibit the mTOR and S6K1 genes of PI3K/Akt/mTOR signaling pathway and so affect the cellular functions like transcription, translation, division, metabolism, metastasis, proliferation, and development of tumor [143]. miR-96 inhibit EMT by targeting astrocyte elevated gene 1 (AEG 1) in Glioblastoma cancer cells [144]. AEG-1 triggers anchorage-independent growth and invasiveness of tumor cells.

Few reports revealed miR-98-5p as an oncogene in non-small lung cancer (NSCLC). Cisplatin emerged as an effective drug for lung cancer, but later drug-resistance and side effects of cisplatin led to the discovery of new drugs. And then the discovery of Epigallocatechin-3-gallate (EGCG) in green tea proved as the chemo preventive agent. EGCG has displayed tumor suppressive effect in the prostate, head, and neck; and lung cancer [145-147]. EGCG is found to enhance the effect of cisplatin and also induce apoptosis in tumor cells. EGCG could improve the therapeutic effect of cisplatin through inhibiting miR-98-5p, signifying that miR-98-5p could be a target in clinical cisplatin treatment of NSCLC [148]. EGCG also increase the capacity of cisplatin by inducing the cisplatin transporter copper transporter 1 (CTR1). NEAT1, a long non-coding RNA (lncRNA) upregulates CTR1 to boost cisplatin sensitivity. Mir-98-5p bind to NEAT1 at the complementary site and lowers the expression of CTR1 [149]. In comparison to NSCLC, the tumor suppressive role of miR-98-5p was observed in pancreatic ductal adenocarcinoma (PDAC). MiR-98-5p was downregulated in the cancerous tissues and it is interpreted that miR-98-5p inhibited PDAC cell proliferation and metastasis by negatively regulating MAPK4 in PDAC cells [150].

Conclusion

Imatinib was found to be superior to conventional medications for CML treatment, but Imatinib resistance led to the development of other TKIs, that appear to overwhelmed Imatinib resistance for many but not all mutations [151-153]. So, the research in this field bent towards gene interference by miRNAs [154,155]. Anti-BCR-ABL RNAi assists Imatinib in inducing cell death in Imatinib-resistant CML cells [153,155].

To search for an alternative treatment, we reviewed miRNAs which regulates the expression of STAT5, Shc, Grb2, Ras, CRKL, CBL and PI3K. These (STAT5, Shc, Grb2, Ras, CRKL, CBL and PI3K) belong to different functional classes of proteins

(tyrosine phosphatase, transcription factor, adaptor protein); and these are selected on the basis of their constitutive activation in the *Bcr-Abl* positive cell lines. Targeting these molecules by miRNAs might effectively enhance chemotherapy-induced cytotoxicity in CML cells, and a time may come when we will be able to control the CML population.

Abbreviations

CCNE: cyclin E; **CDK:** Cyclin Dependent Kinase; **CDKN2B:** Cyclin-dependent kinase 4 inhibitor B; **FOXQ1:** Forkhead Box Q1 protein; **Gab2:** GRB2-associated-binding protein 2; **Grb2:** Growth factor receptor-bound protein 2; **hsa:** *Homo sapiens*; **hTERT:** human telomerase reverse transcriptase; **IκBα:** inhibitor of kappa B; **IKK:** Inhibitor of nuclear factor kappa-B kinase subunit alpha; **JAK:** Janus Kinase; **MAPK:** Mitogen Activated Protein Kinase; **MDM2:** Mouse double minute 2 homolog protein; **MDR:** Multidrug Resistance protein; **MEK:** MAPK/ERK kinase; **mTOR:** mammalian Target Of Rapamycin; **N-Ras:** Neuroblastoma Ras protein; **NEAT1:** Nuclear Enriched Abundant Transcript 1; **NFκB:** nuclear factor kappa-light-chain-enhancer of activated B cells; **PI3K:** Phosphatidylinositol-4,5-bisphosphate 3-kinase; **PIM3:** Pim-3 proto-oncogene, serine/threonine kinase; **PKB:** Protein Kinase B; **PTEN:** Phosphatase and Tensin homolog protein; **PTPN11:** Protein Tyrosine Phosphatase Non-Receptor Type 11; **Rac1:** Ras-Related C3 Botulinum Toxin Substrate 1 protein; **RISC:** RNA-Induced Silencing Complex; **ROCK1:** Rho Associated Protein Kinase 1; **RPS6KB1:** Ribosomal Protein S6 Kinase Beta-1 protein; **RTK:** Receptor Tyrosine Kinase; **SH2:** Src Homology 2; **Shp2:** Src Homology Region 2-Containing Protein Tyrosine Phosphatase 2; **SOCS3:** Suppressor Of Cytokine Signaling 3 protein; **SOS:** Son Of Sevenless protein; **SPHK1:** Sphingosine Kinase 1 protein; **STAT:** Signal Transducer and Activator of Transcription protein; **TEAD:** TEA domain family member 1 protein; **TGF-β:** Transforming Growth Factor Beta; **ZFH1B:** Zinc Finger E-Box-Binding Homeobox 1B protein

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