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REVIEW ARTICLE

miRNAs: EMERGING PLAYERS IN HEMATOLOGICAL DISORDERS

Grace Raji R*., Lincy Edatt and Sameer Kumar V. B.

Department of Biochemistry and Molecular Biology, School of Biological Sciences, Central University of Kerala, Kasargod

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ABSTRACT:

MicroRNAs are the micromanagers of developmental processes capable of modulating different complex regulatory pathways. Many studies have addressed the role of miRNAs in hematopoesis where these tiny non coding RNA molecules has been reported to regulate different stages of hematopoesis and modify the hematopoetic niche. Extensive miRNA deregulation has been observed in different haematological disorders and their aberrant expression has been associated with solid tumors and hematologic malignancies. Moreover, miRNAs being post transcriptional regulators of gene expression, can play dual role as oncogene tumor suppressor gene.

INTRODUCTION: Role of miRNAs in hematopoesis: Multiple evidences show that miRNAs play a significant role in genetic regulation of stem and progenitor cells, thereby playing an important role in the development and functions of hematopoetic cells[7]. They have been reported to act as lineage switch regulators, capable of fine tuning the process of differentiation and adjusting the cell response to stimuli[8].

Many miRNAs has been reported to be deregulated during the process of hematopoesis, and these studies suggests that a particular miRNA or a set of miRNAs are critical in the regulation of lineage differentiation. E.g. During T- cell differentiation, miR-181 family members was reported to be upregulated in the double positive $CD4^+$ $CD8^+$ stage of thymocyte development. These miRNA family members target some genes involved in thymocyte development like Bcl-2, CD-69 and TCRα, where, their levels increased [9]. Other miRNAs like miR-150 and miR 17-92 cluster has been reported to be crucial for B-cell differentiation . miR-150 is selectively expressed in mature resting B-cells, but not in their progenitors; furthermore, B-cell differentiation was reported to be controlled by miR-150 by targeting the transcription factor C-MYB[10].

Another study reported miR-17-92 cluster to regulate B-cell differentiation by targeting the pro apoptotic protein member Bim. Systematic analysis of miRNA expression during erythropoesis revealed a progressive downregulation of miR-150, 155, 221 and 222, with a concomitant upregulation of miR-16 and miR-451[11]. Human granulopoesis has been reported, to be regulated by miR-223, whose transcription is regulated by 2 transcription factors, PU.1 and C/EBPb. Another study has revealed that, miR-424 plays an important role in monocyte development[12,13].

Yet another study has reported that miR-22 can control hematopoesis by negatively regulating TET2 protein levels, through epigenetic mechanisms[14].

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*Corresponding author:
Grace Raji R
Department of Biochemistry and Molecular Biology, School of Biological Sciences, Central University of Kerala, Kasargod

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Pattern of miRNA expression varies specifically at different stages during hematopoetic development, and the biological role of miRNAs in hematopoesis has been studied either by complete inactivation of miRNA formation or by selective targeting of specific miRNAs[15]. Since miRNAs play an important role in regulation of hematopoesis , aberrant expression of these miRNAs can lead to abnormal hematopoetic differentiation resulting in hematological disorders and malignancies. Summarising such role of miRNAs form the subject matter of this review.

miRNAs in hematological malignancies: Hematological malignancies is a wide term that includes blood cell cancers , ie, Chronic lymphocytic leukemia, Chronic myelocytic leukemia, Acute myeloid leukemia, Chronic myeloid leukemia, myelodisplastic syndrome, Multiple myelomas and lymphomas. All these are caused due to aberrant gene expressions, which to some part is regulated by miRNAs[16].

miRNAs and leukemias: *miRNAs in chronic leukemias*: Chronic lymphocytic leukemia (CLL): CLL is the second most common form of leukemia in adults. CLL is characterised by slow accumulation of non-proliferating mature B-lympocytes in blood and bone marrow[17]. In CLL patients, the chromosomal region 13q14 is frequently deleted which contains tumour suppressor genes. One of the candidate genes in this region include the non coding deleted in lymphocytic leukemia 2 (DLEU2) gene[18].

miR 15a/16-1 was found to be downregulated in most cases of CLL, whose target include Bcl-2, an anti-apoptotic protein which in CLL gets overexpressed. miR-15 and miR-16 are ubiquitously expressed from two genes, miR-15a/16-1 on chromosome 13 and miR-15b/16-2 on chromosome 3[19,20]. Other miRNAs reported to be involved in the pathogenesis of CLL are miR29b and miR181b, both of which targets TCL1, an oncogene, which co-activates AKT and takes part in the regulation of many pathways involved in cell survival and death[21]. miR181a together with miR 15a/16-1 cluster can directly target Bcl-2 and play a central role in CLL[22].Another target of miR-15a/16-1 include the tumour suppressor immunoglobulin superfamily member 4 (IGSF4), cyclins E1 and D1[23]. Some potential targets of miRNAs with altered expression pattern in CLL, interact with protein that are overexpressed such as Bcl-2, Mcl-1, P27, Tcl-1 and ZAP70[24].

Chronic myeloid leukemia: Also known as chronic granulocytic leukemia. CML is a clonal bone marrow stem cell disorder, charecterised by proliferation of mature granulocytes and their precursors. It is associated with a characteristc chromosome translocation called philadelphia chromosome.[25] miR 17-92 cluster is mainly involved in the pathogenesis of CML and was reported to be transactivated by BCR-ABL1 and C-MYC dependent pathways. [26]miR203 was found to have a target on ABL1, which is lost in specific hematopoetic malignancies. Re expression of miR-203 reduces ABL1 and BCR-ABL1 fusion protein levels and inhibits tumour cell proliferation in an ABL dependent manner[27].

miRNAs in acute leukemias: *Acute lymphocytic leukemia*: ALL is among the most common malignancy observed in pediatric age which arises due to clonal proliferation of lymphoid progenitors in the bone marrow[28].In ALL also miR-17-92 cluster plays an important role which was found to be overexpressed at the pro B to pre B transition, where it acts to silence the expression of proapoptotic protein Bim, leading to abnormal survival of pro-B lymphocyte[29]. Another set of miRNAs like miR-128a and miR-128b was found to be upregulated and let-7b and miR-223 to be downregulated in ALL. Overexpression of miR-128 has been reported to be correlated with promoter hypomethylation[30]. And therefore pathogenesis of ALL could be attributed to the epigenetic regulation of miRNAs. miR-124a gets silenced in ALL samples whose promoter was found be hypermethylated. Functionally overexpression of miR-124a can

decrease cell proliferation by targeting and inhibiting the expression of cell cycle protein, cyclin dependent protein 6 (Cdk6), thus reducing phospho-Rb. miR-125b-1 was also reported to be involved in the etiology of ALL where it gets inserted in the rearranged immunoglobin heavy chain gene locus[31].

Acute myeloid leukemia: AML is a hematopoetic progenitor cell origin, malignant disorder affecting the myelod lineage[32]. In AML, miR-15a/16 is decreased[33]. Similar to CLL and other forms of cancer, miR-29 is downregulated in AML whose validated targets include the tet1 oncogene, the antiapoptotic Mcl1 and the cyclin dependent kinase Cdk6. Ectopic expression of miR-29 also induces upregulation of the cell cycle inhibitors p15INK4B and ESR1 through demethylation of their promoters by targeting the methyl transferases DNMT3A and DNMT3B and indirectly DNMT1[34,35].

miRNAs and lymphomas: miRNAs are involved in the progression of both Hodgkins and Non-hodgkins lymphomas. In Hodgkins lymphoma, miR-150 was reported to be significantly downregulated, whereas miR- 155 was upregulated and the target genes of miR-155 are AGTR1, FGF7, ZNF537,ZIC3 and IKBKE. Gibcus etal reported a signature of hematological lymphoma specific miRNAs, which included miR 17-92 cluster memebers , miR16, miR21, miR-24 and miR 155[36]. Mir- 155 plays a critical role in the development of lymphomas including Hodgkins, diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma. But its upstream regulating pathway or downstream targets that mediates its malignant effects are however not fully understood. A recent study reported that SHIP1 is a direct target of miR-155 in lymphoma cells and mir-155s upstream regulators include, TNF-α which has increased expression in DLBCL. Upregulation of miR-155 has also been described in non-hodgkins lymphoma[37].Validated targets of this cluster include the proapoptotic gene Bim and the cell cycle inhibitor CDKNIA/p21[38]. miR 17-92 cluster is also associated with non-hodgkins lymphoma, and the transcription of miR-17-92 cluster is regulated by c-myc, where it is frequently over expressed and downregulate the oncosuppressor gene PTEN and BIM[39]. C- MYC can activate miR 17-5p and miR 20a which directly targets E2F1 and promotes cell cycle progression[40].

miRNAs and Multiple myelomas: Multiple myeloma is characterised by a clonal expansion of plasma B-cell in the bone marrow or in extramedullary sites[41]. Recent studies on the role of miRNAs revealed it to be a key player in development of multiple myeloma. It was reported that IL-6 indirectly induces the transcription of miR 21 through STAT3 thereby controling the expression levels of survivin, Bcl-2, and Mcl-1. STAT3 thus exerts its anti apoptotic effect through induction of miR21[42]. Subsequent studies reported that miR-106b-25 cluster, miR 181a/b and miR 32 target a histone acetyl transferase, PCAF, which reversibly acetylates p53. Also miR 17-92 downregulates Bim and 19a/b targets SOCS-1, Silencer of STAT3 and enhances the oncogenic property of multiple myeloma cells[43,44]. Like chronic lymphocytic leukemia, miR 15a/b was found to be downregulated in multiple myeloma, which targets cyclin D1, cyclin D2 and CDC25a[45]. Other miRNAs reported to be increased in multiple myeloma are miR-25 and miR-30d which targets p53. Hyper methylation of promoters of various oncosuppressor miRNAs such as miR 124-1, miR 203 miR 29b has been reported to increase the tumorigenicity of myeloma cells[46].

miRNAs in myeloproliferative disorders: The major myeloproliferative disorders include polycythaemia vera, essential thrombocythaemia and primary milofibrosis, which are clonal stem cell disorders characterised by dis regulated hematopoetic stem cell expansion and production of RBC, WBC and Platelets, individually or in combination[47]. Deregulated miRNA profiles have been reported in myeloproliferative disorders also. In polycythaemia vera, let7a, miR30b, 30c and 150 was found to be down regulated which targets the genes like HMGA2,

HIC2, CCND2, RAS, MYB and IRAK2. upregulated miRNAs include miR182, 143, 145, 223, 26b and 27b which targets the genes like KRAS, HIC2, CHORDC1[48]. The target of let7a is HMGA2, a transcription factor whose disregulation contributes to clonal hamatopoesis[49]. High scored targets of miR150 are MYB and IRAK2 and IRAK2 was reported to be upregulated in polycythaemia vera cells, involved in TLR signalling pathways that interferes with NF- kB[50]. CCND2, a positive regulator of G1 phase promotion of the cell cycle, has been found to be involved in JAK2 V6 17F mediated signalling[51]. Some miRNAs like miR143, mir145 and miR223 are over expressed in all myeloproliferative disorders of mono nuclear cells and abnormally high expression of miR182 in granulocyte of all myeloproliferative disorders[52]. Sustained expression of a single miRNA miR125b or miR155 could cause myeloproliferative disorders by inhibiting apoptosis and expanding hematopoetic stem cell through regulation of TP53 pathway. Deregulated miRNAs contribute to MPN (Myeloproliferative neoplasm) stem cell clone expansion and regulates the differential hametopoetic lineage commitment among different MPN phenotypes[53,54].

Oncogenic and Oncosuppressor miRNAs in haematological malignancies: miRNAs, recently identified master regulators of gene expression, can act both as oncogenes and tumor suppressor genes demonstrating an important role of these non-coding RNAs in the pathogenisis and prognosis of haematological malignancies[55]. miR155 is considered as a oncogenic miRNA because of its over expression in many haematological cancers like B-cell lymphoma, Chronic Lymphocytic Leukemia etc. Another oncogenic miRNA is miR17-92 cluster which undergoes amplification in malignant B-cell lymphoma[56]. miR17-92 cluster can stimulate erythropoetin induced differentiation to proliferation.[57] Members of the miR17-92 cluster directly down regulates the transcription factor E2F1 and exerts a pro-proliferating effect in some circumstances and induces apoptosis in other conditions.[58] Apart from the oncogenic nature, miR17-92 cluster also have tumour suppressor effect by targeting E2F1[59].miR181a was also found to have dual oncogenic / tumour suppressor nature depending on the cellular evolvement[60]. Another important oncosuppressor miRNA reported is miR15a / 16-1 cluster which is deleted or down regulated in majority of chronic Lymphocytic Leukemias which inturn, can negatively regulate cell growth and cell cycle progression[61]. Other oncosuppressor miRNAs include miR223, miR342, miR107 and members of let7 family[62].

miRNAs in Haemoglobinopathies: Sickle cell disease and β thalassemia represent the most common haemoglobinopathies, which are caused due to deficient production of β-globin chain of haemoglobin and γ-globin reactivation and over expression[63]. Recent studies reported that miR96 directly targets γ-globin mRNA and inhibition of miR96 produced a 20% increase in γ-globin expression in erythroid progenitors[64].

Over expression of lin28 represses the let7 family which mediates HbF induction in adult erythroblast through inhibition of BCL11A[65]. Also BCL11A is targeted by miR486-3p to activate γ-globin expression in erythroid cells, associated with β thalassemia[66]. miR210 was also reported to be elevated in patients with β thalassemia and it was demonstrated that miR15a and miR16-1 represses MYB to induce HbF[67].

Circulating miRNAs and haematological disorders: The levels and composition of circulating miRNAs in blood can reflect the presence of malignant and non malignant disorders. Deregulated levels of 3 circulating miRNAs miR155, miR210 and miR221 were found in the serum of patients with DLBCL[68]. It was reported that two miRNAs miR16 and let7a were found in the plasma of patients with myelodysplastic syndrome[69]. Deregulation of 4 miRNAs like miR223 miR128a,

miR128b and let7b is used to differentiate between Acute Myeloid Leukemia and Acute Lymphocytic Leukemia[70]. However in order to reveal the connection of circulating miRNAs with the pathology of haematological diseases, further, specific profiling studies are necessary and this field provides wide scope for biomarker discovery.

miRNAas: Future Perspectives for use in Diagnosis and Therapy of Hematological Disorders: The ability of miRNAs to function as master regulators of hematopoetic landscape makes them a promising diagnostic and prognostic tool in haematological disorders. miRNAs, being short and often highly conserved among multiple vertebrate species, and having multiple targets within cellular networks, they can modulate entire pathways in disease thereby presenting itself as a potential tool for therapeutic targeting. Different approaches are under study for restoring or inhibiting the deregulated miRNAs.

The potential application of anti-miRNA molecules (antagomirs) are studied by different groups in vitro and in vivo. For eg; in CML, the members of miR17-92 cluster like miR18a, miR19b and miR20a are aberrantly expressed. Antimir-18a, antimir19b and antimir20a could successfully antagonise these members.The expression level of the transcription factor E2F1, which is a target of miR20a was increased following treatment with antimir20a. These datas suggest that miR17-92 cluster can act as a significant therapeutic target in CML[71]. Antagomir based inhibition of miR451 was reported in myeloproliferative diseases. Among the targets of miR451, 14-3-3zeta, an intra cellular regulator of cytokine signalling is repressed by miR451, and is upregulated in miR451 deficient erythroblast[72]. Epigenetic regulation of miRNAs by methylation can contribute to a very promising therapeutic target of hypomethylating treatment and a useful tool in differentiating patients with poor prognosis. In ALL, for example, methylation of DNA resulted in down regulation of miR124 and upregulation of its target CDK6 and proliferation of ALL cells, while treatment with 5-aza-2' deoxycytidine results in upregulation of miR124 and down regulation of CDK6[73].

Along with their potential use as therapeutic agents, miRNAs can also play a crucial role in predicting the response to therapy or indicators of clinical outcome of a disease. In CLL patients, prognostic factors such as zap-70 expression, IgVH mutational status and time between diagnosis and treatment are

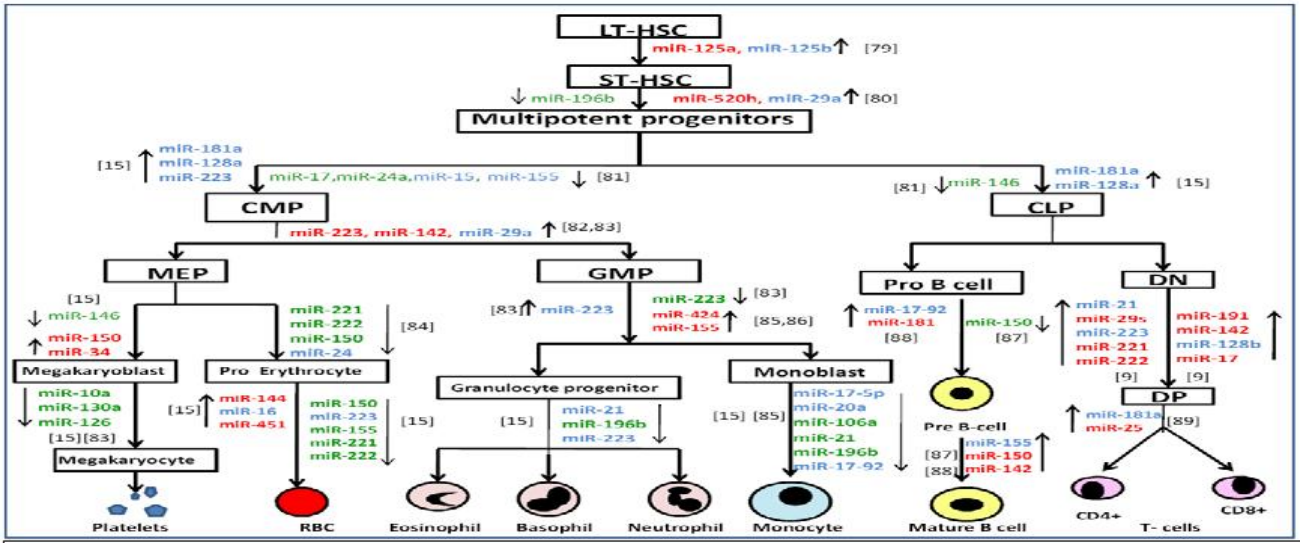

Fig.1Role of different miRNAs in Hematopoesis. The miRNAs that regulate different steps in hematopoesis are indicated in red and green. Upregulated(↑) miRNAs are shown in red and downregulated (↓) miRNAs are shown in green. Among these, the miRNAs that are dysregulated during different haematological disorders are indicated in blue color. **LT HSC**: Long-term hematopoietic stem cell; **ST-HSC**:Short-term hematopoietic stem cell; **CMP**: Common myeloid progenitor; **CLP**: Common lymphoid progenitor; **MEP**: Megakaryocyte-

In addition, the miRNAs like miR29c and miR223 A to C of CLL. So these miRNAs can predict are down

regulated during transition from binet stage treatment free survival and overall survival.[74]

Apart from such diagnostic and prognostic approaches, miRNAs also have specific application in regenerative medicine, where specific miRNAs can be used to generate induced pluripotent stem cells (iPS)[75]. It has been reported that miR372 and miR302 can promote reprogramming of human fibroblasts to iPS by accelerating mesenchymal epithelial transition [76,77]. Another possible application of miRNAs is the in vitro expansion of HSC which can be used in hematopoetic stem cell transplantation, especially in case of small volume transplants[78].

Despite all these approaches, there is a long way to go from the current existing knowledge to the establishment of miRNAs as potent therapeutic, diagnostic or prognostic tools. However further studies and bold initiatives are necessary to unveil the complex regulatory pathways in which miRNAs are involved so as to design useful therapeutic tools.

CONCLUSION

miRNAs are important players in the process of hematopoiesis and other related hematological processes. Therefore a dysregulation in their levels could be detrimental for the normal physiology. An overview of the various miRNAs involved in the process of hematopoiesis and those that are dysregulated during pathological condotions are illustrated in Fig.1.

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