Cancer Letters 454 (2019) 134–145

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

MicroRNA-125 in immunity and cancer

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ARTICLE INFO

Keywords:
MicroRNA
Immune cell
Cancer
Biomarker
Epigenetic

ABSTRACT

MicroRNAs (miRNAs) are small non-coding RNAs that play a wide variety of critical roles in different biological processes by post-transcriptionally regulating gene expression. They access diverse regulatory pathways during various stages of cellular differentiation, growth, and apoptosis, and can contribute to both normal and diseased functions. One important family of miRNAs involved in these functions is the miR-125 family (miR-125a and miR-125b). Investigations have been made to increasingly uncover the mechanisms by which the miR-125 family regulates normal homeostasis and growth in a variety of cell types including immune cells, and how dysregulation of miR-125a and miR-125b can lead to disease pathogenesis and tumorigenesis. In this review, we summarize what is currently known about miR-125a and miR-125b, mainly focusing on their roles in immune cell development and function as well as tumor suppression and promotion.

1. Introduction

MicroRNAs (miRNAs) are a naturally occurring class of small (approximately 22 nucleotides long) non-coding RNAs that regulate post-transcriptional gene expression to control cellular processes, development, cell differentiation, and homeostasis [1]. Multiple steps are involved in the generation of miRNAs [2,3]. Most miRNAs are produced by the canonical biogenesis pathway, which involves transcription by RNA polymerase II to make a primary transcript (pri-miRNA) and cleavage by the microprocessor complex to yield a hairpin precursor miRNA (pre-miRNA) in the nucleus. The pre-miRNA is then exported into the cytoplasm, where cleavage by the enzyme Dicer creates a double-stranded RNA duplex. Only a single strand from the double-stranded RNA duplex forms the mature miRNA and is incorporated into the RNA-induced silencing complex (RISC), which guides the binding of Argonaute (AGO) proteins in the RISC to the 3' untranslated region (UTR) to either repress protein translation or promote mRNA degradation. In addition to canonical miRNA biogenesis pathways, non-canonical microprocessor-independent or Dicer-independent miRNA biogenesis pathways also exist [3]. For example, the microprocessor-independent pathway produces pre-miRNA hairpins from introns [4–7]. Despite miRNAs being mostly involved in the down-regulation of gene expression, there are reports of miRNAs promoting gene expression [8–10]. In addition, relationships between miRNAs and their targets are not always one-to-one in a specific cell type. In fact, a single miRNA may regulate many mRNA targets, and conversely, a single mRNA target also can be regulated by many miRNAs [11].

Since the discovery of the first miRNAs (lin-4 and let-7) in *C. elegans* [12,13], about 2000 miRNAs in the human genome have been annotated. Normal miRNA expression plays important roles in various cellular processes, while miRNA dysregulation leads to disease pathogenesis and progression, such as the development of cancer [11]. One miRNA family that has been significantly investigated is the highly conserved microRNA-125 (miR-125) family, which consists of miR-125a and miR-125b. In humans, there are three homologs, hsa-miR-125a, hsa-miR-125b-1 and hsa-miR-125b-2, which share the same seed sequence but are organized as clusters on different chromosomes (Fig. 1) [11,14]. Hsa-miR-125b-1 and hsa-miR-125b-2 are paralogs, clustered with hsa-miR-100 and hsa-let-7a-2 on human chromosome 11 or with hsa-miR-99a and hsa-let-7c on chromosome 21, respectively. Hsa-miR-125a is located on chromosome 19, in close proximity to hsa-miR-99b and hsa-let-7e. In mice, the miR-125a and miR-125b clusters are localized on chromosomes 17 and 16, respectively [15]. Each member of the miR-125 family has two different mature miRNAs (5p and 3p), derived from the 5′ or the 3' arm of the pre-miRNA. Among these miR-125 variants, miR-125-5p is often more highly expressed than miR-125-3p [16].

The level and function of miR-125 can be up- or down-regulated by

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https://doi.org/10.1016/j.canlet.2019.04.015
Received 19 February 2019; Received in revised form 9 April 2019; Accepted 9 April 2019
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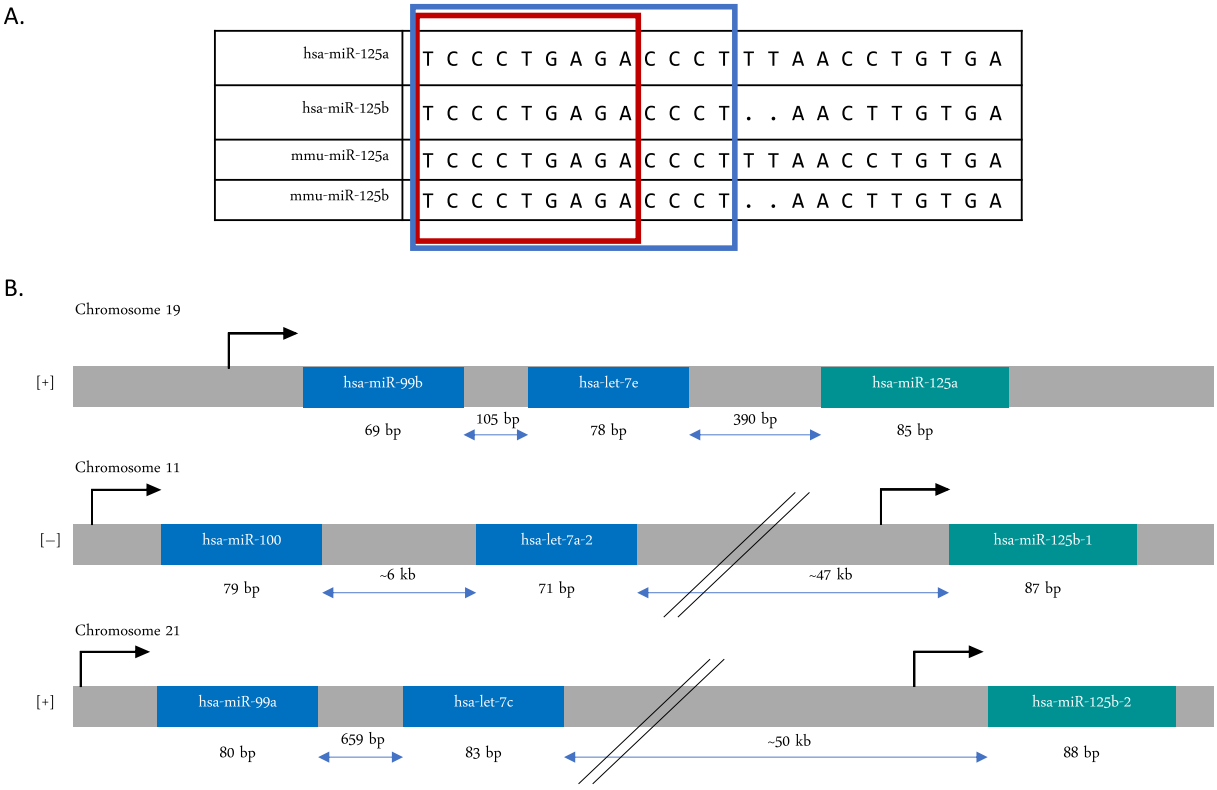

Fig. 1. miR-125a and miR-125b sequence conservation and genomic organization. (**A**). The seed region of miR-125 homologs is highly conserved in the human and mouse genomes (blue box) and throughout other species (red box, other species' sequences not shown). (**B**). Genomic organization of the clusters containing the miR-125 family on human chromosomes 19, 11, and 21 with potential promoter regions indicated. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

a variety of mechanisms, such as chromosome translocation [17,18], RNA methylation [19], single nucleotide polymorphisms (SNPs) [20], lncRNAs [21–24], transcription factors [25] and histone modifications [16]. For example, t(2; 11)(p21; q23) and t(11; 14)(q24; q32) chromosome translocations result in over-expression of miR-125b-1 in myelodysplastic syndrome [17] and acute myeloid leukemia (AML) [17,18]. In addition, methylation of pri-, pre-, or mature miR-125b by RNA methyltransferase NSun2 blocks the processing and function of miR-125b [19]. Potential promoter and enhancer regions have been predicted for miR-125 (Fig. 1b) [25–28], and several transcription factors, such as PPAR-γ, NF-κB, p53 and MYC have been identified [25]. PPAR-γ and CDX2 can bind to the up-stream responsive element of the miR-125b promoter and increase miR-125b expression [29,30]. However, in cutaneous T-cell lymphoma, the oncogene C-MYC suppresses the activity of miR-125b enhancers, resulting in down-regulation of miR-125b [31]. Additionally, levels of miR-125 can be modulated by lncRNAs, such as NEAT1, MEG3, UCA1 and MALAT1 [21–24].

In addition to studies on the regulation of the miR-125 family itself, extensive research has increasingly uncovered the important roles of miR-125 in normal immune functions as well as disease pathogenesis and tumorigenesis (see Table 1). This review will primarily focus on the involvement of miR-125a and miR-125b in the following areas: development and function of immune cells; cancer promotion or suppression in different cell types; chemotherapy drug sensitivity or resistance; and clinical potentials in cancer therapies and treatments.

2. miR-125 in immune cells

The miR-125 family plays important roles in hematopoiesis and immune cell function (Fig. 2a). miR-125 exhibits different levels of expression depending on the types of immune cells and stages of hematopoiesis. In general, miR-125 expression decreases during the hematopoietic cell maturation process. miR-125a is found to be highly expressed in hematopoietic stem cells (HSCs)/multipotent progenitors (MPPs) during the early stage of hematopoiesis in mice and humans [32,33]. miR-125a expression is downregulated in multi-lymphoid progenitors (MLPs) and committed lymphoid progenitor cells at the later stages of hematopoiesis [33]. Similarly, miR-125b is expressed in bone marrow HSCs/MPPs but shut down in the lymphoid lineages [16,34]. miR-125 expression levels play important roles in hematopoiesis. miR-125a overexpression increases HSC/MPP long-term multilineage repopulation and self-renewal by blocking apoptosis pathways [32,33,35]. Similarly, miR-125b can expand HSCs, regulating HSC homeostasis by shifting the balance of TGFβ and Wnt signaling pathways [36]. In addition, miR-125b impairs B cell development and inhibits the development of effector T cells but drives the activation of macrophages [16,37,38]. The miR-125 family also affects granulopoiesis and granulocytic functions [39]. Mechanisms affecting immune cells will be discussed in detail below.

2.1. Granulocytes

Granulopoiesis produces myeloid granulocytes including eosinophils, basophils and neutrophils. During granulopoiesis, HSCs differentiate into multilineage progenitors, producing granulocyte progenitors that subsequently differentiate into mature granulocytes. The miR-125 family is involved in modulating different processes of granulopoiesis and regulating the proliferation of immature granulocytes. During the maturation of granulocyte progenitors, miR-125 expression is downregulated [33,40]. Knockout of the miR-125a gene in mice impairs G-CSF signaling and leads to a decreased percentage of neutrophils in both the bone marrow and the circulatory system [39].

Table 1
Identified miR-125a and miR-125b targets in a variety of cell types.

microRNA	Target gene	Cell/tissue type	Role	Ref.
miR-125a targets				
miR-125a	A20	Pancreatic cells	Chemo-sensitivity to Gemcitabine	[127]
miR-125a	E2F2	Osteosarcoma	Tumor suppression	[91]
miR-125a	FIH1, IRF4	Macrophages	Macrophage polarization	[44]
miR-125a	GALNT14	Ovarian cancer	Tumor suppression	[125]
miR-125a	glypican-4	Kidney cells	Inhibition of cell growth	[150]
miR-125a	HAX-1	Laryngeal cancer stem cells	Reverse Cisplatin chemo-resistance	[137]
miR-125a	Protein phosphatases (PTPN18, PTPN7, PPP1CA, PPP2CA)	Myeloproliferative disease and neoplasm (MPN)	Induce cytokine hypersensitivity	[151]
miR-125a	*Socs3*	Neutrophils	Promote granulopoiesis	[39]
miR-125a	STAT3	Cervical cancer	Tumor suppression	[121]
miR-125a	STAT3	Cervical cancer	Promote paclitaxel sensitivity	[133]
miR-125a	WT1	HSC	Tumor suppression	[152]
miR-125a	Zbtb7a	NSCLC	Tumor suppression	[153]
miR-125a-5p	A20	Macrophages	Macrophage polarization	[43]
miR-125a-5p	ABL2	Cervical carcinoma	Tumor suppression	[122]
miR-125a-5p	BAK1/MLK3	Melanoma	Suppression of intrinsic apoptotic pathway	[126]
miR-125a-5p	BAP1	Breast cancer	Tumor suppression	[113]
miR-125a-5p	BCL2, BCL2L12, MCL1	Colon cancer	Tumor suppression	[85]
miR-125a-5p	BRMS1	Gastric cancer	Inhibit metastasis and invasion of cancer	[109]
miR-125a-5p	Casp2	Various cells	Inhibit apoptosis	[64]
miR-125a-5p	CD147	Thyroid cancer	Tumor suppression	[89]
miR-125a-5p	E2F3	C2C12 myoblast	Inhibit proliferation	[154]
miR-125a-5p	E2F3	Gastric cancer	Tumor suppression	[108]
miR-125a-5p	ESRRA	Oral squamous cell carcinoma	Tumor suppression	[93]
miR-125a-5p	ETS-1	Vascular smooth muscle cells (VSMCs)	Modulation of phenotypic switch of VSMCs	[155]
miR-125a-5p	FUT4	Bladder cancer	Tumor suppression	[156]
miR-125a-5p	HDAC4	Breast cancer	Tumor suppression	[111]
miR-125a-5p	HDAC5	Breast cancer	Tumor suppression	[112]
miR-125a-5p	HK2	Hepatocellular carcinoma	Regulate cell energy metabolism	[84]
miR-125a-5p	IL-6R	Treg cells	Decrease Treg cell sensitivity toward IL-6-Mediated Conversion	[53]
miR-125a-5p	KLF13	Macrophages	Differential activation of macrophages and inflammation	[46]
miR-125a-5p	LIFR	Breast cancer	Stem cell pool expansion	[118]
miR-125a-5p	MARK1	Cervical cancer	Enhance cell migration	[63]
miR-125a-5p	MMP-11	Osteosarcoma	Tumor suppression	[92]
miR-125a-5p	NEDD9	Lung adenocarcinoma	Tumor suppression	[105]
miR-125a-5p	ORP9	Monocytes/Macrophages	Regulation of lipid uptake and inflammatory response	[157]
miR-125a-5p	p38/JNK/ERK	SACC	Tumor suppression	[88]
miR-125a-5p	p53	Breast/Liver/Kidney cancer	Tumor growth	[158]
miR-125a-5p	p53	Multiple myeloma	Tumor growth	[159]
miR-125a-5p	STAT3	Lung carcinoma	Tumor suppression	[104]
miR-125a-5p	STAT3	ESCC	Chemo-sensitivity to Cisplatin	[138]
miR-125a-5p	STAT3	Treg cells	Decrease sensitivity toward IL-6-mediated conversion	[53]
miR-125a-5p	*Stat3, Casp2, Stard13*	Murine liver	Prevent age-associated changes	[160]
miR-125a-5p	Stat3, Il13, Ifng	T cells	Stabilize Treg-mediated immune homeostasis	[54]
miR-125a-5p	TIMP-1	NSCLC	Increase apoptosis/tumor suppression	[106]
miR-125a-5p	TNFR2/CCR2	Treg cells	Inhibit Treg migration	[161]
miR-125a-5p	TP53	Nasopharyngeal carcinoma (NPC)	Inhibit tumor suppression function of TP53	[65]
miR-125a-5p	VEGFA	Colorectal cancer	Tumor suppression	[162]
miR-125a-5p	VEGFA	Gastric cancer	Angiogenesis regulation	[110]
miR-125a-3p	Bcl-2, NF1	THP-1 macrophages	Promote THP-1 cell differentiation and apoptosis	[163]
miR-125a-3p	BRCA1	Breast cancer	Increase Docetaxel chemo-sensitivity	[130]
miR-125a-3p	CDK3	Breast cancer	Tumor suppression	[132]
miR-125a-3p	FUT5, FUT6	Colorectal cancer	Tumor suppression	[86]
miR-125a-3p	Nrg1	Glioma cells	Tumor suppression	[164]
miR-125a-3p	RhoA	Lung cancer	Suppression of tumor cell migration	[103]
miR-125a-3p	TIM-3	AML cell line HL-60	Tumor suppression	[165]

microRNA	Target gene	Cell/tissue type	Role	Ref.
miR-125b targets				
miR-125b	A20 (TNFAIP3)	T cells	Regulate differentiation and reprogramming of glucose metabolism	[50]
miR-125b	BCL2	HCC cells	Tumor suppression	[82]
miR-125b	BCL2	Leukemic B cells	Regulate proliferation	[166]
miR-125b	BCL2	Nasopharyngeal carcinoma cells	Reverse multidrug resistance	[134]
miR-125b	BIK	Monocytes	Reduce mitochondrial respiration	[47]
miR-125b	Bright/ARID3a	Progenitor B cells	Tumor promotion	[79]
miR-125b	CCNJ, CK2-α, ENPEP, MEGF9	Breast cancer	Tumor suppression	[114]
miR-125b	E2F2	Glioblastoma stem cells	Inhibit proliferation	[98]
miR-125b	eIF5A2	HCC cells	Tumor suppression	[80]
miR-125b	EPO/EPOR	Breast cancer	Tumor suppression	[115]
miR-125b	Fes	AML cells	Inhibit cellular differentiation	[167]
miR-125b	ICAM2	Oral squamous cell carcinoma	Decrease proliferation and radioresistance	[168]
miR-125b	IFNG	Naïve $CD4^+$ T cells	Preservation of naïve T cell state	[38]

(*continued on next page*)

Table 1 (*continued*)

microRNA	Target gene	Cell/tissue type	Role	Ref.
miR-125b	IL10RA	Naïve $CD4^+$ T cells	Preservation of naïve T cell state	[38]
miR-125b	IL2RB	Naïve $CD4^+$ T cells	Preservation of naïve T cell state	[38]
miR-125b	IRF4	B cells Myeloma cells	Inhibit differentiation, compromise cell survival	[15]
miR-125b	IRF4	Myeloid and B cells	Induce myeloid and B-cell leukemias	[57]
miR-125b	IRF4	Macrophages	Macrophage activation	[37]
miR-125b	IRF4	Germinal center lymphocytes	Lymphomagenesis	[77]
miR-125b	Lin28A	Hematopoietic cells	Regulation of hematopoiesis	[56]
miR-125b	MAP3K11	Early B cells	Abnormal cellular proliferation	[78]
miR-125b	MMP13	CSCC	Tumor suppression	[96]
miR-125b	MTP18	Monocytes	Promote elongation of mitochondrial network leading to apoptosis	[47]
miR-125b	*Nestin*	NS/PC cells	Modulate proliferation, differentiation and migration	[169]
miR-125b	p53	Colorectal cancer	Inhibit apoptosis	[145]
miR-125b	PIK3CD	Cervical cancer	Tumor suppression	[123]
miR-125b	PIK3CD	Ewing's sarcoma	Tumor suppression	[97]
miR-125b	PRDM1	Naïve $CD4^+$ T cells	Preservation of naïve T cell state	[38]
miR-125b	PRDM1	B cells, Myeloma cells	Inhibit plasma cell differentiation; compromise myeloma cell survival	[15,77]
miR-125b	Sema4C	Paclitaxel-resistant breast cancer	Tumor suppression via regulation of epithelial-mesenchymal transition	[131]
miR-125b	SP7 (osterix)	Vascular smooth muscle cells	Regulation of vascular calcification	[170]
miR-125b	STAT3, Bak1	Murine 32D myeloblast cells	Block granulocytic differentiation and enable proliferation Promote myelopoiesis	[41]
miR-125b	TP53INP1	NSCLC	Promote tumor metastasis	[69]
miR-125b	VE-cadherin	Endothelial cells	Inhibit blood vessel tube formation	[171]
miR-125b	Vps4b	Squamous cell carcinoma	Enhance skin tumor initiation and promote tumor progression	[172]
miR-125b-5p	5-Lipoxygenase	Myeloid cells	Modulation of leukotriene pathway	[173]
miR-125b-5p	A20 (TNFAIP3)	*Brucella abortus*	Suppress *Brucella abortus* intracellular survival	[174]
miR-125b-5p	B7-H4	Macrophages	Modulation of inflammatory state	[175]
miR-125b-5p	BCL2	Gallbladder cancer	Enhance Cisplatin chemo- sensitivity	[139]
miR-125b-5p	LACTB	THP-1 macrophages	Decrease secretion of MCP-1	[176]
miR-125b-3p	S1PR1	B cells	Inhibit B-cell egress from bone marrow	[16]

Target gene	Cell/tissue type	Role	Ref.
miR-125a and miR-125b targets			
A20 (TNFAIP3)	Diffuse large B-cell lymphoma	Tumor promotion	[75]
EIF4EBP1	Ovarian cancer	Tumor suppression	[124]
ERBB2/ERBB3	Breast cancer	Tumor suppression	[117,177]
HER2	Small cell lung cancer	Tumor suppression	[136]
TET2	AML	Regulate malignant hematopoiesis	[74,178]

AML = Acute myeloid leukemia.
Bcl-2 = B-cell lymphoma 2.
Bright = B-cell regulator of immunoglobulin heavy-chain transcription/ARID3a.
CSCC = Cutaneous squamous cell carcinoma.
EPO = Erythropoietin.
EPOR = Erythropoietin receptor.
ESCC = esophageal squamous cell carcinoma.
ESRRA = Estrogen-related receptor α
FIH1 = factor inhibiting hypoxia inducible factor-1α.
HCC = hepatocellular carcinoma.
HEK293T = human embryonic kidney cell line 293T
HK2 = Hexokinase II.
ICAM2 = intercellular adhesion molecule-2.
IRF4 = Interferon regulatory factor 4.
LIFR = leukemia inhibitory factor receptor.
MMP13 = Matrix Metallopeptidase 13.
MARK1 = Microtubule-affinity-regulating kinase1.
NF1 = Neurofibromatosis type 1.
NSCLC = Non-small-cell lung cancer.
NS/PC cells = Neural stem/progenitor cells.
ORP9 = oxysterol binding protein-like 9.
osterix = osteoblast transcription factor SP7.
PIK3CD = phosphoinositide 3-kinase catalytic subunit delta.
SACC = salivary adenoid cystic carcinoma.
TET2 = Ten-Eleven-Translocation 2.
Treg = Regulatory T cells.
Vps4b = Vacuolar protein-sorting 4 homolog B.

Further investigations found that Socs3, a critical repressor for granulopoiesis, is the direct target of miR-125a. Another *in vitro* study using 32D mouse myeloid cells has shown that over-expressed miR-125b blocks G-CSF-induced granulocytic differentiation by targeting STAT3 cofactors c-Jun and Jund [41]. In addition, over-expressing miR-125b in normal granulocytes can lead to the inhibition of granulocytic

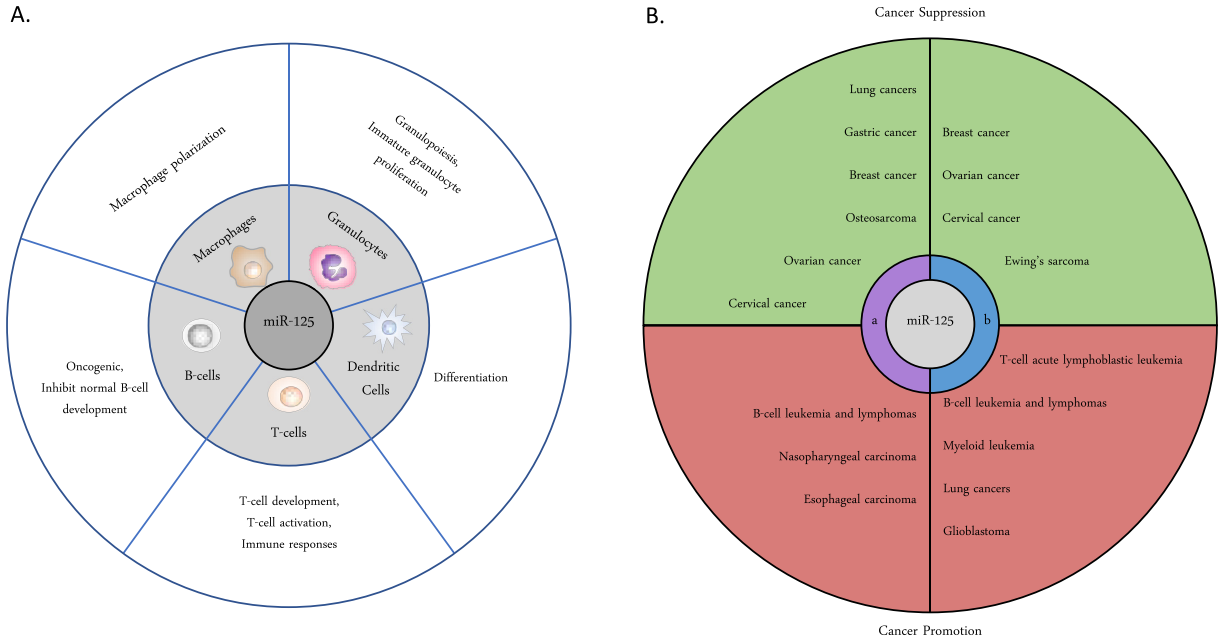

Fig. 2. Functions of miR-125 in immunity and cancer. (**A**). Roles of miR-125 in immune cell development and differentiation. (**B**). Tumor suppressive and oncogenic functions of miR-125 in different cancer cell types.

chemotaxis and LPS induced cell death [40].

2.2. Macrophages

Monocyte to macrophage differentiation involves polarization into two different types of macrophages. The M1 (classically activated) macrophages exhibit a Th1-like phenotype that is pro-inflammatory while the M2 (alternatively activated) macrophages exhibit a Th2-like phenotype that is anti-inflammatory. Stimulating macrophages with Toll-like receptor (TLR) ligands such as LPS and/or IFN-γ results in M1 macrophages, while stimulating macrophages with Th2-like cytokines such as IL-4 results in M2 macrophages [42].

miRNAs play important regulatory roles in macrophage polarization and inflammatory responses. miR-125a is upregulated in M1 macrophages, while it is down regulated in M2 macrophages [43,44]. Temporal patterns of miRNA expression across multiple macrophage polarization phenotypes using bone marrow-derived macrophages have shown increased miR-125a expression in M1 macrophages [45]. However, it is also reported that M2 macrophages obtained by treatment of bone marrow-derived macrophages with M-CSF has a higher expression level of miR-125a-5p [46]. miR-125b is more highly expressed in macrophages than in lymphoid cells and whole immune tissues and promotes M1 macrophage activation [37]. miR-125b is enriched in M1 macrophages and contributes to improved antigen presentation, enhanced T-cell activation, and tumor suppression [37]. miR-125b overexpression in macrophages enhances surface activation markers in response to IFN-γ [37]. It inhibits interferon regulatory factor-4 (IRF4), which is a negative regulator of M1 macrophage activation [37]. In addition, miR-125b regulates M1 macrophage adaptation to inflammation by promoting proinflammation activation and apoptosis via attenuation of mitochondrial respiration [47]. Increased miR-125b upon the activation of TLR4 by LPS can silence the proapoptotic proteins BIK and MTP18, which affects mitochondrial oxygen consumption and dynamics, respectively [47].

2.3. T-cells

T cell development is a multi-stage process. HSC/MPP cells differentiate into common lymphoid precursor (CLP) cells, which then further differentiate into double negative ($CD4^-CD8^-$) and double positive ($CD4^+CD8^+$) thymocytes in the thymus. Through a multi-stage selection process, the immature naïve T cells exit from the thymus as singly positive ($CD4^+$ for helper T cells or $CD8^+$ for killer T cells) cells and further develop into various effector T cells. Although most T cells have T cell receptors (TCRs) composed of α and β chains, a small portion of specialized T cells have TCRs comprised of γ and δ chains [48].

The miR-125 family has different expression profiles in the various T cell types during the T cell development process. miR-125b is more highly expressed in human naïve $CD4^+$ T cells than in memory $CD4^+$ T cells [38]. miR-125b-5p, among other miRNAs, is downregulated in γδ T cells compared to αβ T cells [49]. The different expression profiles play an important role in regulating T cell development. miR-125b can suppress $CD4^+$ T cell differentiation and thus preserve the naïve state of $CD4^+$ T cells via regulation of multiple genes encoding key molecules in the differentiation process [38]. miR-125 also regulates T cell activation and immune responses. miR-125b-5p overexpression in γδ T cells inhibits γδ T cell activation and promotes their apoptosis. Knocking down miR-125b-5p expression facilitated the cytotoxicity of γδ T cells *in vitro* [49]. Overexpression of miR-125b can increase the $CD4^-$ T cell population by targeting A20 (TNFAIP3) and increase T cell glucose metabolism and oxygen consumption [50]. For regulatory T cells to limit excessive inflammation [51,52], sensitivity to inflammatory IL-6-rich conditions is decreased by miR-125a-5p via inhibition of IL-6 receptor and STAT3 expression [53]. In addition, miR-125a can stabilize the immunoregulatory capacity of regulatory T cells via suppression of several effector T cell factors including Stat3, IFN-γ and IL-13 [54].

2.4. B-cells

B cells go through the development process from CLP cells to pro-B cells, pre-B cells, and immature B cells in the bone marrow. After immature B cells enter the circulatory system as transitional B cells, they eventually differentiate into mature pre-immune B cell pools, including follicular, marginal-zone, germinal center and memory B cells [55].

Normal B-cell development requires epigenetic silencing of miR-125b [16]. Expression of miR-125b is evident in bone marrow MPPs

and myeloid cells but shut down in the B-cell lineage. B-cell-specific miR-125b overexpression *in vivo* impairs the release of immature B cells from bone marrow into the blood [16]. Immature B cells are found to be retained in bone marrow sinusoids, leading to increased apoptosis [16]. Further studies identified that S1PR1, a key regulator of the process of immature B-cell release from the bone marrow, is the direct target of miR-125b. Enforced expression of S1PR1 or clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9–mediated genome editing of the miR-125b targeting site in the S1PR1 3′ UTR rescued the miR-125b–mediated defect in B-cell egress [16]. Dysregulation of miR-125b also causes a defect in pre-B cell development [16,56,57]. However, the underlying mechanism for this defect is still unclear. Low expression of miR-125b is associated with repressive histone modifications and/or the absence of active histone modifications in promoter regions of respective coding genes [16], suggesting that the epigenetic regulatory machinery is strictly controlled in order to silence miR-125b expression for normal B-cell development. Consistent with these findings, overexpression of miR-125b inhibits the differentiation of primary B cells into plasma cells [15]. Despite the findings on miR-125b, less is known about the involvement of miR-125a in B-cell development.

2.5. Dendritic cells

Dendritic cells (DCs) are a subpopulation of mononuclear phagocytes involved in triggering the innate and adaptive immune responses. miRNAs regulate the differentiation and functions of DCs, and distinct miRNA groups are expressed in conditioned DCs or in specific subsets of DCs at different differentiation stages [58].

Histone H3K4me3 and H3K27me3 modifications in miRNA transcription start sites (TSSs) participate in regulating the levels of miRNAs in DCs [58]. In human blood DCs, miR-125b is preferentially expressed [59]. When monocyte-derived DCs (moDCs) are treated with TGF-β, the TSS of miR-125b-1 is enriched with H3K27me3, resulting in reduced miR-125b-1 expression [58]. IFN-α treated moDCs also exhibit downregulation of miR-125b, which modulates the expression of Blimp-1. A similar phenotype is also observed in IFN-α treated plasmacytoid DCs (pDCs) [60]. Meanwhile, in murine DCs, miR-125b is downregulated [61]. Mice with miR-125b overexpression in bone marrow show a dramatic increase in the DC population [56]. On the other hand, miR-125a-5p is highly expressed in regulatory DCs (DCregs) from mouse bone marrow. This phenotype is associated with histone H3 acetylation in the promoter region of miR-125a [62]. Despite the extensive studies on miR-125 expression in DCs, the function of miR-125 in DCs requires further investigation.

3. miR-125 and cancer

Extensive studies on the miR-125 family in hematopoiesis and the development and functions of immune cells have linked it to roles in human diseases including autoimmune diseases and cancer. Effects of miR-125a and miR-125b in cancer is cell type dependent (Fig. 2b). miR-125a and miR-125b can be either oncogenic or tumor suppressive, promoting or preventing the growth of tumors at various stages, by affecting cellular differentiation, proliferation, invasion, metastasis, and apoptosis.

3.1. miR-125 promoting cancer growth

An oncogenic miRNA is referred to as an oncomiR. In the case of miR-125a and miR-125b, the miRNAs act as oncomiRs in blood and non-blood cancers in a cell type specific manner. For example, miR-125a has oncogenic properties in non-blood cancers such as cervical cancer [63], colon cancer [64], nasopharyngeal carcinoma [65], and esophageal carcinomas [66,67], while miR-125b is oncogenic in lung cancer [68–70], and glioblastoma [71,72].

A substantial amount of the research on miR-125a and miR-125b as oncomiRs (especially miR-125b) has been conducted on blood cancers. For example, miR-125b has been reported to promote T-cell acute lymphoblastic leukemia (T-ALL) [50,73] and myeloid leukemia [56,57,74], while both miR-125a and miR-125b are reported to cause B-cell leukemia and lymphomas [16,57,75–77]. Molecular mechanisms on blood cancer pathogenesis have also been studied. In B-cell related cancers, for example, diffuse large B-cell lymphoma (DLBCL) is associated with the constitutive activation of the NF-κB pathway via miR-125a as well as repression of tumor necrosis factor alpha-induced protein 3 (TNFAIP3), a negative regulator of NF-κB, by miR-125b [75]. While recent research clearly indicates that epigenetic silencing of miR-125b is required for normal B-cell development, overexpression of miR-125b initially represses B-cell development and reduces pre-B cell output, and continued dysregulation of miR-125b leads to the development of B-cell leukemias or lymphomas [16,57]. miR-125b silencing therefore acts as a mechanism for cancer suppression in B-cells [16], since miR-125b becomes oncogenic when it is expressed in B-cell precursors [78].

There appears to be multiple mechanisms for miR-125b to act as an oncomiR to cause blood cancer. In progenitor B-cells (pro-B cells), miR-125b targets B-cell regulator of immunoglobulin heavy-chain transcription (Bright)/ARID3a to block differentiation, induce abnormal proliferation, and prevent apoptosis [79]. miR-125b also targets tumor suppressors such as MAP3K11 [78] and IRF4 [57]. Interestingly, IRF4 is inhibited by miR-125b in both B-cell leukemia and myeloid leukemia; however, the mechanism of inhibition is distinctly different in each case. miR-125b induces B-cell leukemia by genetically deleting the IRF4 gene [57]. This deletion eliminates the need for miR-125b to be constantly upregulated in order to maintain the oncogenicity of the cancer cells. On the other hand, in myeloid leukemia, miR-125b represses IRF4 expression at the mRNA and protein level (without altering the genomic DNA) in order to enhance myeloid progenitor output and induce tumorigenesis through progenitor cells [57]. Reconstitution of IRF4 expression suppresses miR-125b-induced B-cell and myeloid leukemia [16,57]. In addition to targeting IRF4 in myeloid cells, miR-125b targets Lin28A, a key hematopoietic regulator, to disrupt normal hematopoiesis by skewing the hematopoietic lineage and expanding myeloid cells [56]. miR-125b overexpression can also promote MLL-AF9-driven acute myeloid leukemia through a non-cell intrinsic and miR-125b-TET2-VEFGA pathway dependent mechanism [74]. These studies demonstrated that miR-125 acts as oncomiRs via cell-type specific mechanisms.

3.2. miR-125 suppressing cancer growth

While the miR-125 family is oncogenic in some cancers, it can exhibit tumor suppressive effects on others, such as human hepatocellular carcinoma [80–84], colorectal cancer [85,86], renal cell carcinoma [87], salivary adenoid cystic carcinoma [88], thyroid cancer [89], laryngeal cancer [90], osteosarcoma [91,92], oral squamous cell carcinoma [93], prostate cancer [94], cutaneous malignant melanoma [95], cutaneous squamous cell carcinoma [96], Ewing's sarcoma [97], glioblastoma [98], and gallbladder cancer [99]. By regulating certain pathways associated with cancer growth or inhibiting oncogenic proteins, miR-125a and miR-125b can induce cellular senescence or apoptosis and/or inhibit cancer migration or invasion. In contrast to the studies on miR-125a and miR-125b as oncomiRs in mostly blood cancers, tumor suppression effects have been demonstrated in a wide variety of cancer types through cell-type specific mechanisms. Here, we will review our current understandings of the tumor suppression effects in cancers of the respiratory, digestive, and reproductive systems.

In lung cancer cells, even though miR-125b is oncogenic, miR-125a has been found to be tumor suppressive [100–106]. It directly or indirectly silences several oncogenic pathways and suppresses main tumorigenesis effectors to inhibit cell proliferation, metastasis, and

invasion, and promote cell apoptosis [100]. In addition, the tumor suppressive p53 signaling pathway is activated by miR-125a-3p to promote apoptosis in lung cancer cells [101,102] and the RhoA-actomyosin pathway is directly inhibited to reduce the migratory capacity of non-small cell lung cancer (NSCLC) cells [103]. Negative regulation of STAT3 expression by miR-125a inhibits cancer cell proliferation and invasion, and promotes apoptosis [104].

miR-125a is downregulated in gastric cancer. A germline mutation in the miR-125a coding region is associated with this downregulation [107]. By inducing expression of miR-125a, the proliferation, migration, and invasion of gastric cancer cells can be inhibited [107–110]. miR-125a not only targets BRMS1 to inhibit invasion and metastasis [109], but also targets VEGF-A to regulate angiogenesis in the tissue and thus inhibits tumor growth [110].

In breast cancer (BC), both miR-125a and miR-125b are involved in inhibiting cell proliferation and promoting apoptosis [111–117]. miR-125a does this by directly inhibiting the histone deacetylase HDAC4 [111], downregulating the BC oncogene BAP1 [113], and activating the caspase 9/3 signaling pathway [112]. On the other hand, miR-125b suppresses tumor growth by targeting various oncogenic proteins that are often overexpressed in breast cancer [114–117]. Interestingly, even though miR-125a is a tumor suppressor in breast cancer cells, it promotes cancer in breast epithelial stem cells, suggesting that the miRNA plays a different role in the stem cell and bulk cancer cell populations [118]. Indeed, miR-125a has been found to repress the tumor suppressor LIFR [119,120] in stem cells to regulate stem cell pool homeostasis [118]. In cervical cancer, miR-125a is downregulated, and overexpression of miR-125a will suppress tumor growth, invasion, and metastasis via the regulation of STAT3 and ABL2 [121,122]. Overexpression of miR-125b also decreases cell proliferation, induces apoptosis, and reduces the ability of cells to form tumors by targeting the PI3K/Akt/mTOR signaling pathway, which is key to cell cycle regulation [123]. In the tissue and cell lines of ovarian cancer, expression of miR-125a and miR-125b are significantly decreased compared to normal ovarian tissue [124]. Ectopic expression of miR-125a and miR-125b can suppress tumor growth by inhibiting proliferation, migration, and invasion [124,125].

3.3. miR-125 in drug sensitivity and resistance

Similar to the oncogenic or tumor suppressive effects of miR-125a and miR-125b on various cell types, chemotherapy drug resistance or sensitivity can be enhanced by miR-125a and miR-125b in different cancer types. In BRAF inhibitor (BRAFi) resistant melanoma, miR-125a overexpression promotes BRAFi resistance by suppressing apoptosis in the presence of BRAFi, and miR-125a inhibition leads to partial drug-resensitization in melanoma cell lines [126]. miR-125a also promotes chemo-resistance in pancreatic cells [127] and daunorubicin (DNR) resistance in leukemia cell lines [128]. Similarly, miR-125b overexpression in colorectal cancer cells and head and neck squamous cell cancer cells is associated with cetuximab resistance [129]. On the other hand, in other cancers such as NSCLC [100], breast cancer [130–132], cervical cancer [133], nasopharyngeal carcinoma [134], and human hepatocellular carcinoma [135], drug sensitivity is enhanced or drug resistance is reversed when miR-125a or miR-125b is upregulated [130–140].

3.4. miR-125 as potential diagnostic or prognostic biomarkers

Since abnormal miR-125a and miR-125b expression can result in disease pathogenesis and progression, comparisons between the unique levels of miRNA in healthy and unhealthy cells may be used as a tool for diagnostic or prognostic purposes. Throughout the reports on the miR-125 family and its role in diseases and cancer, the possibility of using miR-125a and/or miR-125b as biomarkers to determine disease status and overall patient survival has been proposed many times. miR-125a has been suggested as a biomarker in cancers such as breast cancer [111], colon cancer [141], hepatocellular carcinoma [142], and non-small cell lung cancer [143], while miR-125b has been suggested as a biomarker in cancers such as hepatocellular carcinoma [80,144] and colorectal cancer [145].

miR-125b is also a potential biomarker for immunotherapy responses. For example, the level of exosomal miR-125b is down-regulated in NSCLC patients treated with immune checkpoint inhibitors PD-1/PD-L1, and its dynamic change might be correlated with the efficacy of immunotherapy in NSCLC [146]. In addition, serum levels of miR-125b have been used to assess the anti-tumor effects of recombinant human (rh) GM-CSF for prostate cancer patients [147] and miR-125b-1 serves as a predictive biomarker for the efficacy of peptide vaccine treatments in colorectal cancer patients [148]. It has been recently reported that melanoma-derived extracellular vesicles containing miR-125a and several other miRNAs can convert monocytes to myeloid-derived suppressor cells (MDSCs). The levels of these miRNAs clustered with the clinical efficacy of PD-1/PD-L1 immune checkpoint inhibitors in melanoma patients, highlighting their potential use as predictors of poor immunotherapy outcomes [149].

Despite the numerous studies on miR-125a and miR-125b as potential diagnostic or prognostic biomarkers, additional research on this topic and further developments for detecting miR-125 levels in a clinical setting are needed before miR-125a and miR-125b can be established as clinically applicable biomarkers.

4. Conclusions

With the extensive research on miR-125a and miR-125b, we have gained great understanding of the miR-125 family's targets and roles in a variety of cell types. We understand that miR-125a and miR-125b regulates cell differentiation, proliferation, and apoptosis in a cell type specific manner. We also recognize that dysregulation of miR-125a and miR-125b can cause diseases such as autoimmune diseases and cancer. Due to the fact that miR-125a and miR-125b themselves are regulated for their expression, and they affect many different cellular pathways to exhibit their biological functions, our current understanding is far from forming a complete picture of the underlying molecular mechanisms. Further research is needed to elucidate the mechanism of how the miRNAs themselves are regulated, and why they behave differently in different cell types. A more thorough understanding of these miRNAs' effects on various cell types will lead to clinical applications of miR-125 for disease diagnostics, treatments, and therapies.

Conflicts of interest

None declared.

Competing financial interests

The authors declare no competing financial interests.

Acknowledgements

We apologize to colleagues whose work was not cited due to space constraints. We thank Brooke Anderson for her helpful suggestions on the manuscript.

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