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Role of MiRNA in the Regulation of Blood Group Expression

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MiRNA · ABO blood group · Blood group antigen expression · Erythropoiesis

Abstract

Background: MicroRNAs (miRNAs) are small, endogenous non-coding RNA molecules that inhibit gene expression through either destabilization of the target mRNA or translational repression. MiRNAs recognize target sites, most commonly found in the 3′-untranslated regions of cognate mRNAs. This review aims to provide a state-of-the-art overview of the role of miRNAs in the regulation of major blood group antigens such as ABH as well as cancer-specific glycans. ***Summary:*** Besides their known roles in the control of developmental processes, proliferation, apoptosis, and carcinogenesis, miRNAs have recently been identified to play a regulatory role during erythropoiesis and blood group antigen expression. Since only little is known about the function of the red cell membrane proteins carrying blood group antigens, it is of great interest to shed light on the regulatory mechanisms of blood group gene expression. Some carrier proteins of blood group antigens are not restricted to red blood cells and are widely expressed in other bodily fluids and tissues and quite a few play a crucial role in tumor cells, as either tumor suppressors or promoters. ***Key Message:*** All available data point at a tremendous physiological as well as pathophysiological relevance of miRNAs in context of blood group regulation. Furthermore, miRNAs are involved in the regulation of pleiotropic genetic pathways such as hematopoiesis and tumorigenesis and thus have to be studied in future research on this subject.

Introduction

The outer membrane of erythrocytes contains numerous proteins that either are anchored via a lipid segment or cross the lipid bilayer at least once [1]. These surface proteins and glycoproteins carry the blood group antigens (shown in Fig. 1) and their specificity is mostly determined by their oligosaccharide or amino acid sequence [2]. Despite the wealth of information on the structures and molecular genetics of blood group carrier molecules, only little is known about the function of most blood groups. Some of the carrier molecules are membrane transporters (i.e., Rh, Kidd, Kx, Diego). The absence of Rh antigens, for example, is associated with structural changes in the erythrocyte membrane that can cause hemolytic anemia, as the Rh protein also maintains the flexibility and flattened shape of erythrocytes, in addition to supporting carbon dioxide transport across the cell membrane [3, 4]. Rh antigens are solely expressed in cells of the erythroid lineage, but most of the other blood group antigens and their carrier molecules are not confined to red blood cells (RBCs) and are widely expressed in bodily fluids and other tissues (shown in

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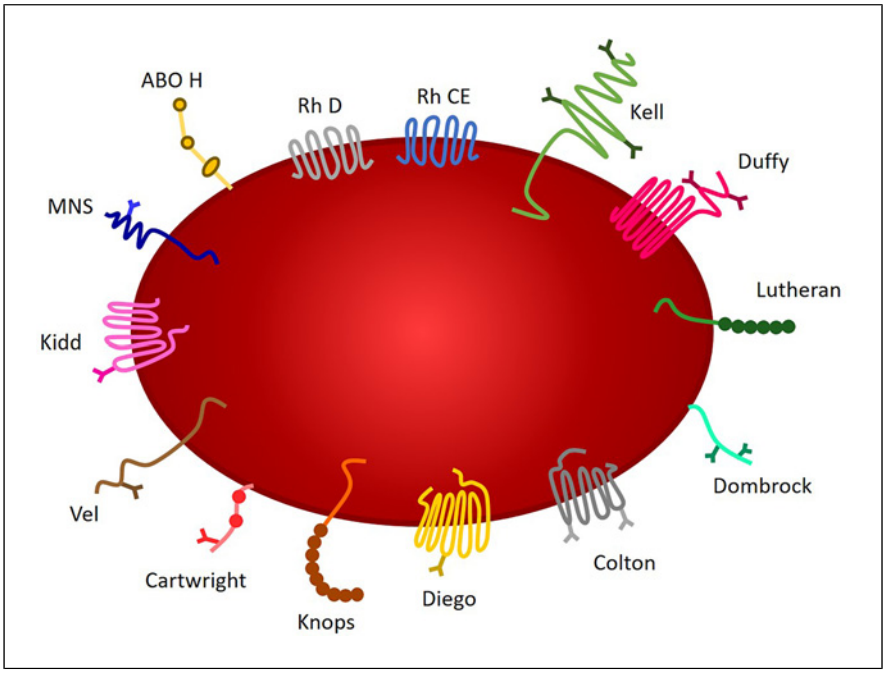

Fig. 1. RBC membrane with representative blood group antigens (modified [2]).

Table 1) [5, 6]. As opposed to Rhesus proteins, the antigens of the ABO [7], the I [8], and also the P1PK system [9] are carbohydrate structures and their synthesis are catalyzed by glycosyltransferases. Some blood group antigens (ABO, KEL, Rh50) are expressed during early erythropoiesis [10] and undergo drastic changes in expression levels during differentiation and maturation of the cells. In recent years, research on the post-transcriptional level in erythropoiesis microRNAs (miRNAs) has emerged as important post-transcriptional regulators of erythropoiesis [11–13]. MiRNAs are small (20–23 nucleotides), often phylogenetically conserved, non-protein-coding RNA sequences that mediate post-transcriptional gene repression by inhibiting protein translation or destabilizing the target mRNA [14, 15]. MiRNAs participate in the regulation of almost all relevant cellular processes, including differentiation, apoptosis, cell proliferation, oncogenic transformation, organ development, and metabolism [16]. The genome of human cells encodes over 1,000 miRNAs, which together regulate approximately 60% of all protein-coding genes [14, 17]. Currently, detection methods of miRNAs comprise quantitative PCR methods and high-throughput analyses such as microarray or next-generation sequencing. In addition, there are first protocols for single-cell miRNA-seq that would contribute significantly to the understanding of molecular regulatory processes, even though single-cell miRNA studies still lag far behind single-cell mRNA studies [18]. Furthermore, the availability of powerful bioinformatics tools such as DIANAmicroT, miRDB, miRanda, mirSVR, and target scan is increasingly improving data interpretation by utilizing a broad spectrum of miRNA-transcription factor (TF) networks, involved in the control of gene regulation.

MiRNA profiling of RBCs revealed the presence of more than 850 miRNAs in mature RBCs [19], whereby the function of miRNAs in erythrocytes has been linked mostly to erythropoiesis [20]. We could show that miRNAs also play an important role in the regulation of ABO blood group antigen expression with pleiotropic effects on erythropoiesis [19, 21]. Since ABO blood groups are characterized by glycoproteins synthesized by the respective ABO transferase, we have demonstrated for the first time that miRNAs are able to regulate glycoprotein expression levels by affecting the transcription level of transferases [19]. MiRNAs have thus far only been reported to directly interfere with the expression level of proteins.

In addition, the expression of certain blood group antigens, such as ABO antigens, undergoes drastic changes in pathological conditions such as tumorigenesis, but again the causative mechanisms are not completely understood [22–24]. At least two different mechanisms are postulated for the downregulation of ABO transcription: allelic loss and epigenetic hypermethylation of the ABO promoter region in a CG island [25–27]. Moreover, further epigenetic regulatory mechanisms of ABO transcription have been proposed since it was shown that histone deacetylase inhibitors reduce ABO expression [28]. The elucidation of HDACI effects in vivo may have a potential utility for reducing ABO antigens on the surface of various cells and organs, thereby reducing the risk of acquiring ABO-associated diseases or improving the outcome of ABO incompatible transplants

Table 1. Function of blood groups, distribution of expression, and number of putative miRNAs that may bind to the genes of the blood group carrier molecules

Blood group system	Encoded by	Red cell function	Tissue distribution	Number of putative miRNAs	MiRNAs with reported relevance for blood group regulation	Regulatory function	References
ABO, H	Transferase A and B, FUT1	Carbohydrate structures which contribute to the glycocalyx	RBCs, platelets, endothelial cells, epithelial cells as soluble form in saliva and other bodily fluids	45	miR-331-3p	Negative regulators of ABH expression	[19]
					miR-1908-5p	Negative regulators of ABH expression	[19]
					miR-215-5p (indirect by targeting RUNX-1) miR-182-5p (indirect by targeting HES-1)	Positive regulators of erythropoiesis	[21]
Rhesus D, CE, RhAG	Rhesus D and CE, RhAG	Membrane transporters	Cells of the erythroid line	93, 15, 52	miR-9	Negative regulator of RhAG Positive regulator of tumor formation	[62]
					miR-98	Negative regulator of RHD	[63]
KEL	KEL, XK	Membrane-bound enzymes	Cells of erythroid and myeloid lineage, lymphoid organs, muscle (both cardiac and skeletal), and the nervous system	9, 157	miR-669m	Negative regulator of XK and erythroid differentiation	[66]
Duffy	ACKR1	Chemokine receptor	RBCs, endothelial cells, epithelial cells of kidney collecting ducts, lung alveoli, and Purkinje cells of the cerebellum, thyroid gland, colon, and spleen	17			
Lutheran	BCAM	Cell adhesion molecules	RBCs, early hepatic epithelial cells, endothelium, hematopoietic cells	161	miR-199a-5p	Negative regulator of BCAM, promotor of preeclampsia, and negative regulator of cutaneous squamous cell carcinoma	[72]
					miR-326 (indirect by targeting EKLF)	Positive regulator of fetal hemoglobin expression	[75]

Table 1 (continued)

Blood group system	Encoded by	Red cell function	Tissue distribution	Number of putative miRNAs	MiRNAs with reported relevance for blood group regulation	Regulatory function	References
MAM	EMP3	Membrane-bound protein	Ubiquitous	29	miR-765	Tumor suppressor of primary breast carcinoma and oral squamous cancer	[77, 78]
JR	ABCG2	BCRP	RBCs, endothelial cells, placenta	124	miR-212	Tumor suppressor	[79]
Dombrock	ADP-ribosyl-transferase 4	Membrane-bound enzymes	RBCs, endothelial cells, liver, spleen	176			
Colton	Aquaporin-1	Membrane transporters	RBCs, thymus, spleen, brain, endothelial cells, smooth muscle cells, pericardium, mucosa	84			
Diego	Band 3 protein	Membrane transporters	RBCs and kidney	62			
Knops	Complement receptor 1	Complement regulation	RBCs, peripheral nerve fibers, leukocytes, dendritic cells, glomerular podocytes	127			
Cartwright	acetyl-cholinesterase	Membrane-bound enzymes	RBCs, thymus, spleen, brain, liver, Islets of Langerhans, kidney	29			
Vel	SMIM1	Structural proteins	RBCs	47			
Kidd	SLC14A1	Membrane transporters	RBCs, thymus, brain, smooth muscle, pericardium, and kidney	133	miR-10a-3p	Positive regulator of cancer	[82]
MNS	Glycophorins	Structural proteins	RBCs, kidney (on the renal endothelium) and epithelium	93			
Lewis	Fucosyltransferases	Cancer-specific glycans			miR-339-5p (FUT1) miR-5193 (FUT1)	Tumor suppressors	[87, 88]
					miR-200b (FUT4)	Tumor suppressor	[90]

Table 2. MiRNA key regulators and their function in early and late erythropoiesis as well as in tumorigenesis [12, 20]

miRNAs	Target genes	Regulatory function
miR-124	TAL1, c-MYB	Suppresses RBC maturation
miR-142	Rac-1	Maintains steady-state erythropoiesis, hematopoietic progenitor cell proliferation, and normal enucleation; abnormal expression and mutations in hematological malignancies
miR-144	KLFD, NRF2, RAB14, MEIS1, COX10, MYC, CAP1	Maintains normal enucleation in erythropoiesis
miR-150	Myb	Inhibits erythropoiesis
miR-155	PU-1, ETS-1, CEBP, SHIP1	Inhibits erythropoiesis; upregulated in acute lymphoblastic leukemia patients
miR-191	RIOK3, MXI1	Regulates RBC enucleation
miR-200a	PDCD4, THRB	Inhibits erythropoiesis
miR-221/222	KIT	Reduces erythroblast proliferation; regulates hemoglobin switching; abnormally expressed in hematological malignancies
miR-222	KIT, BLVRA, CRKL	Inhibits erythropoiesis; upregulated in acute lymphoblastic leukemia patients
miR-223	LMO2	Inhibits erythropoiesis; downregulated in acute lymphoblastic leukemia patients
miR-24	ALK4	Promotes terminal differentiation; upregulated in CBF leukemia samples
miR-326	EKLF	Inhibits HbF synthesis; downregulated in acute lymphoblastic leukemia patients
miR-451	YWHAZ, GATA-2, RAB14, GATA-1, COX10, c-MYC, CAP1	Inhibits the nuclear accumulation and mitochondrial respiration of FOXO3; induces γ-globin gene expression; maintains normal enucleation in erythropoiesis; downregulated in acute lymphoblastic leukemia patients
miR-4732-3p	SMAD2, SMAD4	Promotes cell proliferation during the process of differentiation of erythroid cells
miR-486-5p	FOXO1, PTEN, ANK1	Controls hematopoietic cell growth and survival
miR-669m	AKAP7, SLC22A4, XK	Inhibits terminal erythroid differentiation
miR-9	FOXO3	Blocks erythroid progenitor differentiation; upregulated in acute lymphoblastic leukemia patients
miR-96	ORF of γ-globin	Inhibits γ-globin expression

[28]. Furthermore, some miRNAs act as tumor suppressors or oncogenes by targeting cancer-related genes [29]. Therefore, this review aims to provide a state-of-the-art overview of the role of miRNAs in the regulation of different blood group antigens and cancer-specific glycans.

MiRNAs in Red Blood Cells

For a long time, it was believed that mature RBCs do not contain RNAs. However, an increasing body of evidence show that RBCs express a large number of miRNAs [19, 30] and their function in RBCs has been linked to erythropoiesis [20]. Besides chromatin modifications such as histone acetylation and DNA methylation [31], miRNAs can modulate hematopoietic differentiation, proliferation, self-renewal, and the lineage-specific potential of hematopoietic cells by targeting the expression of TFs and genes involved in the regulation of cell cycle and proliferation [32, 33]. MiRNAs, such as miR-142, miR-144, miR-451, miR-221/222, and miR-155, play an essential role in erythroid differentiation and erythrocyte homeostasis as both positive and negative regulators [12] (summarized in Table 2). Whereas miR-142, -144, and -451 maintain normal enucleation in erythropoiesis, miR-221/222 and miR-155 reduce erythroblast proliferation and inhibit erythropoiesis [12]. Furthermore, miR-4732 promotes cell proliferation during the differentiation process of erythroid cells [30] and together with GATA-binding protein 1 miR-486 acts as a major regulator of erythropoiesis [34]. Erythropoiesis occurs in the bone marrow in special niches called erythroblastic islands, which consist of a central macrophage surrounded by

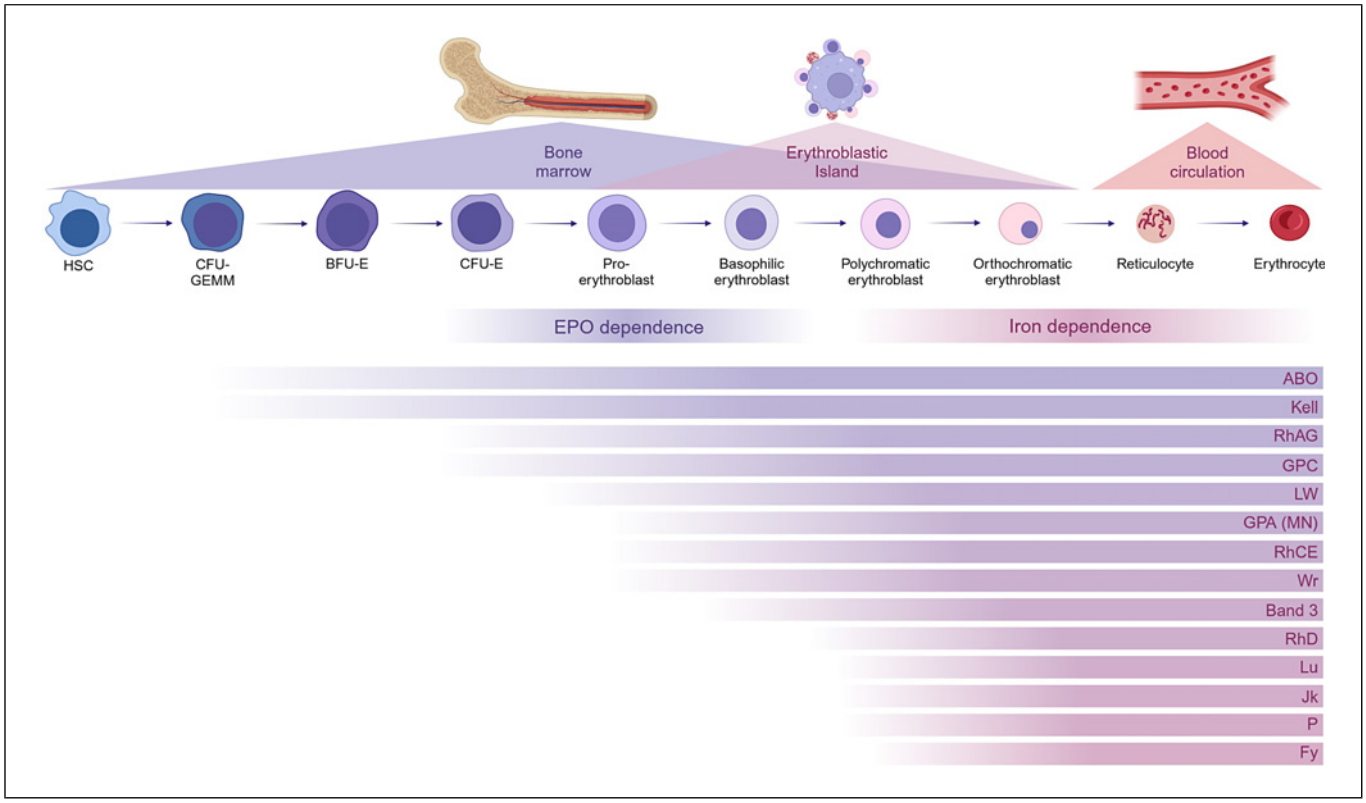

Fig. 2. Schematic illustration of the erythropoiesis. The gradual differentiation of the erythroid cells initially takes place in the bone marrow, from the proerythroblast stage onward within erythroblastic islands. Terminal maturation occurs within the blood circulation. While erythropoiesis is initially EPO independent, EPO dependence increases during erythroid development and gradually turns into an iron-dependence. Onset of blood group expression varies considerably between the blood group systems, suggesting specific functions of the different antigens during erythropoiesis (created with BioRender.com).

developing erythroblasts [35]. Here, erythropoiesis is mainly regulated by erythropoietin (Epo) through binding to its membrane receptor EpoR [10]. Cytokines and cell interactions trigger the cells progressively to activate specific TFs in order to express genes involved in the erythroid phenotype [36]. This leads to a continuous remodeling of the cell surface of differentiating cells, whereby some membrane-expressed components are downregulated whereas other receptors or cell surface markers become transiently or permanently expressed [10]. Since it was shown that the synthesis of blood group-associated proteins occurred at different stages of erythroid differentiation [10, 37, 38], miRNAs have been shown to play a role in the expression of blood group antigens, i.e., ABH [19, 21]. The expression of blood group antigens is a highly dynamic process with changes in antigen expression density throughout the differentiation process [10, 37, 38]. Erythropoiesis starts with hematopoietic stem cells that sequentially differentiate to common myeloid progenitors, megakaryocyte-erythroid progenitors, burst-forming unit-erythroid, and colony-forming unit-erythroid progenitor cells (shown in Fig. 2) [39]. In the second Epo-dependent stage, colony-forming unit-erythroid progenitor cells differentiate through the morphologically distinct nucleated precursors proerythroblast, basophilic erythroblast, polychromatic erythroblast, and orthochromatic erythroblast. The terminal iron-dependent phase comprises the reticulocyte maturation and the ejection of the nucleus [39]. Blood group antigens such as ABH, KEL, and RhAG were already detectable in the Epo-independent phase at day 3 of differentiation. This early onset of Kell glycoprotein expression leads to the assumption of its potential regulatory role during early hematopoiesis and determination of lineage fate [40]. Other antigens such as Fy6 appeared during late phase 1, suggesting a role as a scavenger receptor for cytokines in the bone marrow and circulation [40]. GPA, Wr^b antigen, Rh(D, Cc/Ee), and Landsteiner-Wiener appeared during the Epo-dependent phase and reached their maximum expression between day 8 and 12. In contrast, the expression of Jk^3 and Lu^b first occurred between day 10 and 14 during the Epo-dependent phase [10]. The late appearance of Lu^b indicates its possible involvement in late stage progenitor migration from the bone marrow into the blood circulation [40]. Thus, in addition to disorders of erythropoiesis, dysregulation of miRNAs likely lead to changes in blood group antigen expression dynamics.

MiRNAs mainly exert their biological effects by binding to the target genes and suppressing their translation [20]. Contrary to previous assumptions, studies have shown that mature erythrocytes still have thousands of transcripts that can be regulated by miRNAs. A large number of the highly expressed genes encoded proteins that are strongly associated with erythroid differentiation [41].

MiRNA biosynthesis starts with long primary miRNA transcripts (pri-miRNA) that are transcribed by RNA polymerase II and then processed into precursor miRs (pre-miRNA) by the microprocessor complex, which consists of the proteins Drosha and diGeorge syndrome critical region 8 (DGCR8) (shown in Fig. 3) [33]. After export out of the nucleus to the cytoplasm by exportin-5/Ran-GTP, the pre-miRNA is cleaved by the RNase III-type enzyme Dicer in complex with the double-stranded transactivation response element RNA-binding protein (TRBP) [15, 42]. Finally, the double-stranded miRNA produced by Dicer is incorporated into the RNA-induced silencing complex (RISC) together with Argonaut protein 2 (AGO-2), which selects one strand to become the mature miRNA [42]. It is evident that miRNAs can also be released from RBCs into the circulation mainly carried by AGO-2 and extracellular vesicles and enter the recipient cells to exert different biological effects [20].

Role of MiRNAs in the Regulation of ABO Blood Group Antigen Expression

The ABO system is the clinically most relevant blood group system [2]. In contrast to Rh and other protein antigens, the antigens in the ABO system are oligosaccharides and their synthesis depends on biochemical reactions catalyzed by the A and B transferases coded by the functional A and B alleles at the ABO genetic locus [7]. The ABH antigens are not confined to erythrocytes but are widely expressed in bodily fluids and tissues. However, they are absent in connective tissue, muscle, and the central nervous system [43]. The ABH antigens are expressed in a cell-type-specific manner and undergo drastic changes during the development, differentiation, and maturation of cells in the epithelial and erythroid lineages [44].

Alterations in A/B antigen expression are mainly caused by mutations in the gene structure. However, changes in the transcription of the A/B transferase mRNA, post-transcriptional modifications of the mRNA, changes in the translation of the A/B transferases, post-translational modifications of the enzymes, and changes in the translocation of the enzymes in the Golgi apparatus can also be responsible for differences in A/B antigen expression [7]. Numerous regulatory elements in the DNA sequence of glycosyltransferase have been identified. Specifically, there is evidence for an important role of an enhancer element located 3.8 kb upstream of exon 1 in expression of A/B antigens [45], which contains either one (alleles A1.01 and O.02) or four (alleles A2.02, O.01.01, O.01.02, and B1.01) repeats of 43 bp length [26, 46]. However, in the human erythroleukemia cell line HEL, the activity of this enhancer was barely detected, which suggests that this activity is cell type specific and does not play a role in erythroid cells [47]. Further regulatory elements include a ubiquitous proximal promoter within the ABO CpG-rich region (CpG islets) [27, 48], a cell-type-specific promoter at the 5′ boundary of the CpG islets [47], and expression of an antisense transcript complementary to the genomic DNA of the ABO coding strand [49]. The CpG-rich region within the ABO promoter region has numerous binding sites for TFs. Moreover, its methylation status inversely correlates with the transcription of ABO genes [27, 48]. The protective factors of demethylation include the TF SP1, which is bound to and activated by the ABO promoter. Therefore, mutations in the binding site of SP1 can lead to a reduction of ABO promoter activity [43, 47].

Furthermore, an erythroid-specific regulatory element within intron 1 of the ABO gene, called +5.8-kb site, was identified [50, 51]. This region, with binding sites for the TFs GATA binding factor (GATA)-1 and GATA-2, as well as runt-related transcription factor (RUNX)-1, has a deletion in individuals with an A_m, B_m, and AB_m phenotype. The occurrence of this deletion leads to downregulation of the transcription of the A and B alleles and thus to a reduction of specific antigen expression [50, 51].

In 2020, we showed for the first time a crucial role for miRNAs in the regulation of ABO blood group antigen expression during early RBC maturation from hematopoietic stem cells in the bone marrow [19]. We identified *glycosyltransferase A* and *B* mRNA as direct targets of miRNA-331-3p and -1908-5p. Overexpression of these two miRNAs in hematopoietic stem and progenitor cells (HSPCs) resulted in a significant reduction in the number of blood group A antigens per cell in differentiated RBCs and in a reduction in *glycosyltransferase A* mRNA and protein expression. Additionally, miR-331-3p simultaneously targets the TF SP1 and prevents it from binding to the promoter of the ABO gene [19]. The hypothesis suggests that miR-331-3p is expressed only at marginal levels under physiological conditions, allowing SP1 to bind the ABO promoter and facilitate glycosyltransferase expression (shown in Fig. 4). Upregulation of miR-331-3p and miR-1908-5p results in their binding to and downregulation of SP1 and glycosyltransferase, which in turn inhibits expression of blood group A/B antigens. The results suggest a possible involvement of miR-331-3p in ABH antigen expression regulation first through binding to the 3′UTR of *glycosyltransferase* mRNA and second through regulating the expression of associated TFs. As we were able to demonstrate that overexpression of

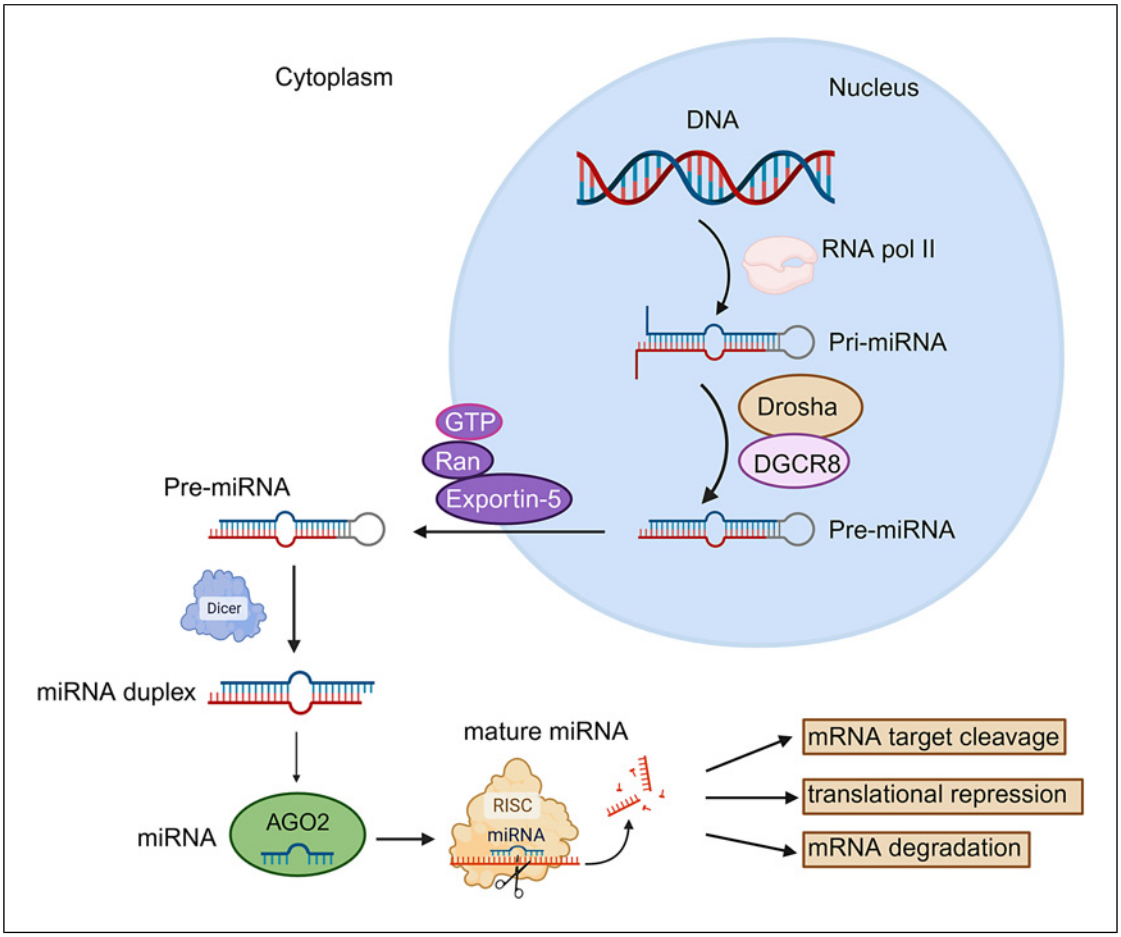

Fig. 3. Overview of the miRNA biogenesis pathway. RNA polymerase II generates primary miRNA (pri-miRNA) transcripts containing hairpins and 5′ and 3′ flanking sequences. The pri-miRNA is cleaved at the stem of the hairpin by the microprocessor complex consisting of DGCR8 and Drosha and liberates a precursor miRNA (pre-miRNA). Exportin 5 facilitates the export of pre-miRNA into the cytoplasm, where Dicer cleaves them within the stem close to the terminal loop and generates a miRNA duplex intermediate. Dicer and an Argonaute (AGO) protein assemble into the RISC loading complex, and one miRNA strand is transferred to the AGO protein, resulting in the formation of RISC (created with BioRender.com).

miR-331-3p in turn causes downregulation of *glycosyltransferase* and *SP1* mRNA, it can be assumed that miRNAs control gene expression by degrading their target mRNA [19]. Further investigation is needed, in order to gain a detailed understanding of the underlying mechanism.

After showing that ABH antigen expression is regulated by miRNAs, it became clear that ABO blood group-associated miRNAs might also affect other biological processes of RBC differentiation. We recently demonstrated for the first time that the ABO blood group directly affects RBC homeostasis through blood group-dependent modulation of erythropoiesis at the miRNA level and corresponding TFs [21]. A large study evaluating the hemoglobin levels of >245,000 first time blood donors showed that the observed differences in blood group-specific erythropoiesis lead to clinically relevant differences in hemoglobin/hematocrit levels in healthy individuals. The differences can be explained by an accelerated in vitro erythropoiesis of HSPCs from donors of blood group *ABO*B1.01* compared to HSPCs from the other ABO blood groups [21]. An indicator for accelerated erythropoiesis in blood group *ABO*B1.01* cells is that the expression of specific miRNAs targeting TF genes (*HES-1* and *RUNX-1*) involved in the inhibition of erythropoiesis [52, 53], such as miR-182-5p and miR-215-5p, was increased (shown in Fig. 5). Upregulation of miR-182-5p leads to an accumulation of erythroid cells by inhibition of the TF HES-1 [52]. Furthermore, it was described that GATA-1 utilizes Ikaros and Polycomb repressive complex 2 to promote HES-1 repression as an important step in erythroid cell differentiation [54]. MiR-215-5p targets RUNX-1 [55], which interacts physically with GATA-1 to repress erythroid differentiation. Consistent with these data, overexpression of miR-215 in HSPCs of blood group A donors resulted in down-regulated mRNA levels of *RUNX-1* and *glycosyltransferase*, as well as decreased blood group A antigen expression and accelerated erythropoiesis [21].

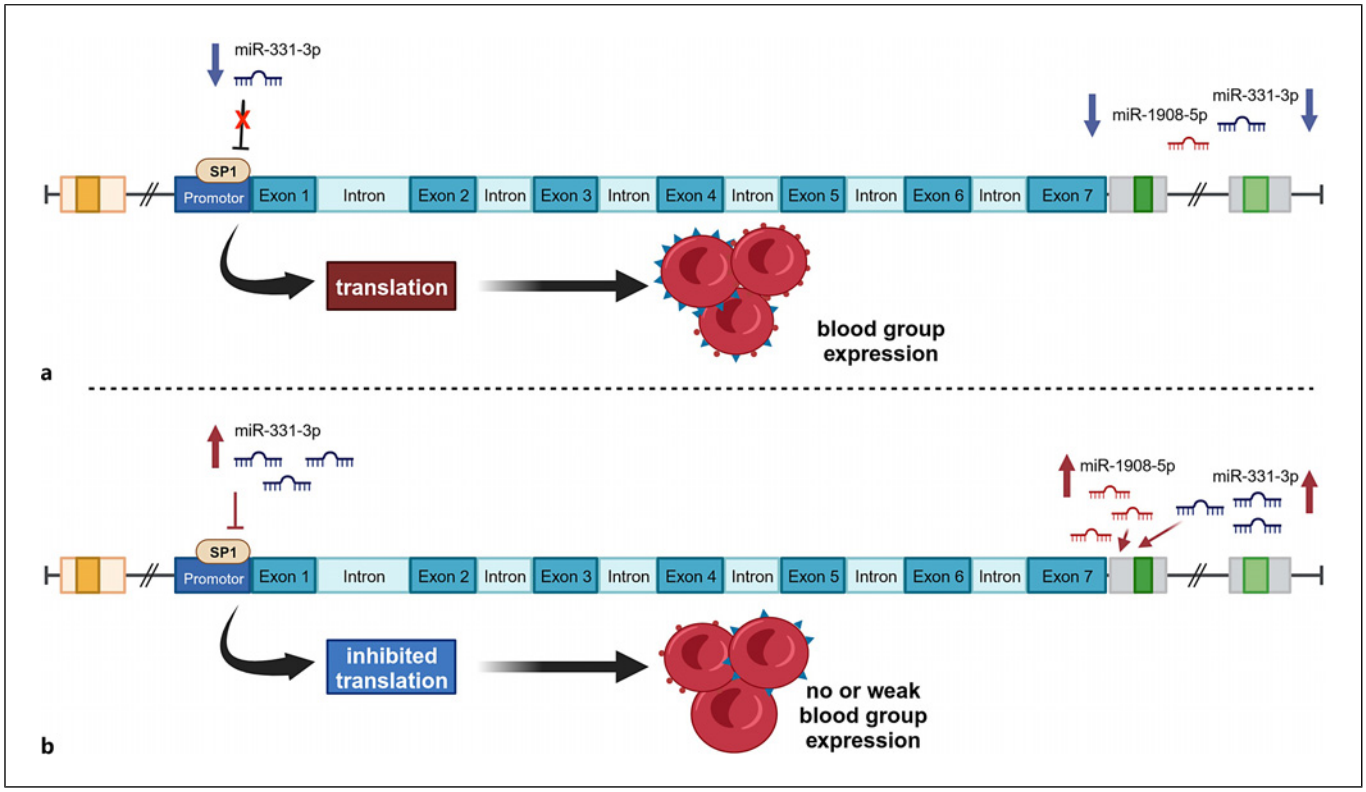

Fig. 4. Proposed mechanism of the regulation of the ABO blood group antigen expression by miRNAs (modified from [19]). **a** In donors of homozygous blood group A genotype, miR-331-3p and miR-1908-5p are repressed, and the TF SP1 can bind to the promoter sequence of the *ABO* gene, leading to normal expression of glycosyltransferase A and blood group A antigen. **b** Overexpression of miR-331-3p and miR-1908-5p inhibits glycosyltransferase A. In addition, miR-331-3p overexpression inhibits the expression of the TF SP1, which in turn downregulates promoter activity of the *ABO* gene, resulting in further gene repression (created with BioRender.com).

An association between ABO blood group antigen expression and erythropoiesis is also known for carcinomas and hematological malignancies [56–59]. Reduction or complete deletion of A/B antigen expression was documented in patients with acute myeloid leukemia (AML), myelodysplastic syndrome, and myeloproliferative disorders including chronic myeloid leukemia [60]. It was proposed that mutations in RUNX-1 might act as dominant negative inhibitors of wild-type RUNX-1, which were responsible for the A antigen loss on RBCs [60]. Nevertheless, it is conceivable that the association of RUNX-1 and miR-215-5p expression could also be a causative explanation for the loss of A/B antigen expression in RUNX-1-mediated hematological malignancies [21]. This is supported by the observation that miR-215-5p-mediated inhibition of RUNX-1 promotes malignant progression in gastric cancer [55]. Loss of A/B antigens was initially reported in gastric cancer [61] and further investigation is needed to clarify a possible role of the interaction of miR-215-5p with its target gene *RUNX-1*. Another long-standing problem in human tumor immunology is termed "incompatible A expression" that means the expression of "A-like antigen" in tumors of O or B individuals [56]. This expression of A-like antigen on tumor cells in non-A individuals may function early during human cancer development as a target of the host immune surveillance and is therefore more susceptible for immunological rejection [56].

Regulation of Other Blood Groups by MiRNAs

Since miRNAs directly interfere with protein expression and blood groups are regularly defined by surface protein expression, it is conceivable that other blood group antigens than ABO may also be regulated by miRNAs. The Rhesus protein RhAG was identified to be a potential target for miR-9 [62]. Overall, 170 putative target genes, including RhAG, showed a significant inverse correlation of the expression of miR-9 in 70 individuals (9 MLL- and 61 non-MLL-rearranged AML cases) and 9 normal controls. Moreover, RhAG was one of the 31 genes that exhibited a significant downregulation in MLL-rearranged AML samples compared with the normal controls [62]. In contrast, a Thai research group analyzed the association of miRNAs and Rh-DEL blood donors with DEL variant in 2017 [63]. Using bioinformatics tools for the prediction of miRNA targeting

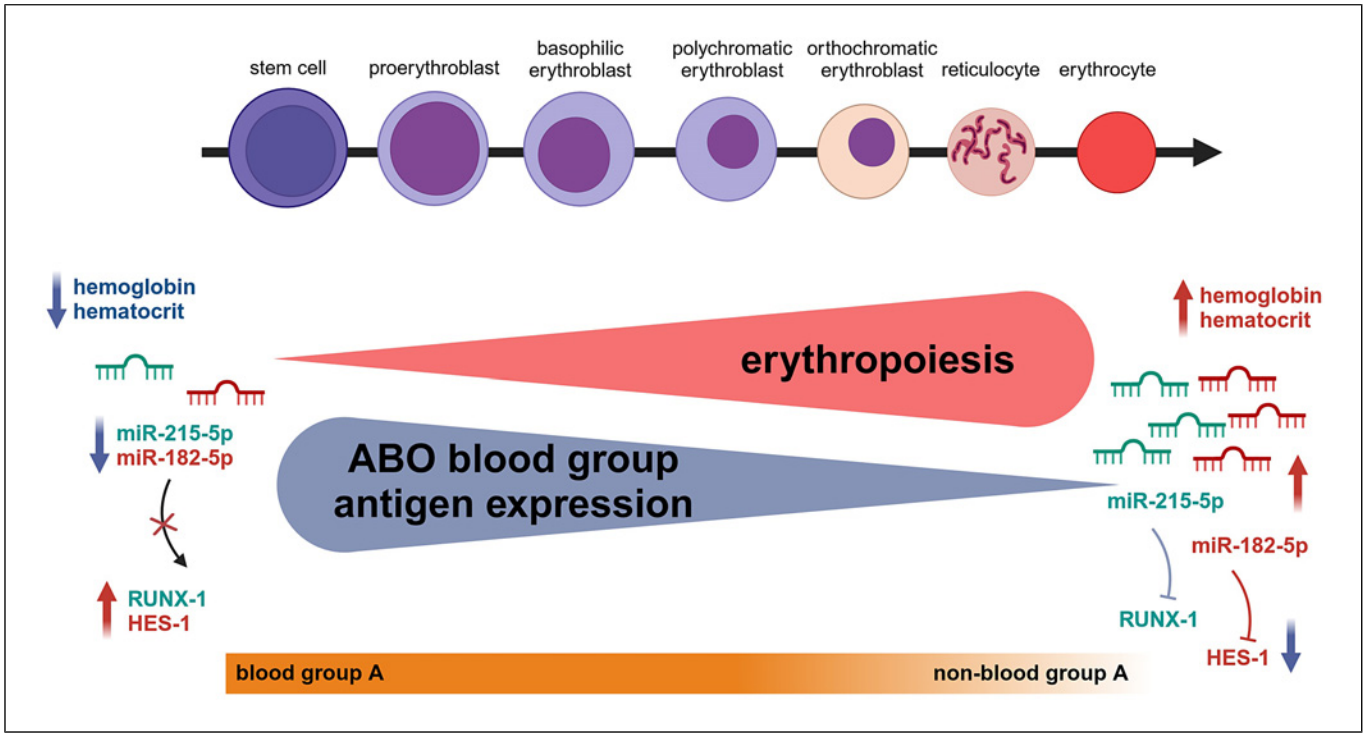

Fig. 5. ABO blood group antigen-dependent modulation of erythropoiesis by miRNAs and target TFs (modified from [21]). Different miRNA repertoires/competitions of HSCs in dependence of the underlying ABO blood group interacts with erythroid lineage-specific TFs and thus affects the velocity and yield of hematopoietic differentiation (created with BioRender.com).

of RHD, they identified miR-98 as the miRNA potentially specific for the 3′ UTR of RHD. However, the relative expression levels of miR-98 among D-positive, D-negative, and DEL subjects showed no statistically significant differences. Since the cohort was small (162 individuals) and other miRNAs could be involved, further investigations are necessary to fully characterize the extent of miRNA regulation in the DEL blood group [63].

Kell antigens consist of a 93-Kd type II transmembrane surface glycoprotein. Kell shares sequence and structural homology with zinc endopeptidases, which are involved in regulating bioactive peptides [64]. Only the antigen Kx is carried by XK, a 440-amino acid protein that spans the membrane 10-fold [65]. In a mouse model, overexpression of miR-669m was shown to inhibit erythroid differentiation. Furthermore, bioinformatic analyses showed that candidate targets of miR-669m involved in the erythropoiesis inhibition are A-kinase anchoring protein 7 (Akap7) and Xk genes [66]. Xk deficiency leads to McLeod syndrome, which is associated with morphological and functional damage of RBCs [67]. This additionally emphasizes the involvement of miRNAs in the regulation of blood group antigens and their impact on the regulation of erythroid differentiation. Although Kell is primarily expressed in erythroid tissues, it is not restricted to erythroid blood cells but is expressed in a broader spectrum of hematopoietic cells including megakaryocyte and myeloid progenitors [64]. As miRNAs are involved in hematopoiesis, it is likely that they are also involved in the regulation of KELL during myelopoiesis and thrombopoiesis.

The antigens of the Lutheran blood group system are expressed as 2 isoforms on the red cell membrane glycoprotein, which is called basal cell adhesion molecule (BCAM) [68]. BCAM may be involved in facilitating movement of maturing erythroid cells from the erythroblastic island of the bone marrow to the peripheral circulation. It may also play a role in the migration of erythroid progenitors from the fetal liver to the bone marrow [2]. BCAM is widely expressed in hematopoietic cells, placenta, kidney, and other tissues [69]. Additionally, BCAM seems to play a key role in tumor progression [70, 71]. BCAM was recently identified as a target of miR-199a-5p in skin keratinocytes in cutaneous squamous cell carcinoma, leading to inhibition of the migratory capability of the skin keratinocyte [72], and placenta, resulting in suppression of trophoblast proliferation, migration, and invasion [73]. Besides direct miRNA-mediated effects on BCAM expression, indirect modulation by miRNA-mediated inhibition of involved TFs (i.e., GATA-1 and Kruppel-like factor 1 [KLF1]) could influence the expression of Lutheran blood group antigens. Alterations in GATA-1 and KLF1 activity by mutations in their gene structure might be associated with severe anemia

and lead to blood group phenotypes with altered Lutheran expression [74]. Erythroid-specific KLF1 is an integral transcriptional activator for erythropoiesis [68] and a direct target of miR-326. Overexpression of miR-326 resulted in reduced KLF1 protein levels, which was associated with elevated expression of γ-globin [75]. However, such an interaction might also lead to decreased level of Lutheran and other blood group antigens (Indian, P1PK, Landsteiner-Wiener, Knops, OK, RAPH, and I blood group systems) regulated by KLF1 [68].

In 2020, Thornton et al. [76] established MAM as a new blood group system and demonstrated an interaction of the epithelial membrane protein 3 (EMP3) with the cell surface signaling molecule CD44. EMP3 is a transmembrane signaling molecule, which is important in the regulation of apoptosis, differentiation, and invasion of cancer cells [77]. The rare but clinically important MAM-negative phenotype is reported to be caused by inactivating mutations in the EMP3 gene [76]. Furthermore, EMP3 was identified to be a target gene of miR-765 in primary breast carcinoma and oral squamous cancer cells, which leads to tumor suppression [77, 78]. Although regulation of EMP3 by miRNAs in the erythroid lineage has not been reported yet, miRNA-dependent regulation of the MAM blood group antigen expression appears conceivable.

The carrier molecule of the Jra antigen of the JR blood group system (ISBT JR 032) has been identified as ABCG2 (ATP-binding cassette super-family G member 2). ABCG2 (also known as CD338) is a breast cancer resistance protein that makes cancer cells more resistant to anticancer drugs [2]. In an in vitro-imatinib-resistance model using the CML cell line K562, ABCG2 was identified as a direct target for miR-212, which is regularly dysregulated in cancer and might function as a tumor suppressor [79]. Since dysregulation of blood group antigens during hematological malignancies was described for the ABO blood group antigens [60], similar mechanisms may also exist for the Jr blood group system possibly by the miRNA-212/ABCG2-axis.

Human solute carrier family 14 member 1 (SLC14A1) gene serves as a urea transporter in the kidney to concentrate urine but is also expressed on RBCs [80] and encodes for the Kidd blood group antigens [81]. Furthermore, it was shown that downregulation of SLC14A1 by miR-10a-3p might involve in the development of FMS-like tyrosine kinase 3 (FLT3) mutation adult AML, which result in poor prognosis in adult AML [82].

Role of MiRNAs in the Regulation of Cancer-Specific Glycan Antigens

Similar to the ABO blood group antigens, Lewis antigens are formed by the addition of specific sugars to an oligosaccharide precursor chain [83]. While fucosyltransferase (FUT) 1 is responsible for production of the precursor substance for the A and B antigens, FUT2 (SE) enables the A, B, and H antigens to be secreted in most bodily fluids and *FUT3* is the gene for the Lewis (Le^a and Le^b) antigens [2]. If both H and *SE* genes are present, the secreted H substance is converted into the Le^b antigen. In the absence of an *SE* gene, the enzyme product of the *LE* gene acts on the precursor H substance giving rise to the Le^a antigen [2]. The antigenic determinants of the ABO and the Lewis systems also exist in a soluble form when the relevant genes are expressed in the respective individual [83]. Lewis antigens can also be sialylated to form sialyl Lewis antigens [84].

As a result of neoplastic transformation, cell membrane glycoconjugates undergo characteristic changes. There are increasing reports of type 2 chain-based structures of the Lewis antigens Le^x (an isomer of Le^a) and Le^y (an isomer of Le^b) and their sialylated forms appearing as "new" antigens in malignant tissue [85, 86]. Several studies have reported associations between miRNAs and FUTs [87–90]. In lung carcinoma cell lines, it was shown that miR-339-5p promoted colony formation and attenuated apoptosis through targeting FUT1 and the downstream protein Le^y [87]. Le^y is involved in various physiological and pathological processes, such as infection, inflammation, and cancer metastasis, which are mediated by glycoconjugates (glycoproteins and glycolipids) on the cell surface [91–93]. The increase of FUT1-mediated Lewis (y) antigen also promotes the proliferation and metastasis of ovarian cancer cells [88]. In this study, miR-5193 was identified as an important downstream regulator for the carcinogenic effect of FUT1 in ovarian cancer because it was downregulated in FUT1-overexpressing ovarian cancer cells and ovarian tumor samples. The interaction of miRNAs with FUT1 enzyme was also suggested to play an important role in colorectal cancer [94] and osteoarthritis [95]. However, the extent of interactions with downstream cancer-specific glycans such as Le^Y needs to be studied in further research on this subject.

The biosynthesis of the tumor-associated sugar antigen Le^Y, which is an α1,3-linkage fucosylated glycan carried by glycoproteins on the cell surface, seems to be also catalyzed by FUT4. MiR-200b was identified as a specific miRNA that inhibited FUT4 expression [90]. In tissue and serum samples of breast cancer patients, FUT4 levels were increased, whereas the levels of miR-200b were decreased. The authors demonstrated that miR-200b decreased α1,3-fucosylation of epidermal growth factor receptor and additionally inactivates the downstream phosphoinositide-3 kinase (PI3K)/Akt signaling pathway [90]. Therefore, miR-200b and FUT4 are considered potential targets in breast cancer and their role in cancer-specific blood group antigen regulation will be the subject of further studies.

Conclusion

The discovery of miRNA-dependent regulation of blood group antigen or their carrier molecule expression is a relatively novel concept. However, all available data point at a tremendous physiological as well as pathophysiological relevance of miRNAs in this context especially as the involved target genes exert pleiotropic effects in both physiological and pathophysiological processes such as hematopoiesis and tumorigenesis. With regard to hematopoiesis, miR-182-5p, -215-5p, and -331-3p and their corresponding TFs modulate ABO blood group-dependent erythropoiesis accounting for blood group-specific differences in hematocrit, which in turn could modulate the adaptation to blood losses. In carcinogenesis, miRNA regulation could play an important role in the expression of differentiation-specific glycan antigens, but also for the appearance of cancer-specific glycan antigens, which could have implications, e.g., for cancer immunotherapy. In conclusion, further exploration of the intricate interplay between blood group regulation and miRNA:mRNA interactions holds great potential for shedding light on various diseases, including myocardial infarction, thrombosis, and infection, which are influenced by blood group-dependent differences. This knowledge could pave the way for advancements in fields of hemotherapy, cancer immunotherapy, and the generation of engineered RBCs.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

R.K. performed the literature search and wrote the manuscript. S.R.K. and J.T. critically read the manuscript and contributed artwork. T.T. conceived the research, assured the funding, and wrote the manuscript.

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