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The role of miR-183 cluster in immunity

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ABSTRACT

MicroRNAs (miRNAs) are essential factors of an extensively conserved post-transcriptional process to regulate gene expression. MiRNAs play a pivotal role in immunity, including controlling the differentiation of various immune cells as well as their immunological functions. The miR-183 cluster, which is comprised of miR-183, -96 and −182, is a miRNA family with sequence homology. These miRNAs are usually transcribed together as a polycistronic miRNA cluster during development and are required for maturation of sensory organs. In comparison to defined sensory-specific role of these miRNAs in normal development, they are frequently overexpressed in several non-sensory diseases, including autoimmune diseases and cancers. Because individual miRNAs of miR-183 cluster have both common and unique targets within functionally interrelated pathways, they can show cooperative or opposing effects on biological processes, implying the complexity of this miR cluster-mediated gene regulation. Therefore, a better understanding of the molecular regulation of miR-183 cluster expression and its downstream networks is important for the therapeutic applications. In this review, we will discuss the characteristics of miR-183 cluster and a wide variety of evidence on its function in immune system. Newer knowledge summarized here will help readers understand the versatile role of miR-183 cluster in this field.

1. Introduction

Many literature indicate that immune system is a fundamental component of the tumor microenvironment which is a crucial aspect of cancer biology contributing to tumor initiation and progression. The certain cells of the immune system, including natural killer (NK) cells, dendritic cells (DCs) and effector T cells, are capable of promoting the elimination of tumors by driving potent anti-tumor immune responses [1,2]. On the other hand, B cells can promote tumor growth and secrete immunoregulatory cytokines, including TGF-β and IL-10 [3]. Furthermore, the immunosuppressive populations of immune cells, such as regulatory T (Treg) cells, attenuate anti-tumor immune responses [4]. Therefore, accurate understanding and control of the immune system is important for the development of cancer immunotherapy.

MicroRNAs (miRNAs) are a large class of non-coding RNAs (20–25 nt) that negatively regulate gene expression of target messenger RNA (mRNA) at the post-transcriptional level [5]. MiRNAs are transcribed from not only individual genes but also several genes which are located adjacent to each other on the chromosome as clusters [6]. Currently, several miRNA clusters have been found to be essential for normal development and pathology of various diseases, including autoimmune disease and cancer [7–13].

In this review, we focus on the one of the miRNA clusters, miR-183 cluster, which is comprised of miR-183, -96 and −182, and discuss its characteristics and functions in immune system. We first state the characteristics of miR-183 cluster, including its genomic organization and conservation, and the regulation of its expression. Next, the expression, functions and targets of miR-183 cluster members in a variety of immune cells and autoimmune diseases are described.

2. Characteristics of miR-183 cluster

MiR-183 cluster consists of three homologous miRNAs, miR-183, miR-96, and miR-182 which are particularly expressed in all major sensory organs including the retina, nose, inner ear, dorsal root ganglion and olfactory epithelia [14–17]. This cluster belongs to a polycistronic miRNA cluster that is located within a 4-kb area on murine chromosome 6q or a 5-kb region on human chromosome 7q32.2 (Fig. 1A) [33]. The three miRNA members of this cluster are oriented in the same order among species and are transcribed in the same direction from telomere to centromere [14,18]. The first human miRNA member of this cluster, miR-96, was discovered in the HeLa human cancer cell line [19]. MiR-183 and -182 were identified in 2003. Bioinformatics analysis allowed the discovery of miR-183 and miR-182 through

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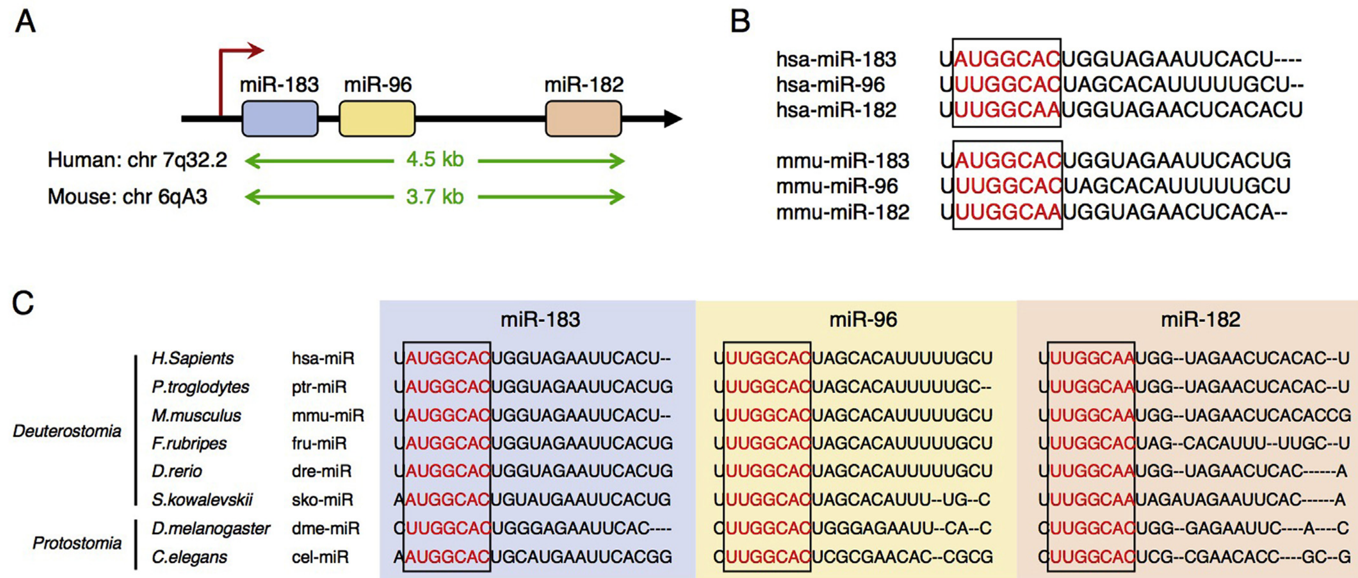

Fig. 1. (A) Chromosomal locations of miR-183 cluster members in human and mouse. (B) Seed sequences of human and mouse miR-183 cluster members. Adapted from Wei et al. Thoracic Cancer 6 (2015) 2–9 [18]. (C) Conservation of miR-183 cluster members. Adapted from Dambal et al. Nucleic. Acids Res. 43 (2015) 7173–7188 [22].

comparison between human or mouse RNAs with Fugu rubripes genome [20]. MiR-183, -96 and −182 were classified as a cluster since these miRNAs are highly co-expressed in the murine retina during development and their chromosomal loci are very close (Fig. 1A) [14,21,22]. Underscoring its functional significance in sensory organs, point mutations in miR-96 resulted in non-syndromic hearing loss in both mouse [23] and human [24]; inactivation of miR-183 cluster in mice resulted in syndromic retinal dystrophy with multi-sensory defects [16]. All members of miR-183 cluster have similar seed sequences (miR-96 and miR-182 are identical) (Fig. 1B). However, minor differences in seed sequences among these members allow them to have independent target mRNAs and distinct functions, suggesting contribution of miR-183 cluster to diverse biological processes such as circadian rhythm, DNA repair, metabolism, apoptosis and immune regulation [22]. Furthermore, next-generation sequencing and comparative genomics have revealed that miR-183 cluster can be evolutionarily traced back ~600 million years ago to protostomes and deuterostomes [25] (Fig. 1C). Therefore, the sequence homology of miR-183, -96 and −182 and the conservation of their genomic organization as a cluster indicates an evolutionary advantage to retaining this miRNA cluster.

3. Regulation of miR-183 cluster expression

The miR-183 cluster members are transcriptionally regulated together as a single polycistronic pri-miRNA. The transcriptional start site (TSS) of miR-183 cluster has not been confirmed yet although several studies suggested its localization in the 5207, 5200, or 5068 bp upstream of miR-183 precursor [26–28], which is in the vicinity of homologous sequence of the transcription start in mouse [16]. Recently, Tang et al. have suggested that the potential TSS of miR-183 cluster maybe localized at the 5112 bp upstream of miR-96, which contains seven binding sites of β-Catenin/TCF/LEF-1 complex [29]. Moreover, previous reports have indicated that three TGF-β response elements at 9–11.5 kb region upstream domain of miR-182, can directly interact with Smad2/Smad4 complex [30]. Throughout the literature, many transcription regulators, including β-catenin/TCF/LEF-1, TGF-β/SMAD, cMAF, FOXP3, STAT3/STAT5, ZEB1, MYCN and HDAC, have been reported to increase or suppress the expression of miR-183 cluster via binding at the upstream of miR-183 in a variety of cells [29–35]. Of note, many of these transcription factors are well known to be involved in the development and functions of immune cells, implying the relationship between miR-183 cluster and immune system.

On the other hand, there is also compelling evidence that the expression of these three mature miRNAs can be regulated individually. For example, transcription factor SP1 increased the expression of miR-182 through the binding to secondary TSS located at the upstream of miR-182 in lung cancer cells [36]. Furthermore, miR-96, but not miR-183 and -182, was negatively regulated by the transcription factor EVI1 via a putative binding site at the 6–7 kb upstream of its sequence [37]. In addition to transcriptional regulation, epigenetic regulation by DNA methylation has been shown to play an important role in the control of gene expression [38]. Of note, there are several CpG islands at the upstream of miR-183 TSS, and the expression of miR-182, but not miR-96 or -183, was regulated by demethylation of a CpG island localized at the 10 kb upstream of miR-183 in human melanoma cell lines [39]. Given the limited number of current reports regarding independent regulation of miR-183 cluster members, further studies are needed for a better understanding of it.

4. miR-183 cluster in immunity

Normally, miR-183 cluster is specifically expressed in sensory cells. This cluster is marginally expressed in immune cells but can be dramatically induced following their activation. All miRNA members of this cluster regulate several pro-inflammatory cytokine pathways which are vital to the immune cell functions. In addition, immune signaling pathway is enriched with target mRNAs of miR-183 cluster members, and several autoimmune diseases have shown aberrant expression of these miRNAs. Here, the examples regarding miR-183 cluster members in T cells, B cells, NK cells, DCs and macrophages are described. The upstream regulators, target genes and functions of miR-183 cluster members in immune cells were summarized in Table 1.

4.1. T cells

It has been reported that global deletion of miRNAs in T cell lineage resulted in impaired T cell development, poor T cell proliferation upon stimulation, aberrant T helper cell differentiation and cytokine production [40]. In 2010, Stittrich et al. have demonstrated that the clonal expansion of activated Th cells following interleukin-2 (IL-2)

Table 1
miR-183 cluster members in immune cells.

Member of miR-183 cluster	Upstream regulators	Immune cell types	Target genes	Functions	References
miR-183 and miR-182	IL-2/STAT5	$CD4^+$ T cells	Foxo1	Promote the clonal expansion of activated Th cells.	Stittrich et al. [34]
miR-182	–	$CD4^+$ T cells	Foxo1	Increases memory T cells and the infiltration of T cells during allograft rejection.	Wei et al. [41,42]
miR-182	–	$CD4^+$ T cells	–	No obvious function in $CD4^+$ T cells.	Pucella et al. [43]
miR-182	IL-4/c-Maf	Th2-associated Treg cells	Cd2ap, BACH2	Reduces IL-2 production and enhance suppressive function.	Kelada et al. [31]
miR-183 cluster	IL-6/STAT3	Pathogenic Th17 cells	Foxo1	Promotes Th17 pathogenicity via regulation of IL-1R1.	Ichiyama et al. [33]
miR-182	–	Activated B cells	–	Drives extra-follicular B cell antibody responses.	Li et al. [49]
miR-183	TGF-b	NK cells	DAP12	Reduces KIR2DS4 and NKp44 expression in NK cells.	Donatelli et al. [50]
miR-183	TGF-b	NK cells	DAP12	Reduces NKG2D, NKp30, DNAM-1, CD107a and IFN-g.	Sadallah et al. [51]
miR-182	–	NK cells from HCC	NKG2A	Increases perforin-1 and cytotoxic activity in NK cells.	Abdelrahman et al. [52]
miR-182	IFN-g/LPS	Human activated DC	–	–	Stumpfova et al. [53]
miR-183	Akt/Foxp3	U937 cell line	β-TrCP	Promotes Sp1 expression and activation of NFkB pathway.	Liu et al. [32]
miR-183	p38/Foxp3	U937 cell line	β-TrCP	Increases Sp1/BAX expression and induce apoptosis.	Huang et al. [54]
miR-96	–	RAW264.7 cell line infected with C. albicans	–	–	Wu et al. [56]
miR-182	–	AM-MDMs infected with F. tularensis	–	Enhances inflammatory gene expression, autophagy and phagocytosis of macrophage.	Gregory et al. [57]
miR-183 cluster	–	RAW264.7 cell line	–	Decreases phagocytosis and intracellular killing activity.	Muraleedharan et al. [58]
miR-183	RANKL	Bone marrow-derived macrophages	HO-1	Induces osteoclastogenesis via increase of TRAP and CTR.	Ke et al. [61]
miR-183 and miR-182	TNF-a	Bone marrow-derived macrophages	Foxo3, Maml1	Promote TNF-a-induced osteoclastogenesis via increase of Blimp1 and NFATc1.	Miller et al. [62]
miR-182	RANKL	Bone marrow-derived macrophages	PKR	Induces osteoclastogenesis via inhibiting IFN-b signaling.	Inoue et al. [63]
miR-182	–	THP-1 cell line	HDAC9	Induces atherogenesis via promotion of lipid accumulation.	Cheng et al. [64]
miR-183	IL-8	THP-1 cell line	ABCA1	Inhibits apolipoprotein AI-mediated cholesterol efflux.	Tang et al. [65]
miR-182	–	RAW264.7 cell line	TLR4	Represses AS progression via inhibiting apoptosis and stress.	Qin et al. [66]

stimulation required the induction of miR-182 mediated by transcription factor STAT5 [34]. The expression of miR-182 increased by 50–200 folds from day 1–2 and reached the peak 3 days after IL-2 stimulation. Of note, this is an example of independent regulation of individual miRNAs since miR-182 expression was only augmented after IL-2 treatment, and miR-96 was not detectable in these activated Th cells [34]. Mechanistically, IL-2-induced miR-182 consequently promoted the clonal expansion of activated Th cells by suppressing post-transcriptionally the expression of its target *Foxo1* mRNA which is a suppressor of proliferation expressed in resting Th cells. Furthermore, *in vivo* studies using an ovalbumin-induced arthritis mouse model showed that specific inhibition of miR-182 by antisense-oligonucleotides (ASOs) led to the improvement of arthritis via limiting the expansion of $CD4^+$ T lymphocytes, suggesting a central role for miR-182 in the physiological regulation of Th cell-mediated immune responses and new therapeutic possibilities [34]. Actually, miR-182 expression was significantly up-regulated in $CD4^+$ T lymphocytes after cardiac transplantation and increased the frequency of $CD4^+CD44^{high}$ memory T cells in allograft recipients as well as the infiltration of T lymphocytes into cardiac allografts via reduction of Foxo1, leading to an aggravation of allograft rejection [41,42]. Therefore, miR-182 may regulate alloimmune responses and be a promising therapeutic target in transplantation. On the other hand, Pucella et al. have recently reported that miR-182 was largely dispensable for T cell-dependent immune responses by using miR-182-deficient mice [43]. The failure to confirm observations derived from previous knockdown experiments by ASOs [34] could be due to off-target effects of knockdown technology. Because miR-183 and miR-96 have similar seed sequences and target mRNAs with miR-182, there is a high probability that they also affect clonal expansion of activated Th cells. To address the possibility of functional compensation, the analysis of mice with deletion of entire miR-183 cluster would need to be performed. Hence, it is still controversial at this time whether miR-182 alone plays a role in T cell-dependent immune responses.

After antigen stimulation, naive $CD4^+$ T cells differentiate into several effector Th subsets with different effector phenotypes to regulate the adaptive immune response, such as Th1, Th2, Treg and IL-17-producing Th cells (Th17) [44]. Several studies have been reported that miR-183 cluster members contribute to the regulation of Th cells differentiation and their functions as well. For example, Kelada et al. have clarified that Th2-associated Treg from type-2 inflamed tissue following *Schistosoma mansoni* infection highly expressed miR-182 by deep sequencing of small RNA species [31]. Functionally and mechanistically, *in vitro* and *in vivo* studies identified that IL-4 induced the expression of miR-182 via transcription factor c-Maf in Th2-associated Treg, which reduced IL-2 production, in part through repression of IL-2-promoting genes [31]. Importantly, specific inhibition of miR-182 in Th2-associated Treg resulted in the failure in controlling Th2-driven airway inflammation as well as Treg-mediated suppression of Th2 proliferation [31]. Collectively, these results indicate that miR-182 can control characteristics within Treg populations and may calibrate their stability and suppressor function after exposure to specific pathogens [31].

Besides Treg, miR-183 cluster also regulates differentiation and pathogenic function of Th17 [33]. A miRNA-sequencing analysis among several Th subsets, including Th1, Th2, Treg and Th17, revealed that miR-183 cluster members were highly expressed in Th17 compared to other Th subsets. Furthermore, the expression of these miRNAs was induced by pro-inflammatory cytokine IL-6 under the TCR stimulation via direct binding of STAT3 at the upstream of miR-183 gene [33]. The over-expression of miR-183 cluster resulted in enhancement of pathogenic cytokines production, such as GM-CSF and IFN-γ, from Th17 during their development and aggravated symptoms of experimental autoimmune encephalomyelitis (EAE), a mouse model for multiple sclerosis (MS) [33]. In contrast, the deficiency of miR-183 cluster reduced severity of EAE symptoms as well as pathogenic cytokines production, suggesting the promotion of Th17 pathogenicity by endogenous miR-183 cluster [33]. Mechanistically, miR-183 cluster in Th17 directly repressed the expression of transcription factor Foxo1 through binding to its putative binding sequences within 3′UTR region of *Foxo1* mRNA [33]. Of note, Foxo1 negatively regulated the pathogenicity of Th17 in part by inhibiting expression of cytokine receptor IL-1R1, which is known to be an important factor for maintenance as well as induction of Th17 pathogenic phenotypes [33]. Together, these findings indicate that miR-183 cluster can drive Th17 pathogenicity in the development of autoimmune disease via inhibition of Foxo1, which is a negative regulator of Th17 pathogenic function and would present promising therapeutic targets in the treatment of many autoimmune diseases. Consistent with above report, Kästle et al. have also rately suggested that miR-183 cluster is markedly up-regulated upon Th17 differentiation by using a miRNA array [45].

4.2. B cells

Both B cell development and function have shown to be regulated by several miRNAs, including miRNA cluster [46–48]. In 2016, Li et al. reported that miR-183 cluster member, miR-182, plays a role in B cell antibody responses [49]. The expression of miR-182 was largely undetectable in naïve B cells, but dramatically induced in activated B cells. Of note, although miR-182-deficient mice had normal B cell development, these mutant mice exhibited a defect of antibody response at early points of time (day7 and day14) after immunization with T cell-dependent antigen NP_{38}-CGG [49]. Mechanistically, the formation of germinal centers was normal, but the generation of extra-follicular plasma cells was defective in the spleens of NP_{38}-CGG-immunized miR-182 deficient mice. Furthermore, mutant mice were also not able to respond to a T cell-independent type 2 antigen, NP_{25}-Ficoll, which typically elicited an extra-follicular B cell response [49]. Taken together, these results indicated that miR-182 plays a critical role in driving extra-follicular B cell antibody responses.

4.3. NK cells

The opposite roles of individual miR-183 cluster members, miR-183 and miR-182, in NK cell function have been reported [50–52]. First, Donatelli et al. have indicated that miR-183 induced by TGF-β silenced NK cell functions, such as tumor cytolysis and perforin polarization to the immune synapse. This result was accompanied by reducing expression of activating surface receptors, KIR2DS4 and NKp44, despite intact cytoplasmic stores of these receptors [50]. Mechanistic analysis has revealed that miR-183 suppressed the transcription/translation of DNAX activating protein 12 kDa (DAP12), which is a key signal adaptor for stabilization and downstream signaling of several activating NK cell receptors, via direct binding to 3′UTR region of *DAP12* mRNA in NK cells [50]. Similarly, Sadallah et al. have also demonstrated that platelet ectosomes (PLT-Ecto) increased miR-183 expression up to 10-fold in NK cells in a TGF-β-dependent manner [51]. The miR-183 reduced the expression of several activating surface receptors, including NKG2D, NKp30, and DNAM-1, via reduction of DAP12 expression and decreased NK cell function, as measured by CD107a expression and IFN-γ production [51]. Collectively, these studies demonstrated that miR-183 is a key factor in TGF-β-mediated inactivation of NK cell functions.

In contrast to the role of miR-183, miR-182 has shown to be over-expressed in NK cells derived from HCC patients. Mechanistically, miR-182 enhanced NK cell cytotoxicity represented in Perforin-1 up-regulation via down-regulation of inhibitory surface receptor NKG2A expression, suggesting that miR-182 is a positive regulator in NK cell function [52].

4.4. DCs and macrophages

The abnormal expression of miR-183 cluster members in DCs and macrophages has been observed under the several conditions. For example, miR-182 was consistently over-expressed in human activated DCs (aDCs) which are stimulated with IFN-γ and LPS, implying the regulation of aDCs function by this miRNA [53]. Furthermore, one group has reported that miR-183 was expressed in U937 macrophage cell line dependent on Akt/Foxp3 pathway and promoted activation of U937 cells through TNF-α-mediated NF-κB activation by inhibiting of β-TrCP expression [32]. Similarly, another group has clarified that an antimalarial drug quinacrine, which is known to have anti-cancer activity, can upregulate miR-183 expression through p38-mediated Foxp3 induction in U937 cells [54]. As a consequence, miR-183 increased Bax expression via suppression of β-TrCP and induced the apoptosis of U937 cells [54].

Macrophages play major roles as sentinels for infectious pathogens and shape the consequential adaptive immune responses [55]. Wu et al. have demonstrated that significant up-regulation of miR-96 was observed in RAW264.7 macrophage cell line infected by *Candida albicans* [56]. Moreover, Gregory et al. have recently proved that over-expression of miR-182 in human alveolar macrophage-like monocyte-derived macrophages (AM-MDMs) induced the expression of pro-inflammatory genes during infection with *Francisella tularensis*. Consequently, miR-182 primed macrophages for increased autophagy and enhanced phagocytosis against *Francisella tularensis*, suggesting a new application for miR-182 in promoting resistance to intracellular pathogens [57]. In contrast, Muraleedharan et al. have showed that miR-183 cluster was expressed in mouse macrophages and human PBMCs, and that deficiency of miR-183 cluster decreased severity of *Pseudomonas aeruginosa*-induced keratitis as well as inflammatory response to *Pseudomonas aeruginosa* infection [58]. Functionally, over-expression or knock-down of miR-183 cluster in RAW264.7 cells resulted in reduction or enhancement of capacity for phagocytosis and intracellular killing of *Pseudomonas aeruginosa,* respectively [58].

In addition to sentinels against infections, macrophages are also known to be a key player in osteoclastogenesis as well as atherogenesis [59,60]. Ke et al. have reported that expression of miR-183 was elevated in bone marrow-derived macrophages (BMMs) during RANKL-induced osteoclast formation [61]. Functionally, mir-183 promoted osteoclastogenesis by directly repressing the expression of heme oxygenase-1 (HO-1) which is a negative regulator for osteoclast-specific genes such as TRAP and CTR [61]. Similarly, Miller et al. have also indicated that both miR-183 and -182 expression was induced by TNF-α stimulation in BMMs, and that miR-182 promoted TNF-α-induced inflammatory osteoclastogenesis [62]. Mechanistically, miR-182 inhibited expression of both Foxo3 and Maml1, which play important inhibitory roles in TNF-α-mediated osteoclastogenesis, via direct binding at their 3′UTR regions. Consequently, miR-182 promoted TNF-α-induced osteoclastogenesis by increase of Blimp1 and NFATc1 expression [62]. Furthermore, Inoue et al. have lately proved that miR-182 positively regulated osteoclastogenesis by inhibiting endogenous IFN-β signaling via targeting protein kinase double-stranded RNA-dependent (PKR) [63]. Therefore, these studies highlight the therapeutic implications of miR-183 cluster inhibition in osteoprotection.

Cheng et al. have found that miR-182 up-regulated LPL expression by directly targeting HDAC9 in THP-1 macrophage cell line and promoted lipid accumulation in atherosclerotic lesions as well as secretion of pro-inflammatory cytokines such as IL-1β, TNF-α and MCP-1, leading to an acceleration of atherogenesis in Apolipoprotein E-Knockout mice [64]. Moreover, Tang et al. have recently demonstrated that IL-8 negatively regulates ATP-binding cassette protein A1 (ABCA1) expression and cholesterol efflux through augmentation of miR-183 expression in THP-1 macrophages, leading to development of atherosclerosis [65]. On the other hand, Qin et al. have indicated that miR-182 was markedly decreased in atherosclerosis (AS) model induced by treatment of oxidized low-density lipoprotein (ox-LDL) in RAW264.7 macrophage cell line [66]. Functionally, miR-182 repressed AS progression through inhibiting oxidative stress and apoptosis via targeting TLR4 expression [66].

Taken together, these observations clarify that miR-183 cluster shows context-dependent functions in regulation of macrophage under the several conditions, suggesting the necessity of further investigations regarding the roles of individual miR-183 cluster members for the clinical application.

5. miR-183 cluster and autoimmune disease

Increasing evidence implicates miRNAs in various disorders by affecting specific target genes. Especially, many miRNAs have been identified as over-expressed or under-expressed in autoimmune diseases such as systemic lupus erythematosus (SLE) [11,12], rheumatoid arthritis (RA) [67] and multiple sclerosis (MS) [68]. In contrast to the seemingly sensory-specific roles of miR-183 cluster members in normal development, they do not appear to be expressed at high levels in most non-sensory tissues. However, individual and multiple members of miR-183 cluster are frequently identified by profiling studies as having high expression in pathologic conditions of autoimmunity. Therefore, research into the role of miR-183 cluster members in *in vitro* and *in vivo* models of autoimmune diseases could provide new insights into therapeutic strategy for diseases.

Dai et al. have demonstrated that three different murine models of SLE showed increased expression levels of miR-183 cluster in splenic lymphocytes derived from diseased mice [69]. Of note, the expression of this miRNA cluster might be regulated by estrogen and relevant to the increased risk of SLE in women since female SLE-model mice (NZB/W_{F1}) and estrogen-treated orchidectomized mice had significantly higher levels of miR-183 cluster compared to intact male SLE mice or placebo-treated orchidectomized mice [70]. Furthermore, Choi et al. have found that both cyclophosphamide treatment and human adipose tissue-derived mesenchymal stem cells (ASCs) transplantation in SLE model mice (C3.MRL-Fas^{lpr}/J) significantly decreased the expression of miR-183 cluster members, anti-dsDNA levels, glomerular C3 deposition, CD138 proportion and the ratio of Th1/Th2 compared with the saline-treatment group, suggesting the involvement of miR-183 cluster in the therapeutic mechanism for SLE [71]. Consistent with mouse studies, Wang et al. have recently reported that miR-182 expression was up-regulated in lupus nephritis (LN) patients while the level of Foxo1 was down-regulated [72]. Importantly, the inhibition of miR-182 by antagomirs in MRL/lpr mice resulted in amelioration of renal structure and function impaired by LN progression, along with the increase of Foxo1 expression [72].

Besides SLE, miR-183 cluster members are also involved in pathogenesis of RA and MS. The specific knockdown of miR-182 by ASOs resulted in the improvement of arthritis by inhibiting expansion of Th cells in the ovalbumin-induced arthritis model mice [34]. Furthermore, Chen et al. have reported that miR-183 was markedly up-regulated in osteoblasts derived from RA patients and may control joint destruction in RA by targeting A-kinase anchoring protein 12 (AKAP12), which is one of the genes involved in protein kinase A signaling, chemotaxis and neovascularization [73]. As mentioned above, the expression of miR-183 cluster was significantly increased in pathogenic Th17 during EAE development, a mouse model for MS [33]. Of note, the deletion of miR-183 cluster attenuated Th17 pathogenicity and relieved symptoms of EAE disease via regulation of Foxo1 and IL-1R1 expression [33]. Moreover, Liguori et al. have lately indicated that miR-182 was significantly up-regulated in peripheral blood of pediatric MS patients compared with pediatric controls, which was correlated with genes involved in immunological functions as well as autophagy-related processes and ATPase activity [74].

In addition, miR-183 cluster members may contribute to the pathogenesis of Graves' disease (GD) as well as Behcet's disease and Vogt-Koyanagi-Harada (VKH) syndrome. In 2015, Qin et al. have clarified that miR-183 was augmented in thyroid tissues of GD patients while the expression of its predicted target genes, such as AKAP12 and ZFPM2, were decreased, providing a new insight into understanding the pathophysiological mechanisms of GD [75]. Recently, one group has indicated that miR-183 and miR-96 were highly expressed in $CD4^+$ T cells from peripheral blood of Graves' orbitopathy (GO) patients [76]. Functionally, over-expression of miR-183 and miR-96 promoted T cell proliferation via decrease of EGR-1 and PTEN expression. In contrast, the inhibition of miR-183 and miR-96 by antagomirs treatment in $CD4^+$ T cells delayed the development of T cell-dependent autoimmune disease [76]. Furthermore, in two rare uveal genetic autoimmune syndromes, there was a single nucleotide polymorphism (SNP) located in pre-miR-182, rs76481776 (CC→TT/CT), that is significantly associated with both Behcet's disease and VKH syndrome, although the functionality of this SNP in these diseases is still unknown [77]. Of note, the expression of mature miR-182 was markedly increased in miR-182/rs76481776 TT/CT genotypes compared to CC genotypes [77]. Furthermore, Hsu et al. have proved that the expression of miR-182 and miR-183 was strongly induced in the eyes of Lewis rats during experimental autoimmune anterior uveitis (EAAU), suggesting the contribution of miR-183 cluster members to this disease [78].

6. Conclusions

The aberrant expression of miR-183 cluster members is frequently observed in pathologic conditions of several autoimmune diseases and cancers although they were originally identified as sensory organ-specific miRNAs. In this review, we presented the pleiotropic roles of miR-183 cluster members in immunity. The individual and multiple members of miR-183 cluster cooperate to regulate various components of pathways related to immune system. Most of the previous reports indicated that miR-183 cluster members play a pathogenic role in autoimmune disorders. Therefore, miR-183 cluster members and their downstream effectors, either individually or as a cluster, have the potential to be promising therapeutic targets in these diseases. However, some studies showed that miR-183 cluster members sometimes exert opposing functions as regulatory genes, implying the complexity of this miRNA cluster. Therefore, further investigations regarding the roles of miR-183 cluster members are still needed to precisely clarify their targets and functions under the various conditions for the clinical application of this miRNA cluster in autoimmune diseases and cancers.

Conflicts of interest

The authors have no conflict of interest.

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