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miRNA-223 at the crossroads of inflammation and cancer

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ABSTRACT

miR-223 is an evolutionarily conserved anti-inflammatory microRNA primarily expressed in myeloid cells. *miR-223* post-transcriptionally regulates many genes essential in inflammation, cell proliferation, and invasion. Recent studies show that *miR-223* is either endogenously expressed or transferred in exosomes or extracellular vesicles to non-phagocytic cells including cancer cells, where it exerts biological functions. In cancerous cells, *miR-223* acts either as an oncomiR promoting tumors or as a tumor suppressor in a context-dependent manner. Taken together, *miR-223* can regulate tumorigenesis at multiple levels, including by suppressing the inflammatory tumor microenvironment and modulating malignancy of cancer cells.

1. Introduction

microRNAs (miRNA, miR) are short, ~22 nt single-strand RNAs that fine-tune gene expression. Due to their pleotropic targeting ability, miRNAs can regulate a network of genes and thus have profound biological impact. miRNAs are first transcribed as long primary transcripts that include conserved palindromic sequences, which fold back on themselves to form an RNA hairpin. The transcript is then processed by DROSHA in the nucleus and DICER in the cytoplasm into mature, double-strand RNAs. The forward and reverse strand are commonly denoted as the -5p and -3p strand. One of the strands is preferentially loaded into the RNA-induced silencing complex (RISC), directing transcript silencing primarily through complementary binding to the 3′ untranslated regions (3′ UTRs) of target mRNAs. Approximately 60% of human genes contain miRNA seed (nucleotides 2–8) binding sites that are conserved in 27 vertebrate species [1].

miR-223 is a highly conserved microRNA in vertebrates. The *miR-223* hairpin resides in the third exon of a noncoding transcript and primarily results in the *miR-223-3p* strand (hereafter referred to as *miR-223* unless specified) [2]. The minor product, *miR-223-5p*, also plays an active role in some disease states, targeting a separate set of genes [3–5]. Expression of *miR-223* is predominantly found in hematopoietic cells, especially granulocytes and their progenitors [6,7]. Transcription of *pri-miR-223* is driven by a conserved core promoter that contains two PU.1 and a single C/EBPα binding site upstream of exon 1 and an ambiguous regulatory element in the second intron [8]. Furthermore, there are 3 PPARγ regulatory elements upstream of *pre-miR*-223 that can directly enhance *miR-223* expression in bone marrow-derived macrophages [9]. Once transcribed, the half-life of *miR-223* is approximately 25 h in transformed 293T cells [10]; however, this could differ *in vivo* or in other cell types.

Based on TargetScan analysis (hsa-r7.2, mmu-r7.1, and dre-r6.2), a bioinformatical tool that ranks potential microRNA targets based on predicted targeting efficacy and conservation [11], *miR-223* have hundreds of conserved binding sites in zebrafish, mice, and humans. A comparative proteomics and transcriptomics analysis suggested that endogenous *miR*-223 might have over 200 different target genes in mice neutrophils [12]. Despite the broad range of targeting, each gene was suppressed only modestly at the protein level, indicating that *miR-223* may fine tune gene expression. Strongly suppressed target genes also have decreased transcript levels, indicating mRNA destabilization as a major mechanism for endogenous *miR-223*-mediated repression. In addition, mRNAs of the most responsive protein targets are reduced in neutrophil progenitor cells [12]. A list of genes that are validated as *miR-223* targets is provided in Aziz et al. [13], and Gao et al., [14]. In addition to cancer and inflammation, *miR-223* potentially regulates chronic kidney disease-mineral and bone disorder [15]; however, this is not a focus of our review.

2. *miR-223* in Innate Immunity and Inflammation

Inflammation is a non-specific immune response to injury or

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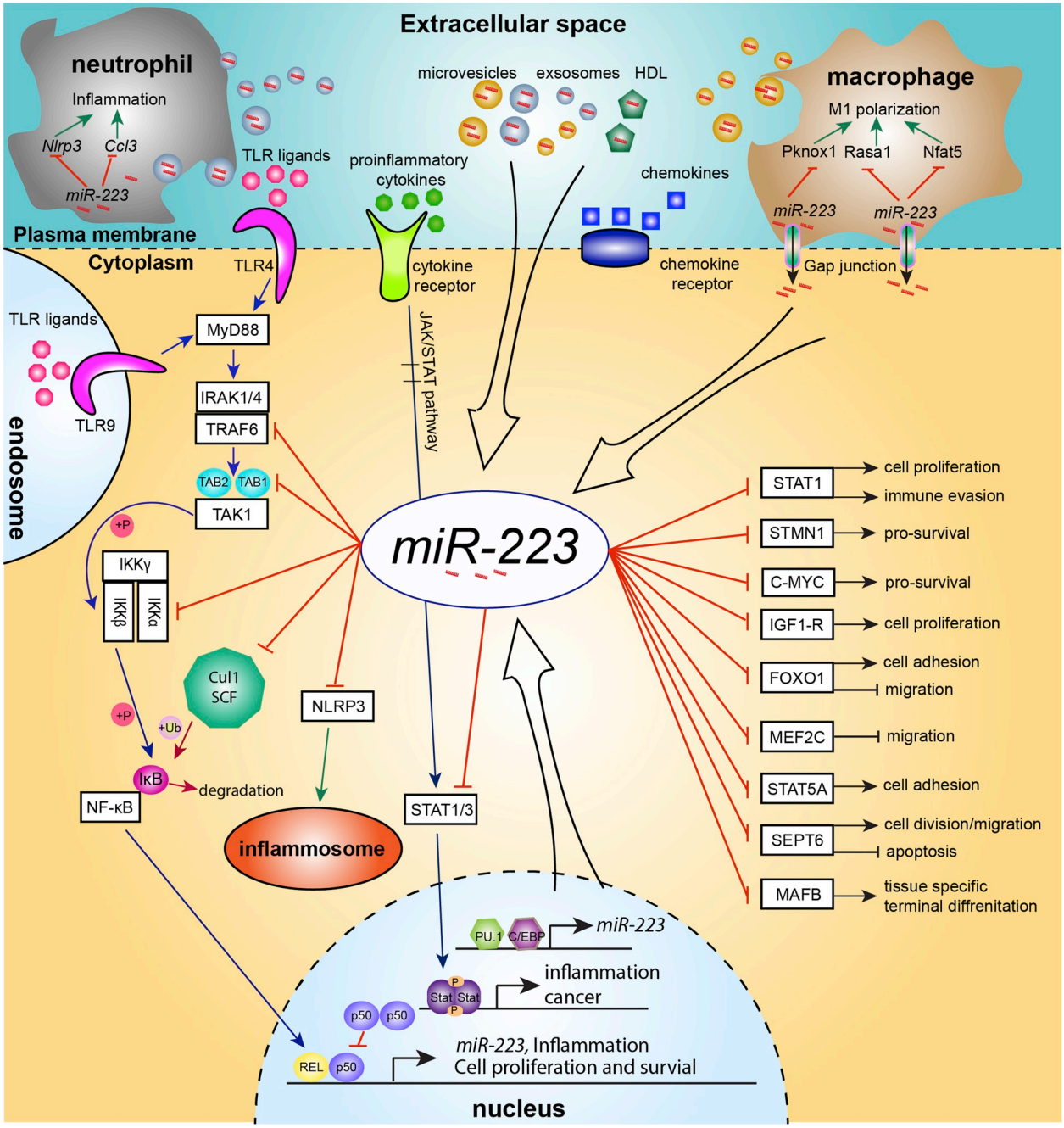

Fig. 1. *miR-223* regulates the canonical NF-κB pathway and other pathways related to cancer. *miR-223* is released from neutrophils and macrophages as a cargo of macrovesicles, exosomes, and possibly high-density lipoproteins (HDL), that can be delivered to phagocytes or non-phagocytic cells. Macrophages, in addition, deliver *miR-223* into recipient cells through gap junctions. *miR-223* is transcribed under the control of PU.1 and C\EBP family transcriptional factors and others, which also contributes to the cytosolic pool of *miR-223*. *miR-223* suppresses the canonical NF-κB pathway by downregulating the expression of components in the signaling transduction pathway. In addition, miR-223 directly targets STAT1 and STAT3 and NLRP3 to suppress the inflammasome activation and production of inflammatory cytokines. In various cancer cells, *miR-223* regulates genes involved in cell proliferation, survival, differentiation, immune evasion, cell adhesion and migration. Note, only selected direct *miR-223* targets are included, and the target genes are different depending on the cell type investigated.

infection, which is detected by pattern recognition receptors such as the Toll-like receptors (TLRs) in sentinel cells, culminating in the activation of the NF-κB and/or the interferon pathways. NF-κB activation leads to the production of inflammatory chemokines and cytokines, which recruit and activate other immune cells including neutrophils, macrophages, and subsequently adaptive immune cells [16–19].

2.1. *miR-223 suppresses inflammation in neutrophils and macrophages*

miR-223 is a negative regulator of neutrophil maturation and activation, although its role in myelopoiesis is still controversial [20]. The first *miR-223* knockout (*miR-223*$^{-/Y}$) was generated in mice [21]. These mice developed spontaneous inflammatory lung pathology with neutrophils that were hypermature and hypersensitive to TLR4 stimulation. The mice were also highly susceptible to *Mycobacteria* [22] due to excessive neutrophil infiltration into the lung and heightened expression of pro-inflammatory cytokines *Cxcl2, Ccl3,* and *Il*-6 by neutrophils (Fig. 1). Furthermore, *miR-223* directly targets *Nlrp3* and negatively regulates inflammasome activation as well as IL-1β release in primary mouse neutrophils [23].

In macrophages, another myeloid cell type where *miR-223* expression level is relatively high, *miR-223* regulates subtype differentiation. In bone marrow derived macrophages of *miR-223*$^{-/Y}$ mice, TLR4-activated M1 (pro-inflammatory) responses were enhanced and IL-4-stimulated M2 (anti-inflammatory) responses were dampened [24]. *miR-223* is downregulated upon TLR4 stimulation, relieving the suppression of its direct target, *Stat3*, which in turn increases the production of pro-inflammatory cytokines [24]. Reciprocally, *miR-223* indirectly downregulates TLR4 protein level and receptor signaling [25]. The transcription factor *Pknox1* is another direct target of *miR*-223 that promotes M1 polarization [9]. IL-4 stimulation upregulates PPARγ to increase the transcription of *pre-miR-223*, which directly silences *Rasa1* and *Nfat5*, positive regulators of the M1 polarization. A recent multi-omics approach has been used to investigate the effects of forced expression and inhibition of *miR-223* in the macrophage RAW264.7 cell line. 120 genes were found to be regulated by *miR-223,* several of which are known to regulate the NF-κB pathway including *Cactin*, *CARM-1*, *MCP-1* and *Ube2g2* [26]. Taken together, *miR-223* inhibits the pro-inflammatory phenotype in both macrophages and neutrophils, thereby suppressing the activation of the innate immune system.

2.2. Extracellular delivery of miR-223

Microvesicles and exosomes transport lipids, proteins, mRNAs, non-coding RNAs, and functional miRNA cargos to target cells [27]. *miR-223* is one of the predominant microRNAs found in microvesicles isolated from human peripheral blood. It possibly originated from peripheral blood monocytes, a major source of circulating microvesicles [28]. Ismail et al. showed that activated human macrophages release microvesicles that deliver *miR-223* as a functional cargo into lung epithelial cells (A549 cell line), fibroblasts (CCL-204 cell line), and endothelial cells (HUVECs). *In silico* analysis of *miR-223* target genes suggested that canonical pathways involved in metabolism, estrogen receptor signaling and degradation of phospholipids could be regulated in the recipient cells [29]. Furthermore, microvesicles from activated THP-1 cells can induce the differentiation of naive THP-1 cells into macrophages [29].

Neutrophils release microvesicles, which induce either pro-inflammatory or anti-inflammatory responses in the recipient cells. In an *in vitro* study, *N*-formyl-Met-Leu-Phe (fMLP) induced the release of extracellular vesicles from circulating human polymorphonuclear leukocytes (PMNs). Co-culturing with stimulated PMNs or treating with the conditioned media, induced the release of pro-inflammatory cytokines IL-6 and IL-8 from human umbilical vein endothelial cells [30]. In agreement with this *in vitro* data, increased microparticle production from circulating leukocytes coincides with enhanced production of IL-6 and monocyte chemoattractant protein-1 from endothelial cells *in vivo* [31]. On the other hand, human neutrophils activated by either fMLP or C5a shed microvesicles, which blocked Lipopolysaccharides (LPS)-induced pro-inflammatory response in co-cultured macrophages [32]. Indeed, *miR-223* is a functional cargo in neutrophil-derived extracellular vesicles *in vivo*. During mechanically induced lung inflammation in mice, PMNs transfer *miR-223* to lung alveolar-epithelial cells, suppressing *PARP-1*, and thereby the detrimental inflammatory cascade during acute lung injury [33].

miR-223 can also be delivered into endothelial cells as a cargo of extracellular high-density lipoproteins (derived from human blood samples with unknown cellular origin), where it directly suppresses the expression of *ICAM-1* and neutrophil attachment to the endothelium [34]. Suppression of *ICAM*-1 by miR-223 has been more recently confirmed in HUVECs transfected with *mir-223* [35]. Taken together, *miR-223* provides an important signal for phagocytes to communicate with themselves and other non-phagocytic cells.

3. *miR-223* in cancer

In contrast to its unified suppressive role in inflammation, *miR-223* is either up-regulated or down-regulated and plays either a pro-tumor or anti-tumor role in different cancers (reviewed in Ref. [14]).

3.1. miR-223 as an oncomiR and tumor suppressor

miR-223 is upregulated in human prostate cancer as well as in multiple prostate cancer cell lines, where *miR-223* directly targets *SEPT6,* a filament-forming GTP-binding protein involved in cell division, polarity and membrane remodeling, to inhibit apoptosis and to promote migration and invasion [36]. In contrast, *miR-223* expression levels are lower in nasopharyngeal carcinoma when compared to healthy cells and patient plasma samples [37]. When a nasopharyngeal cell line (CNE-2) was transfected with *miR-223*, reduced growth rates, colony formation, migration, and invasiveness was observed. This effect was due to *miR-223's* direct suppression of *MAFB*, a transcription factor that regulates early tissue specification and terminal differentiation [37]. Together these studies revealed the various pro- and anti-tumor potential that *miR-223* harbors during tumorigenesis and cancer progression.

3.2. miR-223 in virally induced cancers

In the context of virally induced cancers, *miR-223* also has pro- and anti-cancer qualities. Human Papillomavirus infection upregulates *miR-223* in cervical tissue, reducing cell adhesion and promoting progression of cervical cancer [38]. Conversely, human T-cell Leukemia virus (HTLV-1) downregulates *miR-223*, leading to an increase in the *miR-223* target *STAT-1*, thereby promoting cell proliferation and immune evasion by enhancing MHC-I expression [39]. In the context of Hepatitis B virus-induced Hepatocellular carcinoma, *miR-223* targets pro-survival genes such as *STMN1* [40] and *C-MYC* [41] and restrains cancer growth. The biological consequence of the suppression of *NLRP3* by *miR-223* is also context-dependent. In B cells infected with Epstin-Barr Virus, *NLRP3* suppression enhanced B cell transformation and thereby progression into B cell leukemia [42]. In contrast, in Hepatitis B virus-induced Hepatocellular carcinoma the downregulation of *NLRP3* by *miR-223* inhibited cell proliferation and promoted apoptosis [43].

3.3. miR-223 delivery to tumor cells

Both macrophages and neutrophils are capable of transporting *miR-223* into tumor cells albeit through different mechanisms. Primary human macrophages transfer *miR-223* into HuH7 hepato-carcinoma cells upon direct contact through gap-junctions as determined by *ex vivo* experiments [44]. In these cancer cells, *miR-223* directly targets *STMN1* and *IGF1-R*, inhibiting cell proliferation by over 50% [44]. Neutrophils transfer *miR-223* into A549 lung epithelial carcinoma cells through extracellular vesicles *in vitro*, activating an epithelial-mesenchymal transition program, which results in impaired cell adhesion, increased migration, and invasion through suppressing *FOXO1* and other unknown genes [45].

There are also contradictory results in the literature with respect to *miR-223*'s function in the same recipient cancer cell line. Yang et al., showed that exosomes secreted by M2 polarized macrophages can transport *miR-223* into breast cancer cell lines (MDAMB231 & SKBR3), leading to greater invasiveness [46]. *MEF2C* is a direct target of *miR-223,* and its downregulation can lead to higher nuclear translocation of β-catenin and thereby promotes migration. Pinatel et al., showed that *miR-223* expressing mice embryonic fibroblasts or *miR-223* over-expressing HEK293 cells can transfer *miR-223* into MDAMB231 through conditioned media. Enforced expression of *miR-223*, however, resulted in lower migration rates, invasiveness, and enhanced cell death in anoikis conditions and enhanced the efficacy of chemotherapeutic drugs

[47]. *miR-223* directly targets *STAT5A* and upon silencing of *STAT5A*, similar effects were observed. The discrepancy could possibly be explained by the source of exosome/microvesicles, which mediated *miR-223* delivery. Exosomes from M2 macrophages possibly carry additional cargos that harbor a tumor-promoting function. In addition, many of these studies rely on *in vitro* experimental methods, necessitating further *in vivo* research to confirm the physiological impact of *miR-223* transfer from immune to cancer cells.

4. *miR-223* and the NF-κB pathway

miR-223 modulates the inflammatory response through directly targeting genes mediating signal transduction, including those present in the canonical NF-κB pathway (Fig. 1). Although miR-223 has been implicated in the regulation of the MAPK signaling [35,48], recent findings are still preliminary and contradictory and therefore not included in this review.

4.1. NF-κB in inflammation and cancer

NF-κB proteins are Rel family transcription factors that function as homo- or heterodimers. Their transcriptional activation domain is present in RELA (p65), RELB and c-REL, but not in p50 (a cleavage product of p105, encoded by *NFKB1*) or p52 (a cleaved product of p100, which is encoded by *NFKB2*). As one of the most important molecules linking chronic inflammation to cancer, NF-κB is activated in cancer cells and in the tumor microenvironments of most solid cancers and its role in driving tumorigenesis and anti-tumor immunity has been extensively reviewed [49–54].

4.2. miR-223 suppresses the NF-κB pathway

miR-223 regulates both the canonical and alternative NF-κB pathways. During human monocyte-macrophage differentiation, an increase of the IKKα protein coincides with a decrease of *miR-223*, *miR-15* and *miR-16*. IKKα mRNA is directly targeted by all three microRNAs [55]. Due to the absence of RELB in resting macrophages, the increased amount of IKKα leads to increased processing of p100 and therefore an increase of the inhibitory complexes (p52/p52 or p52/p50), suppressing the alternative pathway. However, upon stimulation with LPS, RELB expression is induced, and the activation of the alternative pathway is enhanced. Transfection of macrophages with a mix of these microRNA mimics, synthetic RNA molecules that mimic endogenous mature microRNAs, suppressed IKKα expression and reduced the activation of the alternative pathway [55]. Although this study investigated the function of all three microRNAs combined, it provided the first evidence that *miR-223* could be a potential regulator of the NF-κB pathway. In mice neutrophils and human neutrophil-like HL-60 lines, *miR-223* also targets *IKKα*, but not *STAT3* [56].

Evidence that *miR-223* suppresses the classical NF-κB pathway was later provided by Liu et al. when they demonstrated that upregulation of *miR-223* suppressed the phosphorylation of RELA in the peripheral blood monocytes from patients with active Tuberculosis [57]. By overexpressing or suppressing *miR-223* in differentiated human myeloid leukemia U937 cells, the authors found an inverse correlation between the level of *miR-223* and RELA phosphorylation, nuclear translocation, and the expression of pro-inflammatory genes (IL-1β, IL-6, TNF-α, and IL-12p40) upon stimulation [57]. *miR-223* deficient neutrophils have elevated expression of TLR9, contributing to the immunopathology in acetaminophen-induced liver damage. Furthermore, the *miR-223* level in neutrophils is elevated specifically by treatment with TLR9 agonists or IL-6. Upon TLR9 ligand treatment, RELA is detected at the *miR-223* promoter region, suggesting a negative feedback loop between the TLR9/canonical NF-κB pathway and *miR-223*, which could possibly restrain the inflammation process.

We have recently generated a *miR-223* knock-out zebrafish line, which exhibits an enhanced neutrophil wound response and delayed resolution of inflammation [58]. Four genes were confirmed as direct targets of *miR-223*: *cul1a/b, traf6, and tab1*. Cul1 is the core subunit of the essential E3 ubiquitin ligase family that mediates the degradation of the IκB. Using an NF-κB reporter line (the promoter is activated by both RelA/p50 and RelB/p52), increased NF-κB activation was noted in the injured epithelium, but not in phagocytes. Endogenous *miR-223* in skin cells and phagocytes coordinate to suppress the NF-κB activation in the epithelium to tune down the magnitude of inflammation. Furthermore, we provided evidence for *miR-223* as a suppressor of the NF-κB pathway in human non-phagocytes, such as the immortalized human bronchial epithelial cells and HEK293 cells [58].

It remains to be determined how phagocytes regulate the NF-κB signal in the basal epithelium. It may likely occur via direct transfer of *miR-223* from phagocytes to epithelial cells, as observed above in mice or *in vitro* [29,34], but could be through other inflammatory mediators such as secreted cytokines. Whereas *miR-223* regulates inflammation through neutrophils, the NF-κB reporter activity was not elevated in the *miR-223* deficient phagocytes, which is somewhat controversial considering the central role of NF-κB in innate immunity [58]. It remains to be determined whether *miR-223* indeed regulates phagocyte function without activating the NF-κB pathway or whether our findings are specific to zebrafish.

Another interesting finding from our study showed that regeneration of tailfins is accelerated in the *miR-223*$^{-/-}$ fish [58]. This relationship between *miR-223*$^{-/-}$ and wound healing has recently been confirmed in mice [59], where *miR-223*$^{-/Y}$ mice display increased repair of *Staphylococcus aureus*-infected wounds. Administration of *miR-223*$^{-/Y}$ neutrophils, or *miR-223* antisense oligos to the infection site improved wound healing, suggesting that *miR-223* can direct wound healing in epithelial cells possibly in both cell-autonomous and non-cell-autonomous manners. It is likely that *miR-223* suppresses the NF-κB pathway also in mice epithelial cells, considering mammary epithelium deficient in I-κBα and therefore with heighted activation of the canonical NF-κB pathway also had increased cell proliferation during development [60].

5. Inflammation drives malignancy

Inflammation is a hallmark and cause of cancer with NF-κB as a molecular lynchpin [61]. Inflammation drives all steps in tumorigenesis, including tumor initiation, promotion, spread and therapy resistance [53]. Cancer, “wounds that do not heal” [62], are chronically inflamed, recruiting and reprogramming myeloid cells into tumor promoting phenotypes and create an immune suppressive microenvironment [63,64]. NF-κB is constitutively activated in many types of cancer, not only in malignant cells, but also in other cells in the cancer microenvironment, including myeloid cells, lymphocytes and fibroblasts. As a result, extensive efforts have been made in developing therapeutics that modulate the NF-κB signaling in cancer [53,54,65,66]. However, NF-κB also promotes anti-tumor immunity in tumor cells [67–69], contributing to the complications in therapeutic intervention using NF-κB blockades.

6. Conclusions and future perspectives

Through sequencing of circulating exosomal miRNAs, the levels of *miR-223* are used to predict the probability of adenocarcinoma of the esophagus [70], colon cancer [71], and breast cancer [72]. However, because of the pleotropic effects *miR-223* within each cancer cell type, it is currently not a predictable oncomiR or tumor suppressor. The therapeutic potential of *miR-223* supplementation or depletion, is not yet clear. *miR-223* suppresses the activation of the canonical and non-canonical NF-κB pathways, STATs and NLRP3 inflammasome and therefore is a potent negative regulator of inflammation. Similar to the use of NF-κB blockades in cancer therapy, therapeutic use of *miR-223* is likely cell-type-dependent and context-dependent. Currently how *miR-*

223 regulates the tumor microenvironment is not characterized in mice or other animal models where *miR-223* is depleted or overexpressed. It is possible that removing *miR-223* from tumor-associated myeloid cells could shift them to a tumor eliminating, pro-inflammatory phenotype [73] and potentiate antitumor immunity [74,75]. On the other hand, depleting *miR-223* could augment inflammation and promote tumor initiation. Although increased tumor incidence was not reported in the *miR-223*$^{y/-}$ mice, it not known whether *miR-223* deficiency will worsen the outcome in cancer prone backgrounds, such as in p53-deficient animals. Over the last 15 years, miRNA therapy has emerged as an alternative means to treat cancer. However, safe and targeted delivery of miRNA mimics and antagomirs still remains a challenge. Viral delivery methods are not ideal for clinical settings due to the risk of inducing strong inflammation. Therapeutic miRNA mimics and antagomirs are conjugated or modified, such as with locked nucleic acid (LNA) to prevent degradation [76,77]. Lipid encasement, aptamer and ligand attachment are used for selective delivery into target cells. Since *miR-223* is likely shuttled between leukocytes and cancer cells within the tumor-immune microenvironment, modulating *miR-223* level in one specific cell type may become a challenge. However, targeting multiple cell types simultaneously can potentially lead to a combined greater benefit. In conclusion, clearly more research, especially in animals, is needed in order to fully understand the biological function of *miR-223* in the tumor microenvironment for specific types of cancer and determine whether up- or down-regulation of *miR-223* could serve as a potential therapeutic.

Conflicts of interest

The authors declare no competing financial interests.

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