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Mini-review

MiRNAs: dynamic regulators of immune cell functions in inflammation and cancer

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ABSTRACT

MicroRNAs (miRNAs), small noncoding RNA molecules, have emerged as important regulators of almost all cellular processes. By binding to specific sequence motifs within the 3′- untranslated region of their target mRNAs, they induce either mRNA degradation or translational repression. In the human immune system, potent miRNAs and miRNA-clusters have been discovered, that exert pivotal roles in the regulation of gene expression. By targeting cellular signaling hubs, these so-called immuno-miRs have fundamental regulative impact on both innate and adaptive immune cells in health and disease. Importantly, they also act as mediators of tumor immune escape. Secreted by cancer cells and consecutively taken up by immune cells, immuno-miRs are capable to influence immune functions towards a blunted anti-tumor response, thus shaping a permissive tumor environment.

This review provides an overview of immuno-miRs and their functional impact on individual immune cell entities. Further, implications of immuno-miRs in the amelioration of tumor surveillance are discussed.

1. Introduction

Since their first description by Lee et al., in 1993, microRNAs (miRNAs) have increasingly gained attention. Our knowledge about their individual functions and the underlying biological principles has developed rapidly [1]. By now, miRNAs have firmly established their role as central regulators of gene expression. They act primarily as inhibitory molecules on their respective target genes, thereby controlling virtually all cellular processes and playing a pivotal role in human diseases including cancer [2–8]. Particularly within the human immune system, miRNAs now are viewed as integral parts of regulatory networks, in homeostasis as well as in disease [9,10]. This is not strictly limited to immunological issues, but also extends to cancer, since the role of miRNAs as mediators of tumor immune escape is a new focus in oncology [11].

MiRNAs are a class of small (~22 nt) non-coding RNA molecules. They post-transcriptionally regulate gene expression by direct targeting of binding sites within the 3′UTR of mRNA transcripts. To date, nearly 2000 human miRNAs have been discovered, and it is estimated that the substantial majority of protein-coding genes is under their control. MiRNA biogenesis is a complex process starting with the transcription of a precursor miRNA (pre-miRNA), which is located either in intergenic regions -equipped with own promoter structures-, or in introns, thus mostly co-transcribed with its respective host gene [12–14]. After several processing steps and translocation into the cytoplasm (Fig. 1 [15]), the mature double-stranded miRNA is generated [16]. One miRNA single-strand molecule is loaded into the RNA-induced silencing complex RISC, enabling it to bind to its target mRNA by base-pairing complementarity of the miRNA 5′ end to the 3′ untranslated region (3′-UTR) of the respective mRNA [16,17]. Binding takes place at typical seed sites consisting of 6–8 nucleotides [2,18–20], or at non-canonical seedless sites [18–20]. This miRNA-mRNA interaction leads either to translational repression or degradation of the target mRNA [21–24].

Targeting networks of miRNAs are rather complex: one miRNA can affect the expression of a multitude of genes. Conversely, one mRNA is usually targeted by many different or related miRNAs. In addition, miRNAs often control multiple targets within one signaling axis, thereby amplifying their regulatory capacity. Many microRNAs are organized and transcribed within miRNA-clusters, containing several functionally cooperating miRNAs, thus exerting synergistic action. Furthermore, not only direct target interaction but also indirect effects via suppression of enzymes or transcription factors may occur. Therefore, miRNA net effects are based on a complex multi layered model, eventually resulting in significant impact on cellular faith [16,29–34]. Importantly, one miRNA may exhibit different effects in different cell types. Evidence was provided for altered 3′UTR length in

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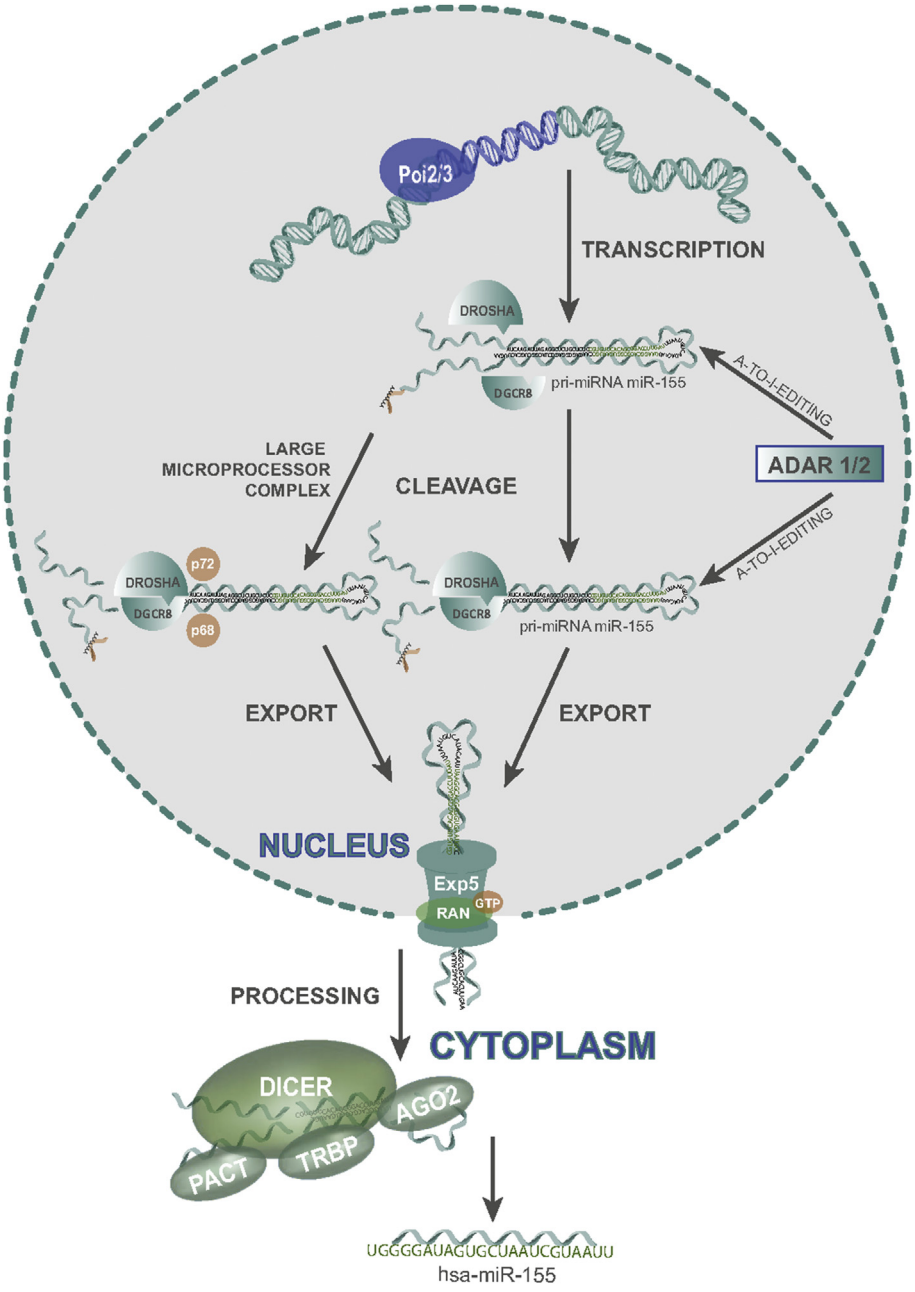


Fig. 1. MicroRNA biosynthesis. The complex process of miRNA biosynthesis is initiated with the transcription of a hairpin-structured primary miRNA (pri-miRNA) by RNA polymerase 2/3. After cleavage through the "microprocessor" complex (DGRC8 and RNAse III Drosha), the newly formed precursor miRNA (pre-miRNA) is exported into the cytosol via Exportin-5/RAN-GTP and finally processed by the RISC loading complex - encompassing Dicer, TAR RNA binding protein (TRBP), protein activator of PKR (PACT) and Argonaute-2 (Ago2) - into mature miRNA transcripts. Alternatively, some pri-miRNAs are further processed by the "large microprocessor complex", comprising Drosha, DGRC8, RNA helicases p68 and p72 as well as double-stranded RNA binding proteins, heterogeneous nuclear ribonucleoproteins and Ewing's sarcoma proteins. In parallel with processing of primary transcripts, miRNA editing through adenosine deaminases acting on RNA (ADAR 1/2) may occur. Through exchange of adenosine (A) for inosine (I), miRNA sequence can be modified, resulting in alterations of miRNA processing steps as well as different miRNA-mRNA binding abilities.

proliferating cells and considerable differences in tissue-specific 3′-UTR regions due to alternative polyadenylation [12,35–38].

Also, cellular microenvironment strongly influences miRNA biogenesis and action. For example, tumor induced hypoxia results in down-regulation of miRNA processing enzymes DICER and DROSHA as well as alterations in RISC catalytic component argonaute 2 (phosphorylation) levels, thus affecting miRNA biogenesis and function [25,26]. On the other hand, hypoxia-induced transcription factors such as HIF1α promote transcription of various microRNAs relevant for hypoxic adaptation [27,28].

In this review, we summarize the current understanding of miRNA involvement in immune cell functions. Due to its strong medical impact, this topic has attracted considerable attention not only with respect to inflammatory diseases but also in the context of cancer. The latter aspect is a nascent field in oncology, as miRNAs secreted by tumors are taken up by immune cells, where they exert inhibitory impact, thus contributing to immune escape of tumors. The first part of this article will present central and important immunological miRNAs - so called immuno-miRs - that control development, proliferation and effector functions of various innate and adaptive immune cells. In the second part, we will focus on tumor-derived miRNAs that impair immune surveillance of tumors.

2. Immuno-miRs: central regulators of immunity

In recent years, a vast amount of miRNAs have been found to be involved in the regulation of immunological key processes encompassing development, lineage commitment, activation, function and ageing of innate and adaptive immune cells [9,39,40]. Within these networks, striking miRNAs and miRNA-clusters have crystallized, that exert pivotal roles in the regulation of gene expression throughout the entire immune system. By targeting cellular signaling hubs (e.g. NF-κB signaling pathways, Fig. 2), these so-called immuno-miRs have fundamental regulative impact in both innate and adaptive immune cells (summarized in Table 1).

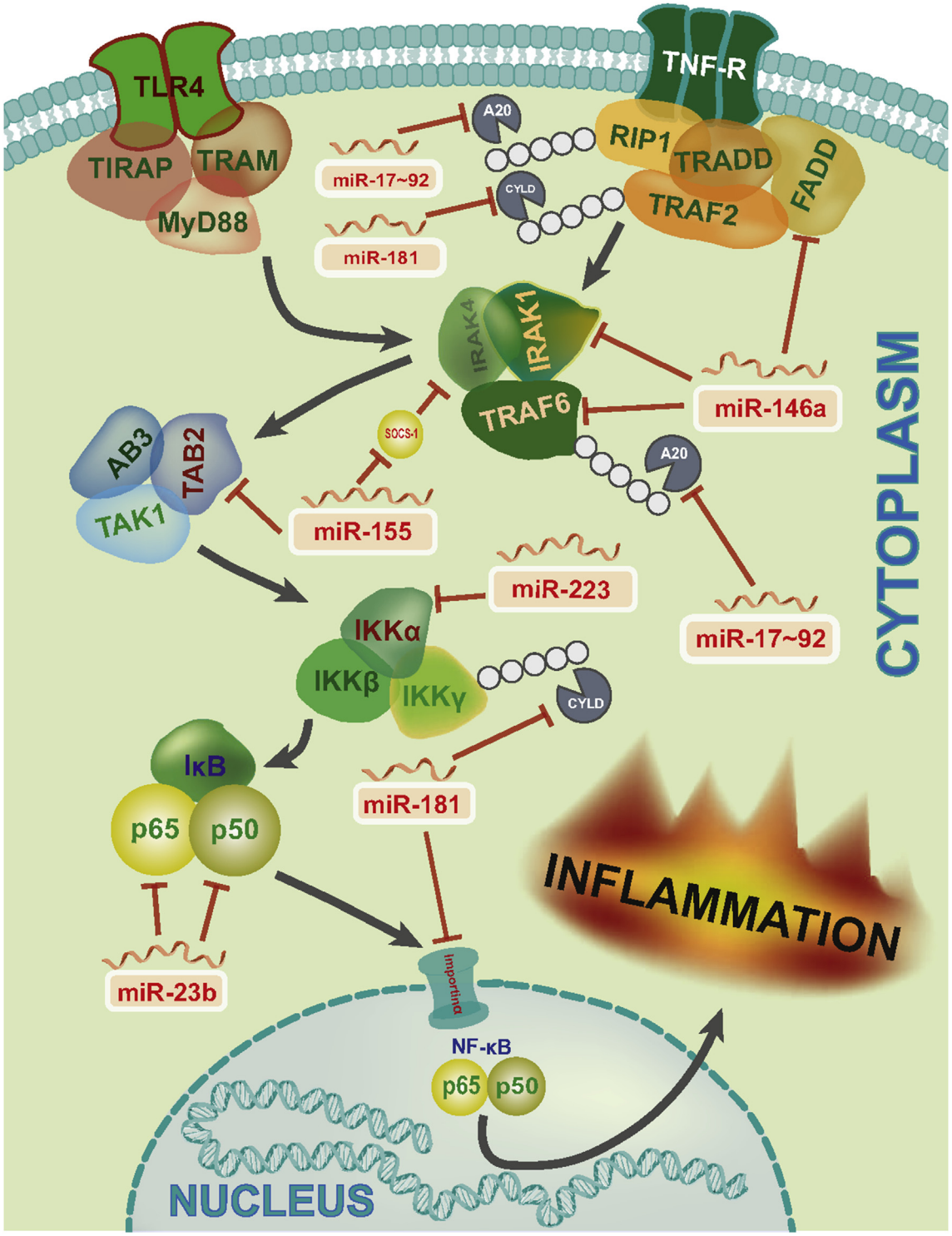


Fig. 2. Regulation of nuclear factor- κB (NF-κB) signaling by immuno-miRs. Several central components within the NF-κB pathway are targeted by miR-146/miR-155-axis, miR-17–92 cluster, miR-223, miR-23 ~ 27 ~ 24 cluster and miR-181, thus regulating inflammation. A20 indicates TNFAIP3 (Tumor necrosis factor, alpha-induced protein 3); CYLD, regulator cylindromatosis; FADD, fas-associated protein with death domain; IKK, IκB kinase alpha; IRAK, interleukin-1 receptor associated kinase; NIK, NF-κB inducing kinase; RIP1, receptor-interacting serine/threonine protein kinase 1; TAB, TGF-beta-activated kinase 1/MAP3K7-binding protein 2; TAK, tat-associated kinase; TGF, transforming growth factor; TIRAP, toll-interleukin 1 receptor domain containing adaptor protein; TLR4, toll-like receptor-4; TNF-R, tumor necrosis factor receptor; TRADD, TNF receptor type 1-associated death domain; TRAF, TNF receptor-associated factor 2; TRAM, toll-like receptor adaptor molecule.

2.1. miR-23 ~ 27 ~ 24 cluster

MiRNAs of this cluster are organized within two paralogues: Mirc11 on chromosome 19 harbouring miR-23a, miR24-2 and miR-27a, and Mirc22 on chromosome 9 encoding miR-23b, miR-24-1, miR-27b [41–43].

Growing evidence suggests a complex interplay between hematopoietic transcription factors and miR-23 ~ 27 ~ 24, influencing the

Table 1
Immuno-miRs and their immunological impact.

Immuno-miR	Immunological effect
miR-23 ~ 27 ~ 24	myeloid lineage commitment ↑ lymphoid cell differentiation ↓ $CD8^+$ T-cell effector function ↓ Th2 response ↓
miR-23 | miR-27	Th1/Th17/Treg differentiation and function ↓
miR-24	Th1/Th17/Treg differentiation ↑
miR-146a	TNFα and IL-6 immune pathways ↓ NF-κB activity ↓ Th1 cell differentiation ↓ Th1 inflammatory response ↓
miR-155	NF-κB activity ↑ T effector cell accumulation and action ↑ Th17 cell function ↑
miR-17–92	Th1 response ↑ T effector cell proliferation and survival ↑ Th2 cytokine production ↑ Treg differentiation ↓ Tfh cell migration, differentiation and function ↑ B-cell development and survival ↑ macrophage differentiation ↓
miR-223	granulocyte inflammatory response ↓ NFκB-, TLR-, and MAPK-signaling ↓ NLRP inflammasome activity ↓
miR-181	TCR signaling power and sensitivity ↑ Th1 cell differentiation ↓ Treg development ↑ dendritic cell response ↓ M2 macrophage polarization ↑

regulation of immune cell lineage commitment. The cluster is transcriptionally induced by PU.1, a central myeloid transcription factor [43], and, in contrast, negatively regulated by lymphoid transcription factors (EBF1, E2A and PAX5) [44]. In turn, cluster miRNAs directly target a number of fundamental lymphoid transcription factors (Runx1, Satb1, Bach1 and Ikzf1), thereby impairing lymphoid cell differentiation and promoting myeloid lineage commitment and cell proliferation [42–47]. Members of the miR-23 ~ 27 ~ 24 cluster exert complex, partially even opposing effects on T-cell immunity. One central feature is repression of Th2 immunity by impairment of IL4 cytokine signaling mediated by all members of the cluster. MiR-24 and miR-27 directly suppress IL4 (miR-24) and the central Th2 transcription factor GATA3, also by targeting BIM1 [48,49]. Pua et al. discovered several more direct targets for miR-24 (Cnot6, Clcn3), miR-27 (Ccnk, Aff4) and miR-24/miR-27 (Ikzf1, Gpr174 and Galnt3), mediating IL4-network-related suppression of Th2 immunity [50]. Regarding other T helper cell subsets, miR-24 has been reported to promote Th1, Th17 and Treg differentiation by targeting TCF1 [48,51], whereas miR-23 and miR-27 have been shown to restrain Treg/Th17 cell differentiation and Th1 functions [48,52,53]. Several studies provided evidence for impaired production and direct targeting of IFNγ by miR-27 [48,54]. In contrast, in patients an increase in IFNγ+ T-cells following overexpression of miR-27 was described [55]. Very recently, this was attributed to a perturbed Treg compartment by Cruz et al. [53].

These partially opposing effects of members of the same miRNA cluster may serve as cluster-intrinsic negative feedback mechanisms, enabling a versatile molecular fine-tuning.

In cytotoxic T-cells, miR-23 ~ 27 ~ 24 is induced directly by TGF-β and indirectly through TGF-β mediated suppression of cMyc [56,57]. The cluster suppresses $CD8^+$ T-cell effector function through direct (miR-24, miR-27a) and indirect (miR-23a) targeting of IFNγ [56,57].

In dendritic cells, miR-27a has been shown to dampen Th1 and Th17 response [58]. MiR-23b acts in the same direction by increasing FoxP3 expression through inhibition of the Notch1 and NF-κB signaling pathways (IκBα phosphorylation) [59].

2.2. miR-146a/-155 axis

miR-146a and miR-155 are abundant in most innate and adaptive immune cells, where they exert strong regulative impact [60–62]. Although not encoded within one genetic cluster, both miRNAs are functionally strongly entangled and thus are viewed to act within a joint functional axis: They form a “yingyang” with miR-146a representing the anti-inflammatory and miR-155 the pro-inflammatory part.

The role of miR-146a as a brake on inflammation has been well defined: By targeting central signaling molecules (IRAK1/2, TRAF6, MyD88, TLRs, NOTCH1), miR-146a negatively regulates both TNFα as well as IL-6 immune pathways, thereby suppressing differentiation processes and inflammatory effector functions in innate immune cells [63–66]. In adaptive immunity, miR-146a has been shown to be a key negative regulator of Th1 cell differentiation [67]. In line with these findings, massive upregulation of IFNγ in miR-146a defective $CD4^+$ and $CD8^+$ T-cells has been observed [68]. MiR-146a-deficient mice develop chronic hyperinflammatory and autoimmune disorders with accumulation of innate immune cells, activated $CD4^+$ and $CD8^+$ T-cells, and autoantibodies. This phenotype is due to a lost targeting of signal transducer and activator of transcription 1 (STAT1), which reduced abilities of Treg cells to suppress IFN-mediated inflammatory Th1 responses [69]. Furthermore, miR-146a has been identified as part of a negative feedback loop limiting NF-κB activity upon T-cell activation via repressing the NF-κB activators TRAF6, IRAK1 [70,71] and FADD. The latter interaction is also mitigating activation-induced cell death (AICD) in T-cells [72].

Pro-inflammatory miR-155, in contrast, is elementary for mounting adequate immune responses [73]. Through direct targeting of suppressor of cytokine signaling-1 (SOCS-1), miR-155 positively regulates IFNγ production in $CD4^+$ and $CD8^+$ T-cells, which was shown indispensable for sufficient T effector cell accumulation and action [68,74]. The interaction with SOCS-1 also has been implicated in conferring Treg fitness [75]. Furthermore, miR-155 contributes to Th17 cell function by suppressing the inhibitory effects of Jarid2 [76]. These findings were further strengthened by analysis of miR-155-deficiency, which resulted in resistance to experimental autoimmune encephalitis, thereby providing evidence for significantly impaired Th1 and Th17 cell response [77].

Based on the fact that miR-146a and miR-155 target elements of the same central immunological hub, namely the NF-κB signaling cascade, Mann et al. provided evidence for a complex spatio-temporal regulatory network in macrophages, consisting of both microRNAs. Activation of NF-κB leads to enhanced expression of miR-155. By targeting of SHIP1 and SOCS1, miR-155 amplifies NF-κB signaling via a positive-feedback loop. With time, also miR-146a levels are upregulated by NF-κB, “switching off” the miR-155 signaling cascade by direct targeting of IRAK1 and TRAF6 [78].

2.3. miR-17 ~ 92 cluster

The miR-17 ~ 92 cluster, located on chromosome 13, encodes a polycistronic miRNA transcript that yields six individual miRNA components: miR-17, mir-18a, miR-19a/b, miR-20a and miR-92 [79]. Individual miR-17 ~ 92 components regulate a variety of cellular processes in a cell type and context-dependent manner [80]. Relevant expression of miR-17 ~ 92 and important functional implications have been described for lymphocytes, monocytes and macrophages [81–83].

miR-17 ~ 92 has revealed as a central pro-inflammatory cluster in T-cell immunity. Induced upon NF-κB activation, cluster members directly target important regulatory molecules of JAK-STAT and NF-κB signaling pathways. As a result, Th1-related IFNγ response is increased, T effector cell proliferation and survival are promoted, cytokine production of Th2 cells (IL4, IL5, IL13) is amplified, and Treg differentiation inhibited [84–89]. Moreover, miR-17 has been shown to provide

strong control on Treg suppressive abilities through targeting the FoxP3 co-regulatory transcription factor Eos [90]. The miR-17∼92 cluster is also essential for B-cell development. Its absence causes increased levels of the proapoptotic protein Bim and inhibits B-cell lymphopoiesis [91]. Furthermore, miR-17∼92 is required for T follicular helper cell (Tfh cell) differentiation, migration and function. By direct targeting of Pten and Phlpp2, miR-17∼92 effectively controls ICOS-PI3K signaling, thus enabling proper Tfh cell migration [92]. Downregulation of key molecules (CCR6, IL1R1/2, IL22) via direct targeting of RORα through miR-17∼92 further supports Tfh differentiation and function [92,93].

Additionally, macrophage differentiation is potently suppressed by miR-17∼92: Through targeting of HIF-1α and HIF-2α, miR-17∼92 decreases HIF-signaling and impairs macrophage differentiation, particularly in inflamed albeit hypoxic tissues [94].

In $CD8^+$ T-cells, another layer of complexity has been added to these regulatory multi-targeting networks of miR-17∼92, as distinct biological functions require a strictly time-dependent cluster expression: In response to acute infections, elevation of miR-17∼92 is required for sufficient cell expansion to counter the pathogens. In protracted states of infection, however, down-regulation of miR-17∼92 is necessary for adequate memory cell response and central memory development [95,96].

2.4. miR-223

MicroRNA-223 is considered a classical innate microRNA [97,98]. In earlier studies, miR-223 was viewed as myeloid-specific with relevant expression only in granulocyte precursor cells and mature granulocytes [99]. Over time, also abundance and functional relevance in monocytes and macrophages has been discovered [60].

Throughout granulocyte cell differentiation, miR-223 levels steadily increase [97]. Johnnidis et al. described neutrophil hyperactivity and hyperinflammatory disorders in miR-223 deficient mice, resulting from direct targeting of the transcription factor Mef2c, suggesting miR-223 to act as a negative regulator of granulocyte production and inflammatory response [97]. Other studies described miR-223 as a modulator within regulatory loops keeping granulocyte differentiation in check [100,101]. In contrast to granulocytes, levels of miR-223 constantly decrease during monocyte/macrophage differentiation. In parallel, miR-223 target IKKα is up-regulated, leading to repression of non-canonical NF-κB signaling, thus preventing hyperactivation of macrophages [102]. Upon stimulation of macrophages, miR-223 is downregulated, which enhances pro-inflammatory cytokine expression (IL1β, IL6, IL18, TNFα) [103,104]. Effects of miR-223 can be put down to a multi-targeting network regulating NFκB-, TLR-, and MAPK-signaling, as well as NLRP inflammasome activity [104,105]. Thus, miR-223 may be regarded as key anti-inflammatory miRNA.

MiR-223 has also been implicated in intercellular signaling by microvesicles. In response to immune challenge, polymorphonuclear cells (PMN) shuttle miR-223 to lung epithelial cells, thereby dampening inflammation during acute lung injury by direct targeting of poly (adenosine diphosphatase-ribose) polymerase-1 (PARP-1) [106]. Also, in patients undergoing cardiac bypass surgery, exosomal miR-223 has been described to suppress inflammation in monocytes by direct binding to NLRP 3′UTR and IL6 coding sequence [107].

2.5. miR-181

In both mature innate and adaptive immune cells, miR-181 is a potent anti-inflammatory miRNA.

In T-cells, miR-181a strengthens T-cell receptor-dependent activation by increasing both power and sensitivity of TCR signaling [108]. These findings are the result of direct negative regulation of several Tyrosine- and ERK-phosphatases by miR-181 [108]. During thymic development, downregulation of miR-181 leads to reduced sensitivity of TCR, which results in maturation of autoreactive T-cells, thus highlighting the importance of miR-181-mediated control of TCR-threshold for T-cell immunity [109]. With respect to $CD4^+$ cells, evidence was provided for miR-181 to inhibit Th1 cell differentiation and to promote Treg development, probably by direct targeting of Smad7, a negative regulator of TGF-β signaling [110]. Mir-181 also impacts immunosenescence. In aged $CD4^+$ T-cells, due to lower levels of miR-181a, dual specificity phosphatase 6 (DUSP6) expression is increased. This leads to dampening of ERK-signaling, resulting in impaired TCR activation and reduced signaling strength [111].

In macrophages, Kruppel-like factor 6 (KLF6) and CCAAT/enhancer binding protein-α (C/EBPα) have been identified as direct targets of miR-181, thus promoting M2 over M1 polarization, including suppression of TNFα and IL1β [110,112]. Further, direct targeting has been confirmed for IL1α [113,114]. In dendritic cells, miR-181 was reported to act anti-inflammatory through direct targeting of TNFα and pro-inflammatory transcription factor c-FOS [115,116].

Generally, anti-inflammatory effects of miR-181 are further mediated by suppression of NF-κB signaling via direct targeting of importin α3 and the lysine deubiquitinase (CYLD) [117,118].

3. MiRNAs as mediators of tumor immune escape

The potential of miRNAs to act as tumor suppressors or oncogenes has been topic of intense research during the last decade [119]. In the recent past, also immunological miRNAs have increasingly gained attention within the context of cancer: These miRNAs are capable to attenuate antitumor immune responses by regulating the expression of immunomodulatory molecules in both tumor and immune cells, thereby facilitating tumor immune escape (summarized in Table 2).

The immune system is equipped with highly evolved mechanisms to control immune responses and to dampen inflammation in order to avoid collateral damage to healthy tissues. This intrinsic “brake” on inflammation encompasses the up-regulation of immune check point- and co-inhibitory molecules, as well as the polarization of immune cells towards immunosuppressive phenotypes. Accumulating data point out, that -under physiological circumstances protective- mechanisms are “hijacked” by tumors to evade immune surveillance. This is accomplished by i) products of tumor metabolism (mainly lactate, NO, and kynurenine) and hypoxia [120–123], and ii) by secretion of immune modulators, e.g. miRNA-, mRNA-, and protein-containing microvesicles/exosomes, which are taken up by immune cells [124]. As a result, suppressive gene signatures in immune cells are induced, and recruitment and functions of immune cell populations are altered towards immunosuppression [125,126]. Moreover, recent studies have highlighted, that expression profiles of tumor cells themselves exhibit specific alterations aiming at hiding from immune attacks, e. g down-regulation of tumor surface antigens, up-regulation of co-inhibitory molecules, and modification of cytokine pathways.

4. Impact of tumor-induced miRNA alterations on individual immune cell subpopulations

Tumor-derived exosomes (TEX) have been intensively investigated in the last few years and it is now well established that they carry immunosuppressive cargos encompassing DNA, mRNAs, proteins, and -importantly- miRNAs, with the above described immuno-miRs being highly abundant [124,127–130]. Stoichiometry of miRNAs in exosomes may differ from that in the tumor cell of origin, suggesting the existence of active secretory mechanisms [127].

Changes in miRNA endowment of immune cells, induced by metabolic products of the tumor microenvironment (TE) or resulting from rapid uptake of TEX, have repeatedly been demonstrated. In mouse experiments, functional consequences of intercellular communication via miRNA transfer were evaluated, thus further corroborating the strong impact of these regulatory miRNA-mediated networks. With respect to the human organism, there is limited but strongly growing

Table 2
Tumor associated miRNAs affecting tumor immune escape.

miRNA	Target	Effects on immunity	Investigated tumor
miR-24-3p	FGF11	Treg induction ↑ Th1/Th17 differentiation ↓ T-cell proliferation↓	nasopharyngeal carcinoma
miR-210	HIF1α	Th17 differentiation ↑	nasopharyngeal carcinoma
	IL16 CXCL12	MDSC recruitment and suppressive function ↑	melanoma/mammary carcinoma
miR-23a	BLIMP-1	$CD8^+$ effector function ↓	lung cancer
miR-34a	CCL22	Treg recruitment ↓	hepatocellular carcinoma
miR-214	PTEN	Treg expansion ↑	various
miR-494	PTEN	MDSC recruitment and suppressive function ↑	breast cancer
miR-20a/-17-5p	STAT3	MDSC suppressive function ↓	colon carcinoma
miR-155	HIF1	MDSC suppressive function ↓	melanoma/lung carcinoma
miR-25-3p	NF-κB pathway?	TAM IL6 production ↑	liposarcoma
miR-92a-3p	NF-κB pathway?	TAM IL6 production ↑	liposarcoma
miR-222-3p	SOCS3	M2 TAM polarization ↑	ovarian cancer
miR-203	TLR4 pathway?	DC cytokine production ↓	pancreatic cancer
miR-212-3p	RFXAP	DC immune tolerance ↑	pancreatic cancer
miR-183	DAP12	NK cell effector function ↓	lung cancer

direct evidence, that cancer-cell-immune-cell communication via miRNAs may significantly contribute to immune escape of tumors. To date, a number of tumor-induced miRNA-mediated functional alterations of individual human immune cell subsets of both adaptive and innate immunity could be shown (summarized in Fig. 3). However, this topic is a nascent field, in particular with respect to immunotherapeutic approaches.

4.1. Lymphocytes

Accumulating data suggests tumor-induced miRNA alterations to affect differentiation and function of both $CD4^+$ and $CD8^+$ T-cells. Recently, miR-24-3p was found to be markedly enriched in exosomes from patients with nasopharyngeal carcinoma as compared to healthy controls. These exosomes inhibited T-cell proliferation and Th1 and Th17 differentiation, whereas Tregs were induced. These effects were mediated via targeting of FGF11. Knockdown of exosomal miR-24-3p reversed these observations [131]. Furthermore, these exosomes decreased IFNγ, IL-2, and IL-17 release from $CD4^+$ and/or $CD8^+$ T-cells [132]. Notably, miR-24-3p levels and effects were increased by hypoxia, thereby further emphasizing the importance of both tumor cells themselves and the TE in miRNA-mediated tumor immune escape. Hypoxia within the TE also induces miR-210, which promotes Th17 differentiation of T-cells via targeting of HIF1α [133].

In patients with advanced lung cancer, miR-23a was found to be up-regulated in tumor infiltrating $CD8^+$ cells. As an underlying mechanism, tumor-derived TGF-β was shown to induce miR-23a, which then suppresses $CD8^+$ T-cell functions by down-regulating its target gene BLIMP-1. Functional blocking of miR-23a enhanced cytotoxic capacity and ameliorated tumor progression [134]. Similarly, tumor-produced TGF-β was found to be the driver of Treg recruitment into the TE in patients with hepatocellular carcinoma via suppression of miR-34a and consecutive enhanced CCL22 production [135]. Treg expansion is also influenced by miR-214, that is secreted by various types of human cancers. In mouse models, tumor-secreted miR-214 turned out to be delivered by microvesicles into recipient T-cells, where it efficiently downregulated phosphatase and tensin homolog (PTEN) and promoted Treg expansion. As a consequence, enhanced immune suppression and tumor implantation/growth in mice was observed [136].

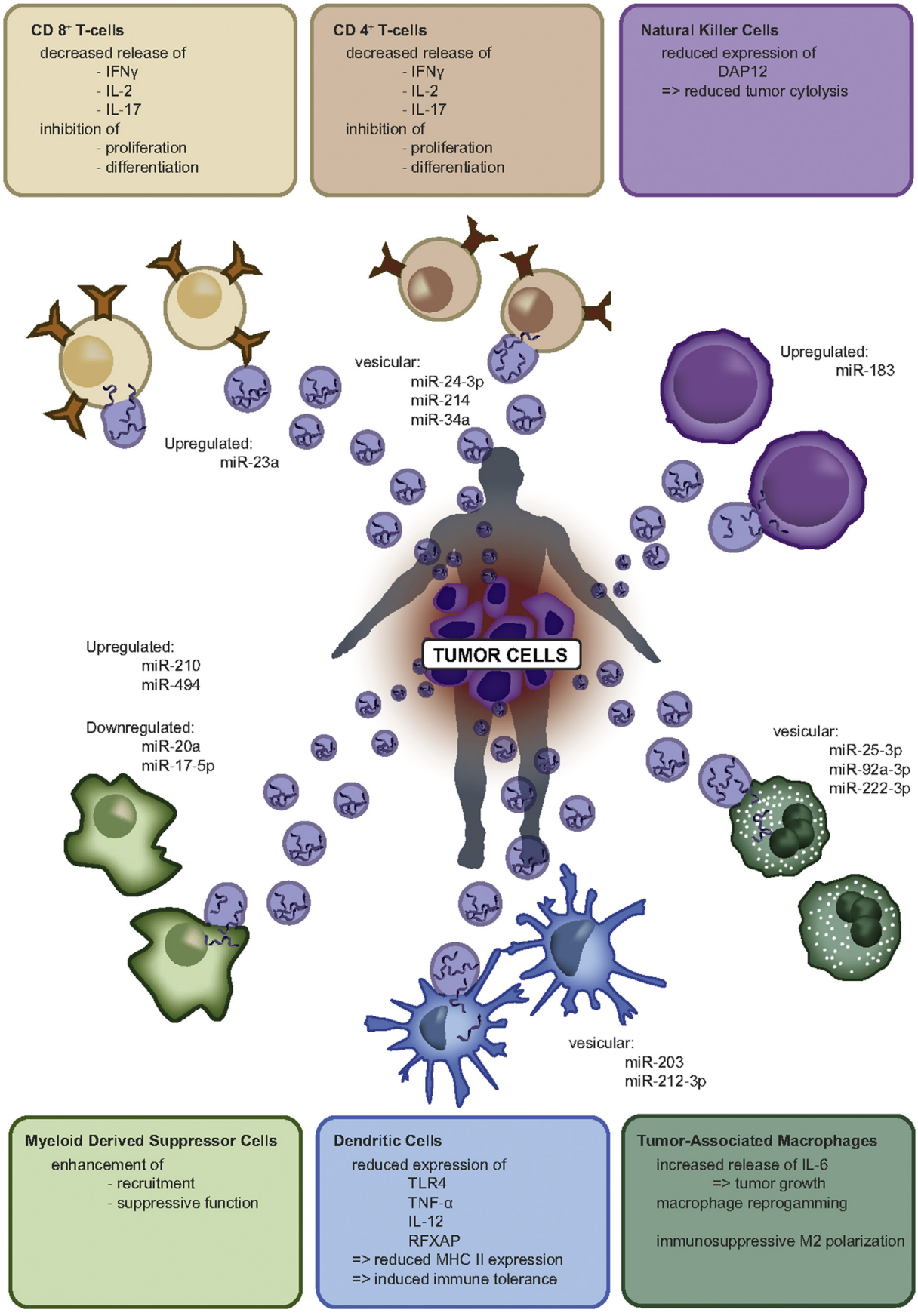
4.2. Myeloid-derived suppressor cells

MDSCs represent immature myeloid cells that accumulate in the tumor environment and suppress adaptive and innate immunity [137]. They thus are regarded as one of the major drivers of tumor immune escape. In rodent models, altered expression of a number of miRNAs in MDSCs within the TE has been shown. Specifically, miR-210 and miR-494, both induced by the TE, are up-regulated. By targeting IL-16 and CXCL12 (miR-210) and PTEN (miR-494), respectively, they enhance MDSC recruitment and suppressive functions [138,139]. MiR-20a and miR-17-5p, on the other hand, were found to be down-regulated in MDSCs. Both miRNAs are restrained by hypoxia [123,140], and their re-expression decreased suppressive features of MDSCs [141]. Also, miR-155 is repressed by the TE, and its deficiency augments the recruitment and functions of MDSCs [142]. As MDSC accumulation and activation of suppressive activities requires various inflammatory factors that are regulated by immuno-miRs (e.g. pro-inflammatory cytokines, signaling pathways including NF-kB, PI3K-Akt and STAT1 [143]), a much larger influence of tumor-induced miRNAs is assumable.

4.3. Tumor-associated macrophages

Tumor-associated macrophages (TAM) have increasingly gained attention as drivers of cancer development and malignant progression. During tumor initiation, they acquire pro-inflammatory properties (M1 phenotype) and contribute to the formation of an inflammatory environment that is mutagenic and promotes growth. During tumor expansion and malignization, macrophages stimulate angiogenesis, enhance tumor cell migration and invasion, facilitate metastasis, and suppress antitumor immunity. In this scenario, TAM mainly display the immunosuppressive so-called M2 phenotype [144]. There exists a large body of evidence that TAM take advantage of immuno-miRs to exert pro-tumorigenic effects by secreting miRNA-containing exosomes, which are taken up by tumor cells [145–148]. Moreover, macrophages - including TAM - functions themselves are substantially influenced by miRNAs [149,150]. Notably, the opposite direction of signaling -via miRNA shuttling tumor to TAM- has been proven [151–155]. A number of studies found tumor-derived exosomal miRNAs to influence TAM functions towards a tumor-promoting direction:

In human samples and cell lines, microvesicle-based secretion of miR-25-3p and miR-92a-3p by liposarcoma cells was demonstrated. These miRNAs then stimulate, in a TLR7/8-dependent manner, the release of IL-6 from tumor-associated macrophages, which in turn boosters liposarcoma growth and invasion [153]. Chen et al. could show that hypoxia within the TE increases secretion levels of miR-940 in exosomes derived from epithelial ovarian cancer. Upon uptake of these exosomes by TAMs, immunosuppressive M2 polarization is induced [152]. Likewise, miR-222-3p was identified to be enriched in exosomes of the same tumors and to contribute to M2 polarization [155]. In pancreatic cancer, tumor-derived miR-155 and miR-125b-2 were found



(caption on next page)

Fig. 3. Tumor immune escape. By using tumor microenvironment (eg. hypoxia) or tumor-derived exosomes, tumor cells alter miRNA expression profiles of innate and adaptive immune cells, thus compromising their immune function. In $CD8^+$ and $CD4^+$ T-cells, up-regulation of miR-23a ($CD8^+$) and vesicular transfer of miR-24-3p, miR-214 and miR-34a ($CD4^+$) leads to reduced effector cytokine secretion and impaired proliferation and differentiation, favouring Treg expansion (upper left and upper middle box). Complex changes of miRNA expression in MDSCs within the TE (up-regulation of miR-210/-494, down-regulation of miR-20a/-17-5p) amplify their suppressive capacity, rendering MDSCs a major tool for tumor immune escape (lower left box). TAM are strongly influenced by tumor-derived exosomal miRNAs: MiR-25-3p and miR-92a-3p enhance IL-6 release from TAM, thereby promoting tumor growth. Other miRNAs (miR-940, miR-222-3p) induce macrophage repolarization towards immunosuppressive M2 phenotype (lower right box). By vesicular delivery of miR-203 and miR-212-3p, antigen-presenting and regulatory capabilities of DCs are diminished due to reduced expression of both MHC II molecules and several elementary cytokines (lower middle box). NK cell tumor cytolysis is hampered via up-regulation of miR-183, induced by TE-derived TGF-β1 (upper right box).

to mediate macrophage reprogramming via exosome-mediated intercellular communication [151].

4.4. Dendritic cells and Natural Killer Cells

Dendritic cells (DCs) are antigen-presenting cells with the ability to regulate adaptive immunity. Whereas immature DCs down-regulate T-cell responses, mature DCs promote activation, proliferation, and differentiation of effector T-cells [156]. DCs have been shown to use exosomal miRNAs as an efficient mechanism of intercellular communication [157]. Pancreatic cancer derived exosomes negatively regulate the expression of TLR4 in dendritic cells via miR-203. Tumor necrosis factor-α (TNF-α) and interleukin-12 (IL-12) also decreased under treatment of exosomes and miR-203 mimics. Similarly, pancreatic cancer-derived exosomes transfer miRNAs to DCs and inhibit RFXAP expression via miR-212-3p, which decreases MHC II expression and induces immune tolerance of DCs [158,159].

Natural Killer Cells are crucial components of the innate immune system, having diverse biological functions which include recognizing and killing of neoplastic cells [160]. Transforming growth factor β1 (TGF-β), that is enriched in the tumor microenvironment, has been shown to induce miR-183 in NK cells, which in turn repressed DAP12 transcription/translation. Consecutively, human NK cells exhibited reduced tumor cytolysis, and perforin polarization to the immune synapse was abrogated [161].

5. Conclusions and future directions

By targeting central signaling hubs, miRNAs are potent regulators of immune cell functions. This has strong implications not only for immune-related diseases, but also for cancer: MiRNA profiles within immune cells are influenced by tumors via secretion/uptake of specific miRNAs or via induction by metabolites, thus weakening immune surveillance of cancer cells. Immuno-miRs could therefore be a valuable diagnostic tool in both immune-related diseases and cancer, and may further expand the emerging concept of “liquid biopsy”. For example, determination of specific miRNA profiles in immune cells could help to assess the current immune status of patients. Moreover, expression analysis of microvesicle-derived miRNAs might even allow diagnosis and classification of tumor entities. It is clear now that elucidation of the complex functional networks of cancer requires analyses going far beyond genomic profiling of tumor tissues. In fact, it is indispensable to obtain a detailed knowledge of the tumor microenvironment - including tumor-derived microvesicles and immune cells. Although further research is necessary to develop these innovative diagnostic concepts and to master possible constraints (such as bias of results by comorbidities), their clinical use is clearly on the horizon.

MiRNAs are currently making their way from bench to bedside. It is an appealing idea to implement miRNA-based strategies into therapeutic approaches to restore immune competence and minimize tumor immune escape. By cell-specific transfer of immuno-miRs, e.g. by use of artificial nanoparticles, cancer-induced alterations of the “miRNome” might be attenuated or even reversed, thus permitting the immune system to overcome tumor immune escape and to participate in tumor elimination. In addition, miRNAs supporting pro-inflammatory or anti-inflammatory immune responses could be shuttled to immune cells, thereby functionally supporting or controlling specific subsets of the immune system. However, finding a safe and efficient strategy of targeted delivery remains a challenge.

Additional research still is required to expand our knowledge of immuno-miRs, thus opening up new avenues for innovative diagnostic and therapeutic approaches in both immune-related diseases and cancer.

Conflicts of interest

The authors declare they have no conflict of interest related to this submission.

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