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Review

miRNAs as novel immunoregulators in cancer

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ABSTRACT

The immune system is a well-known vital regulator of tumor growth, and one of the main hallmarks of cancer is evading the immune system. Immune system deregulation can lead to immune surveillance evasion, sustained cancer growth, proliferation, and metastasis. Tumor-mediated disruption of the immune system is accomplished by different mechanisms that involve extensive crosstalk with the immediate microenvironment, which includes endothelial cells, immune cells, and stromal cells, to create a favorable tumor niche that facilitates the development of cancer. The essential role of non-coding RNAs such as microRNAs (miRNAs) in the mechanism of cancer cell immune evasion has been highlighted in recent studies. miRNAs are small non-coding RNAs that regulate a wide range of post-transcriptional gene expression in a cell. Recent studies have focused on the function that miRNAs play in controlling the expression of target proteins linked to immune modulation. Studies show that miRNAs modulate the immune response in cancers by regulating the expression of different immune-modulatory molecules associated with immune effector cells, such as macrophages, dendritic cells, B-cells, and natural killer cells, as well as those present in tumor cells and the tumor microenvironment. This review explores the relationship between miRNAs, their altered patterns of expression in tumors, immune modulation, and the functional control of a wide range of immune cells, thereby offering detailed insights on the crosstalk of tumor-immune cells and their use as prognostic markers or therapeutic agents.

Abbreviations: MHC, major histocompatibility complex; APC, antigen presenting cells; NK cells, natural killer cells; DCs, dendritic cells; Tregs, regulatory T cells; MDSCs, myeloid derived suppressor cells; PD-1, programmed cell death protein; IL, interleukin; STAT, signal transducer and activator; JAK, janus kinase; TAM, tumor associated macrophages; miRNAs, microRNAs; TME, tumor microenvironment; APC, antigen-presenting cells; AP&P, antigen processing and presentation; APM, antigen processing machinery; TAP1, antigen peptide transporter 1; CTLs, cytotoxic T lymphocytes; HOTAIR, Hox antisense intergenic RNA; CIK cells, cytokine-induced killer cells; DAP12, DNAX activating protein; IDO, indoleamine 2,3-dioxygenase; CTLA4, cytotoxic T-lymphocyte-associated protein 4; iNKT, invariant Natural Killer T cells; NPC, nasopharyngeal carcinoma; PC, pancreatic Cancer; LC, lung Cancer; LiC, Liver cancer; BC, Breast cancer; CRC, colorectal cancer; OC, ovarian cancer; PCa, Prostate Cancer

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1. Introduction

Cancers account for a major cause of death in humans globally, with its prevalence increasing in recent years [1]. By 2012, worldwide cases reached 14.1 million, with a total number of deaths touching 8.2 million, and new cases are expected to stretch to 23.6 million by 2030 [2]. While the primary tumors are mostly treatable, most metastatic tumors are associated with patient mortality. This is primarily due to the lack of therapeutic avenues targeting metastatic tumors and meager understanding of the metastatic process at the molecular and cellular level [3]. Cancers are a complex niche comprising of neoplastic cells, stromal cells including cancer associated fibroblasts (CAFs), endothelial cells, blood & lymphatic vascular cells, adipocytes, neuroendocrine cells, inflammatory immune cells and extracellular matrix (ECM) [4,5]. The crucial cross-talk between cancer cells and stromal cells help shape the fate of tumor progression and metastasis. Moreover, cancer cells sustain cell proliferation and metastasis by various adaptive measures such as evading growth suppression, resistance to apoptosis, angiogenesis, and, more importantly, by escaping immune surveillance [6–8]. The link between cancer progression and the immune system has been established by studies revealing its increased prevalence in patients with diseases such as HIV and AIDS or those on chronic immunosuppressive therapy post-transplant [9].

Immune cells are known to mediate an effective response against tumors in the form of both humoral and cell-mediated cytotoxic responses [10]. This is common to most tumor types, as cancer cells are known to display counteractive immune evasive mechanisms by which they establish their proliferation and metastasis [11]. Immune evasive mechanisms include altering genes and signaling pathways in immune cells involved in tumor recognition and targeting, along with inducing changes in the nearby tumor microenvironment (TME) by releasing various chemical factors that encourage immune suppression [11]. Immune editing mechanisms are thus employed by cancer cells to evade immune surveillance [12]. In addition to proteins and signaling molecules such as interleukins, non-coding RNAs have been recently shown to play a very significant role in regulating the expression of immune-modulatory proteins both in the tumor as well as immune cells, thus establishing yet another layer of complexity associated with immune evasion by tumors [13,14].

With the discovery of lin-4 microRNA (miRNA) in *C. elegans*, studies on the modulation of protein targets by small non-coding RNAs have gained momentum over the last few decades. miRNAs modulate nearly two-third of genes that code for a protein product in a cell at the post-transcriptional level [15,16]. The typical canonical pathway for the biogenesis of miRNAs begins with their transcription by RNA Pol II/III in the nucleus, which generates primary miRNA (pri-miRNA) transcripts composed of repetitive stem-loop structures (60–70 nts) [17,18]. The pri-miRNA transcript is then cleaved by ribonucleases such as Drosha in association with DGCR8, thereby generating separate hairpin-like RNA moieties known as pre-miRNAs [18]. The stem-loop structured pre-miRNAs are then exported from the nucleus to the cytoplasm by the membrane-bound transporter Exportin-5/Ran-GTP complex, where the Dicer endonuclease trims them to generate a double-stranded (ds) miRNA entity [17,18]. The guide strand of the dsRNA, thus, generated is loaded onto the Argonaute protein, which then binds to its complementary region, usually in the 3′ UTR region of the messenger RNA (mRNA) transcripts [19]. The complex is referred to as the miRNA-induced silencing complex, which then recruits other proteins such as GW182, CCR1, and NOT to the mRNA, thus inhibiting translation of the mRNA transcript [20]. Apart from the 3′ UTR region, miRNAs are also known to bind to the 5′ UTR region and the mRNA's coding region, leading to translational repression or mRNA degradation [21].

Considering the vast array of genes/proteins that miRNAs modulate, it is plausible that miRNAs have similar regulatory roles at the post-transcriptional level in altering the immune response to cancer. This review comprehensively describes the role of miRNAs in modulating the response of both immunomodulatory proteins and immune cells and their function in tumour cells' immune evasive strategies and the changes they induce in the TME described so far.

2. The tumor-immune system crosstalk

The crosstalk between cancer cells and immune cells includes a wide variety of regulatory mechanisms established between them, such as alterations in the antigen processing and presentation (AP&P) pathways of antigen-presenting cells (APCs); the expression of co-stimulatory and co-inhibitory cell surface molecules; the signaling pathways of both tumor and immune cells; the synthesis and release of membrane-bound exosomes; and the activities of immune effectors (e.g., B-/T-cells) and immune suppressor cells such as regulatory T cells (Tregs) [22–24]. Moreover, different factors in the TME such as nutrient competition, amino acid depletion and increasingly acidic conditions due to high lactate production can suppress the activities of effector cells such as B-/T-cells, natural killer (NK) cells, and APCs such as dendritic cells (DCs) and macrophages and cause an increase in the immune inhibitory cells such as Tregs, tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs) [25–27]. Moreover, various other tumor-promoting factors such as interleukins (IL-10), TGF-β, prostaglandins, and proteases present in the TME ensure the sustenance of an immune-suppressive TME that attenuates any anti-tumor activity [28,29]. TAMs such as the M2–like macrophage have elevated expression of interleukins such as IL-10 and IL-1Rα, which assists tumor growth and development [30]. Primary TAMs also secrete chemokines such as CCL2 and CXCL12 that recruit effector cells such as monocytes to the TME, and transform them into the M2–like phenotype [30]. DCs, on the other hand, acts as a bridge between the innate and adaptive immune response [31], and can be modulated by different factors such as IL-10, prostaglandins, and VEGF-A within the TME [32–34]. DCs, however, have also been shown to induce anti-tumor activity [35,36]. Immune suppression by MDSCs in the TME is mediated by cytokines such as IL-4, TGF-β, and interferons, thus promoting tumor progression and metastasis [37]. MDSCs can also reduce T-cell homing and priming of DCs and suppress NK cell-mediated cytotoxicity and induce Tregs [38]. T- cell activity is suppressed by cytokines and enzymes secreted by TAMs in the TME [38]. NK cells correspond to innate immune cells in the TME modulated by cytokines such as TNF-α, IL-12, and IFN-α [39]. Several studies have shown miRNAs' role in mediating this complex cellular crosstalk between tumor and immune cells and the importance of their role in immune modulation [40].

3. miRNAs and components of the antigen processing/presentation machinery

Proteins associated with the AP&P pathway are crucial in displaying peptides to circulating $CD8^+$ and $CD4^+$ T cells, thereby enabling the recognition of transformed cells [41]. After recognition, T cells orchestrate a wide variety of immune responses that involve activation of immune cells and release of immune-modulatory molecules. Cancer cells are known to modulate various steps involved in AP&P, thereby ensuring immune evasion and continued proliferation [41]. Non-coding RNAs such as miRNAs have been reported to play crucial roles in modulating various protein targets associated with AP&P and thus influence both tumorigenicity and the immune response [42]. The sections below address the regulation of different protein targets involved in antigen presentation by a wide variety of immunomodulatory miRNAs.

3.1. miRNAs and major histocompatibility complex (MHC)–associated proteins

The major histocompatibility complex (MHC) or the human leukocyte antigen (HLA) such as class I and II MHC play crucial roles in AP&P by displaying cellular peptide moieties to various types of immune cells, thus, enabling the recognition of pathogen-infected cells or tumor cells [22]. Numerous other factors are known to assist in processing peptide moieties such as proteosomes, Transporter associated with Antigen Processing (TAP), etc [43]. In this context, a wide variety of cellular alterations in the AP&P pathways in tumor cells ensure the evasion of immune surveillance, a characteristic hallmark of cancer cells [22]. Recent studies have highlighted the role of miRNAs in modulating the expression of a wide variety of components associated with the antigen processing machinery (APM) in cancer [42]. Like miR-346, miRNAs can modulate the expression of the APM components such as the antigen peptide transporter 1 (TAP1) to regulate the immune response of a cell toward antigens [44].

Furthermore, antigen processing components such as proteasome subunit PSMB8 have been reported to be a direct target of and regulated by miR-451 in lung cancer (LC) cells as confirmed by the Dual-Luciferase reporter assay [45]. The regulation by miR-451 is reflected by altered proliferation, metastasis, and invasion of A549 LC cells by deregulating the target PSMB8 and the inflammatory factors [46]. Moreover, variations in the binding regions of miRNAs located on the 3′ UTR of target mRNAs (associated with APM) can also affect miRNAs function and protein expression. For example, alteration in the sequence of the 3′ untranslated region (3′ UTR) of the HLA-C harboring miRNA recognition sites affects its modulation by miR-148a, and thereby its cell surface expression [47]. Similarly, miRNA-mediated modulation of the immune response has been reported in hepatitis B virus-transformed cells where miR-181a, which is up-regulated in infected cells, regulates HLA-A expression by binding to its 3′ UTR region [48]. The detailed list of the immune-modulatory targets regulated by miRNAs is shown in Table 1. In addition to this, miR-US4–1, a human cytomegalovirus miRNA, has been reported to silence HLA class I expression along with aminopeptidase ERAP1 [49]. The ERAP1 is a target for miR-US4–1, which is involved in peptide processing of the precursors of MHC class I–presented peptides viz. peptide trimming to mature epitopes, thus, suppressing recognition by cytotoxic T lymphocytes (CTLs) [49].

3.2. miRNAs and non-classical class I MHC

Studies have identified several miRNAs that play a regulatory role in non-classical class I MHC molecules. For example, the non-classical class I MHC molecule HLA-G is modulated by miRNAs such as miR-148 and miR-152 in various cancer types [58,88,89]. In addition, HLA-G has also been reported to be induced by TGF-β indirectly via inhibition of miR-152, which has binding sites on the HLA-G 3′ UTR region in gastric cancer (GC) [90]. HLA-G–mediated evasion of immune surveillance in GC may be brought about by suppressing $CD8^+$ T-cells and NK cells [91]. Similarly, indirect activation of HLA-G has been observed by regulating target non-coding RNA Hox antisense intergenic RNA (HOTAIR), inhibited by miR-152 in various cancers [92].

, Moreover, ectopic overexpression of miRNAs viz. miR-148, miR133, or miR152 leads to reduced expression levels of the HLA-G protein, enhancing both the lymphokine-activated killer and NK cell-mediated immune response [58]. Corroborating with these data, studies indicate that variations in the 3′ UTR region of this non-classical class I MHC moiety may affect binding and thus regulation by miRNAs, as described for miRNAs miR-608 and miR-139-3p [93]. MHC class I related molecules such as MICA and MICB are dysregulated in a wide variety of cancers and act as complementary ligands for the stimulatory NK cell receptor NKG2D, thereby promoting cytotoxicity. Studies have

Table 1
miRNAs involved in regulating various immunomodulatory proteins and signaling moieties in cancers.

Immuno-modulatory target	miRNA	Type of cell/model	Refs.
CTLA-4	miR-155	Melanoma	[50, 51]
ICOS	miR-186-5p	Colorectal cancer	[25]
CD28	miR-145	T cells	[52]
TAP1	miR-346	Human airway epithelial cells	[44]
ERAP1	miR-US4-1	Cytomegalovirus-infected human fibroblast	[49]
PSMB8	miR-451	Lung cancer	[45]
BTLA	miR-155	CD4 + T cells	[53]
MICA	miR-20a	Breast cancer	[54]
MICA	miR-25, – 93, – 106b	Hepatocellular carcinoma	[55]
MICB	miR-376	Melanoma	[56]
HLA-G	miR-152	Lung cancer	[57]
	miR-133	Renal cell carcinoma	[58]
	miR-628–5p	Renal cell carcinoma	[58]
HLA-A	miR-181a	Hepatitis B virus-infected liver cells	[48]
HLA-C	miR-148	Lymphocytes	[47]
DAP12	miR-183	Tumor-associated natural killer cells	[59]
B7	miR-21	Colorectal cancer	[25]
	miR-323b	Colorectal cancer	[25]
	miR-186	Colorectal cancer	[25]
B7-H1	miR-138	Colorectal cancer	[60]
	miR-34a	Myeloid leukaemia	[61]
	miR-570	Gastric adenocarcinoma	[62]
	miR-25, miR-93, miR-106b	Bone marrow metastasis	[63]
	miR-34a	Lung adenocarcinoma	[61]
	miR-193a-3p	Malignant Pleural Mesothelioma	[64]
	miR-152	Gastric cancer	[65]
	miR-142–5p	Pancreatic carcinoma	[66]
B7-H2	miR-24	Gastric cancer	[67]
B7-H3	miR-29a	Neuroblastoma	[68]
	miR-29c	Breast cancer	[69]
	miR-187	Renal cell carcinoma	[70]
	miR-124	Osteosarcoma	[71]
TIM3	miR-330–5p	Acute myeloma leukaemia	[72]
CD80	miR-424	Ovarian cancer	[73]
CCL22	miR-34a	HBV-associated hepatocellular carcinoma	[74]
CCL2	miR-126	Breast Cancer	[75]
CXCL12	miR-210	Myeloid-derived suppressor cells	[63]
IL6	miR-210	Myeloid-derived suppressor cells	[63]
ULBP2	miR-34a/c, miR-302c, miR-520c	Melanoma	[56]
STAT3	miR-124–3p	Nasopharyngeal cancer	[76]
PD-1	miR-28	Melanoma/$CD4^+$ T cells	[77]
	miR-15a/16	Glioma/$CD8^+$ T cells	[78]
	miR-21	Tumor grafts	[79]
CD40L	miR-31	Follicular helper T cells	[80]
Signaling moiety targeted	**miRNA involved**	**Model/cell type**	**Ref.**
SOCS3 & IRF2 (JAK/STAT Signaling cascade)	miR-221	Prostate cancer	[81]
JAK2	miR-216a	Pancreatic cancer	[82]
	miR-101	Breast cancer	[83]
SHIP1	miR-155	Primary human NK cells	[84]
STAT1	miR-150	T cells	[85]

(continued on next page)

Table 1 (*continued*)

Immuno-modulatory target	miRNA	Type of cell/model	Refs.
	miR-223		
IRAK/TRAF6	miR-146a	Human NK cells	[86]
IGF1	miR-29b	Colorectal cancer	[87]

shown that MICA and MICB are miRNAs modulated, such as miR-20a and miRNA clusters like miR-25-93-106b [54,55,94]. In addition to promoting the proliferative and angiogenic capacity of tumors, these oncogenic miRNAs (or oncomiRs) are involved in reducing MICA/MICB levels, thus mediating their immune escape from NK cell cytotoxicity [54,55]. In this context, epigenetic changes brought about by histone deacetylase inhibitors such as suberoylanilide hydroxamic acid (SAHA) and SAHA analogs alter expression levels of MIC A/B-associated miRNAs and thus tumor sensitivity to NK cells, have shown promising results in cancer treatment [95].

3.3. miRNAs and co-modulatory molecules

Over the past decade, research has identified co-modulatory, co-stimulatory, and co-inhibitory molecules during the immune response. Co-modulatory molecules often provide the crucial secondary signal that immune cells depend on to mount an effective and controlled immune response [96]. These co-modulatory molecules belong to the immunoglobulin (Ig) superfamily and more prominently include the B7 and tumor necrosis factor (TNF) family members. In B7 family members, the well-described co-modulatory molecules include programmed cell death 1 (PD-1), PD-1 ligand (PD-L1), PD-L2, CD80 (B7–1), CD86 (B7-2), CD28, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and VISTA (or PD-1H) [97]. Co-stimulatory candidate proteins such as CD80 (B7-1), CD86 (B7-2), CD28, ICOS, and B7-H2 are known to be reduced in various tumors such as colorectal cancer (CRC) and gastric cancer [98,99]. In contrast, co-inhibitory molecules such as PD-L1, PD-1, B7-H3/H4, and CTLA-4 are up-regulated in CRC [100–102].

PDL is a co-inhibitory molecule known to be expressed in a wide variety of immune cells such as B-/T-cells, DCs, and TAMs [103]. For instance, increased expression of PD-L1 has been reported on TAMs, a selective group of immunosuppressive cells that promotes T-cell apoptosis and immune escape in ovarian cancer (OC) [104]. Researchers suggest that PDL1 expression is strictly associated with miRNA expression in different cancer types [105]. PD-L1 has been reported to be regulated in various tumors by a wide variety of miRNAs viz miR-424 (in OC), miR-138 (in CRC), and miR-34a (in myeloid leukemia) [60,61,73]. PD-L1 regulation is controlled by a group of miRNAs that include miR-200, miR-197, or miRNA-34 in LC [105]. Expression levels of miR-424, a miRNA that has been widely studied as an immune regulator in many cancers, are found to be inversely correlated with PDL1 and other co-inhibitory molecules that are immune modulators, such as PD-1, CTLA-4, and CD80 [106]. During tumor progression, miR-424 can directly inhibit the binding of PD-1/PD-L1 and CD80/CTLA-4 and induce tumor suppression [106]. Xu et al. demonstrated that miR-424 controls the PD-L1/PD-1 and CD80/CTLA-4 pathways in chemoresistant OC, and its expression is inversely correlated with PD-L1, PD-1, CD80, and CTLA-4 expression [73]. Furthermore, these studies demonstrate that the expression of miR-424 leads to the inhibition of co-inhibitory molecules PD-L1 and CD80 by directly binding to their 3′ UTR regions, along with a concurrent reversal in chemoresistance [73]. Similarly, miR-138 was reported to be downregulated in CRC tissues and accompanied by elevated levels of its target PD-L1, to which it directly binds and causes inhibition through its 3′ UTR region [60]. The gain of function of miR-138 can inhibit PD-L1 expression, leading to reduced cancer cell growth, both in vitro and in vivo tumor models [60]. The aberrant miRNA expression influences co-modulatory molecules, which leads to the generation of an immune response in tumors. Variations in the 3′ UTR regions of co-modulatory molecules that disrupt association with miRNAs also seem to contribute to immune evasion by cancer cells. For instance, polymorphic variations (C to G) at the miR-570 binding site in the 3′ UTR region of PD-L1 (or B7-H1) abrogates its inhibition, resulting in aberrant co-inhibitory PD-L1 protein expression, increased immune evasion, and disease progression in a wide variety of cancers [62,107]. Similar polymorphic variations (T→G, T→C, G→A and G→C) at the miRNAs binding sites in the 3′ UTR regions of various B7 (ligand)/CD28 (receptor) family members have been reported [25,108]. These polymorphic features affect the modulation of individual B7/CD28 members (co-stimulatory and co-inhibitory) by miRNAs such as miR-21, miR-323b, and miR-186, thus affecting tumor progression and immune response [25,109]. Moreover, co-inhibitory molecules such as B7-H3, known to be up-regulated in a wide variety of cancers, are also shown to be modulated by miRNAs, such as miR-29a (neuroblastoma), miR-29c (BC), and miR-187 (renal cell carcinoma) [68–70]. Similarly, the T-cell co-inhibitory molecule T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), known to be overexpressed in cancer cells, is negatively regulated by miR-330-5p in vitro [72]. Variations in the 3′ UTR of the co-stimulatory B7-H2 molecule can provoke its modulation by miRNAs such as miR-24 and contribute to the prevalence of GC [67]. However, other studies seem to correlate the expression of co-stimulatory molecules B7–2 (CD86) and B7–H2 with a poor prognosis of myeloid leukaemias [110]. *In vitro* model studies indicate that brief incubation of the B7-2^{+} leukaemia cell line HL-60 with activated T cells lead to elevated levels of the co-inhibitory PD-L1 and PD-L2, with concomitant reduction of the stimulatory B7-H2 molecule, thereby mediating immune evasion [110]. Thus, the continuously increasing candidates in the B7 co-modulatory family present novel and unique opportunities in therapeutically modulating the immune response for treating a wide variety of tumors.

4. miRNAs and immune cell signaling activation

Numerous proteins associated with the signaling cascade in immune cells have been shown to alter miRNA expression levels, thereby modulating the expression of target genes related to signal transduction, cell proliferation, cellular immune response, and carcinogenesis [111]. Conversely, crucial immune signaling components (e.g., IFN-γ) are also themselves subject to miRNAs regulation [112]. In the context of signaling, miR-221, a key modulator of negative regulatory components, such as SOCS3 and IRF2, of the crucial JAK/STAT signaling cascade is known to be strongly downregulated in prostate cancer (PCa) [81]. These studies have demonstrated that overexpression of miR-221 indirectly activates the JAK/STAT signaling pathway, resulting in improved sensitivity of PCa cells to IFN-γ-assisted growth inhibition [81]. Interestingly, in contrast to its low expression in PCa, miR-221 is known to be overexpressed in various types of tumors such as pancreatic cancer (PC), LC, and liver cancer (LiC) through targeting tumor suppressors such as p27, c-kit, and PTEN, thereby displaying oncogenic characteristics [113,114]. A similar correlation between miRNAs and the IFN-γ signaling pathway's negative regulatory components has been observed for miR-155 (expressed in activated immune cells) and its target inositol phosphatase SHIP1 [84]. Activation of miR-155 by synergistic co-stimulation of NK cells with interleukins such as IL-12/18 can directly inhibit its target protein SHIP1 (differentially expressed in NK cells), thus acting as a positive modulator of IFN-γ production in these cells [84]. Recent studies have demonstrated that miR-150/-223 negatively regulates STAT1 expression and attenuates STAT1-mediated signaling in human T cells [85]. Both miRNAs are downregulated in adult T-cell leukemia (acting as tumor suppressors), corresponding to elevated STAT1 expression levels, a potent factor for leukemia development [115–117]. Restoring the expression of miRNAs suppressed STAT1 expression and thus proliferation in leukemic T cells [85]. In addition to common intermediates such as STATs, miRNAs can

also target components such as IRAK1/TRAF6 associated with the NF-κB signaling pathway [86]. miRNAs such as miR-146a target IRAK1/TRAF6, and the NF-κB signaling cascade is known to negatively regulate IFN-γ levels in human NK cells and keep their production in check and restrain NK cells from overactivation [86]. Furthermore, Janus kinase 2 (JAK2)–modulating miRNAs such as tumor suppressors miR-216a and miR-101 regulate the JAK/STAT signaling cascade and can suppress the growth and enhance apoptosis in PC and breast cancer (BC), respectively [82,83].

Conversely, signaling components of the IFN-γ pathway are also known to modulate miRNA expression levels, thereby assisting in an effective immune response. STATs have been shown in turn to modulate miRNAs such as those observed in miR-155/STAT1 and miR-21/STAT3 regulatory loops [118]. Additionally, IFN-γ is essential in mediating the immunosuppressive property of mesenchymal stem cells (MSCs) that are used to treat various autoimmune disorders [119]. In this context, IFN-γ has been shown to alter the miRNA repertoire of microvesicles released by the MSCs that are crucial in mediating their immunosuppressive effects and, their targets involved in immunomodulation [120]. Moreover, IFN-γ, by modulating the expression of miRNAs such as miR-4448, is known to regulate the expression of MHC class I-related molecules (e.g., MICA) in corneal epithelial cells, resulting in enhanced immune cytotoxicity and thus corneal graft rejection [121]. Intriguingly, IFN-γ is also known to modulate miRNA expression by recruiting various signaling components to their promoter regions. It enhances miR-29b expression by assisting the association of IRF1 to miR-29b promoter regions [87]. Elevated miR-29b manifests in inhibiting its target IGF1 (associated with PI3K/Akt signaling), thus suppressing cell growth and invasiveness in CRC [87]. Table 1 **(bottom)** presents an overview of miRNAs and their respective signaling targets.

5. miRNAs and immune cells

Tumor cells have been known to modulate the properties and functions of immune cells, thus altering the immune response mounted against them. Cancer cells achieve this by changing the miRNA expression profiles of immune cells, thereby suppressing the immune system [42]. Activities of cells such as DCs, B cells, T cells, NKs, and macrophages are repressed, whereas that of immune suppressors such as Tregs; or suppressor T cells, MDSCs, or TAMs are up-regulated [25,26]. The following section describes the various effects miRNAs have on immune cells (Fig. 1).

5.1. miRNAs and Tregs

Infiltration of immune suppressors such as Tregs and concomitant suppression of cytokine synthesis in nasopharyngeal carcinoma (NPC) is associated with reduced expression of miR-124-3p [76]. A similar correlation between tumor progression and suppression of the immune response is reported in mouse tumor models where tumor-derived miRNAs such as miR-214 mediate immune evasion [122]. Microvesicle-mediated delivery of tumor-derived miR-214 into $CD4^+$ T cells in mouse models results in expansion of the immune-suppressive Treg subset, leading to secretion of increased levels of IL-10 and promotion of tumor implantation [122]. Additionally, elevated levels of chemokine CCL22 resulting from reduced expression of miR-34a are also known to attract Tregs in hepatitis-associated hepatocellular carcinoma cells [74]. An immune-evasive microenvironment, thus created, assists metastatic cancer cells to colonize the portal veins. Furthermore, the miR-30b/30d–mediated modulation of GalNAc transferases enhances the metastatic/invasive property of human melanoma cells and promotes Treg infiltration and the production of immune-suppressive IL-10 [123].

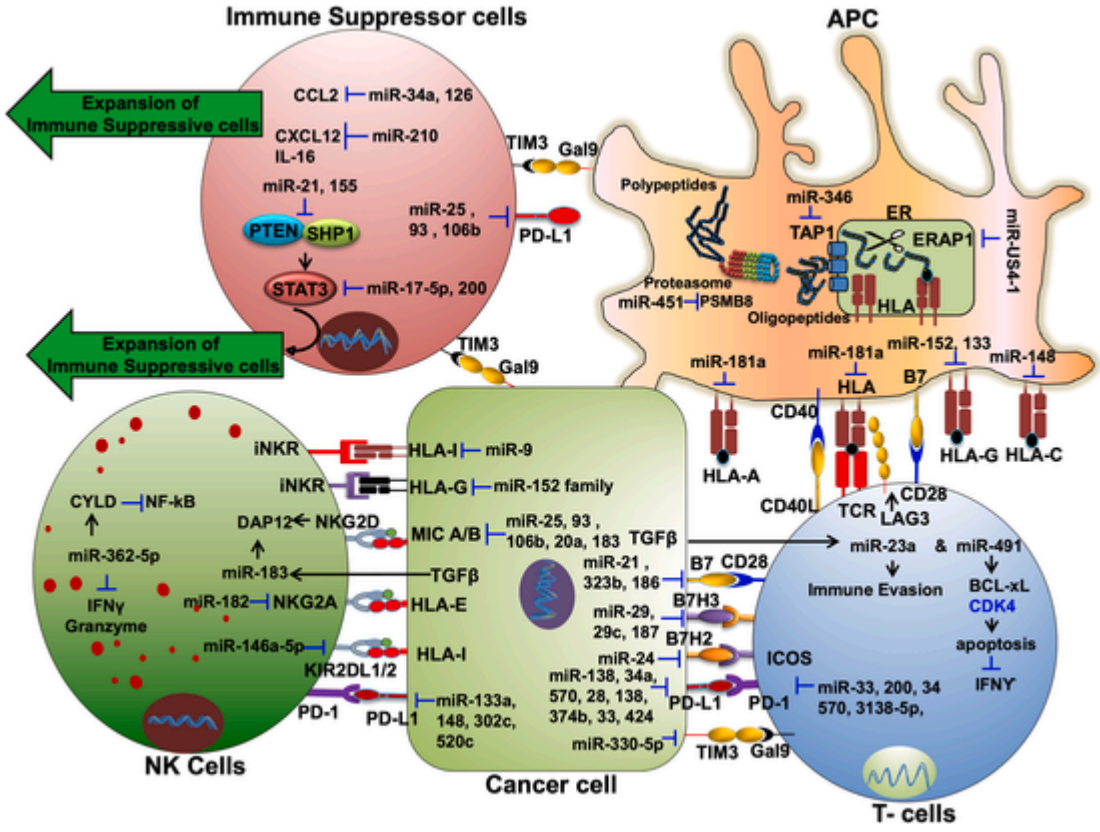

Fig. 1. miRNA-mediated modulation of tumor and immune cells. Modulatory effects of miRNAs on various tumor targets, APCs, NK cells, immune suppressive cells, and T cells. The different immunomodulatory targets include membrane-bound MHC I/II, B-7 family members (e.g., B7-H1, B7-H2, B7-H3), MICA/B, PD-1, and intracellular targets (e.g., TAP1, ERAP1,PTEN, SHIP1, STAT3, CCL2, CXCL12, DAP12).

5.2. miRNAs and cytotoxic T cells

Immune effector cells such as CTLs, which are crucial in restricting tumor metastasis, are suppressed by elevated levels of miR-491 in mouse CRC models [124]. The miR-491 upregulation (induced by tumor-derived TGF-β) induces T-cell apoptosis and decreases IFN-γ production in $CD8^+$ T cells [124]. Moreover, modulation of apoptosis by miR-491 is mediated by its effects on targets such as Bcl-xL and CDK4 [124]. Similarly, tumor-derived TGF-β-mediated overexpression of miRNAs (e.g., miR-23a in tumor-infiltrating $CD8^+$ T cells) and immune evasion have been reported in LCs [125]. Therefore, immunotherapy involving the inhibition of miR-23a expression in CTLs corresponded with reduced tumor progression and improved immune competence.

5.3. miRNAs and natural killer cells

Besides regulating CTLs, miRNAs also play a pivotal role in modulating the immune response of effector cells such as NK cells. miRNAs such as miR-374b have been recently shown to regulate the anti-tumor activity of immune effector cells such as $CD3^+/CD56^+$ cytokine-induced killer (CIK) cells, which are NK-like T cells produced upon induction by IL-1/2 and IFN-γ [126]. The study demonstrated that the overexpression of miR-374b or inhibition of its target PD-1 limits hepatic carcinoma and restores the tumor-targeting property of CIK cells [126]. Loss of miR-374b activity has also been associated with progression and therapeutic resistance in PC [127]. Overexpression of miRNAs such as miR-133a and miR-148a are known to promote NK cell-mediated anti-tumor activity in renal cell carcinoma [58].

Similarly, miRNA-mediated activation of NK cell immune response/cytotoxicity has been described for miR-34a/c and miR-302c and miR-520c in melanoma, myeloid leukemia and triple-negative BC cells, respectively [128,129]. The human TME-derived immunosuppressive cytokine TGF-β regulates the DNAX activating protein (DAP12), which is crucial for NK cell surface receptor stabilization and the subsequent downstream signaling cascade, thus resulting in the repression of tumor cytolysis [59]. TGF-β achieves this by activating miR-183 that targets DAP12 expression levels and thus inhibits the NK cell effector immune response [59]. Furthermore, nucleofection-mediated overexpression of miR-362–5p has been correlated with enhanced NK cell-mediated immune effector functions such as improved synthesis of cytotoxic effector products IFN-γ, granzymes, and perforins [130]. In addition, miR-362–5p mediates its effect on the NF-kB signaling pathway by modulating the expression of its target CYLD, a negative regulator of the NF-kβ signaling cascade.

Moreover, miRNAs such as miR-150 have been reported to differentially modulate the development of NK and TCRα expressing invariant NKT (iNKT) cells [131]. Whereas miR-150 promotes phenotype maturation, activation, and development of NK cells, iNKT cells are suppressed in the thymus and lymphoid organs [131]. It is pertinent to mention that miR-150 exerts its differential effect on NK and iNKT cell lineages via its target protein c-Myb, which is evident from a study that showed that the heterozygous null mutants of c-Myb recapitulate the phenotype of the miR-150 transgenic mice [131].

5.4. miRNAs and myeloid immuno-suppressors

miRNAs are also known to regulate the recruitment and the activity of MDSCs within the TME [132]. The tumor suppressor miR-140 inhibits the immune check-point molecule PD-L1 to suppress osteosarcoma by reducing MDSCs and Tregs' infiltration to the TME [133]. Corroborating with this, miR-140 is reported to be significantly downregulated in osteosarcoma [133]. STAT3, which is crucial in regulating the expansion of MDSCs, is known to be regulated by miRNAs such as miR-17–5p and miR-20a [134]. Overexpression of miR-17–5p/miR-20a in MDSCs alleviated their suppressive role against specific $CD4^+/CD8^+$ T cells in vitro and in vivo. In correlation with this, tumor-associated factors inhibited the expression of both miR-17–5p and miR-20a, thereby favouring MDSC expansion [134]. Likewise, miR-126, by inhibiting the chemokine ligand 2 (CCL2), suppresses the recruitment of tumor-infiltrating inflammatory monocytes (of myeloid lineage) to the TME and thus metastasis [75]. Moreover, miRNA clusters such as miR-25-93-106b are also known to regulate MDSCs by targeting proteins such as PD-L1 and chemokines such as CXCL12 [63]. In contrast, the tumor-promoting potential of MDSCs or their immunosuppressive properties is enhanced by hypoximiRs (hypoxia-induced miRNAs), such as miR-210, that mediate their effect by targeting proteins such as CXCL12 and IL16 [135]. Overexpressing miR-210 or blocking its targets IL16 or CXCL12 in MDSCs improves their immunosuppressive activity (T-cell suppression) in vivo, thus promoting tumor growth [135]. miRNAs such as miR-21 and miR-155 overexpressed in MDSCs induced from the bone marrow have been shown to synergistically modulate the expression of their targets such as phosphatase and tensin homolog (PTEN) and SHIP1, thereby promoting STAT3 activation [136]. This enhances the expansion of MDSCs and thus tumor progression. Moreover, both the monocytic and granulocytic subpopulations of MDSC are reported to be induced by these miRNAs [136].

6. Exosomal miRNAs and immune modulation

Cancers are known to hijack the body's immune system to propagate themselves by various methods such as promoting inflammation and using and expanding immunosuppressive cells and proteins to evade the immune response. In this context, tumors are known to employ miRNAs to interact with and attenuate the body's defense systems, the immune cells, and vice versa. Exosomes, extracellular secreted vesicles composed of a wide variety of biomolecules, mediate the crosstalk between cancer cells and immune cells of the TME, thus regulating tumor progression [137]. Exosomes, therefore, act as intercellular vehicles transporting immunomodulatory miRNAs between tumor -immune cells (Fig. 2).

Tumor exosomes released by melanoma cells have been shown to modulate both cytokine secretion and the T cell receptor (TCR) signaling cascade in $CD8^+$ T cells [138]. The secreted exosomes contain miRNAs such as miR-3187-3p, miR-498, and miR-149, which modulate TCR signaling and TNFα secretion, thereby suppressing $CD8^+$ T-cell cytotoxicity and promoting tumor immune evasion [138]. More recently, studies have indicated that melanoma-derived exosomes modulate the transcript profiles of CTLs and eventually their mitochondrial respiration, thus altering their metabolism and immune activity [139]. Exosomal miRNAs derived from tumors in NPC have been shown to suppress the proliferation of T helper cells such as Th1 and Th17. On the other hand, they promote the expansion of immune suppressors such as Tregs [140]. Similar suppression of the T-cell immune response and the promotion of tumor progression in NPCs are mediated by exosomal miR-24-3p, which directly targets FGF11 [141]. These studies have also suggested that exosomal miR-24-3p acts as a promising prognostic marker associated with NPC. Apart from their direct effects on T cells, exosomal miRNAs secreted by tumor cells are also known to indirectly modulate T cell function via other immune cell subtypes present in the TME. For instance, exosomal miR-23a-3p secreted by LiC cells suppresses T-cell activity, albeit indirectly by modulating PD-L1 expression (via the miR-23a-PTEN-AKT pathway) in macrophages in the TME [142]. By targeting PTEN expression, miR-23a-3p increases phosphorylated AKT levels and thus PD-L1 expression [142].

Tumor-associated macrophages (TAMs) that infiltrate the TME are known to regulate most of the hallmarks of cancers such as angiogenesis, growth, immune regulation, and metastasis by secreting exosomes enriched in miRNAs [143]. Exosomal miR-29a-3p and miR-21–5p released from TAMs have been shown to directly and synergistically inhibit STAT3 expression in $CD4^+$ T cells, otherwise crucial for their dif-

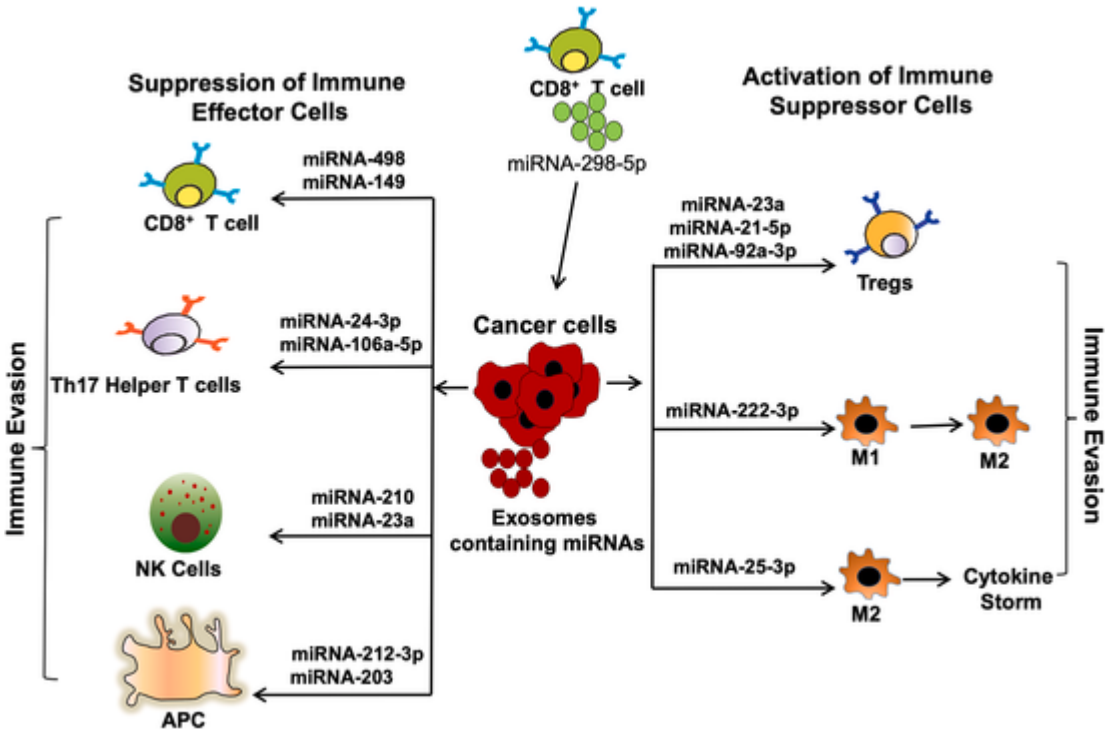

Fig. 2. Schematic describing the effect of tumor-derived exosomal miRNAs on various types of immune cells. Activities of immune effector cells such as T cells, NK cells, and APCs are suppressed, whereas immunosuppressors such as Tregs and TAMs are activated. miRNAs associated with the modulation of each cell type are shown. Also depicted is the effect of exosomes released in turn from T cells.

ferentiation into immune effector T helper 17 (Th17) cells [143]. This increases the Treg/Th17 cell ratio, thereby creating an immunosuppressive TME that promotes epithelial OC (EOC) progression. Other exosomal miRNAs, such as miR-222–3p, secreted by EOC cells, have been shown to induce the polarization of macrophages to a tumor-promoting M2 phenotype, thereby facilitating cancer progression [144]. Exosomal miR-222-3p achieves this by modulating the SOCS3/STAT3 pathway and downregulating its target gene SOCS3 [144]. Furthermore, liposarcoma-derived miR-25-3p and miR-92a-3p (by modulating Toll-like receptors 7/8) are known to stimulate M2-TAMs to release proinflammatory cytokines such as IL6 that favor liposarcoma proliferation and metastasis [145]. These studies have also suggested that exosomal miR-25-3p and miR-92a-3p act as biomarkers for liposarcoma [145]. Consistent with these studies, LC-derived exosomal miRNAs such as miR-29a and miR-21 are also known to target TLR-7/8, affecting TNF-α and IL-6 secretion and thus TAM polarization [146].

On the other hand, immune effector cells are also known to secrete miRNA- enriched exosomes to mediate an effective anti-tumor response. Cytotoxic extracellular vesicles (EVs) released from activated $CD8^+$ T cells have recently been shown to promote apoptosis in mesenchymal tumor stromal cells, thus restricting fibroblastic stroma assisted–tumor progression and metastasis [147]. The EVs engulfed by the mesenchymal tumor stroma are known to be enriched in miR-298–5p, which is considered to be responsible for their apoptotic depletion [147]. Therefore, $CD8^+$ T cells display additional effector mechanisms to regulate the TME apart from their usual cytotoxic activity against cancer cells.

The NK cells that play a crucial role in host rejection of tumors are known to be attenuated and display a diminished anti-tumor response in cancer patients [148]. Some essential factors responsible for host rejection are the reduced expression of cytotoxicity receptors such as NKG2D, which govern the NK cell response [51]. Hypoxic intratumoral-derived exosomes containing miR-210 and miR-23a along with TGF-β have been shown to reduce the expression of these activating cytotoxicity receptors in NK cells, thus attenuating their anti-tumor response [149]. These studies have further indicated that tumor-derived exosomal miR-23a directly targets CD107a in NK cells, thereby mediating a supplementary immunosuppressive role [149]. Similar suppression of surface NKG2D cytotoxicity receptors on NK cells (and $CD8^+$ T cells) has also been observed to be mediated by exosomes secreted by prostate tumors [150]. Conversely, NK cells are also known to release exosomes expressing various cytotoxic markers capable of mounting an effective anti-tumor response [151].

APCs such as DCs crucial in generating and regulating an immune response are also known to be modulated by exosomal miRNAs [152]. For example, pancreatic tumor-derived exosomal miR-212-3p has been shown to suppress the expression of the MHC II complex on DCs by modulating targets such as regulatory factor X-associated protein (RFXAP), a crucial protein involved in MHC II transcription [153]. Interestingly, these studies have also indicated that several hundred mRNA transcripts are dysregulated in exosome-treated DCs relative to immature DCs [154]. In addition to this, PC is also known to secrete exosomal miR-203, affecting TLR4 expression on DCs and establishing immune evasion [155].

7. Immunomodulatory miRNAs and cancer therapeutics

Immune cells (e.g., DCs, macrophages, APCs) are known to release exosomes enriched in a wide variety of proteins such as MHC-I/II, B7s, and ICAMs, which are capable of inducing an effective immune response in neighboring cells [156]. In addition to this, immune effector cells are also known to secrete exosomes enriched in miRNAs (as discussed above) that have emerged as novel immunotherapeutic tools that can be used against several cancers. More recently, studies have shown that exosomes secreted by macrophages, in the presence of DCs, are capable of inducing both the CD4 + and CD8 + T-cell response in vitro [157]. Intriguingly, miRNAs have also been shown to be sorted in a much more selective manner. For instance, miRNAs such as miR-671–5p [158] and miR-760 [159] were mostly enriched in exosomes

associated with cancer. miR-335, on the other hand, was found to be enriched selectively in exosomes secreted by primary DCs [160]. Such exosomal miRNAs have been shown to have promising results in therapeutic applications against cancer. For instance, exosomal nanoparticles derived from NK cells have been shown to carry and efficiently restore miR-186 expression levels, thus improving the NK cell-mediated cytotoxic response and reducing tumor growth [161].

Furthermore, as exosomes also play a significant role in the crosstalk between cancer cells and their microenvironment, current therapeutic strategies have also focused on ways to inhibit either the release or the uptake of exosomes from tumors, thus severing cell-to-cell communication. For example, rab27 silencing has been shown to block the exosomal release of miR-494 and, therefore, tumor growth and progression in melanoma [162]. Inhibitors of exosome biogenesis, such as GW4869, have also been reported to target the exosomal miR-501 biogenesis involved in promoting tumorigenesis in GC [163]. Alternatively, endocytosis inhibitors that block the cellular uptake of exosomes have been shown to successfully inhibit the uptake of myeloma-derived exosomes by stromal cells, thus severing cell-to-cell communication in the TME and serving as a potential alternative therapy [164].

Various clinical trials are also underway (see ClinicalTrials.gov). An ongoing pilot study (NCT02507583) currently underway uses exosomes enriched with antisense RNA moieties as an immunotherapeutic tool to treat human patients with malignant glioma. The study suggests that the said immunotherapeutic intervention will have more significant benefits and reduced risks relative to the treatment options currently available for glioma. Another ongoing investigation (NCT03608631) uses iExosomes derived from mesenchymal stem cells enriched with siRNAs as an alternative treatment option for metastatic pancreatic ductal adenocarcinoma with a $Kras^{G12D}$ mutation. Nevertheless, the crucial role of exosomal miRNAs in cancer progression, metastasis, and immune evasion makes them exciting candidates for designing novel treatment against various cancers.

Moreover, exosomal miRNAs such as miR-21 have been shown to act as biomarkers indicative of treatment efficacy in non-small cell LC [165]. These studies revealed that elevated serum levels of miR-21 corresponded with acquired resistance against cytotoxic agents such as EGFR and tyrosine kinase inhibitors. Corroborating with this, studies indicate that silencing miR-21 expression improved cancer cells' radio sensitivity to ionizing radiation by suppressing the PI3K/Akt signaling cascade, thus establishing the critical role of miRNAs in predicting therapeutic outcomes [166].

8. miRNAs and immuno-modulatory biomolecules

In addition to regulating the proteins involved in the AP&P machinery, miRNAs also affect immune cell activity in the TME by various immunomodulatory biomolecules. One such immune metabolite, the enzyme indoleamine 2,3-dioxygenase (or IDO) associated with tryptophan metabolism in the TME, has been reported to promote the development of numerous immune suppressors such as Tregs 90 and $CD19^+$ DCs [167] along with suppressing effector cells such as cytotoxic $CD8^+$ T cells [168], thus attenuating the anti-tumor response. In this context, studies have shown that ectopic expression of miRNAs such as miR-448 by directly targeting and reducing IDO1 levels in CRC cells increased the activity of $CD8^+$ T cells and resulted in an effective immune response [168]. Similar miRNA-mediated suppression of the immune-metabolite IDO1 has been reported for tumor-suppressive miR-153 [169]. Its overexpression, coupled with the use of therapeutic chimeric antigen receptor T cells, has shown promising applications (e.g., miR-448) in improving T-cell cytotoxicity in vitro and suppressing tumor progression in vivo [169].

9. Conclusions

In recent years, the importance of miRNAs in the post-transcriptional regulation of various crucial cellular and physiological processes such as growth, development, proliferation, oncogenic transformation, tumor suppression, and immune modulation has been established. In the context of cancers, increasing evidence has suggested and established the critical role of miRNAs in modulating the behavior of both effector and immune suppressor cells. The pan cellular role of miRNAs in regulating targets associated with immune evasion by tumors, targets involved in an effective immune response by immune cells, or target proteins related to crosstalk between tumor and immune cells has revealed an altogether new layer of post-transcriptional regulatory mechanisms that exist in a cell. In addition, a deeper understanding of the roles of immune-modulatory miRNAs would also help develop more contemporary and effective therapeutic approaches against cancer cells and improve the efficacy of known drugs by reducing chemoresistance. This review also addresses the role of exosomal miRNAs in modulating the immune effector and immune suppressor cells. Apart from modulatory functions, exosomal miRNAs are emerging as novel predictive and diagnostic markers for various cancers. The therapeutic applications of an ever-increasing list of exosomal miRNAs have opened up novel prospects for anti-cancer treatments. The discovery of newer immune-modulatory miRNAs and their associated targets could also improve our understanding of "ways and means" that cancer cells employ to proliferate and highjack the immune system or those used by immune cells to establish an effective anti-tumor immune attack. A better understanding of immune modulation by miRNAs can lead to the design of better therapeutic strategies.

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Competing Interests

The authors declare that they have no competing interests.

Contributions

S.N.L., M.A.M and M.H: Conceived and designed the review's content and contributed to manuscript writing and editing; S.N.L., M.A.M., A.A.B., and N.A.W: Prepared the scientific material, wrote the manuscript, and generated figures. T.K., S.N., M.S., S.H., P.B., B.C.D., D.B., R.R., M.F.P., W.E.R., M.A.S., M.A.M and M.H: Critically revised and edited the scientific contents. All authors read and approved the final manuscript.

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