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REVIEW ARTICLE

Immunomodulatory MicroRNAs in cancer: targeting immune checkpoints and the tumor microenvironment

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Cancer immunotherapy represents a promising new era in cancer management due to the relatively high safety margins and selectivity, compared to the classical cancer chemotherapeutic agents. However, there is an imperative need to overcome tumor resistance in order to improve clinical outcomes and maximize the benefits of cancer immunotherapy. The interaction between the programmed cell death-1 (PD-1) receptor and its ligand PD-L1 is a vital immune checkpoint that is often adopted by cancer cells to undergo immune evasion. PD-1/PD-L1 signaling is regulated at multiple levels through the crosstalk with other immune targets or relevant signaling partners involved in the cancer progression. Among the significant epigenetic players that are implicated in modulating the immune system are microRNAs (miRNAs). A complex system of these noncoding RNAs regulates the gene expression at the post-transcriptional level and plays a significant role in the modulation of both innate and the adaptive immune systems. The expression profile of immune-modulatory miRNAs might be useful as a predictive biomarker for the response and clinical outcomes in cancer immunotherapy. Therefore, in the current review, we highlighted the role of miRNAs in cancer immune evasion through a critical discussion of their impact on key immune checkpoints as well as the role of miRNAs in cancer progression and resistance.

Abbreviations
BCC, breast cancer cells; CDK, cyclin-dependent kinase; CRC, colorectal cancer; CTLA-4, T-lymphocyte–associated antigen 4; EBV, Epstein-Barr virus; HCC, hepatocellular carcinoma; HIF-1α, hypoxia-inducible factor-1α; HLA, human leukocyte antigens; IFN-γ, interferon gamma; IL, interleukin; MDSCs, myeloid-derived suppressor cells; MHC, major histocompatibility complex; NK, natural killer; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PTEN, phosphatase and tensin homolog; RCC, renal cell carcinoma; STAT, signal transducer and activator of transcription; TGFβ1, transforming growth factor beta1; TNF-α, tumor necrosis factor-alpha.

Introduction

The characterization of Lin-4 *Caenorhabditis elegans* in 1993 was the starting point for the microRNAs (miRNAs)-based gene regulation concept [1]. Approximately 60% of protein-coding genes in humans are regulated by miRNAs [2]. Most of miRNAs are generated through the canonical pathway, a sequential process through which the primary transcript (pri-miRNA) is synthesized by RNA polymerase II or RNA polymerase III and cleaved by Drosha (RNase III nuclear enzyme) and DGCR8 complex [3]. Pre-miRNA, the precursor miRNA, forms a characteristic hairpin double-strand of 60- to 70 nucleotides and is exported out of the nucleus through the effect of Exportin-5. Dicer (RNase III enzyme) would then cleave the pre-miRNA, with the aid of TRBP/PACT proteins, to produce a 22-base pair double-stranded RNA molecule [4]. Once the mature strand is incorporated into the RNA-induced silencing complex with Argonaute protein, the whole complex would attack the target messenger RNA [5]. miRNAs bind to the coding sequences 3′ or 5′ UTR of the target mRNA, leading to translation inhibition or target mRNA degradation [6]. miRNAs can also be involved in translation upregulation, through direct or indirect miRNAs-mediated inhibition of gene repression. However, it is strictly dependent on cell type, cell cycle, and the presence of additional mRNA UTR sequences [7].

Immunotherapy represents a promising new era in cancer management. Instead of targeting cancer cells, immunotherapy preferably aims at the immune checkpoints interrupting the interaction between the programmed cell death protein 1 (PD-1) and its ligand, PD-L1(or PD-L2) [8]. PD-1 protein is found on the surface of many immune cells, while PD-L1 is expressed by several cell types, including cancer cells [9]. PD-L2 has a more limited expression profile compared to PD-L1. It is present on the surface of dendritic cells, macrophages, and mast cells [10]. The association of PD-1 to PD-L1 inactivates T cells and halts the immune system [11]. PD-L1 overexpression has been identified as a mechanism for immune evasion [12]. Inhibiting PD-1/PD-L1 immune checkpoint offers a promising strategy with hopeful clinical applications [13]. Until now, there are no approved therapeutic agents that specifically target PD-L2. In many clinical trials, PD-1/PD-L1 inhibitors showed superior efficacy and safety compared to the traditional chemotherapeutic agents [14,15]. However, the low response rates and the development of resistance are still among the major challenges encountered by this class of anticancer agents. Extensive research efforts are dedicated to understand the resistance mechanisms for immune checkpoint inhibitors and to develop efficient biomarkers for response prediction.

Immune-modulatory effects of miRNAs in cancer

Various reports showed that tumor-suppressor miRNAs are implicated in the control of antitumor immune response through the regulation of immune checkpoints such as PD-1, PD-L1, and T-lymphocyte–associated antigen 4 (CTLA-4). Some of the miRNAs target either PD-1 or PD-L1 checkpoint proteins, while others target both PD-1 and PD-L1 simultaneously, such as miR-33 and miR-BART cluster. miRNAs are also implicated in the regulation of key immune cells within the tumor microenvironment. Those include macrophages, myeloid-derived suppressor cells (MDSCs), and natural killer (NK) cells in addition to regulating tumor antigen processing for the major histocompatibility complex (MHC) restricted presentation. Herein, we are summarizing the up-to-date data in this regard, as depicted in Fig. 1.

miRNAs regulation of PD-L1 checkpoint protein

The mechanisms of cancer immune evasion include PD-L1 overexpression as a result of the disruption of its 3′-UTR in several types of cancer such as leukemia, lymphoma, and gastric adenocarcinoma. Kataoka *et al.* [16] demonstrated that viral infections like human papillomavirus (HPV) and viral-DNA integration contribute to the aberrant transcription of PD-L1 with subsequent tumor immune escape. In that study, the authors highlighted the genetic basis of post-transcriptional regulation for PD-L1-mediated immune evasion and suggested that PD-L1 3'-UTR disruption could be utilized as a genetic marker for cancers capable of escaping the immune surveillance [16].

miRNAs direct regulation of PD-L1 expression

The expression of PD-L1 immune checkpoint is regulated at the epigenetic level through multiple miRNAs which bind to its 3′UTR resulting in translation repression. miR-142-5p inhibits the expression of PD-L1 by tumor cells directly through binding to its 3'UTR, which subsequently stimulates the antitumor immunity and leads to the suppression of pancreatic cancer growth *in vivo* [17]. Another inhibitor for PD-L1 expression is miR-138-5p, which can be considered

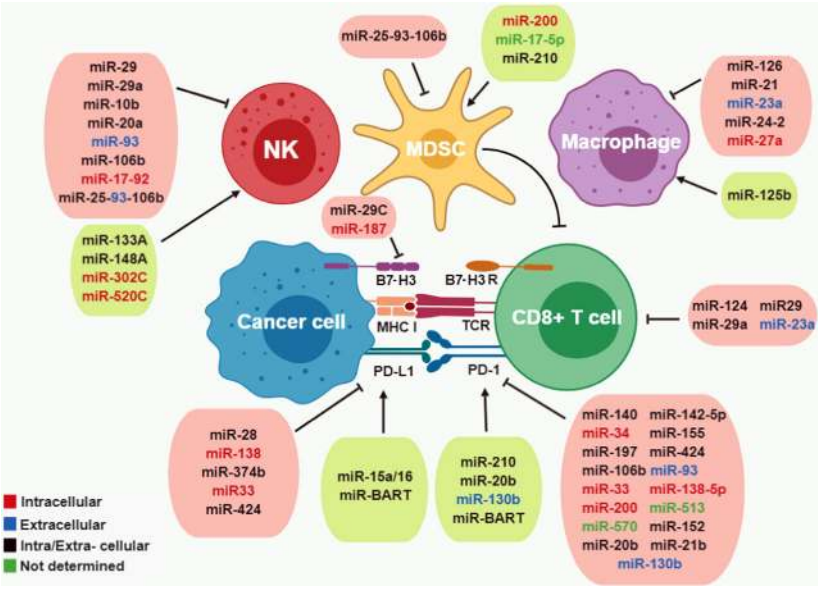

Fig. 1. Tumor microenvironment regulation by miRNAs. Modulatory effects of miRNAs on NK cells, MDSCs, tumor-associated macrophages, and CD8+ T cells. Regulation of the different molecular immune targets and checkpoints by miRNAs including MHC-I, TCR (T-cell receptor), PD-1, PD-L1, B7-H3 (CD276). The colored legend on the bottom-left panel indicates the sites of action of the depicted immunomodulatory miRNAs.

as a tumor suppressor that is commonly deficient in colorectal cancer (CRC) and linked to poor clinical outcomes [18]. This miRNA is the 5′ end-transcript of the precursor miRNA-138. The expression of miR-138 is also reduced in squamous cell carcinoma of the head and neck, thyroid, and ovarian tumors [19,20]. miR-138-5p was recently identified as one of the key miRNAs dysregulated in renal cell carcinoma (RCC) [21]. miR-138-5p mimics were shown to inhibit the cell proliferation and invasion of RCC cell lines [22]. Additionally, miR-138-5p was found to altered among benzo-a-pyrene-induced miRNA profile changes in lung epithelial cells [23]. Therefore, the use of miR-138-5p mimics is anticipated to be important in modulating the antitumor immunity in both RCC and lung cancer. miR-513 is commonly downregulated in patients with chronic biliary inflammation [24]. This miRNA inhibits the expression of PD-L1, in addition to hindering interferon gamma (IFN-γ)-mediated PD-L1 expression in the cholangiocytes. Therefore, miR-513 can block the malignant transformation in these cells [25]. Furthermore, the low expression of miR-513 was coupled with PD-L1 overexpression in retinoblastoma [26]. Recent studies showed that miR-513 hinders cell invasion and metastasis in endometrial cancer and that it is implicated in gemcitabine resistance in bladder cancer [27,28]. These findings support the potential utility of miR-513 mimics to target these cancer types. miR-570 is another inhibitor of PD-L1 expression, which is commonly downregulated in hepatocellular carcinoma (HCC) [29]. miR-570 mimics have shown antiproliferative and antiangiogenic effects in HCC, *in vivo* [30]. Additionally, they enriched both the blood and the cancer tissues with $CD8^{+}IFN\text{-}\gamma^{+}T$ cells [30]. miR-152 is a direct inhibitor of PD-L1 expression [31]. It is a tumor-suppressor miRNA that was recently reported to exhibit both antiproliferative and antimetastatic effects. The underlying mechanisms for such activity were reported to be through Kruppel-like factor 5 regulation [32], Akt/ERK signaling suppression in cervical cancer, and CRC [33]. miR-152 also suppresses non-small cell lung cancer (NSCLC) proliferation via the downregulation of fibroblast growth factor (FGF) [34]. Low level of miR-152 in gastric cancer patients was related to poor prognosis with a higher incidence of metastasis [35]. miR-34 family encompasses miR-34a, -34b, and -34c, which directly target PD-L1 and inhibit its expression [36]. This tumor-suppressor family of miRNA is induced by p53, and its level was reported to be lower in NSCLC and acute lymphocytic leukemia [37]. This low expression of miR-34 was correlated with the overexpression of PD-L1 on the tumor cells [38]. Additionally, miR-34a modulates the immune exhausted CD8+/PD-1+T-cells resulting in enhanced production of IFN-γ and tumor necrosis factor-alpha (TNF-α) [38]. The induction of miRNA-155 expression, via exposing the cells to the proinflammatory cytokines TNF-α and IFN-γ, suppresses the expression of PD-L1 in both lymphatic endothelial cells and fibroblasts [39]. miR-155 was also reported to activate STAT3 signaling and promote breast cancer cells (BCC) progression [40,41]. miR-155 is a vital component of the inflammatory response that is dysregulated in various cancer types such as BCC, CRC in addition to B-cell lymphoma [42] and such perturbations are linked to poor prognosis [42].

miRNAs indirect regulation of PD-L1 expression

miRNAs indirectly modulate the PD-L1 expression through the epigenetic regulation of upstream signaling pathways such as phosphatase and tensin homolog (PTEN)/PI3K/Akt and signal transducer and activator of transcription (STAT). Low expression of PTEN leads to upregulation of PD-L1 in cancer cells. miRNAs-20b, -21, and -130b downregulate PTEN expression and hence enhance PD-L1 expression. The levels of miRNAs mentioned above are significantly higher in CRC cells, in comparison to normal cells [43]. PTEN is also a target for miR-214a, which modulates the expansion of T-regulatory cells in solid tumors [44]. The downregulation of PTEN by miR-221/222 activates Akt/NF-κB/COX-2 pathway in BCC *in vivo* and *in vitro* [45]. Both miR-21 and miR-181-1b inhibit PTEN through STAT3 pathway in CRC [46]. miR-21 also regulates macrophages polarization via curbing the IFN-γ-induced STAT1 signaling [47]. miR-23a/24-2/27a modulate macrophage polarization in BCC through the Janus kinase (JAK)/STAT pathway [48]. Besides, macrophages are partly activated by miR-125b [49]. miR-197 indirectly inhibits the expression of PD-L1 via the suppression of the cyclin-dependent kinase (CDK) CKS1B/STAT3 signaling axis [50]. The expression of miR-197 is dysregulated in various cancers, including lung, pancreatic, and thyroid cancers, and its downregulation is linked to poor overall survival and chemoresistance [51]. The upregulated miR-21 in BCC suppressed lymphocytes migration via the inhibiton of activated STAT3 (PIAS3)/STAT3 signaling [52]. The elevated miR-21 expression has been linked to poor survival in six different cancer patient cohorts, including HCC, RCC, pancreatic, lung adenocarcinoma, low-grade glioma, and glioblastoma multiforme [47]. miR-124 is also immunologically related to glioma, through inhibiting T-cell proliferation via its effect on STAT3 [53].

To sum up, miRNAs involved in PD-L1 regulation can work either in a direct manner by targeting the 3′-UTR of PD-L1 or indirectly through the regulation of PD-L1 upstream pathways like PTEN/PI3K/Akt or JAK/STAT. It is noteworthy that a subset of miRNAs which include miR-140, miR-126, miR-210, and miR-25-93-106b cluster have dual regulatory effects in tumor immune evasion since they are implicated in controlling PD-L1 expression as well as the modulation of MDSCs. Targeting those immune-modulatory miRNAs could be a valid approach to enhance the antitumor immunity and achieve a better therapeutic response in hard-to-treat cancers like HCC. According to the aforementioned data, there are multiple miRNAs (miR-34, -570, -20b, -21b, -130b) that were reported to be dysregulated in HCC. Those miRNAs can lead to the upregulation of PD-L1 expression and enhancing the HCC tumor immune escape [30,47,54].

It is worthy of mentioning that miR-34a mimics (MRX34) have been tested in phase I clinical trial as liposomal preparations in patients with advanced solid tumors including HCC and they have raised safety concerns due to immune-related adverse events [55,56]. However, the administration of dexamethasone as a premedication has improved the tolerability of MRX34 [54]. The tested regimen has shown promising antitumor effects in patients with advanced solid tumors that are refractory to standard treatment. One HCC patient achieved a prolonged confirmed pathologic response that lasted for 4 years, while four patients demonstrated stable disease that lasted greater than or equal four cycles[54]. The outcomes of this study could help in the optimization of the treatment protocols, and the development of an appropriate premedication course for the anticipated adverse effects to improve the tolerability of MRX34 or other miRNAs mimics that would be tested in the future.

miRNAs regulation of PD-1 checkpoint protein

The miRNA cluster miR-15a/16 is localized at chromosome 13q14, and it plays an immune regulatory role in both physiological and inflammatory conditions [57]. The aberrant expression of miR-15 and -16 was initially demonstrated in patients with chronic lymphocytic leukemia, then extended to several types of solid tumors such as prostate cancer and gliomas [58]. The downregulated expression of miR-15a/16 in CD8+ T cells resulted in low expression of PD-1 in addition to high activity as evidenced by boosted proliferation and production of cytokines such as IFN-γ, interleukin-2 (IL-2), and TNF-α [57]. The deficiency of miR-15a/16 inhibited tumor expansion and prolonged the survival in a mouse model of glioma [57]. T-cell exhaustion is a condition of poor T-cell effector function that occurs in various chronic infections and in cancer as a result of sustained expression of inhibitory receptors [1]. miR-28 was shown to regulate T-cell exhaustion via controlling the expression of inhibitory receptors such as PD-1 and T-cell immunoglobulin domain and mucin domain 3. The inhibition of miR-28 led to the upregulated expression of such inhibitory receptors [59]. Furthermore, the upregulation of miR-28-5p was linked to poor overall survival and shorter disease-free periods in patients with CRC, independent from the clinicopathological features of the tumor or the therapeutic protocol [60]. Wei *et al.* [61] have indicated that

miR-138 targets the 3′UTRs of PD-1 and CTLA-4, inhibiting their expression. The cytotoxic CTLA-4 is another crucial molecular target for classical immunotherapy, and it acts as a negative regulator for T-cells. Transfection of glioma cells with miR-138 markedly decreases the expression of immune checkpoint molecules, boosting the anticancer immune response and resulting in tumor shrinkage [61]. Moreover, the aberrant expression of miR-138 was linked to fulvestrant and tamoxifen resistance in BCC [62].

miRNAs regulation of PD-1 and PD-L1 checkpoint

Some miRNAs have been found to mutually regulate PD-1 and PD-L1 checkpoint proteins. Epstein-Barr virus (EBV) miR-BART cluster, which includes miR-BART-2, -4, -5, -18 and -22, was found to be expressed by solid tumors like CRC and gastric cancer and was associated with poor prognosis [63]. It is noteworthy that solid tumors with positive expression of miR-BART cluster show a prominent upregulation of PD-1 and PD-L1 immune checkpoint proteins [63]. For example, miR-34a is downregulated by EBV, which enhances the PD-L1 expression and so the immune evasion [64]. Interestingly, patients with high levels of EBV-miRNA have also parallel high expressions of PD-1, PD-L1, transforming growth factor beta 1 (TGFβ1), IL-10, IFN-γ, and TGFβ2, which make them good candidates for immune checkpoint therapy [65]. Additionally, EBV-encoded miRNAs mediate immune evasion through targeting other cellular immune factors [66]. These miRNAs as miR-BHRF1-2, 2-5p, 10-3p, and 11-5p interfere with the host immune system at many levels, including T-cell differentiation, activation and recognition, B-cell differentiation, NK cell activity, and antigen processing. Moreover, EBV-encoded miRNAs enhance the immune exhaustion by boosting the generation of IL-10, TGF-β, and IFN-γ [63]. There are many other virus-modulated miRNAs that change the expression of PD-1/PD-L1 such as miR-4717 which is encoded by hepatitis-B and could significantly downregulate PD-1 in lymphocytes isolated from chronic hepatitis-B patients with the polymorphic variant GG [67].

miR-33 is another miRNA that targets PD-1 and PD-L1, inhibiting their expression through the interaction with 3'UTR of both. miR-33 is known to play a role in lipid metabolism [68]. The upregulation of miR-33a was found to be coupled with the downregulation of PD-1 immune checkpoint and better outcomes in lung cancer patients [68]. Moreover, miR-33a has a tumor-suppressor function via reducing the expression of β-catenin [69]. Additionally, miR-424 was identified as a potential immune checkpoint inhibitor targeting PD-L1/PD-1 and cluster of differentiation 80 (CD80)/CTLA-4 interactions [70]. miR-195 and miR-16 overexpression have been correlated with recurrence-free survival in prostate cancer patients. The levels of both miR-195 and miR-16 are negatively correlated with the expression of the immune checkpoints PD-1, PD-L1, and CTLA-4 [71]. The restoration of miR-195 and miR-16 expression exhibited synergistic antitumor effects in syngeneic orthotopic prostate cancer murine model. The underlying mechanisms for such effect were attributed to inhibiting PD-L1 expression, boosting the expansion of cytotoxic CD8+ T cells, while inhibiting MDSCs and regulatory T cells (T-reg) [71].

miRNAs regulation of MDSCs

It is noteworthy that some of the miRNAs that regulate PD-L1 immune checkpoint are also involved in the control of the activity and the recruitment of the immunosuppressive MDSCs to the tumor microenvironment. Those miRNAs include miR-140, miR-126, miR-210, and miR-25-93-106b cluster. The mammalian target of rapamycin signaling inhibitor miR-140 exhibits immune-mediated antitumor effect via inhibiting PD-L1 expression. Such inhibition enriches the tumor microenvironment with CD8+ antitumor T cells and reduces the infiltration of MDSCs. The level of miR-140 was markedly downregulated in osteosarcoma [72]. The immunosuppressive potential of MDSCs in CRC is opposed by the effect of miR-20a/miR-17-5p on STAT3 [73]. miR-126, on the other hand, suppress the recruitment of inflammatory monocytes via downregulation of the expression of chemokine (C-C motif) ligand 2 (CCL2) [74]. Furthermore, miR-25-93-106b cluster is upregulated via the effect of danger signals activated by total body irradiation and ischemia-induced injury. This miRNA cluster inhibits the receptiveness of bone marrow stromal niche to metastatic cancer cells through targeting CXCL12 [75]. The members of this cluster are negative regulators of PD-L1. The expression of PD-L1 in MDSCs and pancreatic carcinoma was found to be downregulated upon treatment with miR-93 or miR-106b mimics. The percentage of PD-L1+ myeloid cells has been shown to be higher in miR-25-93-106b knockout mice in comparison to wild-type mice [75]. The upregulation of miR-210 in MDSCs by hypoxia-inducible factor-1α (HIF-1α) augments their immunosuppressive functions by increasing the expression of PD-L1 and boosting the production of IL-10 and IL-6 [76].

miRNAs modulation of NK cells

Unleashing the NK cells represent an essential aspect for boosting the antitumor immunity. miR-374b downregulation has been linked to cancer aggressiveness and resistance to therapy in various cancers of the gastrointestinal tract, including CRC, pancreatic, and gastric cancer [77,78]. The overexpression of miRNA-374b can halt the progression of hepatic tumors through downregulating the expression of PD-1 by cytokine-induced NK cells and restoring their antitumor activity [79]. Likewise, the overexpression of miR-133A and miR-148A induces tumor cell death via activation of NK cells in RCC [80]. Furthermore, the suppression of NK and T cells is observed in various types of solid tumors, including neuroblastoma, due to the expression of the inhibitory glycoprotein Cluster of Differentiation 276 (CD276) (B7-H3). miR-29 and miR-29a were reported to target and inhibit B7-H3 in these immune cells, which reverses the tumor immune evasion [81,82]. On the other hand, miR-29c target B7-H3 in BCC [83]. B7-H3 can also be a target for miR-187, which inhibits cell survival in RCC [84]. In addition, miR-24 was reported to inhibit CD275 (B7-H2) in BCC [85]. miR-34a and miR-34c also enhance NK-cell killing activity against melanoma cells by targeting UL16 binding protein 2 (ULBP2)[86]. Moreover, miR-302c and miR-520c target the same protein and enhance the tumor cell susceptibility to NK-mediated cytotoxicity [87].

miRNAs regulation of tumor antigen processing for MHC restricted presentation

Tumor immune evasion is not restricted to the upregulation of immune checkpoint proteins. Multiple mechanisms have been proposed, including classical and nonclassical MHC-I molecules expression dysregulation. In addition, other mechanisms such as the manipulation of molecules were involved in MHC-1 processing and antigen presenting machinery such as the proteasome subunits Proteasome Subunit Beta 8 and 10 (PSMB8 and PSMB10), human antigen peptide transporter 1 TAP1 protein, and miRNAs. For instance, miR-9 controls peptide processing and presentation by targeting IFN-induced genes and MHC-I molecules. Other miRNAs that are implicated in the modulation of human leukocyte antigens (HLA) class 1, APM components, and IFN-induced genes expression include miR-346, miR-451, and miR-148a [88]. Contrary to the classical HLA class I molecules, HLA-G antigen overexpression, and heterogeneity are associated with poor prognosis and response to therapy. Seliger *et al*. have reviewed miRNAs that regulate the expression of HLA-G, such as tumor-suppressive miRNA family miR-148 [89]. Moreover, the inhibition of MHC class I chain-related protein A/B (MICA/B) expression and NKG2D NK-cell receptor ligands is another mechanism of immune suppression targeting NK cells cytotoxicity. A recent report has identified a novel miRNA, miR-183 that targets MIC A/B in lung cancer [90]. Similar modulation has been reported for miR-10b in BCC [91], miR-20a in ovarian cancer [92], and miR-25-93-106b, miR-20a, miR-93, miR-106b and miR-17-92 cluster in HCC [93,94].

miRNAs role in cancer development and progression

The dysregulated expression of miRNAs in tumors can modulate several pathways involved in cancer progression and metastasis. According to the target gene, miRNA may act as an onco-miR or a tumor-suppressor miRNA [95]. In the following section, we are discussing different miRNAs implicated in cancer development, metastasis, and angiogenesis. Although the expression of PD-1/PD-L1 expression is associated with immune escape, interestingly an emerging role in cancer development and progression has been reported in several cancer studies [96]. Therefore, it is crucial to deeply understand the regulatory role of miRNAs in this complex interaction.

The role of miRNAs in cell cycle regulation

The dysregulation of miRNAs has been associated with alterations in genes governing cell cycle progression in many tumors. Several studies indicated promising outcomes for the use of PD-L1 inhibitors in combination with CDK 4/6 inhibitors such as abemaciclib [12,97]. The inhibition of CDK4/6 enhances the immune system against cancer cells as it promotes cytotoxic T cell-mediated clearance of tumor cells and upregulates the expression of antigen-presentation genes in hormone receptor-positive BCC [97,98]. In this section, we are highlighting a subset of miRNAs that are implicated in the regulation of CDK4/6 in both cell cycle progression and immune evasion.

The PD-L1 inhibitor, miR-34a, has been reported to downregulate CDK6 expression in NSCLC [99]. High levels of miR-34a are linked to a long progression-free survival in adenocarcinoma patients [99]. miR-200 reverses the immune exhaustion of CD8+ T cells by targeting PD-L1, resulting in its marked downregulation [37]. The downregulated expression of miR-200 in NSCLC cells is also linked to PD-L1 overexpression

and higher scores for epithelial to mesenchymal transition (EMT) [37]. miR-200a forced expression has been reported to suppress the expression of CDK6 in metastatic melanoma cells [100]. In addition, miR-200a downregulation in melanoma cells is associated with disease progression and a high number of lymph node metastases [100]. It is noteworthy that MYC proto-oncogene induces hypermethylation of miR-200b promoter leading to its repression in triple-negative BCC [101]. The depletion of miR-200 halts pancreatic β-cell differentiation and initiates EMT leading to augmented tumor invasion *in vivo*, in an insulinoma mouse model through Zeb1 regulation [102]. The overexpression of miR-6883 in CRC cells resulted in reduced levels of CDK4 and 6 with subsequent cell cycle arrest at G0/G1 phase [103]. Besides, miR-9 is downregulated in patients with oral squamous cell carcinoma [104]. Furthermore, forced expression of miR-9 induces G0/G1 cell cycle arrest and suppresses cancer cell migration. The use of miR-9 mimics significantly downregulates CDK6 and cyclin D1 in oral squamous cell carcinoma cells and halts cell proliferation [104]. miR-9 is also implicated in the downregulation of other pro-survival signals, including the transcription factor NF-kB in the colon, gastric, and ovarian cancers [105,106]. As discussed above, miR-9 also regulates antigen-presentation genes and MCH class-1 molecules [106]. Collectively, the pivotal role of these miRNAs in the regulation of CDK4/6 function underscores the importance of miRNAs in the cell cycle progression and immune evasion, which encourages further supporting studies for the use of combinations of miRNA mimics and immune checkpoints inhibitors.

The role of miRNAs in modulating angiogenesis

Angiogenesis is a vital process in promoting tumor expansion and metastasis, via the creation of new blood vessels that provide tumor cells with nutrients and oxygen [107]. Ample evidence indicated that several miRNAs control the angiogenesis process. In BCC, Camps *et al.* [108] demonstrated that miR-210 is overexpressed under hypoxia through HIF-1α and von Hippel-Lindau (VHL)-dependent pathways. The study also suggests that miR-210 can serve as a prognostic marker for breast tumors. Exosomes isolated from hypoxic multiple myeloma cells showed upregulation of miR-135b, which could enhance angiogenesis via interfering with a factor inhibiting HIF-1. Conversely, miR-519c, miR-20b, and miR-107 have been reported to suppress vascular endothelial growth factor (VEGF) and HIF-1α expression under hypoxia and thus negatively regulate angiogenesis. These findings are in harmony with the fact that cancer patients who overexpress miR-519c have a better prognosis [109]. Similarly, miR-107 in human colon cancer tissues negatively regulates HIF-1β expression as well as tumor angiogenesis under the control of p53 (Fig. 2) [110]. Together, the interplay between angiogenesis and cancer immune evasion has been investigated in many preclinical studies, which highlight the synergistic effect of immune checkpoint blockade in combination with antiangiogenic agents [111,112]. Inspired by promising animal studies, many clinical trials are underway to explore the combination of different compounds that target immune checkpoints and angiogenesis (NCT03024437, NCT02659384, NCT02873962, NCT02017717).

The role of miRNAs in counteracting cancer cell apoptosis

Tumor cells have evolved several strategies to resist apoptosis via interference with the tumor-suppressor p53, proapoptotic signals and as well as upregulation of antiapoptotic factors. The dysregulation of p53 or its associated miRNAs has been reported to confer resistance against apoptosis in cancer cells. Pichiorri and co-workers have reported downregulation of miR-192, miR-194, and miR-215 as central to the progression of multiple myeloma via triggering the degradation of p53 [113]. Yan *et al.* [114] have demonstrated that upregulation of miR-17-92 cluster in tumor cells can evade hypoxia-triggered apoptosis. Moreover, apoptosis is induced by the overexpression of miR-101 in human BCC via modulating JAK2 [115] and by miR-124-3p in nasopharyngeal carcinoma via modulating STAT3 and its downstream targets [116]. Similarly, miRNA-145 targets STAT1 in colon cancer cells, inhibiting their proliferation [117].

miRNAs can induce apoptosis resistance by inhibiting various elements of the extrinsic apoptotic pathway. Hatley *et al.* [118] reported that miR-21 is overexpressed in K-Ras–dependent lung cancers, which downregulates the expression of Fas ligand, a pivotal element in the extrinsic pathway of apoptosis. The ectopic expression of miR-21 has been reported to guard against gemcitabine-evoked apoptosis in advanced pancreatic cancer [119]. The same miRNA is involved in the resistance of human epidermal growth factor receptor-2–positive BCC to trastuzumab through its inhibitory effect on PTEN and PDCD4 [120]. In acute myeloid leukemia, miR-590 has been characterized as an onco-miRNA due to its ability to downregulate Fas ligand expression [121]. Razumilava

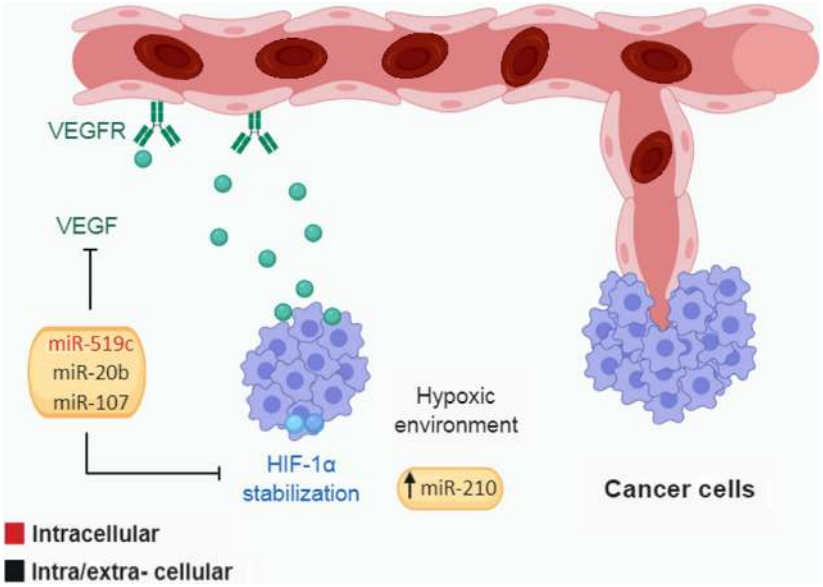

Fig. 2. The role of miRNAs in promoting angiogenesis. Several miRNAs are involved in the angiogenesis regulation in tumors. These miRNAs are overexpressed in hypoxic conditions and can regulate angiogenesis through the modulation of HIF-1α and VEGF. The colored legend on the bottom-left panel indicates the sites of action of the depicted immunomodulatory miRNAs.

and co-workers demonstrated that overexpression of miR-25 could counteract apoptosis in cholangiocarcinoma cells via downregulating TNF-related apoptosis-inducing ligand death receptor-4 [122]. In several tumors, miRNAs can interact with the proapoptotic signals, for example, Bax and PUMA or the anti-apoptotic factors, for example, Bcl-2 to hinder apoptotic cell death. Zhang *et al.* [123] have demonstrated that miR-221/222 can circumvent apoptosis in human glioblastoma cells via downregulating the protein expression of PUMA gene, verifying that miR-R221/222 can be a possible target for glioblastoma management. On the other hand, low expression of miR-15a and miR-16-1 has been characterized in chronic lymphocytic leukemia; an event that increases the protein amount of Bcl-2, resulting in the resistance to apoptosis (Fig. 3) [107]. It is noteworthy that some of apoptosis regulatory miRNAs that are mentioned in this section have also been implicated in the modulation of immune targets as discussed above. Some examples include miR-17-92 cluster which targets MIC A/B in HCC [93,94] and miR-125b, which play a role in the activation of macrophages [49].

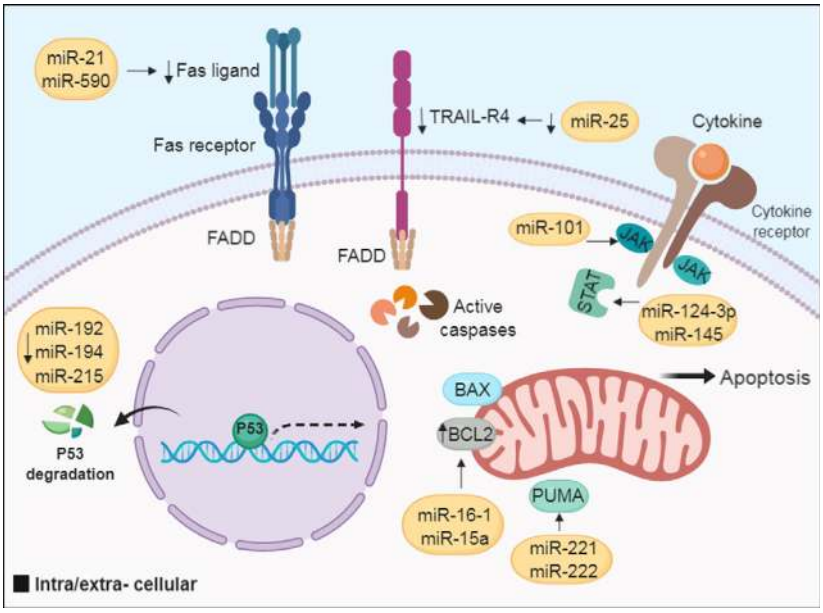

Fig. 3. The role of miRNAs in counteracting cancer cell apoptosis. The resistance against apoptosis in cancer cells is mediated through many miRNAs, which regulate the expression and function of several apoptosis/survival key-proteins such as p53, JAK/STAT, BCL-2 family, and death receptors.

Table 1. Immune-modulatory miRNAs that are downregulated in cancer. TAP-1, transporter associated with antigen processing 1.

	miRNAs	Action	Target	Reference
1	miR-9	Downregulated in colon, gastric, ovarian and nasopharyngeal carcinoma	NF-kB, β2-microglobulin, TAP-1, PSMB8	[105,106]
2	miR-17	Caused shift of G1-S phases of the cell cycle. and impairment of T-cell response in lung cancer	E2F family STAT3	[139,140]
3	miR-19a-3p	Caused macrophage polarization in BCC	Fos-related antigen 1	[48]
4	miR-23a/24-2/27a	Promoted M1 and M2 breast cancer macrophage polarization	A20, JAK1, STAT6	[48]
5	miR-29	Inhibited NK and T-cell function in various solid tumor	B7-H3	[81]
6	miR-29a	Inhibited T cell and NK cells in neuroblastoma	B7-H3	[82]
7	miR-29c	Regulates the immunomodulatory response by suppressing the expression of B7-H3 in BCC	B7-H3	[83]
8	miR-34a	Helped in the regulation of T-reg recruitment in hepatocellular tumor cells	CCL2	[55,56]
9	miR-34a/c	increased NK-mediated killing of melanoma cells	ULBP2	[86]
10	miR-34a/c	enhanced the cytotoxic effects of lymphocytes in melanoma and other tumor cells	ULBP2	[55]
11	miR-20a/miR-17-5p	alleviates the immunosuppressed effect of MDSCs in CRC	STAT3	[73]
12	miR-101	Stimulated the apoptosis and curbed the proliferation of BCC	JAK2	[115]
13	miR-124	Impaired the T-cell proliferative response in glioma cancer cells	STAT3	[53]
14	miR-124-3p	Inhibited the growth and boosted the apoptosis of nasopharyngeal carcinoma cells (NPC)	STAT3	[116]
15	miR-126/126a	Decreased CCL2 expression and suppressed the inflammatory monocyte recruitment in BCC	Stromal cell-derived factor-1 alpha	[74]
16	miR-133/miR-148a	Increased the NK and lymphokine-activated killer cell-mediated cytotoxicity in RCC	HLA-G	[80]
17	miR-135a	Inhibited gastric cancer proliferation	JAK2	[141]
18	miR-150/miR-223	Modulated IL-2 signaling in adult T-cell lymphoma/leukemia cells	STAT1	[142]
19	miR-155	Increased the recruitment of MDSC cells in melanoma and Lewis lung cancer	HIF-1α	[125]
20	miR-187	Inhibited cell survival and growth of RCC	B7-H3	[84]
21	miR-199a	Increased cytokine production in ovarian cancer	IκB kinase β	[143]
22	miR-214a	Modulated the expansion of T-reg cells in various solid tumors	PTEN	[44]
23	miR-520c, miR-302c	Enhanced the susceptibility of tumor cells to NK cell-mediated cytotoxicity	MIC A/B and ULBP2	[87]

miRNAs role in driving cancer cell invasion and metastasis

Kong *et al*. have reported that tissue specimens of invasive breast cancer overexpress miR-155. This miRNA has an essential function in TGF-β–triggered key events of metastasis, such as EMT, cell migration, and invasion. miRNA-155 mediates such effects through targeting RhoA GTPase, which is a key regulator of cellular polarity and tight junctions. Thus, miR-155 has been suggested as a therapeutic target for the management of BCC [124]. The same miRNA is also related to the recruitment of the immune suppressor MDSC cells in melanoma and Lewis lung cancer, through targeting HIF-1α [125]. In similar regards, patients with metastatic breast tumors have displayed increased expression of miR-9, signifying its crucial role in the process of metastasis. Via direct binding to 3'-UTR, miR-9 downregulates E-cadherin in BCC, which activates β-catenin signaling and enhances cellular motility and invasiveness [126]. miR-9 is also implicated in cancer immune evasion via modulating MHC-1 antigen presentation as discussed above [88]. Patel and Gooderham have revealed the involvement of IL-6, miR-21, and miR-29b to maintain inflammation and induce invasion in CRC [127]. Conversely, the expression of miR-200 is repressed in invasive breast cancer tissues with a higher chance for metastasis. This can be attributed to the intervention of miR-200 family with E-cadherin transcriptional repressors, which suppress the cellular migration [128]. Likewise, the downregulation of miR-29b has been linked to invasive CRC [129]. Moreover, new metastasis

Table 2. Immune-modulatory miRNAs that are upregulated in cancer. CYLD, cylindromatosis (turban tumor syndrome); IRF, interferon regulatory factors; SOCS, suppressor of cytokine signaling; TAP1, human antigen peptide transporter 1.

	miRNAs	Action	Target	Reference
1	miR-10b	Decreased the NK-mediated killing of breast tumor cells	MIC B	[91]
2	miR-20a	Decreased NK-mediated cytotoxicity of ovarian tumor cells	MIC A/B	[92]
3	miR-221/222	Increased breast cancer stem-like cells propagation	MIC A/MIC B	[92]
4	miR-21	Suppressed lymphocyte migration and chemokine production, thus increasing the resistance to breast cancer immunotherapy	PIAS3	[52]
5	miR-21/miR-29b	Enhanced the expression of proinflammatory immune cells in CRC	IL-6	[127]
6	miR-24	Caused the inhibition of B7-H2 in gastric cancer	B7-H2	[85]
7	miR-29b	Its upregulation enhanced the expression of IRF-1 and, its suppression caused a reduction of IFN-γ which enhance apoptosis in CRC	IRF-1	[129]
8	miR-34a	Inhibited the expression of PD-L1 and increased the resistance to chemotherapeutics agents in AML	PD-L1	[36]
9	miR-25-93-106b cluster	Suppressed the MHC class I polypeptide-related sequence A (MIC A) gene in HCC	MIC A	[93]
10	miR-20a/miR-96/miR-106b	Decreased NK-mediated killing of hepatocellular tumor cells	MIC A	[94]
11	miR-125b	Enhanced macrophages activation	IRF-4	[49]
12	miR-138-5p	Worked as tumor suppressor in CRC	PD-L1	[18]
13	miR-145	Inhibited colon cancer cells	STAT1	[117]
14	miR-146a	Decreased the inflammation in gastric cancer	IL 1 receptor associated kinase 1 TNF receptor-associated factor 6, IL-8	[144]
15	miR-152	Downregulated FGF2 and suppressed the proliferation of NSCLC	HLA-G	[34]
16	miR-155	Activated STAT3 signaling and curbing early steps of BCC progression	SOCS1, SH-2 containing inositol 5′ polyphosphatase 1	[40,41]
17	miR-181-1b	Inhibited PTEN and CYLD tumor suppressor through the STAT3 pathway, which is controlled by IL-6 in BCC	CYLD	[46]
18	miR-183	Suppressed MICA/B expression	MIC A/B	[90]
19	miR-200	Suppressed the metastasis and EMT by enhancing T-cell immunosuppression in NSCLC	PD-L1	[37]
20	miR-216a	Inhibited pancreatic cancer growth and boosted apoptosis	JAK2	[145]
21	miR-221	Overexpressed in Prostate cancer, therefore proposed as a prognostic factor	SOCS3, IRF2	[82]
22	miR-223	Promoted the invasion of BCC	Myocyte enhancer factor 2 C-β-catenin pathway	[132]
23	miR-346	Decreased TAP-1 function which is necessary for proper MHC class I-associated antigen presentation	TAP-1	[146]
24	miR-362-5p	Enhanced and regulated NK cells functions	CYLD	[147]
25	miR-375	Decreased gastric cancer proliferation	JAK2	[148]
26	miR-424	Enhanced T-cell activation in ovarian cancer	PD-L1, CD80	[70]
27	miR-451	Inhibited the proliferation, metastasis, invasion and inflammation related genes in lung cancer and glioma metastasis	PSMB8	[131]
28	miR-494	Increased the accumulation of MDSCs in BCC	PTEN	[130]

miRNA modulators were identified in breast, lung, prostate, and glioma cancers such as miR-494, miR-223, miR-221, and mi-451, respectively [82,130–132].

As highlighted above miRNAs are involved in tumor progression either via the modulation of tumor immune evasion or through orchestrating pathways that control cell cycle, angiogenesis, and cell invasion or both. Given that complex role, understanding the regulatory networks of miRNAs in cancer is anticipated to contribute positively to the development of better therapeutic approaches. In the next section, we are highlighting some examples for the use of miRNAs

profile as a potential prognostic tool in the setting of cancer immunotherapy.

miRNAs as diagnostic and prognostic tools

There is a growing interest in the use of the dysregulated miRNAs expression profile as a prognostic tool. Circulating miRNAs (C-miRNAs) have emerged as potential markers for cancer diagnosis and follow up [133]. The prominent stability, accessibility, and noninvasiveness of C-miRNA were the main advantages beyond acquiring a huge clinical interest [134].

There are several clinical attempts to investigate the potential link between miRNAs expression profile and patients' response to immune checkpoint inhibitors such as nivolumab and pembrolizumab to seek biomarkers for the response to therapy. Costantini *et al*. investigated potential biomarkers related to nivolumab therapy in NSCLC by assessing plasma levels at baseline and 2 months after therapy initiation. The elevated level of soluble PD-L1 and reduced level of soluble granzyme B were associated with poor prognosis and shorter overall survival [135]. miRNA profile analysis linked the downregulated expression of miRNA-320b and -375 to nivolumab clinical benefit in NSCLC patients [135]. In a separate study, next generation sequencing-based miRNA profiling in serum samples from nivolumab-treated NSCLC patients (n = 20) identified a signature of seven miRNAs (miR-215-5p, miR-411-3p, miR-493-5p, miR-494-3p, miR-495-3p, miR-548j-5p, and miR-93-3p). The identified signature was linked to better overall survival (> 6 months) [136]. These data need further verification by extending the biomarker studies to a larger cohort of nivolumab-treated patients and by investigating the possible relevance in patients with different types of solid tumors other than NSCLC.

The analysis of serous exosomal miRNAs from patients with melanoma showed significant upregulation of miRNA-532-5p and miRNA-106b expression levels in melanoma patients versus healthy volunteers and the advanced stage disease (III–IV) versus early stage (I–II) [137]. The expression of both miRNAs was also significantly different in patients who received pembrolizumab compared to control [137]. Based on these data, further studies are encouraged to correlate between the expression of these exosomal miRNAs (miR-532-5p and-106b) and the response of melanoma patients to pembrolizumab. The data generated from the studies discussed above highlight the significance of investigating plasma or exosomal miRNAs profile signatures as a tool for the diagnosis and prediction of therapeutic response of cancer immunotherapies.

Conclusions and future recommendations

Despite the impressive success that has been reached in the development of immune checkpoint inhibitors and the subsequent approvals in a broader range of cancers, about 40–60% of cancer patients do not benefit from such treatment [12,138]. For example, the overall response rate to treatment with anti-PD-1 immune checkpoint inhibitors pembrolizumab or avelumab monotherapy in patients with triple-negative breast cancer that is positive for PD-L1 is 18.5%

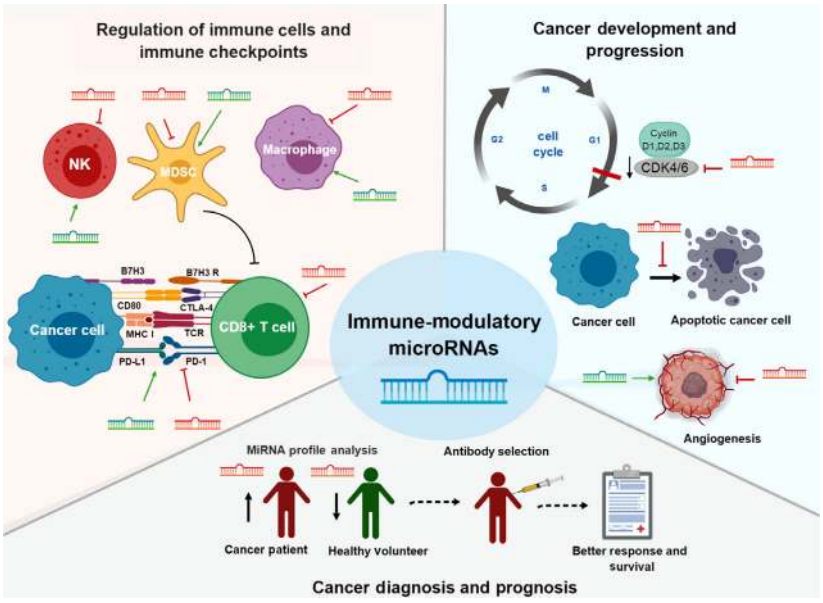

Fig. 4. Schematic diagram depicting the role of immune-modulatory miRNAs in the regulation of immune cells and immune checkpoints, cancer development, progression, and diagnosis.

($n = 27$) and 44.4% ($n = 9$) [12]. Also, the cost of immunotherapeutic agents is higher than the other conventional therapies, and their use is associated with the development of some immune-related adverse effects [15]. Therefore, finding efficient biomarkers that aid in optimal patient selection is still on the top-ranked research concerns that are extensively studied. As discussed in the current review, miRNAs modulate several aspects of the antitumor immune response including immune checkpoints (PD-1, PD-L1, and CTL-A4), immune cells (macrophages, MDSCs, and NKs) and tumor antigen-processing machinery (Tables 1 and 2, Fig. 4). Based on these data, miRNAs could be the missing link in the chain of potential biomarkers that predict the effective tumor response to immune checkpoint inhibitors (Fig. 4). Future studies comparing miRNAs' expression profiles in patients who respond to such therapies to nonresponders will be beneficial to disclose the potential benefit of miRNAs in this regard. Additional studies to compare the miRNAs' expression profiles in specimens from diagnostic biopsies versus tissue specimens obtained after receiving an immune checkpoint inhibitor will help to disclose the potential role of miRNAs in tumor resistance to immunotherapy. miRNAs can also be easily assessed in plasma samples pre- and post-treatment, which highlights their potential role as a noninvasive biomarker for monitoring the response to therapy with immune checkpoint inhibitors. Developing a better understanding of the complex interplay between miRNAs and the different players in the antitumor immune response will ultimately contribute to closing some gaps regarding this aspect and help in the development of more optimized cancer immunotherapy protocols.

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Conflict of interest

The authors declare no conflict of interest.

Authors contributions

All authors contributed toward literature review, manuscript generation, critical revision of the manuscript, and illustrations.

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