Chapter 3

The Role of Immune Modulatory MicroRNAs in Tumors

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Additional information is available at the end of the chapter

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Abstract

Tumors could evade the control of $CD8^+$ T and/or NK cell-mediated surveillance by distinct immune escape strategies. These include the aberrant expression of HLA class I antigens, coinhibitory or costimulatory molecules, and components of the interferon (IFN) signal transduction pathway. In addition, alterations of the tumor microenvironment could interfere with a proper antitumoral immune response by downregulating or inhibiting the frequency and/or activity of immune effector cells and professional antigen presenting cells. Based on the identification as major mediators of the posttranscriptional silencing of gene expression, microRNAs (miRNAs) have been suggested to play a key role in many biological processes known to be involved in neoplastic transformation. Indeed, miRNA expression is frequently deregulated in many cancer types and could have tumor-suppressive as well as oncogenic potential. This review focused on the characterization of miRNAs, which are involved in the control of the immune surveillance or immune escape of tumors and their use as potential diagnostic and prognostic biomarkers as well as therapeutic targets. Moreover, miRNAs can have dual activities by affecting the neoplastic and immunogenic phenotype of tumors.

Keywords: APM, IFN, immune escape, microRNA, tumor microenvironment

1. Introduction

Tumors have developed different strategies to evade immune recognition by cytotoxic T lymphocytes (CTLs) as well as natural killer (NK) cells. This is caused by alterations of the tumor itself, changes of the tumor microenvironment (TME), reduced frequency, and impaired function of diverse immune subpopulations. The processes leading to immune evasion of tumors are diverse and could be associated with structural alterations and/or deregulation of genes/proteins from tumor cells, but also from different immune cells important for recognition and killing of tumor cells or in the induction of immune suppression. The identification of microRNAs (miRNAs), involved in the RNA interference (RNAi)-based control of these

immune modulatory molecules, clarified the complexity of the mechanisms conditioning tumor immune escape. This review is focused on the identification and characterization of immune modulatory miRNAs (im-miRNAs) in tumors, thereby altering the antitumoral immune response by miRNAi-mediated RNAi.

2. The MHC class I antigen processing and presentation machinery (APM)

The major histocompatibility complex class I (MHC) molecules present an array of peptide epitopes for surveillance by $CD8^+$ T cells. These peptides are classically derived from proteins synthesized in the cytosol. Upon proteasomal degradation of ubiquitinated proteins, the yielded peptides are then transported into the endoplasmic reticulum (ER) via the heterodimeric peptide transporter associated with antigen processing (TAP). The peptide transport into the ER is ATP dependent and sequence specific. The TAP heterodimer associates in ER with a number of other proteins to form the peptide loading complex (PLC). These include the chaperone tapasin, which recruits MHC class I heavy chain (HC)/β_2-microglobulin (β_2-m) dimers and calreticulin. The peptides are either trimmed by ER-resident aminopeptidases or directly loaded onto MHC class I molecules [1]. Upon peptide loading, the PLC dissociates from the trimer consisting of the MHC class I HC, β_2-m, and peptide is then transported via the trans Golgi to the cell surface and exposed to $CD8^+$ CTLs [1].

3. Immune stimulatory and immune inhibitory molecules and immune response

An effective T-cell response requires two signals. The first is mediated by the interaction with MHC class I antigens on the antigen-presenting cells (APC), and the second is mediated by the interaction of B7 family members on APC with CD28 or CTLA4 on T cells. The prototypes of B7 family members are B7-1 (CD80) and B7-2 (CD86). During the last years, the B7 family was growing consisting of B7-H1 (PDL-1), B7-H2, B7-H3, B7-H4, and B7-H6 molecules [2, 3]. While B7-H1 and B7-H4 represent coinhibitory molecules, B7-H2 was identified as costimulatory molecule, which is mainly expressed on B cells, monocytes and dendritic cells (DC): B7-H2 binds to the receptor ICOS, which results in activation of T cells through phosphatidylinositol-3-kinase-dependent signal transduction pathways and in the induction of Th2 cell-mediated immune response, proliferation, and cytokine production [4]. The role of B7-H3 is currently controversially discussed and depends on the cell types analyzed, demonstrating either costimulatory or coinhibitory activity. Regarding B7-H4, its expression is primarily restricted to activated T cells, B cells, monocytes, and DCs [5, 6]. B7-H4 is not detected in the majority of normal tissues and cells but is overexpressed in a variety of tumor tissues. B7-H6 has been identified as ligand for the NK cell receptor NKp30 and is detectable on surface or in the cytosol of tumor cells and as soluble factor in the peritoneal fluid [7], while it is not expressed on healthy cells. The interaction of B7-H6 with NKp30 is involved in NK cell

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responses [8]. It is noteworthy that many other coinhibitory molecules have also been identified and their role on immune responses is currently under investigation [2, 3].

4. Features of the interferon-γ-mediated signal transduction

Interferons (IFN) are a group of pleiotropic cytokines that play a key role in the intercellular communication during innate and adaptive immune responses, in particular in the host defense against viral and bacterial infections and neoplastic transformation [9]. The IFN family could be classified into type I and type II IFNs, which differ in their activity regarding immune modulation [10].

IFN-γ belongs to the type II IFN and is a central regulator of immune responses by controlling and modulating the expression of targets essential for cell-cell communication and cellular interactions. It is secreted by activated T cells, NK cells, and macrophages and induced by DC and monocytes stimulated with bacterial cell wall components [11]. IFN-γ exerts its activity by binding to its heterodimeric receptor consisting of IFN-γ-R1 and IFN-γ-R2 subunits [12, 13]. This results in the dimerization of the receptor subunits followed by activation (transphosphorylation) of the receptor-associated tyrosine kinases JAK1 and JAK2 belonging to the Janus kinase (JAK) family and phosphorylation and dimerization of the JAK-associated STAT1 transcription factor. The activated STAT1 is translocated into the nucleus and recruited to the IFN-γ-activated sequence (GAS) element of the promoters of the STAT1 target genes leading to their transcriptional activation.

IFN-γ-regulated genes can be classified into primary and secondary responsive genes. Primary responsive genes are induced early due to the binding of STAT dimers to the GAS element in the promoter region of target genes, like IRF1, CXCL9, and CXCL10 [14]. IRF1 binds to IFN-stimulated response elements (ISRE) and modulates gene induction of the secondary responsive genes. IFN-γ induced the transcription of MHC class I and class II antigens and of many APM components and at high concentrations could lead to a caspase-dependent apoptosis. In addition, IFN-γ is involved in amplifying toll-like receptor (TLR) signaling by increasing or inhibiting the transcription of TLRs, chemokines, and cytokines [15, 16]. Furthermore, IFN-γ promotes the induction of SOCs proteins (suppressor of cytokine signaling), which inhibit IFN-γ signaling by a negative feedback loop, resulting in the inactivation of JAK1 and JAK2 [17]. Moreover, IFN-γ signaling is controlled by inhibiting JAK1, JAK2, and IFN-γ-R1 via dephosphorylation mediated by SH2-domain-containing protein tyrosine phosphatase 2 [18], by proteasomal degradation of JAK1 and JAK2 [18] and by inhibition of STAT1, which is mediated by the protein inhibitor of activated STAT1 [19].

5. Distinct levels of tumor immune escape

Tumors have developed different strategies to escape immune surveillance, which could occur at the level of immune cells, tumor micromilieu, and the tumor itself (Figure 1). The frequency,

activity, and function of $CD8^+$ and $CD4^+$ T lymphocytes, DC, NK cells, and B cells are often downregulated in peripheral blood of tumor patients, while the number of immune-suppressive myeloid-derived suppressor cells (MDSC), NKT cells, and regulatory T cells (Treg) is upregulated [20-23].

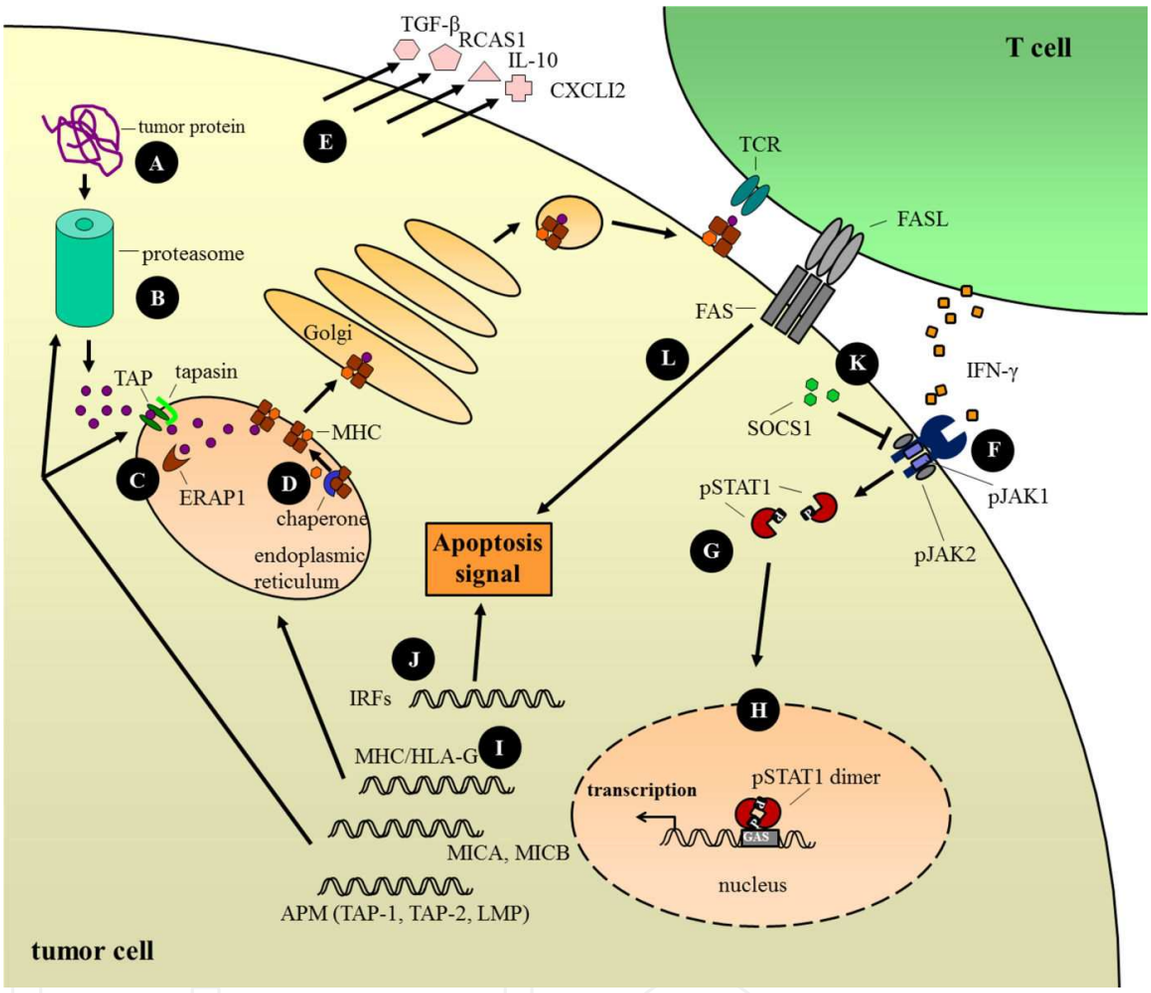

Figure 1. Tumor immune escape mechanisms containing (A) loss of tumor antigen expression; (B) variations in tumor antigen processing; (C) defects in the peptide transporter TAP, chaperone tapasin, and protease ERAP1; (D) defects in expression of MHC class I heavy chain and β_2-microglobulin; (E) release of anti-inflammatory cytokines; (F) downregulation of IFN-γ-R1, JAK1, JAK2, STAT1, and STAT2; (G) altered phosphorylation states of STAT1; (H) impaired upregulation of IFN-γ regulated genes (MHC class I, APM); (I) upregulated expression of HLA-G; (J) altered methylation pattern of IRF; (K) overexpression of SOCS1; and (L) protection from T-cell-mediated apoptosis.

The tumor microenvironment (TME) consists of various cellular and soluble factors and is of clinical relevance since its composition significantly correlates with the tumor patients' outcome. These include different cellular components, such as fibroblasts, blood vessels, immune cells, stroma cells, extracellular matrix, and soluble factors such as immune-suppressive cytokines, like interleukin (IL)-10, transforming growth factor (TGF)-β, metabolites, arginase and prostaglandin, hypoxia, and pH, which negatively interfere with the antitumoral immune responses.

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In tumors, an aggressive and deregulated growth of neoplastic transformed cells, which overexpress proangiogenic factors, such as the vascular endothelial growth factor (VEGF), leads to the development of organized blood vessels. These blood vessels are fundamentally different from the normal vasculature. Tumor-associated fibroblasts (TAF) represent the major constituents of the tumor stroma and produce growth factors, including the VEGF and inhibitory cytokines that activate extracellular matrix thereby contributing to the tumor growth.

Furthermore, cancer is often driven by inflammation mediated by monocytes and tumor-associated macrophages (TAM), which belong to the innate immune cells. Macrophages could be classified in type 1 and 2 macrophages. While M1 macrophages express a series of proinflammatory cytokines, chemokines and effector molecules, the M2 macrophages express a wide array of anti-inflammatory molecules, including IL-10, IL-35, TGF-β, and adenosine. TAMs are mainly of the M2 phenotype and secrete different cytokines, chemokines and proteases, which promote tumor angiogenesis, growth, metastasis as well as immune suppression.

In addition to TAM and TAF, MDSC represent a heterogeneous population derived from myeloid progenitors [20]. They can promote tumor growth by enhancing angiogenesis or suppression of innate and adaptive immune responses. Regarding the innate immune cells, MDSCs suppress NK cell cytotoxicity, promote M2 macrophage differentiation, and modulate the priming activity of mature DC [24]. Moreover, MDSCs suppress T-cell responses by induction of apoptosis, secretion of immune modulatory factors, modulation of amino acid metabolism, restriction of T-cell homing, and induction of Treg [25-28]. Tregs suppress the activity of immune cells and maintain immune tolerance to self-antigens. They express CD4, CD25 and FoxP3 [22]. The elevated numbers of Tregs in cancer is due to their efficient migration into the tumor sites [29], local expansion in the tumor environment[29], and *de novo* generation within the tumor [30].

5.1. Alterations of the tumors

Immune escape mechanisms include loss or downregulation of HLA class I antigens and/or components of the antigen processing machinery (APM), upregulation of nonclassical HLA-G and HLA-E antigens, and coinhibitory molecules, including PDL-1, as well as alterations of signaling transduction cascades, including in particular the IFN signaling pathway [31]. The frequency of these different mechanisms highly varied between tumor (sub)types and is often correlated with a worse prognosis and reduced survival of tumor patients.

5.1.1. MHC class I abnormalities

The classical MHC class I pathway and the APM components are involved in eradication of developing tumors [32]. Since $CD8^+$ CTLs recognize and eliminate cells presenting tumor antigens via HLA class I molecules, loss of HLA class I expression results in evasion of CTL-mediated cell death [33]. Abnormalities of HLA class I antigens are often due to downregulation of various components of the MHC class I APM, in particular of TAP, tapasin, β_2-m, and MHC class I HC. Structural alterations of these components are rare, while MHC class I defects

are mainly due to deregulation of the different components, which could be controlled at the transcriptional, epigenetic (methylation, acetylation), posttranscriptional (e.g., microRNAs, protein degradation), or posttranslational (phosphorylation) level.

HLA-G has been demonstrated as a nonclassical HLA class I antigen, which is in general only expressed on immune privileged organs, but also on many tumors of distinct origin [34]. The overexpression of HLA-G or secretion of soluble HLA-G are directly associated with tumor progression and reduced patients' survival. It suppresses antitumoral immune responses by binding to receptors of various immune populations, thereby inhibiting the sensitivity to CTL- and NK cell-mediated lysis in particular [34]. In contrast, tumor cells with deficient expression of classical HLA class I molecules are eradicated by NK cells.

5.1.2. Check points as important regulators of immune response

During carcinogenesis, members of the B7-family play a key regulatory role of both stimulatory and inhibitory T-cell responses, which depends on the available B7 ligand and receptor on the respective target and immune cells [35, 36]. Interestingly, B7-H1 and B7-H4 were often overexpressed on tumors leading to impaired immune recognition. By interaction with these coinhibitory molecules, the intensity of the T-cell responses is reduced by raising the threshold of activation, halting proliferation, enhancing apoptosis, and inhibiting the differentiation of effector cells [37].

5.1.3. Role of IFN-γ in cancer immunogenicity

Abnormalities of MHC class I expression on tumor cells due to the downregulation or loss of APM component expression are common mechanisms, by which tumor cells can escape from anti-tumor-specific immunity [38, 39]. In addition, tumor cells are often not susceptible to treatment with IFN-γ, which could be due to structural alterations or deregulation of constituents of the IFN signal pathway. Several studies confirmed that defects in the IFN-γ receptor signaling cascade could be occur at multiple steps of this pathway, including lack of the expression of the IFN-γ-R1, abnormal forms of JAK2, lack of expression of JAK1 [40], altered phosphorylation, repressed STAT1 expression, and overexpression of SOCS1. The latter results in an increased negative feedback regulation of the IFN-γ signal cascade. The defects in the IFN-γ receptor signaling cascade caused impaired expression of IFN-γ regulated genes.

Previous studies demonstrated that IFN-γ responsive genes are frequently downregulated in tumor cells due to impaired IRF1 expression as well as defective transcriptional and posttranscriptional regulation of components involved in the IFN-γ signal transduction pathway. The loss of the IFN-γ-mediated upregulation of TAP in a renal cell carcinoma is associated with the lack of IRF1 and STAT1 binding activities as well as JAK1, JAK2, and STAT1 phosphorylation [41]. This impaired IFN-γ-mediated phosphorylation could not be restored by JAK1 and/or JAK2 gene transfer. Furthermore, an impaired STAT1-phosphorylation associated with the loss of IFN-γ-mediated MHC class I upregulation was also reported in melanoma and colorectal carcinoma cells [42].

IFN-γ treatment is able to restore the expression of many genes belonging to the MHC class I APM [43, 44]. As a consequence, anti-tumor-specific immune responses can be induced, suggesting that IFN-γ acts as key regulator of immunogenicity [45]. Its antitumoral activity includes also the induction of apoptosis and inhibition of cell proliferation by STAT1 activation, which induces expression of cell cycle inhibitor, CDKN1A [46]. In addition, the IFN-γ-mediated upregulation of MHC class I antigens could be due to DNA demethylation of MHC class I APM genes, suggesting that IFN-γ acts as an epigenetic modifier of APM components [47]. Therefore, IFN-γ is a major player in the regulatory network combating tumor cell proliferation and tumor survival.

6. Features of miRNAs

miRNAs are small noncoding ~22 nucleotide long regulatory RNAs encoded in the human genome, which control the posttranscriptional gene expression by binding to the 3′-untranslated region (UTR) of mRNA of target genes, thereby affecting their stability and/or their translation [48]. An individual miRNA could target numerous cellular mRNAs, while single miRNA can be regulated by several proteins [49, 50]. miRNAs have emerged as key players in the posttranscriptional control of gene expression and based on their prediction appear to be directly involved in the expression of at least 50% of all protein-coding genes in mammals [51].

A strong relationship between miRNAs and human cancer has been developed during the past years. High throughput analysis allows the comparison of miRNA expression pattern in normal and tumor tissues demonstrating global changes within the miRNA expression in different malignancies. Interestingly, the miRNA genes were frequently located at fragile sites and cancer-associated chromosomal regions. The deregulation of the biogenesis and expression of miRNAs is involved in the initiation as well as progression of tumors, metastasis formation, and therapy resistance [52]. Furthermore, miRNAs can participate in reprogramming components of the tissue tumor microenvironment (TME) in order to promote tumorgenicity [53]. In the following sections, miRNAs are described as powerful RNAi inducing regulators of immune modulatory genes involved in escape from immune surveillance. Moreover, this review highlights some miRNAs and their roles in immune escape and discusses these miRNAs as putative targets for (immune) therapy (Figure 2).

6.1. Antigen processing and presentation machinery and miRNAs

Recent studies showed identified miRNAs able to affect the expression of APM components. Microarray analysis of miRNA-9 overexpressing nasopharyngeal carcinoma cells demonstrated that miRNA-9 controls the expression of components of the classical MHC class I pathway. miRNA-9 targets many IFN-induced genes and MHC class I APM molecules, such as the proteasome subunits PSMB8 and PSMB10, TAP1, β_2-m, HLA-B, HLA-C, and the nonclassical HLA-F and HLA-H antigens [54]. However, the binding of miRNA-9 to the 3′-UTR of these molecules has not yet been shown. miRNA-9 is involved in the cellular differentiation [55] and

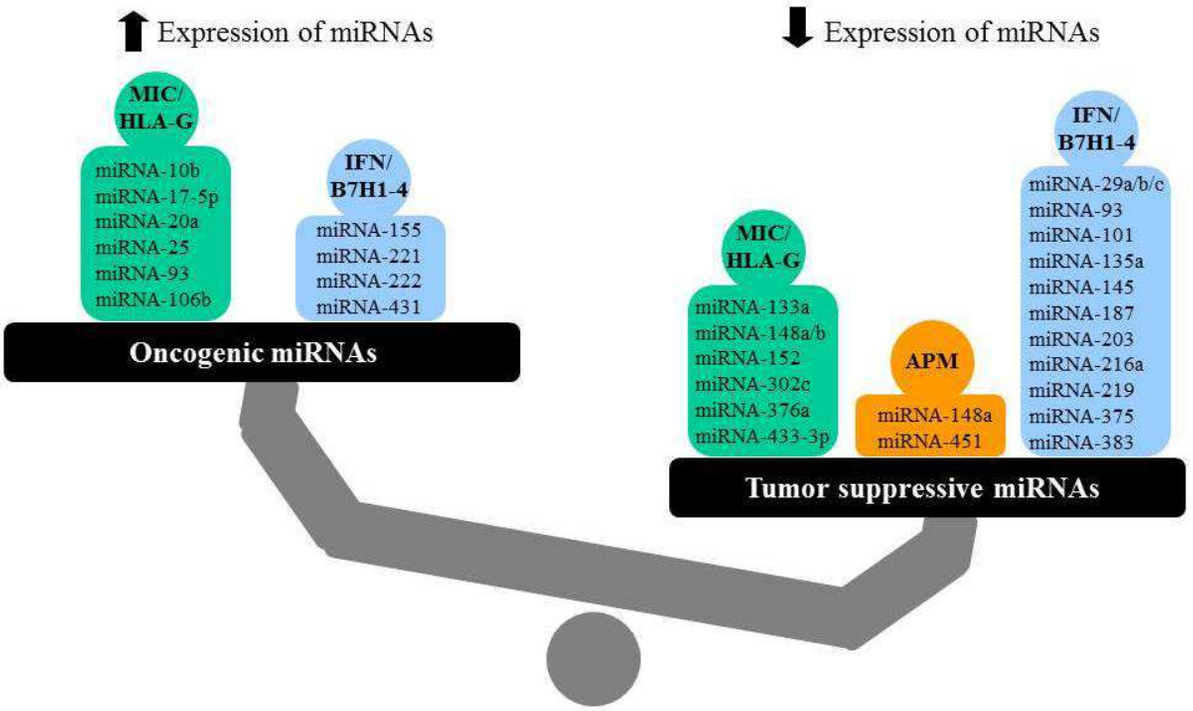

Figure 2. Scale of miRNAs targeting immune pathways in cancer exhibit an imbalance of tumor-suppressive miRNAs, which occur more frequent than oncogenic miRNAs as per knowledge from today. Oncogenic miRNA are highly expressed in cancer, while tumor-suppressive miRNAs possess a reduced expression.

aberrantly expressed in many cancer types breast cancer[56], colon cancer [57], nasopharyngeal carcinoma [58], and melanoma [59], suggesting that the decreased miRNA-9 expression is associated with tumor suppressor activity. In contrast, miRNA-9 expression is increased in brain cancer [60] and in Hodgkin's lymphoma [61], implying an oncomir potential. Furthermore, miRNA-9 has been shown to regulate the proliferation [56, 60-62] epithelial-mesenchymal transition (EMT), invasion and metastasis [62-64], apoptosis [56], tumor angiogenesis [63-64], and evasion of immune surveillance in many cancer types [54]. Although the function of miRNA-9 in the classical MHC class I pathway has still to be characterized in extent, miRNA-9-mediated regulation of APM deficiencies might be at least partially responsible for the T cell-mediated immune escape.

Besides miRNA-9, the ER stress-induced miRNA-346 modulates the expression of APM components and IFN-induced genes as shown by miRNA arrays. Functional studies revealed that TAP1 is a direct target of miRNA-346 using overexpression and RNAi knockdown experiments with miRNA mimic and miRNA inhibitors. The ER stress-mediated MHC class I-associated antigen presentation decrease might be explained by increased miRNA-346 expression [65], although the function of miRNA-346 in cancer has not yet been fully analyzed.

The inflammation and overexpression of miRNA-451 are associated with the carcinogenesis of lung cancer. A decrease in the proliferation, invasion, and metastatic potential of lung cancer cells was detected after the overexpression of miRNA-451. In addition, the proteasome subunit

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PSMB8 has been identified as a direct target of miRNA-451 using both bioinformatics and dual luciferase reporter assays. This was confirmed by miRNA-451-overexpressing lung cancer cells, demonstrating a reduced PSMB8 protein expression. These data suggest that miRNA-451 inhibits the development and metastasis of lung cancer [66].

There are variations that exist in the 3′-UTR of HLA-C, which modulate the miRNA-binding capacity and consequently the HLA-C surface expression. miR-148a has been shown to bind to the HLA-C 3′-UTR. Next to cancer, the miRNA-148a expression is associated with the control of HIV [67-70]. Furthermore, miRNA-181a is upregulated in Hepatitis B virus infected cells and has a binding site in the 3′-UTR of the HLA-A gene, which might be a target of miRNA-181a [71]. Moreover, viral DNA or RNA can encode miRNAs, e.g., miRNA-US4-1 from the human cytomegalovirus, which targets the amino-peptidase ERAP1, thereby blocking CTL response [72].

6.2. Control of HLA-G and MHC-related proteins by miRNAs

Recently, a number of HLA-G-specific miRNAs have been identified, which belong to the miRNA-148 family consisting of three members, miRNA-148a, miRNA-148b, and miRNA-152. These miRNAs have been shown to act as tumor suppressors in many tumors, including prostate, ovarian, endometrial, and colorectal cancer [69, 73, 74]. In addition, other miRNAs such as miRNA-133, miRNA-548, and miRNA-628 have been identified to inhibit HLA-G expression. The HLA-C-regulating miRNAs are involved in inducing T and/or NK cell responses and have a tumor-suppressive capacity. Moreover, some of the HLA-G-regulated miRNAs are inversely expressed when compared to HLA-G in tumor lesions and are associated with disease progression [74].

The cytotoxicity of NK cells is determined by activating and inactivating signals. The ligands of the activating NK cell receptor NKG2D are the major histocompatibility complex class I-related molecules (MIC) A and B and the human cytomegalovirus UL16-binding proteins (ULBP) [73]. The expression of MICA and MICB is controlled by several oncogenic miRNAs, like miRNA-10b, miRNA-17-5p, miRNA-20a, miRNA-25, miRNA-93, and miRNA-106b, which increase the proliferative, invasive, and angiogenic potential of tumors [73, 75-83] and affect the NK cell cytotoxicity. The tumor-suppressive miRNA-302c, miRNA-376a, and miRNA-433-3p showed a reduced expression in cancer and target the 3′-UTR of MIC [73, 84-87]. Furthermore, the expression of ULBP is regulated by many tumor-suppressive miRNAs, e.g., miRNA-34a/c, miRNA-140-5p, miRNA-302c, miRNA-409-3p, and miRNA-433-p, and by the oncogenic miRNA-650 [73, 83, 85, 87].

6.3. Control of B7 family members by miRNA

The expression of B7 family members is subject to the regulatory control of miRNAs: B7-H1 could act as a costimulatory molecule, which is expressed on B cells, T cells, macrophages, and DCs [88], and acts as a ligand for PDL-1. miRNA-513 targets B7-H1 and inhibits its expression by translational repression [89]. In this context, Tamura and coworkers identified an association between low expression of B7-H2 and the escape from immune surveillance indicating

that B7-H2 has a potential role in tumorigenesis. B7-H2 [90] is a direct target of miRNA-24, which inhibits B7-H3 expression and therefore is involved in cancer immune evasion. B7-H3 is an immune regulatory molecule, which is often overexpressed in different cancers and associated with metastasis and poor prognosis [91, 92]. Its expression could be posttranscriptionally regulated by miRNA-29c. The miRNA-29c-mediated downregulation of B7-H3 expression was found in breast cancer and acts therefore as tumor-suppressive miRNA [93]. Furthermore, another B7-H3-regulating miRNA, miRNA-187, has been identified in clear renal cell carcinoma, and its expression is downregulated in this disease [94]. The coinhibitor B7-H4 functions as a negative mediator of immune responses. So far, no information exists about the role of miRNAs in the regulation of B7-H4 expression. In addition, miRNAs binding to the 3′-UTR of B7-H6 have not yet been identified.

6.4. Control of the IFN-γ pathway by miRNAs

The regulation of IFN-γ signaling includes negative as well as positive regulators, such as kinases and phosphatases as well as transcription factors. A main regulatory role of IFN-γ signaling is attributed to miRNAs, affecting genes involved in proliferation, differentiation, signal transduction, immune response, and carcinogenesis [50, 95].

IFN-γ can modulate the expression levels of miRNAs and to regulate miRNAs at the level of miRNA biogenesis [96], whereas miRNAs can inhibit IFN expression directly or indirectly. In addition, studies have confirmed that miRNAs are able to target components of the IFN-γ signaling pathway and components of the JAK/STAT-pathway can regulate miRNAs simultaneously. The latter has been described by controlling miRNA expression via transcription factors, such as c-myc, the hypoxia-induced factor (HIF), and STATs [97]. The contribution and regulatory role of miRNAs in IFN-γ signaling is still under investigation and an emerging research area. Here, to highlight the regulatory function of miRNAs in the IFN-γ signaling pathway, the functional role of miRNA-155 has been described in more detail.

miRNA-155 proceeding from the non-protein-coding transcript of the *BIC* gene RNA is required for the normal function of B, T, and DC [98. 99], and its expression is increased during B cell, T cell, macrophage, and DC activation [100]. miRNA-155 has been shown to regulate IFN-γ production in NK cells, while its disruption or knockdown suppressed IFN-γ induction of NK cells [101]. Additional studies reported that miRNA-155 also downregulates IFN-γ-R expression [102]. Furthermore, STAT1 upregulates miRNA-155, which in turn downregulates SOCS1, a negative inhibitor of JAK1 [103]. These findings illustrate that a single miRNA can regulate several target mRNAs of the IFN cascade and miRNAs can be regulated by a number of targets.

miRNA regulating components of IFN-γ signaling pathway mainly act as tumor-suppressive miRNAs. An antiproliferative effect of miRNA-375, which affects JAK2 protein expression, has been recently described [104, 105]. Furthermore, miRNA-135a expression was downregulated in gastric cancer cell lines, while its overexpression results in inhibition of gastric cancer cell proliferation by targeting JAK2 [106]. Thus, miRNA-135a may function as tumor suppressor by regulating JAK2 expression in gastric cancer cells [107]. Several studies confirmed other miRNAs targeting JAK2, including miRNA-216a, which is known to inhibit cell growth and

promote apoptosis of pancreatic cancer cells by regulating JAK2/STAT3 signaling pathway [108, 109], as well as miRNA-101, which promotes apoptosis of breast cancer cells by targeting JAK2 [110]. Similar results were found for STAT1 and miRNA-145 [111]. miRNA-145 is reported to be downregulated in several cancers [112, 113] and has STAT1 as direct target [111]. Moreover, STAT1 is able to upregulate miRNA-29 family members in melanoma cells, which inhibit melanoma cell proliferation by downregulating CDK6 [114].

Further studies confirmed that miRNA-223 and miRNA-150 are equally involved in IFN-γ signaling, but their role in cancer cells is still controversially discussed. Both miRNA-150 and miRNA-223 could exert oncogenic or tumor-suppressive activity. In hepatocellular carcinoma, acute myeloid leukemia (AML) [115] and gastric mucosa-associated lymphoid tissue lymphoma miRNA-223 expression is repressed [116], while an upregulation of miRNA-223 has been recently described in T-cell acute lymphocytic leukemia (T-ALL) [117]. In this context, Moles and coworkers [118] demonstrated that both miRNA-223 and miRNA-150 target STAT1 3'-UTR and reduce STAT1 expression, which in turn results in reduced expression of IFN-γ-regulated genes. The expression of miRNA-150 is upregulated in $CD19^+$ B cells from chronic lymphocytic leukemia [119, 120], while in chronic myeloid leukemia [121, 122], ALL [123] and mantel cell carcinoma miRNA-150 is downregulated. Moreover, miRNA-150 is upregulated in adult T-cell leukemia/lymphoma cells. This discrepant expression pattern of miRNA-223 and miRNA-150 suggests that both miRNAs could act as oncogenic as well as tumor suppressor miRNAs, which are dependent on the cellular context.

6.5. Role of miRNAs in immune cell function

Cancer cells upregulate and downregulate different miRNAs in immune cells to limit the antitumor response. It is well known that tumor cells reprogram the myeloid compartment to evade the immune system and promote tumorigenesis. This might be partially mediated by alterations in the miRNA expression pattern. The miRNA-155 modulates the immune response mediated by T cells, NK cells, B cells, and antigen presenting cells, such as macrophages and DC [124]. Furthermore, miRNA-155 expression has been found to be downregulated in TAMs [125], but also in hepatocellular carcinoma. The restoration of miRNA-155 in macrophages leads to enhanced T-cell function by targeting the suppressor of cytokine signaling. Other miRNAs, like miRNA-142-3p, miRNA-125b, and miRNA-19a-3p, are often downregulated in TAMs, thereby limiting the tumor infiltration of macrophages and reducing the therapeutic effect of adoptive transfer. The restoration of miRNA-125b in macrophages enhances antitumor response by targeting the IFN-regulatory factor 4, which promotes the M2 macrophage phenotype [126].

Recently, miRNAs have been identified to play a role in MDSC that regulate immune suppression within the tumor microenvironment. miRNA array analysis identified a number of deregulated miRNAs, e.g., miRNA-494, which suppresses the antitumor $CD8^+$ T-cell responses due to response to TGF-β. miRNA-494 targets PTEN in MDSC, which is responsible for the enhanced immune suppression of $CD8^+$ T cells [127]. Furthermore, a number of other miRNAs are downregulated in MDSC [128], which promote the differentiation of myeloid cells and regulate immune-suppressive signaling pathways.

In addition, miRNAs have been demonstrated in tumor-infiltrating lymphocytes. The suppression of T-cell activity is due to different mechanisms, including the dysregulation of miRNA expression. In $CD4^+$ T cells from tumor bearing mice and tumor patients, the expression of miRNA-17-92 family members was reduced, while T cells derived from miRNA-17-9 transgenic mice demonstrated a superior type 1 phenotype [129]. Furthermore, the expression of miRNA-155 was shown to promote antitumor responses. miRNA-155 in combination with miRNA-146a could upregulate the IFN-γ production of T cells. Furthermore, cancer cells could regulate miRNAs in T cells in order to modulate antitumor T-cell responses. In order to escape immune surveillance, cancer cells alter the expression of transcription factors, surface receptors, soluble chemokines/cytokines, and miRNAs to support the immune system. The downregulation of miRNA-124 increases Treg infiltration and reduces cytokines production through an altered expression of STAT3, which represents a target of miRNA-124. In contrast, tumor-secreted miRNA-214 induces Treg. Regarding NK cells, the TGF-β-inducible miRNA-183 affects NK cell activity [130]. Thus, the regulation of miRNAs within the cancer cell alters the TME through manipulation.

7. Conclusion and future perspectives

Taken together, during the past years, the posttranscriptional control of gene expression by miRNAs has gained relevance as key regulator in a wide variety of physiological and pathophysiological processes due to the role of miRNA-mediated RNAi not only in differentiation, proliferation, apoptosis, immune responses but also in viral and bacterial infections as well as neoplastic transformation (Table 1). A deregulated expression of miRNAs has been often found in tumors of distinct origin, which have been classified into oncogenic or tumor-suppressive miRNAs known to play an essential role in cancer initiation and progression. Therefore, these miRNAs could act as potential biomarkers and therapeutic targets in cancer. *In silico* prediction analysis further proposed that many miRNAs could target different immune modulatory molecules expressed either on tumor cells or on different immune cell subpopulations.

As summarized, an emerging relevance of miRNAs in mounting the tumor immune escape by altering the communication between cancer cells, immune cells, and other components of the TME has been demonstrated. This leads to another level of complexity due to the involvement of miRNAs in the interaction between cancer cells and immune cells. These miRNAs might not only provide new insights into tumor growth and progression as well as antitumoral immune responses but also represent promising therapeutic targets for (immune) therapy. To date, many cancer-deregulated miRNAs have been identified in particular in cancer cells and also in components of the TMA. However, their role in modulating the antitumor immune responses has not yet been characterized in detail. Although the majority of the miRNA alterations detected are dedicated to cancer cells, there is already evidence that miRNAs of infiltrating immune cells also particularly influence tumorgenicity. The identification of further im-miRNAs as well as their functional characterization might lead to a plethora of novel candidate biomarkers for monitoring of immune responses, which might be also potentially used for targeted RNAi therapy.

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miRNAs	target	biological impact of the miRNA					literature
		proliferation	invasion	apoptosis	angiogenesis	tumor suppressor/ oncogenic	
let-7c	JAK2	n.d.	n.d.	n.d.	n.d.	n.d.	[131]
miRNA-9	HLA-B, HLA-C, HLA-F, HLA-H, PSMB8, PSMB10, B2M, JAK1, IRF-1			controversially discussed			[54, 132]
miRNA-10b	MICB	up	up	down	up	oncogenic	[73, 76, 77]
miRNA-15a	FOXP3	down	down	up	down	tumor suppressor	[133-137]
miRNA-16	FOXP3	down	down	up	down	tumor suppressor	[133-135, 138, 139]
miRNA-17-5p	MICA	up	up	down	up	oncogenic	[73, 80, 83]
miRNA-20a	MICA, MICB	up	up	down	up	oncogenic	[73]
miRNA-24	B7-H2	n.d.	n.d.	n.d.	n.d.	n.d.	[140]
miRNA-25	MICA	up	up	down	up	oncogenic	[78, 81, 141, 142]
miRNA-29	STAT1, B7-H3	down	down	up	down	tumor suppressor	[114, 143]
miRNA-29b	IRF-1	down	down	up	n.d.	tumor suppressor	[144]
miRNA-29c	B7-H3	n.d.	n.d.	n.d.	n.d.	tumor suppressor	[93]
miRNA-34a	CD44, ULBP2	down	down	up	down	tumor suppressor	[73]
miRNA-34c	ULBP2	down	down	up	n.d.	tumor suppressor	[73]
miRNA-93	MICA	up	up	down	up	oncogenic	[73, 75]
miRNA-93	JAK1	down	down	n.d.	n.d.	tumor suppressor	[145]
miRNA-101	JAK2	down	down	up	n.d.	tumor suppressor	[110]
miRNA-106b	MICA	up	up	down	n.d.	oncogenic	[75, 79, 82, 146, 147]
miRNA-133a	HLA-G	down	down	up	n.d.	tumor suppressor	[73, 148, 149]
miRNA-135a	JAK2	down	n.d.	up	n.d.	tumor suppressor	[76, 106]
miRNA-140-5p	ULBP1	down	down	n.d.	n.d.	tumor suppressor	[73, 150]
miRNA-143	CD44	down	down	up	down	tumor suppressor	[151-155]
miRNA-145	CD44, JAK1, STAT1	down	down	up	down	tumor suppressor	[111, 156-160]
miRNA-146a	CD40-L	down	down	up	up	tumor suppressor	[161-165]
miRNA-148a	HLA-C, HLA-G	down	down	up	down	tumor suppressor	[68, 73, 166]
miRNA-148b	HLA-G	down	down	up	down	tumor suppressor	[73]
miRNA-150	STAT1			controversially discussed			[118, 121]
miRNA-152	HLA-G	down	down	up	down	tumor suppressor	[73]
miRNA155	CTLA4, STAT1	up	up	down	up	oncogenic	[167-172]
miRNA-187	B7-H3, ALDH1A3	down	down	up	n.d.	tumor suppressor	[94, 173]
miRNA-199a	CD44	down	down	up	down	tumor suppressor	[174-178]
miRNA-203	CD44, IRF-1	down	down	up	down	tumor suppressor	[179-184]
miRNA-216a	CD44, JAK2	down	down	up	down	tumor suppressor	[109, 128, 185, 186]
miRNA-219	JAK2	n.d.	n.d.	n.d.	n.d.	tumor suppressor	[187]
miRNA-221/222	STAT2, IRF-2, TIMP2	up	up	down	up	n.d. (oncogenic)	[188-191]
miRNA-223	STAT1			controversially discussed			[115, 117, 118]
miRNA-302c	MICA, MICB, ULBP2	down	n.d.	up	down	tumor suppressor	[85, 87]
miRNA-328	CD44	down	down	up	down	tumor suppressor	[192-195]
miRNA-330	CD44	down	down	up	n.d.	tumor suppressor	[196, 197]
miRNA-346	TAP1	n.d.	n.d.	n.d.	n.d.	n.d.	[65]
miRNA-373	CD44			controversially discussed			[198-200]
miRNA-376a	MICB, HLA-E	down	down	up	n.d.	tumor suppressor	[84, 86, 201]
miRNA-375	JAK2	down	down	n.d.	n.d.	tumor suppressor	[168, 202-204]
miRNA-383	IRF-1	down	n.d.	up	n.d.	tumor suppressor	[205]
miRNA-409-3p	ULBP1	down	down	n.d.	n.d.	tumor suppressor	[73]
miRNA-431	JAK1, STAT2	up	n.d.	n.d.	n.d.	oncogenic	[206]
miRNA-433-3p	MICB, ULBP1	down	down	n.d.	n.d.	tumor suppressor	[73]
miRNA-451	PSMB8	down	down	up	n.d.	tumor suppressor	[128]
miRNA-491	CD44	down	down	up	up	tumor suppressor	[207-209]
miRNA-512-3p	CD44	down	down	up	n.d.	tumor suppressor	[202, 210]
miRNA-513	PD-L1, B7-H1	n.d.	n.d.	n.d.	n.d.	n.d.	[89]
miRNA-520b	MICA	down	n.d.	n.d.	n.d.	n.d.	[73]
miRNA-520c	MICA, MICB, ULBP2, CD44			controversially discussed			[62, 211]
miRNA-570	PD-L1			controversially discussed			[212, 213]
miRNA-608	CD44	down	down	up	n.d.	tumor suppressor	[214, 215]
miRNA-650	ULBP1	up	up	n.d.	n.d.	oncogenic	[73]
miRNA-708	CD44			controversially discussed			[216, 217]

Table 1. Identified miRNAs involved in the tumor immune escape and their tumor–associated function. Controversially discussed miRNAs are found as tumor suppressors in some cancer types, while exhibiting oncogenic properties in other cancer types. n.d., no data.

8. Abbreviations

APC, antigen presenting cell; APM, antigen processing machinery; β_2-m, β_2-microglobulin; CDKN, cyclin-dependent kinase inhibitor; CTL, cytotoxic T lymphocyte; CXCL, chemokine (CXC motif) ligand; DC, dendritic cell; GAS, IFN-γ-activated sequence; HC, heavy chain; HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; IRF, interferon regulatory factor; ISRE, IFN-stimulated response element; im-miRNA, immune modulatory miRNA; JAK, janus kinase; LMP, low molecular mass polypeptide; MAPK, MAP kinase; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; MIC, major histocompatibility complex class I-related molecule; miRNA, microRNA; NK, natural killer cell; PD, programmed death; PDL, PD ligand; PLC, peptide loading complex; STAT, signal transducer and activator of transcription; SOCS, suppressor of cytokine signaling; TAF, tumor-associated fibroblast; TAM, tumor-associated macrophage; TAP, transporter associated with antigen processing; TGF, transforming growth factor; TLR, toll-like receptor; TME, tumor microenvironment; Treg, regulatory T cell; ULBP, human cytomegalovirus UL16-binding protein; UTR, untranslated region; and VEGF, vascular endothelial growth factor.

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