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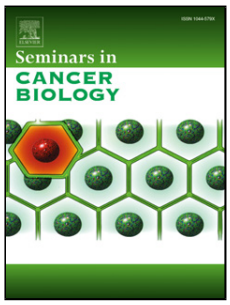

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Radhakrishnan Vishnubalaji, Hibah Shaath, Ramesh Elango, Nehad M. Alajez

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Noncoding RNAs as potential mediators of resistance to cancer immunotherapy

Radhakrishnan Vishnubalaji[1§], Hibah Shaath[1,2§], Ramesh Elango [1], and Nehad M. Alajez[1,2*]

[1]Cancer Research Center, Qatar Biomedical Research Institute (QBRI), Hamad Bin Khalifa University (HBKU), Qatar Foundation (QF), PO Box 34110, Doha, Qatar
[2]College of Health & Life Sciences, Hamad Bin Khalifa University (HBKU), Qatar Foundation (QF), Doha, Qatar.

[§]Authors contributed equality
*Correspondence and requests for materials should be addressed to N.M.A. (email: nalajez@hbku.edu.qa)
Nehad M Alajez
Cancer Research Center
Qatar Biomedical Research Institute
Hamad Bin Khalifa University (HBKU)
Qatar Foundation, Doha, Qatar, 00000.
Email: nalajez@hbku.edu.qa
Tel: +974 4454 7252
Fax: +974 4454 0281

Abstract

Substantial evolution in cancer therapy has been witnessed lately, steering mainly towards immunotherapeutic approaches, replacing or in combination with classical therapies. Whereas the use of various immunotherapy approaches, such as adoptive T cell therapy, genetically-modified T cells, or immune checkpoint inhibitors, has been a triumph for cancer immunotherapy, the great challenge is the ability of the immune system to sustain long lasting anti-tumor response. Additionally, epigenetic changes in a suppressive tumor microenvironment can pertain to T cell exhaustion, limiting their functionality. Noncoding RNAs (ncRNAs) have emerged over the last years as key players in epigenetic regulation. Among those, microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) have been studied extensively for their potential role in regulating tumor immunity through direct regulation of genes involved in immune activation or suppression. In this review, we will provide an overview of contemporary approaches for cancer immunotherapy and will present the current state of knowledge implicating miRNAs and lncRNAs in regulating immune response against human cancer and their potential implications in resistance to cancer immunotherapy, with main emphasis on immune checkpoints.

Keywords

MicroRNA, miRNA, lncRNA, cancer immune therapy, immune checkpoint inhibitors

1. Introduction

In recent years, substantial evolution in the field of cancer therapy has emerged, steering mainly towards immunotherapeutic approaches, replacing or in combination with classical therapies such as chemotherapy, radiotherapy and surgery [1]. Active immunotherapy involves stimulating the immune system to target cancer cells through specific antigen recognition, while passive immunotherapies aim to enhance an existing anti-tumor immune response in the tumor microenvironment. Despite the progress and unprecedented achievements in the field of cancer immune therapy, resistance remains a major clinical challenge. A number of mechanisms have been implicated in this scenario, which include, but not limited to, intrinsic mechanisms (i.e. weak immune response against the tumor); adaptive (i.e. tumor adapts itself to evade immune therapy); or acquired (i.e. in which tumor responds initially to the treatment, but later on develops a mechanism to resist immune therapy) [2].

Noncoding RNAs (ncRNAs) have emerged over the last several years as key players in epigenetic gene regulation. Among those, microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) have been studied extensively for their potential role in regulating various cellular processes under normal and pathological conditions. In the context of tumor immunity, a large number of miRNAs, and to a lesser extent lncRNAs, have been identified as potent regulators of tumor immunity though direct regulation of genes governing the balance between immune activation and suppression. In this review, we will provide an overview of current cancer immunotherapy approaches and present the current state of knowledge implicating miRNAs and lncRNAs in regulating immune response against human cancers and their potential implications

in resistance to cancer immunotherapy, with main emphasis on immune checkpoints (ICs) regualtion.

2. Cancer immunotherapy

Over the past few decades, the role of the immune system in combating human malignances has been well established. Central to tumor immune response are antigen presenting cells (APCs) and T cells. Functioning as mediators, they are involved in foreign antigen recognition, digestion and presentation. However, the immune system on its own may not be able to eliminate the tumor as a result of immune evasion or immune suppression, and may need assistance in steering T cell functions to better efficacy. Approaches implemented to confer anti-tumor immunity in patients with various malignances will be discussed.

2.1. Adoptive T cell therapy

Adoptive T cell therapy (ATC), autologous or allogeneic, is based on the isolation of tumor infiltrating T cells from the tumor microenvironment of cancer patients. Antigen specific expansion through incubation with growth factors such as IL-2 allows for the reinfusion of larger numbers of effector T cells back into the same patients tumor microenvironment [3]. An early study highlighting the potential for ATC was conducted in 1988, which showed regression in metastatic melanoma in 60% of cases, with a response time of up to 13 months [4]. An increase in efficacy was observed during clinical trials adopting this therapy with additional lymphodepletion prior to T cell infusion [5]. Lymphodepletion aids in the removal of any immune competitors such as myeloid-derived suppressor cells (MDSCs) and T regulators cells, which maintain tolerance to tumors. It also facilitates the eradication of cellular sinks, increasing

access to homeostatic cytokines as a mechanism of enhancing the effect of antigen specific T cells [6].

2.2. T Cell Receptor (TCR)-Genetically Modified T-Cell Therapy

Over the past years, T cell therapy has been directed towards genetically engineering T cells, rather than expanding existing tumor infiltrating lymphocytes (TILs), to instigate a faster, stronger and more specific response [7, 8]. Modifying the TCR *in vitro* to target tumor antigens specifically can be a challenge as many are also expressed on normal cells. Cancer testis antigens therefore provide promising targets as they are not naturally expressed in somatic cells, rather only in the germline, but have shown to be re-expressed on tumor cells [9]. T cells engineered to recognize cancer-testis antigen New York Esophageal Squamous Cell Carcinoma-1 (NY-ESO-1) and L Antigen Family Member-1 (LAGE-1) have been used in multiple myeloma trials with promising outcomes. Eighty percent of the cohort tested showed a clinical response, with a progression free survival median of 19.1 months [10].

2.3. Chimeric antigen receptor (CAR) Genetically-Modified T Cell Therapy

CAR-T cell therapy has gone through multiple generations of enhancements, empowering its therapeutic potential. In the same way as TCR engineering, autologous T cells are extracted and genetically enhanced via viral vector transduction with genes encoding a specific antibody directed against a known cancer antigen to be integrated into the T cells and expressed on their surface. CAR-T cells possess the added advantage of being MHC independent, and can therefore target cancer cells that would otherwise evade immune therapies successfully via loss of MHC molecules [11]. The first generation of CAR-T cells was essentially a single chain variable

fragment (scFv) fused to a CD3 signaling domain required for T cell activation, however, without co-stimulation, T cell anergy is common [12]. Second generation CAR-T cells overcame this issue with the addition of a CD28 co-stimulation molecule added to the CD3 signal 1, improving T cell activation and longevity through proliferation and cytokine secretion. The use of second generation CAR-T cells gave favorable outcomes pertaining to higher efficacy of tumor cell eradication and immune persistence [13]. CAR-T cells have been developed further with the inclusion of additional co-stimulatory molecules (third generation CAR-T cells) and cytokine mediated killing (fourth generation CAR-T cells), with the ability to secrete pro-inflammatory cytokines to targeted tumor tissue, eliciting the recruitment of innate immune cells for an even stronger immune response [14].

Extensive research and clinical trials gave rise to the first FDA approved CAR-T cell therapy in 2017 [15]. Tisagenlecleucel, used in the treatment of B-cell acute lymphoblastic leukemia (ALL) and Diffuse large B-cell lymphoma (DLBCL), is engineered to target CD19 antigen commonly expressed on B cells, with a 4-1BB co-stimulatory domain. The phase 2 trial, JULIET, in which 93 patients received Tisagenlecleucel, saw 40% of patients reach complete remission and 12% with a partial response to the treatment. Relapse free survival was estimated at 65% and although this came with substantial adverse effects in most patients (such as cytokine release syndrome (CRS)), no deaths were directly attributed to Tisagenlecleucel [16].

Dual CAR-T cell therapy has recently demonstrated promising results. A study by Yan *et al*., was conducted on 21 patients who received a CAR-T cell infusion of humanized anti-CD19 with murine anti-BCMA (B-cell maturation antigen) in a subset of multiple myeloma patients. Ninety-five percent of participants responded to the treatment in one form or another; complete,

very good, or partially (57%, 24% and 14%, respectively). No deaths were reported; however, the majority of patients experienced CRS [17].

Bi-specific T-cell engagers (BiTEs) are another class of genetically engineered T cells whose functionality is MHC-independent [18]. The mechanism of action, unlike other CAR-modified T cells, is to simultaneously bind T cells and the tumor antigen, stimulating T cells for cytotoxic granules, granzymes and cytokine production, triggering close-proximity tumor cell apoptosis. Blinatumomab, a BiTEs which includes constructs specific for both CD19 and CD3 has been used for the treatment of hematological malignancies [19]. A study by Keating *et al*., highlighted the importance of FDA-approved Blinatumomab as a 'bridging' therapy in patients with relapsed or refractory B acute lymphoblastic leukemia (B-ALL) with minimal residual disease (as a replacement for chemotherapy), which was reduced to negligent levels in most patients (93.3%) [20].

2.4. Monoclonal antibodies

One way of stimulating the immune system into action is by artificially increasing the amount of antibodies in circulation. Monoclonal antibodies can facilitate several mechanisms of action which include acting as a cell surface receptor antagonist, inhibiting signaling, reducing proliferation and inducing apoptosis [21]. Alternatively, they can serve as immune cell recruiting markers.

Cancer therapy using monoclonal antibodies have been a great success with the manufacture of known and specific antigens, such as anti- human epidermal growth factor receptor 2 (HER-2), used in some breast cancers. Trastuzumab (Herceptin®) is an anti-HER2

used in cases of HER2 positive breast cancers with adequate results. HER2 is overexpressed in approximately 15-20% of all breast cancers [22], providing a good target for an antagonist, inducing antibody-dependent cell-mediated cytotoxicity (ADCC). When given in combination with chemotherapy, Trastuzumab was well tolerated and gave a median duration response of 9.1 months [23].

As a development to using monoclonal antibodies, conjugated antibodies whereby different agents can be attached, using the antibody as a homing vehicle to deliver substances such as radiotherapies and chemotherapies specifically to tumor cells [24]. In this manner, adverse effects experienced using chemotherapies are minimalized. The first drug of its kind to be approved by the FDA, Ibritumomab tiuxetan (Zevalin®), is an example of radioimmunotherapy (RIT), used in the treatment of some types of non-Hodgkin lymphoma. A recent report on patients in advanced stages shows 30% survival without relapse after an 8-year long follow up [25], which gave encouraging indications of the success achieved by conjugated monoclonal antibodies.

2.5. Immune checkpoint Inhibitors

Adaptive immunity encompasses an intricate system of stimulatory and inhibitory signals, operating in harmony as a mechanism for the body's' self-preservation and some cancer cells have shown the ability to bypass this immunosurveillance [26], leading to the progression and possible malignancy of cancer cells. This is feasible due to the dysregulation of ICs, mediated by interactions between T cells, APCs and cancer cells. TCRs recognize MHCs on APC's, initiating T cell priming and activation. A secondary stimulation is needed for the survival of the T cell, which also dictates its function [26, 27]. Inhibitory molecules can alternatively bind, facilitating

a block in T cell activation, leading to T cell anergy; a natural mechanism protecting the body against autoimmune diseases [28]. Immune checkpoints are a class of surface molecules implicated in regulating immune response under normal and pathological conditions [29]. Herein, we discuss a panel of well-studied immune checkpoints in the context of anti-tumor immune response.

2.5.1. CTLA4 (cytotoxic T-lymphocyte-associated protein 4)

Cytotoxic T-lymphocyte-associated protein 4 (CTLA4) is one of the most widely studied immune inhibitory molecules found on the surface of T cells. In an active state, B7 molecule on APCs is able to bind CD28 found on T cells leading to their activation and proliferation. In competition with CD28, CTLA4 ligand binds B7 with greater affinity, inhibiting T cell activation and acting as an immune checkpoint [30]. To prolong T cell activation to utilizing it for cancer therapy, immune checkpoint inhibitors (ICIs) have been used to impede CTLA4 interactions with B7, favoring CD28-B7 T cell activation longevity. CTLA4 was first demonstrated to enhance antitumor response in a *Ctla4*-knockout mouse study [31]. A subset of mice treated with anti-CTLA4 showed complete eradication of their induced tumors by day 17 and even exhibited tumor rejection upon subjection to secondary challenges.

Anti-CTLA4 monoclonal antibody, Ipilimumab, is the first FDA approved ICI used to treat patients with advanced melanoma. In a 2010 study by Hodi *et al*., a cohort of 676 patients with late stages of melanoma were treated with ipilimumab either in combination or alone. Whereas alternative therapy gave a mean overall survival of 6.4 months, the inhibition of immune checkpoint with anti-CTLA4 ipilimumab gave rise to a 10 month overall survival [32]. In a more recent study, which pooled the data from over 10 ipilimumab clinical trials, and with a

follow up of up to 10 years, survival curves had started to plateau after 3 years of taking the treatment, after which the risk of death became minimal [32, 33]. It has been suggested that CTLA4 inhibitors could have more than one mode of action. The introduction of anti-CTLA4 such as ipilimumab and tremelimumab have been associated with a decrease in T regulatory cells (Tregs) levels [34, 35].

2.5.2. PD1 (Programmed cell death protein 1)

The second immune receptor target to show promise in the field of immunotherapy, particularly in melanoma and non-small cell lung carcinoma (NSCLC), is PD1 (CD279). Expressed on the surface of activated T cells, and similarly to CTLA, PD1 acts as a negative regulator of the immune system to maintain homeostasis by suppressing inflammatory activity and supporting tumor escape [36]. FDA approved anti-PD1 drugs, such as Pembrolizumab and nivolumab, block PD1 binding to its ligands, PD-L1 (B7-H1, CD274) and PD-L2 (B7-DC, CD273). Antibodies have also been developed that target these ligands found on tumor cells as an alternative route to blocking this interaction, which promotes T effector cell activation [37]. Reports show increased progression free survival and overall survival in response to anti-PD1 treatment in patients with PD-L1 positive tumors [38, 39]. A phase 3 study on 418 previously untreated patients with metastatic melanoma showed significant improvement in survival after 1 year of administrating anti-PD1 drug nivolumab (72.9%) in comparison to 42.1% survival in patients undergoing chemotherapy (dacarbazine). Immune based therapy also showed 7% less occurrence of adverse effects such as fatigue and nausea [40].

2.5.3. Lymphocyte-activation gene 3 (LAG3)

LAG3, binds to MHC Class II molecules with greater affinity than CD4, attenuating T cell activation and proliferation [41]. Ongoing clinical trials have used anti-LAG3 as either a monoclonal antibody or as a LAG3-Ig fusion protein to inhibit its ligation to MHC II. mAb BMS-986016 shows encouraging efficacy with patients responding to this mAb in combination with nivolumab, even after initial treatment with other ICI's. A significant increase in survival can be observed with IMP321, a LAG-3Ig fusion protein, as a mono-therapy in renal cell carcinoma [42].

2.5.5. Other promising Immune checkpoint

Numerous other immune checkpoints are being exploited for cancer immune therapy, these include but are not limited to T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), signal transducer and activator of transcription 3 (STAT3), V-domain Ig suppressor of T cell activation (VISTA) and B- and T-lymphocyte attenuator (BTLA). However the efficacy of targeting those immune checkpoints in comparison to targeting the classical CTLA-4, PD-1, and PD-L1 remains to be addressed.

Overall, immunotherapy and specifically the use of ICIs has shown substantial promise. However, strategies improving the efficacy of these therapies is essential for unresponsive patients or those with acquired immune resistance. Epigenetic modulators have been shown to influence the tumor microenvironment via manipulation of chromatin structure and enhancing cell surface expression of immune checkpoints. The use of epigenetic drugs can therefore sensitize cells to immunotherapeutic responses. Delving deeper into epigenetic regulation, the role of non-coding RNAs (ncRNAs) in the effectiveness and resistance to cancer immunotherapy

is still being unraveled. In following chapters, we will provide an overview of miRNA and lncRNA biogenesis and function. We will also present the current state of knowledge concerning the regulation of ICs by ncRNAs in the context of tumor immune response, and future development of ncRNA-based strategies to overcome resistance to cancer immunotherapy.

3. Noncoding RNAs

NcRNAs represent a class of RNA species, which lack protein translation potential. NcRNAs are classified according to their product size and function into microRNAs (miRNAs), circular RNAs (circRNAs), long noncoding RNAs (lncRNAs), piwi-interacting RNAs (piRNAs), small nucleolar RNAs (snoRNAs), small nuclear RNAs (snRNAs), transfer RNAs (tRNAs), ribosomal RNAs (rRNAs) and small interfering RNAs (siRNAs) includes endogenous siRNAs (endo-siRNAs) and exogenous siRNAs (exo-siRNAs) [43-45]. In this chapter, we will provide an overview of miRNA and lncRNA biogenesis and function. We will also present the current state of knowledge concerning the regulation of ICs by ncRNAs in the context of tumor immune response.

3.1. MicroRNA biogenesis and function

MiRNAs are a class of small (~21-nucleotide-long) RNAs involved in post-transcriptional regulation of gene expression, hence play a crucial role in regulating several cellular and biological processes under normal and pathological conditions [46, 47]. The majority of miRNAs are located within the introns of coding genes, however a significant number of miRNAs are derived from exons of coding, as well as from the exons and introns of non-coding genes [48]. MiRNAs are typically generated through the canonical pathway and are transcribed by RNA

polymerase II or RNA polymerase III in the nucleus (Fig. 1a), processed by Drosha/DGCR8 nuclear complex enzyme from pri-miRNAs into pre-miRNAs (Fig. 1b)[49]. The originated pre-miRNA is actively translocated into the cytoplasm through exportin-5 mediated mechanism (Fig. 1c), which are then converted into miRNA duplex of ~20-bp nucleotide long through Dicer cleavage (Fig. 1d)[49, 50]. The complementary strand is usually degraded, while the remaining strand representing mature miRNA, is then incorporated into the miRNA-induced silencing complex (miRISC), leading to silencing via mRNA degradation or translational repression through interaction with the 3' untranslated regions (UTR) of the target mRNA (Fig. 1e)[51-54]. MiRNAs have emerged as dominant regulators of gene expression in several human diseases, including cancer [55, 56]. In the context of tumorigenesis, miRNAs can act as tumor suppressors, through modulation of oncogenic cellular processes, or as oncogenes, through suppression of anti-tumor cellular pathways [57, 58]. Aside from that, miRNAs are also implicated in shaping the immune system through direct regulation of innate and adaptive immune systems [59]. The role of miRNA in regulating immune response to cancer will be discussed later on in this review.

3.2. LncRNA biogenesis

Long non-coding RNA (LncRNA) represents a class of RNA species which are transcribed predominantly by RNA polymerase II, with a length exceeding 200 nucleotides and have no apparent protein-coding role [60]. Current GENCODE database (version 31) revealed the existence of approximately 17,904 lncRNAs and 14,739 pseudogenes in the human genome. LncRNAs play a crucial role in diverse biological systems through genomic imprinting, cell cycle regulation, cell differentiation, and has been linked to a number of human diseases [44, 61, 62]. LncRNAs can be transcribed from their own promoters as well as from enhancer or

promoter sequences shared with separately transcribed coding and non-coding genes (Fig. 1f-i)[63-66]. LncRNAs lacks the strongly translated open reading frames (ORFs); however, numerous lncRNAs are poly adenylated at their 3' end and possess a 5′ cap, resembling protein-coding genes, in relation to post-transcriptional processing [66]. Recent ribo-seq and mass spectrometry data suggested a possibility of translational ability of lncRNAs, through the presence of small ORFs encoding for short peptides [67, 68]. In contrast to mRNAs, lncRNAs can localize to several nuclear parts (eg, chromatin, subnuclear domains, and nucleoplasm) along with the cytoplasm or both nuclear and cytoplasmic parts [69]. In the cytoplasm, lncRNAs are oftentimes associated with protein coding gene translation and stability, thus controlling protein expression. However, in the nucleus, lncRNAs are interconnected with chromatin modifications, RNA processing, and transcriptional regulations [70]. LncRNAs can be classified on the basis of their transcript length, mRNA similarity and relationship with marked protein-coding genes, as well as in relation to distinctive features, including differences in biogenesis and regulatory mechanisms, *cis*-regulatory activities and RNA-binding domains [71-74]. Additionally, lncRNAs are classified according to their position relative to well-known mRNAs or biogenesis loci. In that regard, lncRNAs can be divided into four major categories (Fig. 1f-i): 1) long intergenic/intervening lncRNAs (lincRNAs) which are transcribed from intergenic regions and do not overlay mRNAs; 2) enhancer RNAs (eRNAs), both are unrelated transcription units located to the adjacent mRNAs; 3) antisense lncRNAs (natural antisense transcripts; NATs or as lncRNA) which represents lncRNAs that completely or partially overlap with mRNAs and are transcribed across the complementary strand of exons of protein coding genes; and 4) intronic lncRNAs which represent lncRNAs that exist in the introns of protein coding genes [75, 76].

3.3. LncRNA function

A number of mechanisms have been proposed for how lncRNAs mediate gene regulation. Generally, lncRNA act in *cis*, by regulating the chromatin state of nearby genes (Fig. 1j), through its ability to modulate regulatory elements at that particular locus [77]. One of the best studied examples of a *cis*-acting lncRNA is X chromosome inactivation for dosage compensation mediated by X-inactive specific transcript (Xist) during early embryonic development in females [78]. In this regard, the transcribed Xist lncRNA spreads across the entire X chromosome in female mammals, leading to the deposition of repressive mark and subsequent inactivation of almost the entire chromosome [79]. Alternatively, lncRNA can function in *trans* through regulation of gene expression across the genome. One of the best studied examples of *trans* regulation is regulation of HOXD gene by HOX Transcript Antisense RNA (HOTAIR) lncRNA transcribed from the HOXC locus [80]. This repression is mediated via the recruitment of the polycomb repressive complex 2 (PRC2) to the HOXD locus and subsequent deposition of repressive chromatin state. Other mechanisms have been proposed where certain lncRNA can shape the chromatin structure to modulate various steps in gene regulation. One such example is the metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) lncRNA, oftentimes localizes to nuclear speckles [81], hence act as a scaffold that facilitates the positioning of nuclear speckles at active gene loci, which could enhance the recruitment of splicing machinery to nascent transcripts. However, Malat1-deficient mice did not exhibit significant splicing abnormalities, therefore better understating of the role of MALAT1 in gene regulation warrant further investigations [82]. In addition to the aforementioned mechanisms, lncRNAs have the ability to regulate the abundance of other RNA species through base-pairing interactions. LncRNAs can act as endogenous sponges to titrate the abundance and hence the activity of miRNAs (Fig. 1k). One such example is the inhibition of let-7 family of miRNAs by the

imprinted H19 lncRNA by acting as competing endogenous RNA (ceRNA) or molecular sponge in mammalian cells [83].

4. NcRNAs as epigenetic regulators of immune checkpoints

Accumulation of genetic and epigenetic alterations, in addition to the existence of unique tumor antigens, provides an opportunity for the immune system to distinguish cancerous cells from their non-cancerous counterparts. Effective anti-tumor immune response is dictated by the balance between stimulatory *vs*. inhibitory signals. Induction of peripheral tolerance is controlled by specific IC molecules, including PD1 receptor and its ligands PD-L1 and PD-L2, CTLA-4, TIM3, BTLA, and LAG3 [84-87]. Recently, along with PD-L1 and PD-L2, there are eight more B7 family members identified: B7.1 (CD80), B7.2 (CD86), B7-H2 (ICOSL), B7-H3 (CD276), B7S1 (B7-H4, B7x, or Vtcn1), B7-H5 (VISTA, GI24 or PD-1H), B7-H6 and B7-H7 (HHLA2) [88]. The blockade of these ICs is transforming cancer therapeutics. Recently, clinical studies have highlighted the agonists (antibodies) of co-stimulatory pathways or antagonists of inhibitory pathways to boost antigen-specific T cell responses in patients with advanced cancers, as highlighted previously in this review [85].

A myriad of studies demonstrated IC networks targeting by miRNA and lncRNA in the context of human cancers (summarized in table 1). Just a decade ago, miR-29a from 3 isoforms of miR-29 (a, b, c) family was recognized as the first miRNA candidate whose expression inversely correlated with B7-H3 protein in several solid tumors (neuroblastoma, sarcomas, brain tumors), and was found to directly target B7-H3 3′-UTR [89]. In agreement with those data, inverse regulation between miR-29c and B7-H3 was observed in cutaneous melanoma [90]. Using high-throughput approach, Nygren and colleagues screened 810 miRNA mimics for their potential to target B7-H3 and identified 13 miRNAs (miR-214, miR-363*, miR-326, miR-940,

miR-29c, miR-665, miR-34b*, miR-708, miR-601, miR-124a, miR-380-5p, miR-885-3p, and miR-593) which directly targeted B7-H3 3'-UTR in two BC cell lines [91]. However, the contribution of those identified miRNAs in the context of immune escape in BC patients warrants further investigation. In clear cell renal cell carcinoma (ccRCC), overexpression of miR-187 decreased B7-H3 expression and inhibited proliferation and tumor progression. Remarkably, 100% of the patients with high expression of miR-187 achieved 5 year survival, while only 42% of patients with low miR-187 expression reached the 5 year survival point [92].

Under normal physiological conditions, PD-L1 is expressed at varying levels in cells of the myeloid lineage, such as DCs, macrophages, and myeloid-derived suppressor cells, but not in normal tissues. In contrast, PD-L1 protein is rich in various human cancer cells and is upregulated by the pro-inflammatory cytokine interferon-gamma. PD-L1 enhances apoptosis and inhibits activation and proliferation of antigen-specific human T-cell clones and enhanced the growth of PD-L1+ tumors *in vivo* [93]. Sequencing of gastrointestinal cancers such as esophageal, gastric, colorectal, hepatocellular, and pancreatic cancers revealed elevated PD-L1 expression through the frequent guanine- to- cytosine somatic mutation in the PD-L1 3′-UTR, leading to loss of post-transcriptional and translational regulation inflicted by miR- 570 [94]. Subsequent studies confirmed that single nucleotide polymorphisms (SNPs) in miR- 570 target sites (miRSNPs) could affect the binding of miR- 570 to its target and contribute to the increased risk of gastric cancer (GC) [95]. Other studies have confirmed miR-152 and miR-200b to directly target PD-L1 3′- UTR and to inversely correlate with PD-L1 expression in GC patients [96, 97]. In a study by Pyzer *et al*., miR-200c and miR-34a were found to suppress PD-L1 expression in acute myelocytic leukemia (AML). Interestingly, MUC1 was shown to regulate miR-200c and miR-34a processing rather than transcription [98]. Concordantly, Chen and

colleagues revealed miR-200 to directly target PD-L1. Interestingly, ZEB1, an inducer of epithelial to mesenchymal transition (EMT) and inducer of metastasis, was found to repress miR-200, therefore alleviates PD-L1 repression and subsequently promotes immunosuppression and metastasis of LC [99]. In GC, miR-186 was found to regulate PD-L1 expression indirectly through HIF-1α [100]. In lung cancer, tumor immune evasion was found to be controlled by TP53/miR-34/PD-L1 axis where TP53 induced miR-34, which in turn downregulated PD-L1 expression [101]. Concordantly, therapeutic delivery of MRX34 (miR-34 mimic) increased TILs and particularly increased the number of CD8+ cells *in vivo*, when combined with radiotherapy [101]. Similarly, miR-34a was also found to targets PD-L1 expression in acute myeloid leukemia [102]. In one study, miR-197 was found to be downregulated in platinum-resistant NSCLC, thus implicating this miRNA in the promotion of chemoresistance, tumorigenicity, and metastasis [103]. Loss of miR-197 promoted CKS1B/STAT3-dependent activation of oncogenic mediators (Bcl-2, c-Myc, and cyclin D1) as well as activation of PD-L1, therefore forced expression of miR-197 sensitized drug-resistant PD-L1 positive cells to chemotherapy [103]. In contrary, while inverse correlation between miR-197 and PD-L1 expression was observed in squamous cell carcinoma, patients with T4 stage exhibited low PD-L1 and high miR-197 expression, suggesting miR-197 as an unfavorable prognostic marker [104]. MiR- 3127- 5p is another miRNA which was shown to exert tumor promoting role in LC cell [105]; however, miR- 3127- 5p was found to stimulate STAT3 phosphorylation and to induce the expression of PD- L1, leading to suppression of T cell proliferation and the induction of suppressor T cells and chemoresistance [106]. In malignant pleural mesothelioma, miR-15a, miR-16, and miR-193a mimics downregulated PD-L1 mRNA and protein expression *in vitro* and their expression inversely correlated with PD-L1 expression in patients' specimens [107]. In colorectal cancer (CRC),

downregulated miR-138-5p is frequently found and is associated with poor clinical outcome [108]. Mechanistically, miR-138-5p mimics suppressed PD-L1 expression and suppressed tumor growth *in vitro* and *in vivo* [108]. In an independent study, miR-148a-3p was found to negatively regulate tumor PD-L1 expression, whereas loss of miR-148a-3p contributed to the immunosuppressive tumor microenvironment [109]. In melanoma, elevated PD-L1 expression was associated with BRAF and MEK inhibitor resistant phenotype. Interestingly, miR-17-5p was shown to directly target PD-L1, suggesting loss of miR-17-5p as a potential mechanism leading to the acquisition of BRAF and MEK inhibitor resistant phenotype [110]. In RCC, miR-497-5p was shown to regulate PD-L1 expression and to suppress tumor cell proliferation, colony formation and migration and to induce apoptosis *in vitro* [111]. In bladder cancer, suppression of miR-145 increased PD-L1 expression and promoted stemness properties and invasion of BC cells [112]. In cervical cancer, miR-140, miR-142, miR-340, and miR-383 directly inhibited PD-L1 expression, while miR-18a promoted PD-L1 expression indirectly through regulation of PTEN, WNK2 and SOX6 [113]. In diffuse DLBCL, miR-195 inhibited PD-L1 expression and promoted IFN-γ and TNF-α, by T cells *in vitro* [114]. In chemoresistance ovarian cancer, miR-424(322) suppressed PD-L1 and CD80 expression through direct binding to their 3'-UTR, whereas forced expression of miR-424(322) reversed chemoresistance through suppression of PD-L1 [115]. In NSCLC, PD- L1 expression was shown to be regulated in a miR- 181a/Cbl- b and miR- 940/c- Cbl ubiquitin ligases dependent manner [116]. In laryngeal cancer, miR-217 inhibited cell migration, invasion, proliferation, apoptosis, EMT, and angiogenesis, which was associated with downregulation of AEG-1 and PD-L1 [117]. Those data highlighted an important role for miRNAs in regulating PD-L1 expression in the context of tumor immune response.

Although large amounts of literature investigated miRNA-dependent PD-L1 regulation, other immune checkpoints have been studied as well. In a recent study, TIM-3 was found to regulate macrophage polarization through regulation of STAT1-miR-155-SOCS1 network [118]. In AML HL-60 cell model, miR-330-5p was shown to directly target TIM-3 mRNA [119]. In chordoma, patients with high miR-455-5p and negative Gal9 expression experienced longer survival times. Mechanistic studies identified miR-455-5p as negative regulator of Gal9, a TIM-3 inhibitor [120]. In glioma, miR-138 directly targeted CTLA-4 and PD-1 and inhibited tumor growth *in vivo* [121]. Global miRNA profile between PD1+ and PD1- T cells isolated from lymph nodes and spleen of melanoma tumor-bearing mice revealed the downregulation of miR-28, miR-150 and miR-151-5p. Predominantly, miR-28 mimic suppressed the expression of PD-1. Additionally, miR-28 inhibition increased the expression of PD1, TIM- 3 and BTLA of exhausted T cells and regulated the PD1+ Foxp3+ and TIM3+ Foxp3+ exhaustive regulatory T cells *in vitro* [122]. In a study by Zang *et al*., the rs10204525 single-nucleotide polymorphism (SNP) within PD1 3'-UTR was linked to chronic HBV infection. Interestingly, in lymphocytes from chronic HBV patients with the rs10204525 genotype GG, miR-4717 suppressed PD-1 expression and increased TNF-α and interferon IFN-γ secretion [123].

LncRNAs have also been implicated in IC regulation. In pancreatic cancer, LINC00473 and PD- L1 were upregulated, whereas miR- 195- 5p was downregulated. LINC00473 silencing suppressed tumorigenesis through enhancing miR- 195- 5p- targeted downregulation of PD- L1, and subsequent activation of CD8+ T cells [124]. In NSCLC tissues, the expression of MALAT1 exhibited negative correlation with miR-200a-3p and positive correlation with PD-L1 expressions. Additionally, MALAT1 promoted proliferation, migration, and invasion of NSCLC cells through sequestering endogenous miR-200a-3p [125]. In GC, UCA1 lncRNA

promoted tumor cell proliferation and migration, and inhibited apoptosis, through direct binding to PD-L1-inhibiting miRNAs (miR-26a, miR-26b, miR-193a and miR-214) and subsequent increase in PD-L1 expression. *In vivo*, UCA1-KO GC tumors formed smaller tumors, and exhibited higher levels of miR-26a, miR-26b, miR-193a and miR- 214 expression [126]. In lung cancer, NKX2-1-AS1 negatively regulated endogenous PD-L1 and PD1 expression, through interfering with NKX2-1 protein binding to the PD-L1 and PD1 promoter and subsequent suppression of their transcription and cell migration [127]. In CRC, MIR17HG promoted tumorigenesis and metastasis *in vitro* and *in vivo*. Pulldown experiments revealed binding of MIR17HG to PD-L1 in the SW620 and HCT116 cell models [128]. Similarly, Hsa_circ_0020397 (circRNA) was observed to promote CRC viability and invasion through suppression of endogenous miR-138, and subsequent upregulation of TERT and PD-L1 [129]. In PBMCs from patients with HCC, NEAT1 and TIM-3 were upregulated compared to healthy controls. Direct interaction between NEAT1 and miR-155 was observed in CD8+ T cells, leading to TIM-3 upregulation, while suppression of NEAT1 decreased tumor growth in HCC mice, thus implicating the NEAT1-miR-155-TIM-3 circuit in HCC pathogenesis [130]. In addition to protein coding PD-L1, there are three non-coding transcripts as per the latest ENSEMB assembly, namely CD274-203, CD274-204, and CD274-205. Thus far we have no information if those transcripts exert any biological function and if they have the capacity to act as decoys for PD-L1 targeting miRNAs, which warrants further investigation.

5. ncRNAs and regulation of immune cell differentiation and function

Better understanding of the role of lncRNAs in regulating the immune system under physiological and pathological conditions could provide new ncRNA-based therapeutic venue

for human cancers. A large number of ncRNAs have been investigated for their role in regulating immune cell differentiation and function. In this chapter we will present selected examples of miRNAs and lncRNAs with well-established role in regulating the immune system. Potential implications of such regulatory elements in cancer immunity will be discussed.

5.1 miRNAs and regulation of the immune system

Earlier studies have shown an essential role for miRNAs in the function and long term reconstitution capabilities of hematopoietic stem cell [131]. In particular, forced expression of miR-125b was shown to induce myeloproliferative disease and subsequent progression to myeloid leukemia in mice which in part is mediated through suppression of Kruppel-like factor 13 (Klf13) and BCL‐2‐modifying factor (Bmf) [131, 132]. MiRNAs has also been implicated in the regulating the innate immune system. For instance, miR-155 was shown to control macrophage differentiation and function [133]. Lipopolysaccharide (LPS) induces miR-155 expression, which in turn downregulates Aryl Hydrocarbon Receptor Nuclear Translocator Like (ARNTL) leading to proinflammatory response. During granulocyte differentiation, Nuclear Factor I A (NFI-A) was shown to bind to miR-223 promotor and to sustain low level of its expression, whereas when replacement by CCAAT Enhancer Binding Protein Alpha (C/EBPalpha) in response to retinoic acid (RA) stimulation, miR-223 expression increases promoting granulocyte differentiation [134].

Similarly, a number of miRNAs have been implicated in the differentiation and function of the adaptive immune system. A pivotal role for miR-181a in regulating T cell development and sensitivity has been described. Inhibition of miR-181a expression in immature T cells reduced their sensitivity to peptide antigens and impaired positive and negative thymic selection.

Concordantly, enhanced miR-181a expression in mature T cells increased their sensitivity, mediated via downregulation of multiple phosphatases, leading to elevated steady-state levels of phosphorylated signaling molecules [135]. Several miRNAs were also shown to regulated T cell differentiation. For instance, miR-17-92 cluster was shown to regulate T_H1 function [136], miR-24 and miR-27 were shown to regulated T_H2 function [137], while miR-326, miR-301, and miR-21 were shown to regulate T_H17 differentiation and function [138-140].

MiRNAs can also regulate B cell development and function. Eelier studies revealed miR-181 to be expressed predominantly in B-lymphoid cells in the mouse bone marrow. Concordantly, forced expression of miR-181 in hematopoietic stem and progenitor cells led to increased B-cell lineage differentiation in vitro and in vivo [141]. In contrary, forced expression of miR-150 in hematopoietic stem cells, had minimal effects on T cell, granulocyte, and macrophage development; however significant impairment in B cell development was observed [142]. Subsequently, miR-150 was also shown to control B cell differentiation through targeting MYB transcription factor [143]. In addition to B cell development, miR-155 was shown to inhibit Spi-1 Proto-Oncogene (SPI1), also known as PU.1, expression, leading to suppression of Pax5 plasma cell differentiation [144].

Given this well-established role for various miRNAs in regulating the innate and adaptive immune system, several studies implicated various miRNAs in shaping the immune system and tumor immunity. For instance, miR-155 was shown to promote, while miR-146a inhibited both CD4+ and CD8+ T cell antitumor responses. Mechanistically, miR-155 targets Ship1 in T cells, leading to IFNγ repression [145]. Therefore, a more comprehensive understanding of the role of

various miRNAs in regulating immune cell differentiation and function in the context of remains to be fully understood.

5.2 lncRNAs and regulation of the immune system

Recent studies have highlighted a role for lncRNAs in regulating immune cell differentiation and function. For instance, loss-of-function of lnc-DC decreased the DC differentiation and their ability to enhance T cell activation. Mechanistically, lnc-DC binds directly to cytoplasmic STAT3 and promotes STAT3 phosphorylation on tyrosine-705, therefore preventing STAT3 from being dephosphorylated by SHP1 [146]. Pro-inflammatory cytokines IFNγ and TNFα were shown to be crucial for antigen presentation [147]. Collier et al. revealed that T_H1 can produce and highly express Ifng along with lncRNA Tmevpg1 (NeST, IFNG-AS1), and IFNG-AS1 is essential for T_H1-lineage–specific expression of IFNG. Knockdown and overexpression of IFNG-AS1 significantly affected IFNG, whereas silencing of IFNG did not affect IFNG-AS1 [148]. TNFα that induce DC cell maturation was found to be induced by linc1992 (THRIL; TNFα and hnRNPL-related immunoregulatory lncRNA), which is highly expressed by in THP1 macrophages. A negative feedback regulation loop was shown between THRIL and TNFα, where over expression of TNFα downregulated THRIL, whereas silencing of THRIL decreases TNFα [149]. The balance between T effector cells and T regulatory cells regulates the final result of immune response. Many lncRNAs have been found to regulate immune cell differentiation during immune priming and activation, particularly in lymphocyte differentiation and activation [150]. In diabetic pancreatic cancer (PaC), lncRNA CECR7 regulates the expression of CTLA4 by targeting miR-429 [151]. Similarly, in gastric cancer, linc-POU3F3 stimulates the differentiation of Tregs through activation of the TGFβ pathway [152].

Also, lnc-SGK1 and SGK1 were detected in T cell of gastric tumor and peripheral, and moreover related with Helicobacter pylori infection and high-salt diet (HSD). Lnc-SGK1 stimulates T_H2 and T_H17 and reduced T_H1 differentiation through SGK1/JunB signaling, and was associated with poor prognosis of GC patients [153]. According to the findings of Zhang and his colleagues, linc-MAF-4 regulated T_H1/T_H2 differentiation and was implicated in the pathogenesis of multiple sclerosis, through regulation of encephalitogenic T cells [154]. Interestingly, Linc-MAF-4 lncRNA was shown to regulates MAF BZIP Transcription Factor (MAF) transcription via recruitment of chromatin modifiers Lysine Demethylase 1A (LSD1) and Enhancer Of Zeste 2 Polycomb Repressive Complex 2 (EZH2) Subunit and consequently skewing the differentiation of T cells toward the T_H2 phenotype through suppression of MAF expression [155]. Spurlock and his colleagues identified T_H2 locus control region (TH2-LCR) lncRNA cluster, consisting of four alternatively spliced transcripts, to be essential for the expression of genes encoding T_H2 cytokines. Th2-LCR lncRNA stimulated the formation of H3K4Me3 marks at several genomic regions of IL4, IL5 and IL13 hence stimulating the differentiation into T_H2 cells [156]. Moreover, many evidences suggest that lncRNAs involve in the migration and infiltration of immune cell in cancer. Particularly in T_H2 subset, CCR1, CCR2, CCR3 and CCR5 genes are important for their migration. LincRNA expression profiling from early T cell progenitors to terminally differentiated helper T cells identified a number of subset-specific lincRNAs. Interestingly, lincR-Ccr2-5′AS regulated the migration of T_H2 cells to the lung [157]. Fas (APO-1) is a tumor necrosis factor receptor that has a key role in the extrinsic pathway of apoptosis when activated by its ligand FasL [158]. Sehgal et al have shown that the level of lncRNA Fas-AS1 inversely correlated with the expression of the soluble Fas (sFas) in B-cell lymphoma [159]. Additionally, lncRNAs can also regulate various important cell signaling pathways, including

regulation of P53 by Damage Induced Long Noncoding RNA (DINO) and Linc-RoR, NF-κB by NF-KappaB Interacting LncRNA (NKILA) and PTGS2 Antisense NFKB1 Complex-Mediated Expression Regulator RNA (PACERR), AKT by AK023948 and LINK-A, and NOTCH by NOTCH1 Associated LncRNA In T-Cell Acute Lymphoblastic Leukemia 1 (NALT) regulatory network [160]. Given this broad regulatory activity inflicted by lncRNAs in shaping the immune system, ongoing research in this domain will ultimately uncover the importance of lncRNAs in regulating tumor immunity and their potential utilization to improve the efficacy of current immunotherapy approaches.

6. ncRNAs and resistance to cancer immunotherapy

Just as cancer cells have evolved to master immune evasion, some cancer types have developed resistance to immune-based therapies. In cases where ICIs have contributed to initial remission, longer follow ups have recorded late relapse, highlighting cancer cells' ability to acquire resistance [161]. It is important to understand why there is such heterogeneity in responses to ICIs. Total or partial loss of MHC molecules on the surface of APCs could be a contributing factor aiding ICI resistance by disrupting antigen presentation, consequently affecting the generation of active T cells for immune response [162]. In addition to this, cancer cells by their very nature are prone to high spontaneous mutation rates. For instance, patients who developed resistance to anti-PD1 treatments exhibited mutations in Janus kinases 1 and 2 (JAK1/JAK2), causing cells to lose their responsiveness to external stimuli [162].

In a study by Huber *et al*., a set of eight miRNAs (miR-146a, miR-155, miR-125b, miR-100, let-7e, miR-125a, miR-146b, and miR-99b) derived from melanoma extracellular vesicles (EVs) were able to convert monocytes into MDSCs, associated with resistance to treatment with

ICIs. Interestingly, the basal level of those miRNAs in plasma correlated with the efficacy of CTLA-4 or PD-1 blockade, suggesting those miRNAs as potential predictors of treatment response [163]. In an independent study, prostaglandin E2 (PGE2) released by doxorubicin-resistant BC cells stimulated the expansion of MDSCs, through activation of miR-10a production, and subsequent activation of AMPK signaling to promote expansion and activation of MDSCs, leading to immune resistance [164]. In a recent study, long intergenic noncoding RNA for kinase activation (LINK-A) was shown to attenuate protein kinase A-mediated phosphorylation of TRIM71 E3 ubiquitin ligase and subsequent reduction in the antigen peptide loading complex (PLC). Interestingly, triple negative breast cancer (TNBC) Patients resistant to PD-1 blockade exhibited elevated LINK-A and downregulated PLC expression, suggesting a plausible link between LINK-A and resistance to immune checkpoint inhibitors [165].

Potential utilization of miRNAs to enhance anti-tumour T cell therapy has been tested in a number of experimental models. Sasaki *et al*., reported exogenous expression of miR-17-92 to promote the survival and production of IFN-γ by human T-cells [166]. In a follow-up study, Ohno *et al*., demonstrated enhanced protection in a human glioblastoma model by CAR-T cells engineered to co-express miR-17-92 cluster [167]. Dudda *et al*., reported miR-155 overexpression to enhance the antitumor CD8 T cell response, through suppression of cytokine signaling-1 (SOCS-1) [168]. In a study by Ji *et al*., miR-155 was shown to enhance PRC2 activity, indirectly through downregulation of Ship1 and increased expression of Phf19, a PRC2-associated factor [169]. TGFβ signaling is critical for the suppressive function of MDSCs [170]. Ishii *et al*., reported direct regulation of TGFβ receptor II (TβRII) by miR-130a and miR-145, whereas exogenous expression of miR-130a and miR-145 in MDSCs decreased tumor metastasis, through downregulation of their type 2 cytokines in MDSCs accompanied by the

increase in IFNγ-production by CD8+ T cells, leading to prolonged anti-tumor immunity in preclinical mouse models [171]. Therefore the use of genetically-modified CAR-T cells expressing miR-17-92 or miR-155 as well as therapeutic delivery of miR-130a and miR-145 mimics to MDSCs might provide novel therapeutic opportunity for human cancers by overcoming resistance inflicted by the tumor microenvironment. In the context of cancer therapy, MRX34, a miR-34 mimic, is the first to enter phase I clinical trials to treat patients with advanced stage IV multiple cancer [172]. The results from the trial show that MRX34 treatment, with dexamethasone premedication, exert antitumor activity in a subset of patients with refractory advanced solid tumors; however the study was subsequently terminated due to immune-related adverse effects [172, 173]. Interestingly, miR-34 was shown to target PD-L1, therefore whether combination of MRX34 and IC would achieve better clinical outcome remains to be addressed. Taken together, those data have implicated various miRNAs in resistance to cancer immunotherapy inflicted by the tumor microenvironment and demonstrated possible utilization of miRNA-based approaches to enhance CAR-T cell therapy.

7. Conclusions

Throughout this review, we have accumulated literature core to the understanding of contemporary cancer immunotherapy approaches, as well as the latest findings associated with the use of immune checkpoint inhibitors. Our emphasis on the use of ncRNAs as a tool in cancer immunotherapy reinforces the need for further exploration of these epigenetic regulators with regards to immune checkpoint inhibition and resistance to cancer immunotherapy. Recent advanced in epigenetic research could lead to the identification of additional ncRNAs potentially

associated with tumor immunity, which provides a step in the right direction for the advancement of our knowledge pertaining to cancer immunotherapy and resistance.

In the current review, we provided a plethora of data implicating ncRNAs in regulating immune checkpoints. However, the precise contribution of ncRNA-mediated epigenetic regulation of immune checkpoints to resistance to immune therapy remains to be fully explored. A number of key questions pertaining to the precise role of ncRNAs in mediating resistance to cancer immunotherapy remains to be address. For instance, are acquired and adaptive resistance to cancer immunotherapy associated with alteration in ncRNAs in patients? What is the contribution of such mechanisms to resistance compared to other mechanisms? (i.e. clonal selection, etc). Is resistance mediated through changes in ncRNAs in the tumor or in immune cells, or both? Are such changes pre-existing or *de novo*? Are ncRNAs the drivers of resistance? Isolation of various immune subsets from patients through the course of treatment in conjunction with transcriptome and functional investigation might shed some light on the precise role of ncRNAs in this process for their potential utilization to monitor disease progression and therapeutic interventions.

Conflict of Interest statement:

The authors declare no conflict of interest.

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Figure legends

Figure 1. MicroRNA and LncRNA biogenesis and function. Pri-miRNA is transcribed by RNA polymerase II/III in the nucleus **(a)**, which is subsequently cleaved by Drosha into pre-miRNA **(b)**, followed by its export into the cytoplasm via exportin-5 **(c)**. The stem-loop is cleaved by Dicer **(d)**, producing a double-stranded structure of miRNA and antisense miRNA*. Antisense miRNA*is typically degraded, whereas the long (~22 nt) mature miRNA strand is incorporated into the miRNA-induced silencing complex (mRISC, **e**), leading to mRNA degradation or translational repression. Intergenic **(f)**, enhancer **(g)**, intronic **(h), or** antisense **(i)** lncRNAs are transcribed from the indicated promoter and are involved in gene regulation through acting in the nucleus **(j)** or cytoplasm **(k)**.

Figure 2. lncRNA-miRNA-IC network. Schematic representation of the interaction of the indicated lncRNAs, miRNAs, and immune checkpoints in the context of cancer-immune interaction. Arrow-headed and bar-headed lines indicate activation or inhibition, respectively. Solid lines indicate direct, while dotted lines indicated indirect relationship.

Fig 1

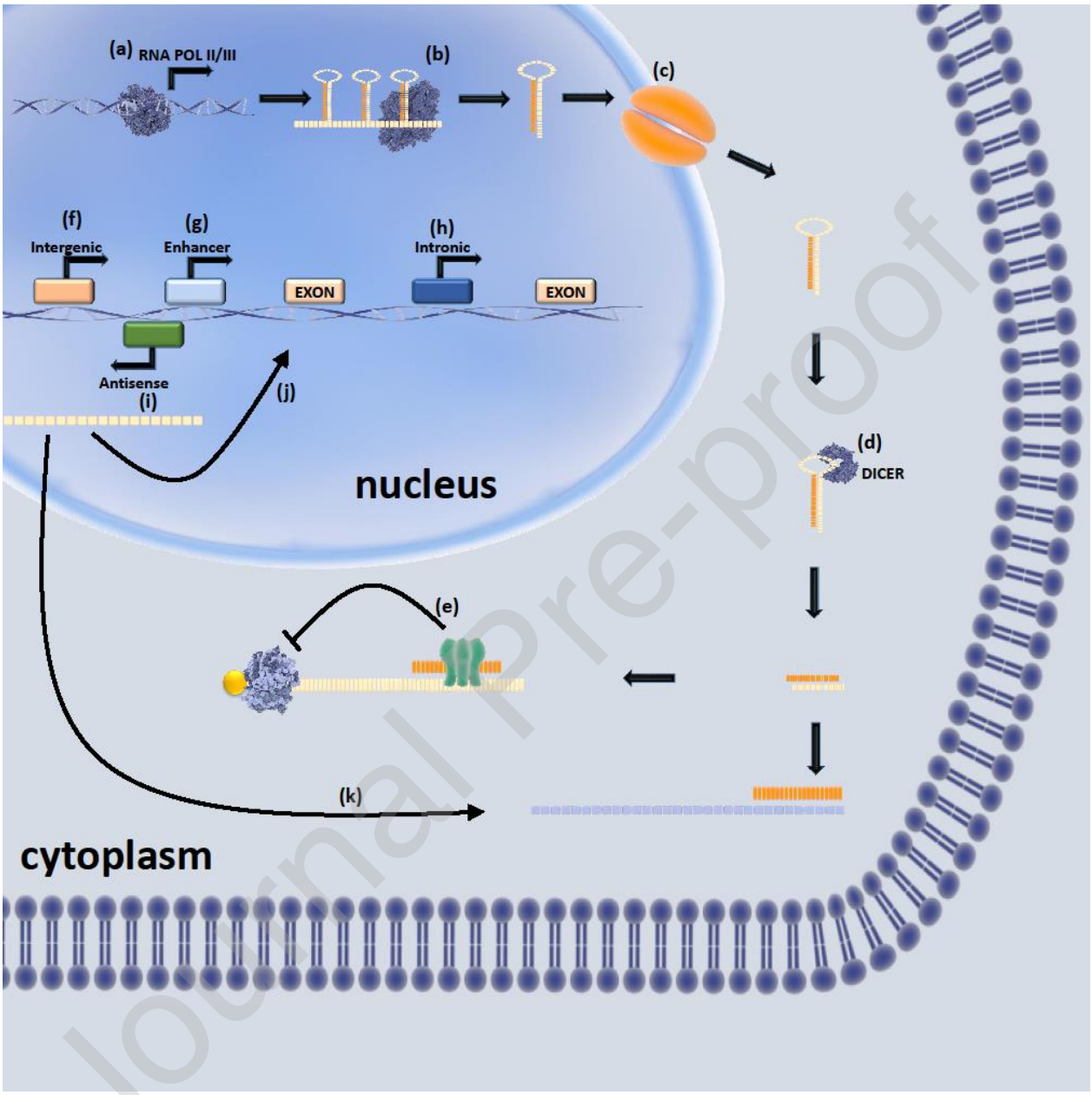

Fig 2

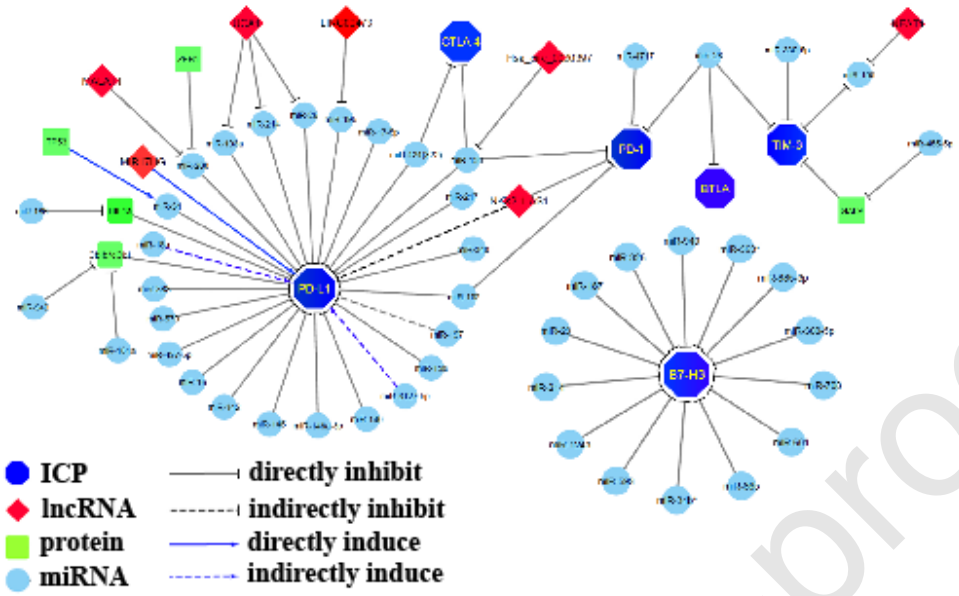

Table 1. **MiRNA and lncRNA targeting immune checkpoints in the context of cancer immune response.**

No.	miRNAs	Cancer Types/Sources	ICP	Studies	Functions	References
1	miR-29a (miR-29b and miR-29c)	Neuroblastoma and other solid tumors (sarcoma and brain tumors)	B7-H3	in vitro	B7-H3 correlated inversely with miR-29 levels in both cell lines and tumor tissues tested. MiR-29a directly target B7-H3 3'UTR, and knock-in and knock-down of miR-29a led to down-regulation and up-regulation, of B7-H3 protein expression, respectively.	[129]
2	miR-29c	Cutaneous melanoma (primary melanomas(n=30) and metastatic melanomas(n=67))	B7-H3	in vitro	MiR-29c expression level inversely correlated to B7-H3	[130]
3	miR-214, miR-363*, miR-326, miR-940, miR-29c, miR-665, miR-34b*, miR-708, miR-601, miR-124a, miR-380-5p, miR-	BC (142 patients from DBCG82bc and 101 from MicMa cohorts)	B7-H3	in vitro	A panel of thirteen miRNAs efficiently downregulating B7-H3 expression in two BC cell lines. High expression of miR-29c predicted reduced risk of death in BC in a univariate and multivariate	[131]

	885-3p, and miR-593				analysis.	
4	miR-187	Renal cell carcinoma (108 patients)	B7-H3	in vitro and in vivo	Over-expression of miR-187 decreased B7-H3 mRNA level and suppressed in vitro proliferation, and in vivo tumor growth	[132]
5	miR-570	GC (205 gastric adenocarcinoma patients and 393 non-cancer controls)	PD-L1	Single nucleotide polymorphisms (SNPs) in putative microRNA (miRNA) target sites (miRSNPs)	Luciferase reporter assay indicated that this SNP might be responsible for aberrant B7-H1 protein expression in gastric cancer by disrupting the interaction between miR-570 and B7-H1 mRNA.	[135]
6	miR-152	GC (42 patients)	PD-L1/PD-1	in vitro	miR-152 directly bind to B7-H1 3′ untranslated region in GC and inhibited B7-H1 expression. Furthermore elevation of miR-152 enhanced T cells proliferation and effector cytokines production via	[136]

					inhibiting B7-H1/PD-1 pathway.	
7	miR-152 and miR-200b	GC (96patients)	PD-L1	in vitro	miR-152 and miR-200b target B7-H1 and suppress B7-H1 expression in gastric cancer cells	[137]
8	miR-200c and miR-34a	AML	PD-L1	in vitro and in vivo	MUC1 is inhibiting PD-L1 expression via its upregulation of MiR-200c and miR-34a.	[138]
9	miR-200	LC (for in silico 230 patients data were used and further validated in 42 patients tissues)	PD-L1	in vitro and in vivo	Suppressor of EMT and metastasis, targets PD-L1. moreover, ZEB1 (EMT activator) transcriptional repressor of miR-200, relieves miR-200 repression of PD-L1 on tumor cells, leading to CD8+ T cell immunosuppression and metastasis	[139]

10	miR-186	GC (18 normal GT, 17 HDAC tissues and 16 cases of PDAC tissues)	PD-L1 (through HIF1a)	in vitro and in vivo	Overexpression of miR-186 downregulated PD-L1 and glycolytic rate-limiting enzyme HK2, PFKP content and activities by inhibiting HIF-1α, and suppressed tumor growth	[140]
11	miR-34a	NSCLC (patients details not available, 3 patients for each group, in silico 81 patients TCGA analysis)	PD-L1	in situ hybridization, in vitro and in vivo (p53R172HΔg/+K-rasLA1/+ syngeneic mouse model)	p53 regulates the tumor immune response by regulating PDL1 via miR-34	[141]
12	miR-34a	AML (44 patients)	PD-L1	in vitro	PD-L1 specific T cell apoptosis was reduced by miR-34a transfection, miR-34a regulate PD-L1 expression by targeting PD-L1 mRNA	[142]

13	miR-197	NSCLC (29 lung tumor samples with corresponding normal lung tissues for the miRNA microarray analysis and 177 lung tumor samples for validated cohort study)	PD-L1	in vitro and in vivo	downregulation of miR-197 is associated with chemoresistance and survival. miR-197/CKS1B/STAT3-mediated network drive tumor PD-L1 expression	[143]
14	miR-197	OSCC (45 male patients and 23 female patients)	PD-L1	Clinicopathologic implications	PD-L1 correlated inversely with miR-197 but correlated positively with TILs. High T stage (T4) tumors had low PD-L1 expression but had high miR-197. In cohort, high miR-197 was associated with poor overall survival, whereas PD-L1 associated with good overall survival.	[144]
15	miR-3127-5p	NSCLC (64 patients)	PD-L1	in vitro	microRNA-3127-5p induces PD-L1 elevation through regulating pSTAT3 expression	[146]

16	miR-15a, miR-16 and miR-193a-3p	Malignant pleural mesothelioma (MPM), (74 patients)	PD-L1	in vitro	miR-15a and miR-16 are predicted to target PD-L1, and mimics transfection downregulated the PD-L1 mRNA and protein in MMP model. miR-193a-3p, with an alternative G-U-containing target site, also caused PD-L1 downregulation.	[147]
17	miR-138-5p	CRC (21 patients tissues)	PD-L1	in vitro and in vivo	mssociated with advanced clinical stage, lymph node metastasis and poor overall survival	[148]
18	miR-148a-3p	CRC (395 patients and data from TCGA)	PD-L1	in vitro	miR-148a-3p is potential negative regulator of PD-L1 expression, particularly in dMMR/MSI-H CRC and reduced IFN-γ-induced PD-L1 expression.	[149]
19	miR-17-5p	MM	PD-L1	in vitro and in vivo	PD-L1 upregulation was due to post-transcriptional events controlled by miR-17-5p, which showed an inverse correlation with PD-L1 mRNA	[150]

20	miR-497-5p	Renal cell carcinoma (30 patients)	PD-L1	in vitro	miR-497–5p targets PD-L1 and knock-down promotes aggressive tumour behaviours in in-vitro	[151]
21	miR-145	Bladder Cancer	PD-L1	in vitro	Lower expression of miR-145 increases PD-L1 mRNA stability. Enhancing stem-like property and invasion through regulating PD-L1 mRNA stability and expression via ATG7/autophagy/FOXO3A/miR-145 axis.	[152]
22	miR-140, miR-142, miR-340 and miR-383 (miR-18a indirect activator)	Cervical cancer	PD-L1	in vitro and in vivo	PD-L1 is directly repressed by the miR-140/142/340/383 tumor suppressors, while it is indirectly induced by miR-18a	[153]
23	miR-195	Diffuse large B-cell lymphoma (DLBCL) (20 patients)	PD-L1	in vitro	Overexpressed miR-195 suppressed PD-L1 and promoted the secretion of IFN-γ and TNF-α, but decreased IL-10 and PD-1+T cells rate in the co-culture model of T cells and OCI-Ly-10 cells.	[154]

24	miR-424(322)	OC (for in silico TCGA 489 patients data were used and furthre validated in 42 patients tissues)	PD-L1 and CD80/CTLA-4	in vitro and in vivo	miR-424(322) expression is inversely correlated with PD-L1, and also directly regulate PD-L1 and CD80. Influences PD-L1-associated T-cell apoptosis and regulates the immunocyte production	[155]
25	miR-181a and miR-940	NSCLC (133 patients)	PD-L1 (through inhibition of Cbl-b and c-Cbl)	immunohistochemistry and in vitro	miR-181a and miR-940 indirectly upregulate PD-L1 through inhibition of Cbl-b and c-Cbl and induction of the STAT3/AKT/ERK signaling.	[156]
26	miR-217	laryngeal cancer	PD-L1	in vitro and in vivo	Inhibits laryngeal cancer metastasis through downregulation of AEG-1 and PD-L1.	[157]
27	miR-155	CRC (validated in 16 patients and 11 normal tissues)	Tim-3 inhibits miR-155	in vitro and in vivo	STAT1 acts as a key signaling adaptor linking Tim-3 signaling to miR-155 during macrophage polarization	[158]

28	miR-330-5p	AML	Tim-3	in vitro	miR-330-5p has high predicted ability to silence TIM-3 gene expression. MiR-330-5p is able to strongly silence TIM-3 expression in HL-60 cell line.	[159]
29	miR-455-5p	Chordoma (93 patients)	TIM-3 (indirectly through GAL9 inhibition)	in vitro	Positive correlation between TIM-3 and miR-455-5p expression, lower expression of miR-455-5p upregulated the expression of Gal9 in chordoma and then induce the apoptosis of TIM-3+ lymphocytes and lower TIM-3+ TIL densities.	[160]
30	miR-138	Glioma	CTLA-4 and PD-1	in vitro and in vivo	miR-138 inhibiting the expression of CTLA-4, PD-1, and FoxP3 in transfected human CD4+ T cells.	[161]

31	miR-28	Melanoma	PD-1, TIM-3 and BTLA	in vitro and in vivo	PD1 expression was decreased after transfection with miR-28 mimic. MiR-28 regulating T cell exhaustion by PD1, TIM-3 and BTLA of exhausted T cells. MiR-28 also regulating the PD1+ Foxp3+ and TIM-3+ Foxp3+ exhaustive Treg cells in vitro.	[162]
32	miR-4717	Hepatitis B virus (HBV) infection and hepatocellular carcinoma (HCC)	PD-1	In silico	miR-4717 allele-specifically regulate PD-1 expression through interaction with the 3' UTR of PD1 mRNA	[163]
33	LINC00473 (LncRNA)	pancreatic cancer (PC) (134 patients)	PD-L1	in vitro	LINC00473 and PD-L1 are upregulated, whereas miR-195-5p is downregulated in PC. LINC00473 silencing blocked the PC progression through enhancing miR-195-5p-targeted downregulation of PD-L1.	[164]

34	MALAT1 (LncRNA)	NSCLC (113 patients)	PD-L1	in vitro	MALAT1 is negatively correlated with miR-200a-3p and positively correlated with PD-L1. MALAT1 promoted proliferation, mobility, migration, and invasion of NSCLC cells via sponging miR-200a-3p.	[165]
35	UCA1 (LncRNA)	GC (40 patients)	PD-L1	in vitro and in vivo	UCA1 repressed miR-26a/b, miR-193a and miR-214 expression through direct interaction and then up-regulated the expression of PDL1. UCA1-KO GC cells formed smaller tumors, had higher miR-26a, −26b, −193a and − 214 level, reduced cell proliferation and increased apoptosis in xenograft mouse model.	[166]

36	NKX2-1-AS1 (LncRNA)	NSCLC, patients adenocarcinomas (AC, n = 8) and squamous cell carcinomas (SCC, n = 8)	PD-1/PD-L1	in vitro	NKX2-1-AS1 expression is higher in lung adenocarcinomas than in squamous cell carcinomas. NKX2-1-AS1 negatively regulates PD-1/PD-L1 signaling and adherens junction pathways. NKX2-1-AS1 impairs binding of NKX2-1 protein to the CD274 gene promoter. NKX2-1-AS1 inhibits transcription from the CD274 proximal promoter and reduces NKX2-1-mediated activation of CD274 transcription and does not change the histone methylation landscape of the CD274 promoter.	[167]

37	MIR17HG (LncRNA)	CRC (6 patients)	PD-L1	in vitro and in vivo	MIR17HG directly binds to PD-L1. mRNA expression levels of PD-L1 was indistinguishable from control following either MIR17HG overexpression or knockdown, whereas westernblot showed increased PD-L1 expression following MIR17HG overexpression and decreased PD-L1 expression following knockdown in CRC model.	[168]
38	Hsa_circ_0020397 (circRNA)	CRC	PD-L1	in vitro	Hsa_circ_0020397 regulates colorectal cancer cell viability, apoptosis and invasion by promoting the expression of the miR-138 targets TERT and PD-L1.	[169]

39	NEAT1 (LncRNA)	Hepatocellular carcinoma (HCC), 20 patients	TIM-3	in vitro and in vivo	NEAT1 and Tim-3 were up-regulated and miR-155 was lower in PBMCs of patients with HCC. Down-regulation of NEAT1 restrained CD8+T cell apoptosis and enhanced the cytolysis activity through the miR-155/Tim-3 pathway. Repression of NEAT1 suppressed tumor growth in HCC mice.	[170]