Immune Checkpoint Gene Regulation by microRNA in Cancer

Subjects: Oncology

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Currently, the search for new promising tools of immunotherapy continues. In this regard, microRNAs that influence immune checkpoint gene expression in tumor and T-cells. An important feature of miRNA is its ability to affect the expression of several genes simultaneously, which corresponds to the trend toward the use of combination therapy. MiRNAs regulate gene expression by blocking mRNA translation. An important feature of miRNA is its ability to affect the expression of several genes simultaneously, which corresponds to the trend toward the use of combination therapy.

Keywords: microRNA ; immune checkpoint ; immunotherapy

1. Introduction

Immunotherapy is an innovative method of cancer treatment. As a result of experiments and clinical trials, it has been found that immunotherapy can increase progressionfree survival and overall survival. However, this method of treatment is effective in a limited number of patients, and in addition, it can cause severe adverse reactions due to hyperreactivity of the immune system [1]. In this regard, research is underway to develop new therapeutic approaches based on targeting immune checkpoints (ICs). Tumor cells have the ability to generate ligands that can bind to co-inhibitory receptor molecules. This interaction suppresses the antitumor immune response, allowing the tumor to “escape” from the immune system. In order to increase the effectiveness of immunotherapy, the FDA approved a number of regimens, including a combination of two IC inhibitors, a combination of IC inhibitors and targeted therapy drugs, as well as antitumor bispecific antibodies [2][3]. It has been shown that in combination therapy regimens, patients experienced a higher response rate compared to monotherapy [4]. In addition, the search for a more promising immunotherapy approach is currently ongoing. In this regard, microRNAs (miRNAs) are considered. According to recent studies, miRNAs influence IC gene expression and are important regulators in both T-cells and tumor cells [5]. MiRNAs regulate gene expression by binding to the 3’-UTR of their mRNA [6][7][8]. MiRNAs can also affect IC expression indirectly, through molecules of different signaling pathways, such as PTEN, IFR-1, and others [9]. It is also important that one miRNA can affect several genes [5][10]. Here presents a entry of miRNAs that interact with IC genes, analyzes their regulating IC expression in tumors of various types of cancer, and identifies miRNAs that act on several IC genes simultaneously. Due to these properties, miRNA-based therapy may become an alternative to the combination of targeted drugs in the future. In addition, miRNAs are considered that are capable of simultaneously regulating the expression of targeted therapy genes along with IC genes. These issues have not been previously analyzed in existing reviews of miRNAs as IC regulators [11][12][13][14][15]. The researchers have reviewed more than 200 miRNAs that regulate ICs in tumors of various types.

Table 1. The miRNAs interacting with IC genes in different types of cancer.

Immune Checkpoint	microRNA	Cancer	Reference
PD-1	miR-374b, miR-4717	Liver cancer	[16][17]
PD-1/PD-L1	miR-183	RCC	[18]
	miR-138-5p, miR-200b, miR-429, miR-508	Lung cancer	[19][20]

Immune Checkpoint	microRNA	Cancer	Reference
PD-L1	miR-142-5p	PC, OC	[21][22]
	miR-497-5p	ccRCC	[23]
	miR-20-b, miR-21, miR-130b, miR-138-5p, miR-148a-3p, miR-191-5p	CRC	[24][25][26][27]
	miR-195, miR-424-5p, miR-497, miR-873, miR-3609	BC	[28][29][30][31]
	miR-17-5p, miR-146a	Melanoma	[32][33]
	miR-15a, miR-15b, miR-16, miR-193a-3p, miR-320a	Pleural Mesothelioma	[34][35]
	miR-155, miR-195, miR-214	B-cell lymphoma	[36][37][38]
	miR-16, miR-195	Prostate cancer	[39]
	miR-34a, miR-34b, miR-34c, miR-140, miR-200, miR-200a-3p, miR-3127-5p	Lung cancer	[40][41][42][43][44]
	miR-34a	AML	[45]
	miR-23a-3p, miR-570	Liver cancer	[46][47]
	miR-375	HNSCC	[48]
	miR-145	OC, bladder cancer	[49][50]
	miR-513a-5p	Retinoblastoma	[51]
	miR-105-5p, miR-152, miR-200b, miR-200c, miR-570	GC	[52][53][54][55][56]
	miR-18a, miR-140, miR-142, miR-340, miR-383	Cervical cancer	[57]
	miR-217	Laryngeal cancer	[58]
	miR-20b-5p	Models of lung and BC	[59]
	miR-194-5p	PC	[60]
PD-L1+B7-H3	miR-326	Lung cancer	[61]
PD-1, CTLA-4	miR-424	OC	[62]
	miR-138-5p	Glioma	[63]
CD80/CTLA-4	miR-424	CRC	[64]
PD-1, PD-L1, CTLA-4	miR-33a	Lung cancer	[65]
PD-1, BTLA, Tim-3	miR-28	Melanoma mouse model	[66]
BTLA	miR-32	OC	[67]
Tim-3	miR-498	AML	[68]
IDO1	miR-153, miR-448	CRC	[69][70]
Gal-3	miR-424-3p	OC	[71]
	miR-128	CRC	[72]
Gal-9	miR-22	Liver cancer	[73]
	miR-15b-5p, miR-455-5p, miR-1237, miR-1246	CRC	[74][75]
ICOS (B7-H2)/ICOSL	miR-24	GC	[76]

Immune Checkpoint	microRNA	Cancer	Reference
	miR-29 (a, b and c)	Neuroblastoma, sarcoma, brain tumors	[77]
	miR-145	Lung cancer	[78]
	miR-28-5p, miR-29a, miR-128, miR-145, miR-155/miR-143, miR-187, miR-192, miR-335-5p, miR-378, miR-1301-3p	CRC	[79][80][81][82][83]
	miR-187	ccRCC	[84]
	miR-29c	Melanoma, CRC	[85][86]
B7-H3	miR-29c, miR-34b, miR-124a, miR-125b-2, miR-214, miR-297, miR-326, miR-363, miR-380-5p, miR-506, miR-555, miR-567, miR-593, miR-601, miR-665, miR-708, miR-885-3p, miR-940	BC	[87]
	miR-539	Glioma	[88]
	miR-124	Osteosarcoma	[89]
	miR-506	Mantle cell lymphoma	[90]
	miR-214	Multiple myeloma	[91]
	miR-29, miR-1253	Medulloblastoma	[92][93]
	miR-199a	Cervical cancer	[94]
B7-H5 (VISTA, BTNL2)	miR-125a-5p	GC	[95]
	miR-155/miR-143, miR-1207	CRC	[80][96]
B7-H4 (VTCN1)	miR-7–5p, hsa-let-7c, hsa-let-7f-5p, miR-17–3p, miR-21–3p, miR-21–5p, miR-24–1-5p, miR-27b-3p, miR-31–3p, miR-31–5p, miR-33a-5p, miR-33b-5p, miR-122–3p, miR-130b-3p, miR-138–1-3p, miR-148a-3p, miR-149–3p, miR-183–3p, miR-186–5p, miR-196a-5p, hsa-miR-204–3p, miR-299–5p, miR-302a-3p, miR-302e, miR-335–3p, miR-335–5p, miR-361–5p, miR-374c-5p, miR-483–3p, miR-513a-5p, miR-519e-3p, miR-520d-5p, miR-525–5p, miR-615–3p, miR-642a-5p, miR-744–5p, miR-937, miR-1246, miRPlus-G1246–3p, miR-1260a, miR-1265, miR-1284, miR-1290, miR-1973, miR-2115–3p, miR-2116–5p, miR-3178, miR-3202, miR-3646, miR-3651, miR-3676–3p, miR-3685, miR-3686, miR-4258, miR-4279, miR-4284, miR-4288, miR-4290, miR-4306, miR-4324	PC	[97]
B7-H6 (NCR3LG1)	miR-93, miR-195, miR-340	BC	[29]
B7-H7 (HHLA2)	miR-3116, miR-6870-5p	ccRCC	[98]

Footnotes: RCC—renal cell cancer; PC—pancreatic cancer; OC—ovarian cancer; CRC—colorectal cancer; BC—breast cancer; AML—acute myeloid leukemia; HNSCC—head and neck squamous cell cancer; GC—gastric cancer.

2. The Features of Immune Checkpoint Gene Regulation by microRNA in Cancer

The results of accumulated data analysis demonstrate a significant relationship between the action of miRNAs on ICs genes and the type of tumor—only about 14% (95% CI: 9.8–20.1%) of the studied miRNAs regulate the expression of specific IC in more than one type of cancer.

Currently, there are numerous studies underway to identify miRNAs that are the most promising as immunotherapy agents. In vivo experiments have repeatedly shown that miRNA-based therapy leads to significant tumor regression. Although miRNA has not yet entered the arsenal of antitumor agents used in practice, some results are encouraging. Thus, the miR-155 inhibitor has performed well in clinical trials. The study of miR-138 is promising. Ongoing research on miR-34a may also lead to a positive result. Thus, there is the prospect of using miRNA as a therapeutic agent in cancer immunotherapy regimens. At the same time, the ability of miRNAs to inhibit several genes can lead to adverse events. To

overcome this, it is important to expand data of the spectrum of miRNA targets in a particular type of cancer. Additional studies of the miRNA–genes interaction features and the search for an optimal miRNA mimic structure are necessary, thus allowing an increase in the efficiency and selectivity of interaction with the mRNA of target genes. It can increase the effectiveness of therapy, as well as reduce the dose of the drug, thereby reducing its side effects.

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