

Review

Functions of non-coding RNAs in regulating cancer drug targets

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Abstract

With the development of precision medicine, the efficiency of tumor treatment has been significantly improved. More attention has been paid to targeted therapy and immunotherapy as the key to precision treatment of cancer. Targeting epidermal growth factor receptor (EGFR) has become one of the most important targeted treatments for various cancers. Comparing with traditional chemotherapy drugs, targeting EGFR is highly selective in killing tumor cells with better safety, tolerability and less side effect. In addition, tumor immunotherapy has become the fourth largest tumor therapy after surgery, radiotherapy and chemotherapy, especially immune checkpoint inhibitors. However, these treatments still produce a certain degree of drug resistance. Non-coding RNAs (ncRNAs) were found to play a key role in carcinogenesis, treatment and regulation of the efficacy of anticancer drugs in the past few years. Therefore, in this review, we aim to summarize the targeted treatment of cancers and the functions of ncRNAs in cancer treatment.

Key words non-coding RNA (ncRNA), immune checkpoint inhibitor, EGFR, precision medicine, drug resistance

Introduction

Cancer has become a major disease that threatens human health because of its high morbidity and mortality. The traditional treatments, including surgery, radiotherapy and chemotherapy, have great limitations [1]. In addition, due to the immune deficiency of the body or immune damages caused by operation, radiotherapy or chemotherapy, the new and residual cancer cells cannot be removed in time, leading to further development of the disease caused by proliferation, spread and metastasis. With the comprehensive application and popularization of new technologies, precision medicine, especially in the field of cancer, is entering a stage of rapid development. Precision medicine is an individual diagnosis and treatment strategy based on personal genome information and relevant internal environment information such as proteomics and metabolomics [2]. The arrival of the precision treatment era brings hope to targeted treatments of various cancers.

At present, precision treatment of cancers mainly includes treatment based on driving cancer gene, angiogenesis and immunotherapy. Epidermal growth factor receptor (EGFR), a typical model of targeted therapy, is closely related to the occurrence and development of cancers. Statistics have shown that there are either overexpression or active mutations of EGFR in about 30% of solid

tumors, including lung cancer, breast cancer, head and neck squamous cell carcinoma and glioblastoma. Targeting EGFR has become one of the most important treatments for various cancers [3].

In recent years, with the illustration of the mechanism of tumor cellular immune escape, immunotherapy, particularly immune checkpoint inhibitors, has shown incomparable advantages in tumor treatment. It is reported that programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) blockades have achieved remarkable anti-tumor effects in various tumor types, yet drug resistance and side effect to these inhibitors have made the treatments more difficult [4].

Based on the study of genome microarray, whole genome and transcriptome sequencing, at least 90% of the genome is transcribed [5]. However, less than 2% of the whole genome sequence has the function of coding protein, and the number of non-coding RNAs (ncRNAs) is much larger than that of coding RNAs. Non-coding RNAs refer to the RNA molecules that do not have the ability to encode proteins, but play a role in the life activities of organisms, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) [6,7]. In 2011, Salmena *et al.* firstly proposed the hypothesis of the interaction between protein-coding

messenger RNA (mRNA) and ncRNA called “competing endogenous RNA (ceRNA)”, indicating ncRNA that contains microRNA respond element (MRE) can relieve the inhibition of miRNA to the target mRNA by binding with miRNA. In addition, lncRNA and circRNA can also bind with miRNA through MRE to reduce the available binding sites between miRNA and target genes, that is, lncRNA and circRNA can also be used as ceRNA to indirectly regulate the expression level of target genes [8]. Therefore, non-coding RNAs can be considered to have important functions in the occurrence and development of tumors.

In this review, we aim to summarize the targeted treatment of cancers and the functions of non-coding RNAs in cancer treatment.

EGFR as a Successful Target in Precision Medicine

EGFR is a member of the HER family and belongs to receptor tyrosine kinase. In non-small cell lung cancer (NSCLC), 10% ~ 35% of patients contain EGFR gene mutation. Thus, EGFR has become an important therapeutic target. More and more tyrosine kinase inhibitors (TKIs) have been developed and used in clinical trials and first-line treatment of malignant tumors such as NSCLC. In the early 2000s, Gefitinib, one of the epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), was approved by Food and Drug Administration (FDA). Since then, the study of NSCLC enters a fast track to precision therapy [9]. The first-generation EGFR-TKIs in China mainly include Gefitinib, Erlotinib and Icotinib. Gefitinib was licensed in China in 2005, followed by Erlotinib and Icotinib in 2007 and 2011 respectively. However, with the continuous use of TKI preparations, some patients have developed drug resistance [10]. The main mechanism of drug resistance is EGFR gene mutation, in which the incidence of Thr790Met (T790M) mutation in exon 20 is as high as 50% ~ 65% [11]. The second-generation EGFR-TKIs, including Afatinib and Dacomitinib, can irreversibly bind to the targets and enhance the therapeutic effect. Although the first-generation and second-generation molecular targeted drugs have significantly prolonged the median remission time, the vast majority of patients eventually developed drug resistance, of which the secondary mutation of T790M accounts for 50% ~ 60% of all drug resistance mechanisms [12]. The third-generation EGFR-TKIs are novel targeted therapeutic drugs which are highly selective and effective against EGFR-TKI, including Osimertinib, Rociletinib and Almonertinib, but acquire T790M resistance as well. Among them, Almonertinib (HS-10296) is an innovative drug independently developed by Haosen Pharmaceutical Company. It has just been approved in China on March 18, 2020 for the treatment of locally advanced or metastatic NSCLC adult patients with advances in previous EGFR-TKI treatment and positive T790M mutation. It is the second third-generation EGFR-TKI innovative drug approved to be marketed in the world. In conclusion, EGFR-TKIs have led to the

development of precision medicine for lung cancer (Table 1).

Regulation of EGFR by non-coding RNAs

Regulation of EGFR by miRNAs

miRNAs are about 22 nucleotides in length and exert a function on biological processes, including the development of cancers [13,14]. RNA polymerase II/III transcribed miRNAs to form pre-miRNAs, and then pre-miRNAs are processed by the microprocessor complex (RNA binding protein DGCR8 and ribonuclease III enzyme Drosha). After the export, Dicer and TRBP cleave pre-miRNA to form the mature miRNA complex [15,16]. miRNAs can be used as tumor oncogenes or tumor suppressor factors. In the process of gene expression, they serve as essential post-transcriptional regulators which have great effects on tumors.

The miR-200 family is an miRNA family that has been studied in various malignant tumors, including ovarian cancer, colorectal cancer and lung carcinoma [17]. It was found that the decline of miR-200a in NSCLC cells can directly target the 3'-UTR of EGFR and downregulate its expression level to inhibit migration and invasion in NSCLC [18]. In order to confirm that EGFR is the real target of miR-200a, the authors performed luciferase report analysis using the original 3'-UTR sequence and its mutant version of EGFR mRNA. The results showed that EGFR 3'-UTR is indeed the direct target of miR-200a. Additionally, wound-healing assay, cell invasion assay, MTS assay and BrdU incorporation assay were performed to indicate that the viability and proliferation of the three NSCLC cell lines were significantly inhibited after miR-200a transfection [18]. Another research revealed that miR-200a contributes to the downregulation of G protein α inhibitory subunit 1 (Gai1) and influences EGFR expression [19].

miR-34a, located in the lp36.23 region of the chromosome [20], is a tumor suppressor with deletion or down-regulation of expression [21]. It is well known that miR-34a can significantly inhibit tumor progression, such as breast cancer [22], NSCLC [23], and squamous cell carcinoma of head and neck [24]. According to quantitative real-time PCR (qRT-PCR) performed in 60 patients with NSCLC and corresponding para-cancerous tissues, Li and her colleagues [24] demonstrated that miR-34a is downregulated in NSCLC cell lines. They found that miR-34a inhibits NSCLC tumor growth and metastasis through targeting EGFR, which indicates that miR-34a may not only become molecular targets for the treatment of NSCLC, but also become a useful prognostic or progressive marker for NSCLC. In glioblastoma, miR-219-5p is downregulated. Moreover, over-expression of miR-219-5p inhibits cell proliferation through inhibiting EGFR by directly binding to its 3'-UTR and downregulating the activity of RTK pathway [25]. miR-1231 expression, inversely correlated with EGFR expression level, is downregulated in human glioma tissues. Bioinformatics prediction and luciferase assay re-

Table 1. EGFR-TKIs approved for use

EGFR-TKI	Type	Year of approval	Acquired mutation
Gefitinib	First-generation	2003/NMPA	T790M
Erlotinib	First-generation	2005/NMPA	T790M
Afatinib	Second-generation	2013/FDA 2017/NMPA	No
Dacomitinib	Second-generation	2019/NMPA	No
Osimertinib	Third-generation	2015/FDA 2017/NMPA	C797S
Almonertinib	Third-generation	2020/NMPA	No

vealed that EGFR is a direct target of miR-1231 [26]. The inhibitory effect of miR-1231 on the PI3K/AKT pathway and G1 phase can be blocked by EGFR overexpression [26]. It has also been demonstrated that miR-221 is upregulated in temozolomide-resistant and radiation-resistant glioblastoma, and miR-221 can downregulate the expression of EGFR to mediate drug resistance to temozolomide and radiotherapy, making it a potential target for further targeted therapy [27]. miR-566 [28], miR-7 [29], miR-181b [30] and miR-615 [31] have also been demonstrated to regulate EGFR expression.

Regulation of EGFR by lncRNAs

Long non-coding RNAs (lncRNAs) are non-coding RNAs with a length greater than 200 nt [32]. lncRNAs are also involved in chromatin modification, gene regulation, transcriptional activation and interference, as well as invasion, metastasis of tumors and drug resistance. They play a key role in the occurrence and development of tumors [33].

LNC-EGFR, upregulated in patients with tongue cancer, has been proved to play an important role in the diagnosis and treatment of tongue cancer [34]. Colony formation assay and cell proliferation assay showed that LNC-EGFR gene knockout could inhibit the colony formation ability and cell viability of human tongue cancer cell lines. LNC-EGFR inhibits the apoptosis of human tongue cancer cells by positively regulating EGFR. This study suggested that LNC-EGFR may provide new insights into the development of therapeutic strategies for tongue cancer. Another research revealed that LNC-FAM201A was significantly upregulated in the tissues of patients with radiotherapy-resistant NSCLC, and FAM201A silencing could inhibit the proliferation and further apoptosis of NSCLC cells under X-ray irradiation *in vivo* and *in vitro*. In addition, the levels of EGFR and hypoxia inducible factor 1 α (HIF-1 α) were increased when FAM201A competitively targeted miR-370. After FAM201A gene knockout, EGFR and HIF-1 α were inhibited, and radiosensitivity was enhanced [35]. The expression of lncRNA-UCA1 in hypoxia-resistant gastric cancer (HRGC) cells was upregulated to promote their migration. Bioinformatics analysis and luciferase reporter assay revealed that miR-7-5p could bind to specific sites of UCA1 and regulate EGFR [36]. UCA1 directly interacts with miR-7-5p to inhibit the degradation of EGFR mRNA. Therefore, UCA1 enhances EGFR expression and promotes cell migration. Wang and colleagues [37] found that lncRNA EGFR-AS1 stimulated the growth and invasion of bladder cancer cells via suppressing the degradation of EGFR mRNA, indicating that lncRNA EGFR-AS1 can be used as a promising diagnostic marker for bladder cancer. SNHG16, a novel recognized lncRNA, was verified to be upregulated in human malignant carcinomas [38]. Researchers found that SNHG16 acts as a ceRNA to sponge miR-373-3p and regulate EGFR through activating PI3K/AKT pathway, thereby exerting oncogenic function. lncRNA MYLK-AS1, as an upstream regulator of EGFR/HER2, promotes the migration, proliferation, and invasion of HCC cells via activating the EGFR-ERK1/2 signaling pathway [39]. The expressions of lncRNA KRT16P2 and EGFR were both obviously upregulated in laryngeal squamous cell carcinoma (LSCC), and KRT16P2 inhibited EGFR expression through suppressing miR-1294 expression, indicating that KRT16P2/miR-1294/EGFR influences the proliferation, invasion, and migration of LSCC cells [40]. Other lncRNAs, such as LPP-AS2 [41], LINC01485 [42], LINC00152 [43] and ARAP1-AS2 [44], also have a close relationship with EGFR.

Regulation of EGFR by circRNAs

Circular RNAs (circRNAs) are produced by the “back splicing” of

the precursor mRNA (pre-mRNA) transcripts, becoming covalently closed, circular single-stranded RNAs [45]. According to their origin, they can be divided into three types, being exonic circRNAs (ecRNAs), intron circRNAs (ciRNAs) and exon-intron circRNAs (EiRNAs) [46]. The expressions of target genes are regulated by circRNAs at the transcriptional or post-transcriptional level by interacting with other molecules or miRNAs [47]. Many circRNAs are involved in tumorigenesis and become new tumor markers and therapeutic targets [48].

circRNA ciRS-7 was found to be abnormally upregulated and abundantly sponge miR-1299 in esophageal squamous cell carcinoma (ESCC). miR-1299 can directly bind to the 3'-UTR of EGFR, thus affecting its downstream Akt-mTOR pathway. Meng and his colleagues [49] observed that ciRS-7 could inhibit autophagy of ESCC cells induced by starvation or rapamycin, and miR-1299 could promote autophagy of ESCC cells. Another research revealed that circular RNA CDR1-AS, closely associated with the EGFR/PI3K signaling pathway, was upregulated in lung adenocarcinoma (LUAD) tissues and cell lines [50]. In LUAD patients, the expression of CDR1-AS was high and related to the insensitivity of pemetrexed (PTX) and cisplatin (CDDP). CDR1-AS promoted the chemical resistance of PTX and CDDP through the EGFR/PI3K signaling pathway. In osteosarcoma cancer, the expression of cir-ITCH is significantly upregulated, and cir-ITCH can increase the expression of EGFR via reducing the level of miR-7 [51]. circ-ATP8A2 is markedly enhanced in cervical cancer (CC). Ding *et al.* [52] demonstrated that circ-ATP8A2 sponged miR-433 to suppress EGFR expression at post-transcriptional level and promote cell progression by the miR-433/EGFR axis. CircHBEGF acts as a miR-646 sponge to regulate EGFR expression in human trabecular meshwork cells (HTMCs) [53]. In gastric cancer (GC) cells and tissues, circ_0081143 expression is increased, and circ_0081143 sponges miR-497-5p to modulate EGFR expression, indicating that circ_0081143 is a new potential target for GC treatment [54] (Figure 1).

EGFR-TKI resistance and non-coding RNAs

EGFR-TKI resistance and miRNAs

As previously mentioned, most patients eventually develop acquired drug resistance after a period of treatment. In recent years, more and more miRNAs were found to be related to EGFR-TKI resistance, suggesting that miRNAs may become new targets or promising predictive biomarkers for anti-EGFR therapy. In addition, miRNA-based therapy is considered to be a reasonable and potentially effective treatment for targeted EGFR.

Studies have shown that miR-21 is upregulated in NSCLC and participates in the regulation of lung cancer cell growth and invasion. Li *et al.* [55] found that miR-21 was highly expressed in NSCLC cell line PC9GR with EGFR deletion mutation (delE746-A750) and EGFR-TKI resistance, and negatively correlated with the expression of PTEN and PDCD4. In addition, there is a close relationship between miR-21 and the activation of PI3K/AKT signal pathway. Notably, NSCLC patients who acquired EGFR-TKI resistance at the beginning had higher serum miR-21 levels than the baseline. Additionally, in EGFR mutant NSCLC cell line, miR-21 downregulated the expression of PTEN, which promoted the tumorigenesis of lung cancer. The expression of miR-21 leads to poor prognosis and shorter overall survival (OS), and overexpression of miR-21 reduces the sensitivity of Gefitinib by downregulating PTEN and activating the PI3K/AKT signal pathway, while downregulation of the ex-

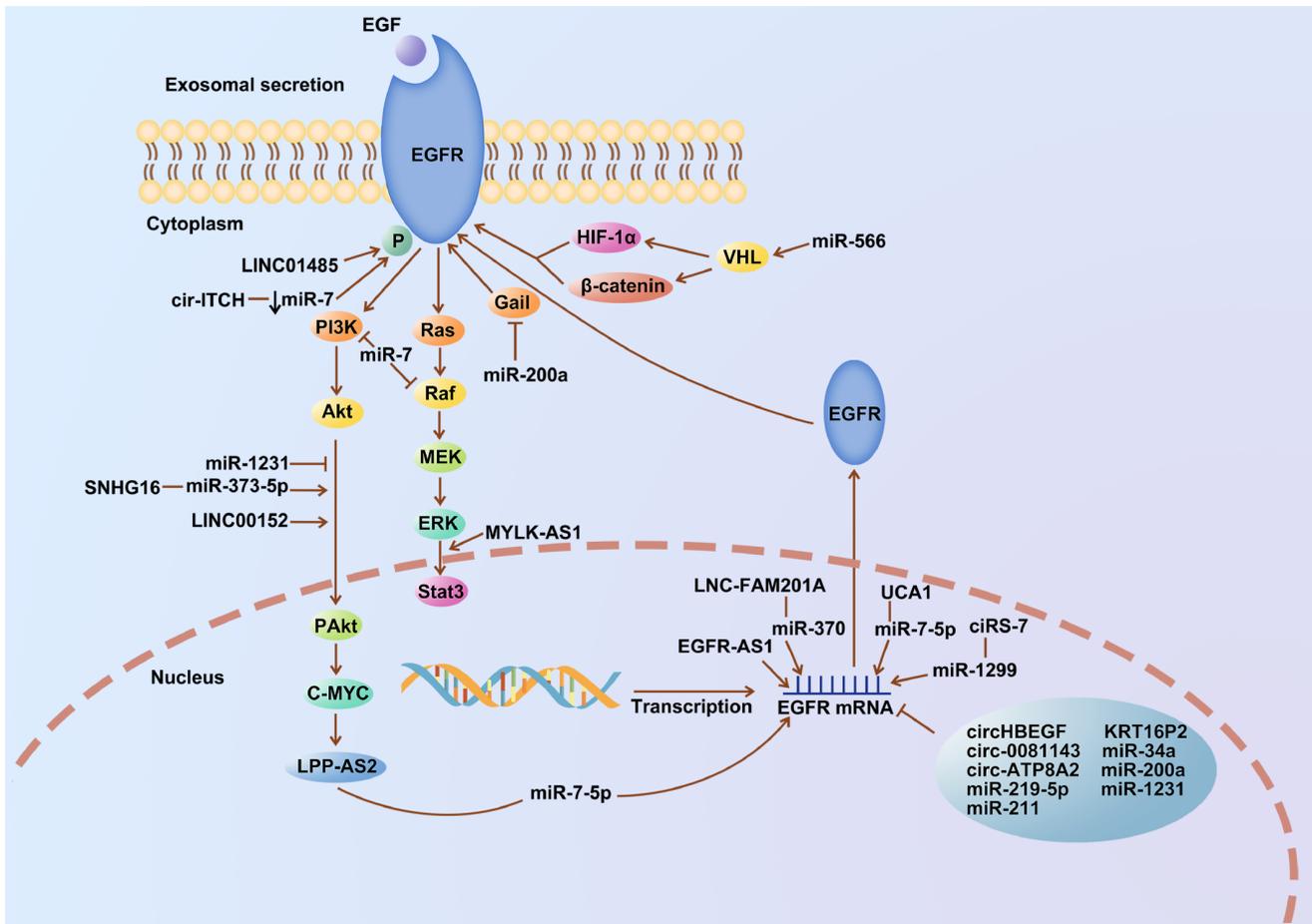


Figure 1. Non-coding RNAs involved in regulation of EGFR in cancer Non-coding RNAs mainly regulate EGFR by targeting EGFR receptor through PI3K/AKT pathway, Ras/ERK pathway, Gail and HIF-1 α / β -catenin, or directly targeting EGFR mRNA.

pression of miR-21 can increase the sensitivity of Gefitinib by up-regulating the activity of PTEN and inhibiting the PI3K/AKT signal pathway [56]. Similar to miR-21, miR-214 is also involved in the regulation of acquired resistance of Gefitinib by regulating PTEN and PI3K/AKT signal pathways [57]. In Erlotinib-resistant (ER) cells, the expression of miR-506-3p is decreased significantly. It can counteract EGFR-TKI resistance by downregulating Sonic Hedgehog (SHH) signaling and increasing the expression of E-cadherin. The miR-506-3p/SHH axis may become a new target for the treatment of EGFR mutant lung cancer in the future [58]. Wang *et al.* [59] found that miR-200c-3p can enhance the sensitivity of EGFR-TKIs by regulating the epithelial-to-mesenchymal transition (EMT) process. With the development of resistance to EGFR-TKI treatment, the expression of miR-146b-5p in lung cancer cells was significantly increased. EGFR-TKI-induced apoptosis can be promoted by ectopic expression of miR-146b-5p. miR-146b-5p inhibits the nuclear factor kappa B (NF- κ B) activity and the production of NF- κ B-related IL-6 and IL-8 by targeting IRAK1, and miR-146b-5p is negatively correlated with IRAK1 which can reverse the effect of miR-146b-5p on the sensitivity of EGFR-TKI. In summary, the miR-146b-5p/IRAK1/NF- κ B signaling plays an important role in accelerating EGFR-TKI resistance [60]. miR-1 remarkably inhibits the effect of EGFR-TKI, and researchers found that upregulated miR-1 develops EGFR-TKI resistance by suppressing tumor immune microenvironment (TIME). Therefore, miR-1 can be used as a useful clinical marker to predict

the efficacy of immunotherapy in patients with lung adenocarcinoma resistant to EGFR-TKIs [61]. In xenografts, the growth of tumor induced by H1650-acquired Gefitinib-resistance (H1650GR) can be inhibited by Gefitinib combined with miR-30a-5p mimics. Therefore, the combination of Gefitinib and miR-30a-5p may play a key role in overcoming EGFR-TKI resistance [62]. It was also reported that the anticancer effect of Gefitinib on NSCLC cells was improved by miR-1262 [63]. Meanwhile, miR-150 [64], miR-17 [65], miR-483-3p [66], miR-608 and miR-4513 [67] were also found to contribute to EGFR-TKI resistance.

EGFR-TKI resistance and lncRNAs

In recent years, much attention has been paid to the research on lncRNAs and drug resistance. A large number of lncRNAs have been proved to be related to drug resistance [68,69].

lncRNA BC087858 is an intergenic lncRNA located near the *FOXC1* gene, an important gene in the development of tumors. lncRNA BC087858 may be related to EGFR-TKI resistance through epithelial-to-mesenchymal transition (EMT), as *FOXC1* can promote EMT [70,71]. Wang *et al.* [72] found that the resistance of NSCLC cells to Gefitinib can be affected by the overexpression of MIR31HG lncRNA via activating the EGFR/PI3K/AKT pathway, and then cell proliferation, apoptosis and cell cycle are affected. lncRNA UCA1, first identified in bladder cancer cells and upregulated in lung cancer, can induce non-T790M acquired resistance to EGFR-TKIs by activating the AKT/mTOR pathway [73,74]. Meanwhile, knock-

down of *UCA1* can enhance E-cadherin expression [75], indicating that lncRNA *UCA1* regulates the resistance to EGFR-TKIs also by activating EMT [74]. lncRNA *GAS5*, significantly downregulated in lung adenocarcinoma tissues, is also related to EGFR-TKI resistance. Researchers found that *GAS5* enhanced Gefitinib-induced cell death in EGFR-TKI-resistant lung adenocarcinoma by downregulating IGF-1R expression. Therefore, *GAS5* may play a novel role in the development of drug resistance to Gefitinib, and overexpression of *GAS5* can reverse this resistance [76]. A long non-coding RNA, *HOTAIR*, is obviously decreased in lung cancer cells and patients with EGFR-TKI resistance, while overexpression of *HOTAIR* can restore the sensitivity of Gefitinib in cells [77]. lncRNA *SNHG15* was reported to alter Gefitinib resistance of lung adenocarcinoma cells via regulating miR-451/multidrug resistance protein 1 (*MDR-1*) [78]. In clinical patients with EGFR-TKI resistance, lncRNA *H19* acts as an obviously downregulated lncRNA. The downregulation of lncRNA *H19* results in Erlotinib resistance via enhancing the phosphorylation of AKT [79]. *LINC00460* acts as a ceRNA of miR-149-5p to promote EGFR-TKI resistance and the knockdown of *LINC00460* can restore the effect of EGFR-TKI in Gefitinib-resistant NSCLC cells [80]. Chen *et al.* [81] found that lncRNA *CASC9* expression was upregulated in both Gefitinib-resistant and Gefitinib-sensitive cells. *In vitro* and *in vivo* Gefitinib sensitivity can be restored by *CASC9* inhibition, but overexpression of *CASC9* promotes Gefitinib resistance via repressing *DUSP1*, a tumor suppressor. Moreover, ectopic expression of *DUSP1* improves the sensitivity of Gefitinib by inhibiting the ERK pathway. *BLACAT1*, a novel lncRNA, plays an important role as an oncogenic lncRNA and is related to EGFR-TKI resistance. A study demonstrated that knock-out of *BLACAT1* gene reversed the drug resistance to Afatinib of NSCLC cells by regulating the STAT3 signal pathway [82]. Another study indicated that lncRNA *LOC554202* upregulated the expression of miR-31 and decreased the sensitivity of NSCLC cells to Gefitinib [83].

Immune Checkpoint Inhibitors as New Targets

In recent years, tumor immunotherapy has developed rapidly domestically and internationally. It is considered to be another important treatment method with a significant effect on tumors after surgery, radiotherapy and chemotherapy. In 2013, the journal of Science announced that immunotherapy was a breakthrough in cancer treatment [84]. It has been widely used in the treatment of many kinds of malignant tumors, such as ovarian cancer [85], melanoma [86], Hodgkin lymphoma [87] and NSCLC [88]. A variety of immunotherapeutic approaches have been developed in the medical field recently, including cellular immunotherapy, personalized tumor vaccine and immune checkpoint inhibitors [89]. Among them, immune checkpoint inhibitors, PD-1 [90] and CTLA-4 [91], were considered as anti-cancer drugs. In 2018, the Nobel Prize in Physiology or Medicine was awarded to James P. Allison and Tasuku Honjo who discovered their roles in cancers.

Immune checkpoints are protective molecules in the human immune system, which act as a brake to prevent inflammatory damage caused by excessive activation of T cells. Immune checkpoint inhibitors can achieve an anti-tumor effect by inhibiting immune checkpoints activity, releasing immune brake in the tumor micro-environment, and re-activating T cell immune response to tumors, which also makes it a new weapon against tumors [92].

Immune checkpoint molecules such as PD-1, CTLA-4, TIM-3 [93]

and LAG-3 [94] are important signaling molecules that mediate immune escape of tumor cells, so these checkpoint inhibitors have important functions on many kinds of cancers, such as melanoma [95], renal cancer [96], and gastric cancer [97]. At present, several PD-1/PD-L1 and CTLA-4 monoclonal antibodies have been approved for clinical use around the world.

Anti-PD-1 antibodies

PD-1 is a glycoprotein expressed on T cells, B lymphocytes, NK cells, monocytes and dendritic cells [4]. The ligands of PD-1 are PD-L1 and PD-L2 that are usually expressed on tumor cells [98]. PD-1 inhibitors mainly include Nivolumab and Pembrolizumab. Nivolumab has become the most attractive immune checkpoint inhibitor after Ipilimumab because of its remarkable clinical efficacy in many types of tumors. Camrelizumab, a potent anti-PD-1 monoclonal antibody developed locally in China, Jiangsu Hengrui Medicine, is a humanized IgG4 antibody against PD-1 that inhibits the binding of PD-L1 and PD-L2 to PD-1 [99]. On June 19, 2020, it was officially approved in China for first-line treatment of advanced NSCLC and second-line treatment of advanced esophageal squamous cell carcinoma.

Anti-PD-L1 antibodies

PD-L1 is highly expressed in many tumors. By interacting with receptors PD-1 and B7.1 (also known as CD80) expressed on activated T cells, PD-L1 can transmit inhibitory signals that lead to the inactivation or non-function of T cells [100]. Antibodies of anti-PD-L1 hinder the interaction of PD-L1 with PD-1 and CD80 [98]. Atezolizumab is a humanized IgG1 monoclonal antibody against PD-L1 [101]. Atezolizumab was approved by FDA in 2016 in the second-line setting for patients with advanced-stage NSCLC and metastatic urothelial carcinoma (MUC). On May 18, 2020, FDA approved Genentech's Atezolizumab as a first-line monotherapy for certain people with metastatic NSCLC who were confirmed to have high PD-L1 expression and no EGFR or ALK gene mutation [102]. Durvalumab was qualified for a breakthrough drug by FDA in 2017 for the treatment of advanced urothelial cancer and unresectable stage III NSCLC [103]. In 2019, China also approved Durvalumab for the treatment of unresectable stage III NSCLC after simultaneous radiotherapy and chemotherapy.

Anti-CTLA-4 antibodies

CTLA-4 (CD152), mainly expressed on activated T cells (CD4⁺, CD8⁺, helper and killer T cells), is a homodimer glycoprotein receptor induced by T cells, which can interact with B7-1 (CD80)/B7-2 (CD86) ligands on the surface of APCs [104]. When combined with CD80/CD86, CTLA-4 can negatively regulate T cell activation, resulting in the downregulation of T cell response. Therefore, blocking CTLA-4 can reactivate T cell immune response and play an anti-tumor role. At present, the main CTLA-4 inhibitors are Ipilimumab and Tremelimumab, where Ipilimumab was the earliest immune checkpoint inhibitor approved by the FDA and used in the clinic for the treatment of melanoma. In May 2020, several research results (CheckMate-227, CheckMate-9LA, and CheckMate-568) of the combination of PD-1 antibody Nivolumab and CTLA-4 antibody Ipilimumab (O + Y regimen) in the first-line treatment of lung cancer were announced in the Annual Meeting of the American Society of Clinical Oncology (ASCO). According to the results of these trials, FDA approved two indications of double immunotherapy (O + Y

regimen), both of which are used in the first-line treatment of advanced NSCLC (Table 2).

Non-coding RNAs Related to Immune Checkpoints

As previously mentioned, immune checkpoints, which are related to the occurrence of autoimmune diseases, transmit negative regulatory signals to activated T cells and consequently prevent excessive immune response, thereby keep the immune balance of the body and maintain the immune tolerance of self-tissues [105]. Early studies have shown that the expression of PD-1 and PD-L1 is related to the efficacy of PD-1/PD-L1 inhibitors [106]. In the context of tumor immunity, a large number of miRNAs, and a small degree of lncRNAs, are considered to be effective tumor immunoregulatory factors by directly regulating the balance between immune activation and immunosuppression. Therefore, it is critical to explore the non-coding RNAs' potential implications in anti-tumor immunity.

miRNAs regulate immune checkpoints

miRNAs have also been implicated in the regulation of immune checkpoints. It has been reported that about 2500 miRNAs are capable of modulating biological processes by targeting various genes [107]. In gastric cancer, miR-186 indirectly regulates the expression of PD-L1 through HIF-1 α [108]. The down-regulation of miR-138-5p expression is common in colorectal cancer (CRC) and is related to poor clinical prognosis. In terms of mechanism, miR-138-5p mimic can inhibit the expression of PD-L1, thus inhibiting tumor growth *in vitro* and *in vivo* [109]. miR-135, a tumor promoter, up-regulates the expression of PD-L1 via inhibiting TRIM16 (a target gene of miR-135), resulting in immune evasion of cancer cells [110]. miR-33a, with tumor-suppressive activity, inhibits the progression of cancer cells and improves survival rate through downregulation of the PD-1/PD-L1 axis [111]. miR-200 restrains PD-L1 to improve the sensitivity of cancer cells to immunotherapy [112]. Two functional miR-155 binding sites were found in the PD-L1 3'-UTR. Endogenous miR-155 controls the level of PD-L1 induced by IFN- γ and TNF- α . IFN- γ combined with TNF- α therapy results in tumor inhibition via enhancing the expression of miR-155 to suppress PD-L1 [113]. miR-140 is downregulated in NSCLC cells, while PD-L1 is upregulated. Researchers found that overexpression of miR-140 inhibits PD-L1 expression by straightly binding to 3'-UTR [114]. miR-3127-5p induces the up-regulation of PD-L1 expression by regulating the expression of pSTAT3 [115]. Other miRNAs including miR-93-5p [116], miR-140-3p [117], miR-21 [118], miR-4717 [119],

miR-28 [120], miR-138 [121], miR-374b [122], miR-17-5p [123], miR-152 [124] also have key relationships with the PD-1/PD-L1 axis.

As for CTLA-4, investigators adopted luciferase expression assay and found that miR-138 could bind to the 3'-UTR of *CTLA-4*. Overexpression of miR-138 in both CD4⁺ and CD8⁺ T cells resulted in reduced expression of CTLA-4 [121]. miR-155, another direct target of CTLA-4, is known for its immune-regulating properties. Huffaker and colleagues found that immune checkpoint blocking antibodies can restore the anti-tumor immunity of miR-155-TCKO mice. The enhanced expression of miR-155 can be used to improve anti-cancer immunotherapy [125].

lncRNAs regulate immune checkpoints

It was reported that lncRNAs can affect different biological processes by regulating different genes, which is important in effective cancer therapy [126]. In ovarian cancer cells, lncRNA HOXA transcript at the distal tip (HOTTIP) enhances the expression of IL-6 by binding to c-Jun and then increases the expression of PD-L1, which attenuates anti-tumor immunity, leading to the migration, proliferation and metastasis of cancer cells [127]. In pancreatic cancer, lnc00473 and PD-L1 expressions are upregulated and miR-195-5p expression is downregulated. lnc00473 silencing suppresses tumorigenesis by enhancing miR-195-5p targeting to downregulate PD-L1 and then activate CD8⁺ T cells [128]. In gastric cancer, lncRNA UCA1 directly binds to miRNAs (miR-26a, miR-26b, miR-193a and miR-214), and then increases PD-L1 expression, promotes the proliferation and migration of tumor cells, and inhibits apoptosis [129]. lncRNA EMX2OS induces Akt3/PD-L1 axis by down-regulation of miR-654-3p [130], an onco-suppressor factor in ovarian cancer cells [131], resulting in reduced anti-tumor immunity. lncRNA MALAT1, an oncogene factor, activates PD-L1 by decreasing the expression of miR-200a, resulting in immune escape of lung cancer cells [132]. In diffuse large B cell lymphoma (DLBCL), lncRNA SNHG14 is upregulated. SNHG14 acts as miR-5590-3p sponge to upregulate Zinc finger E-box binding homeobox 1 (ZEB1) which promotes DLBCL cell immune evasion by activating SNHG14 and PD-L1. Hence, SNHG14/miR-5590-3p/ZEB1 contributes to immune evasion through regulating the PD-1/PD-L1 axis [133]. lncRNA XLOC_003810 suppresses the PD-1/PD-L1 pathway in patients with myasthenia gravis-related thymoma [134]. lncRNA MIR155 host gene (MIR155HG) was reported to have a relationship with PD-1/PD-L1/CTLA-4 in various cancers [135]. Other mod-

Table 2. Immune checkpoint inhibitors approved for use

Immune checkpoint inhibitor	Generic name	Trade name	Manufacturer	Year of approval
Anti-CTLA-4	Lpilimumab	Yervoy	BMS	2011/FDA
Anti-PD-1	Pembrolizumab	Keytruda	MSD	2014/FDA
	Nivolumab	Opdivo	BMS	2014/FDA
	Cemiplimab	Libtayo	Regeneron	2018/FDA
	Toripalimab	Tuo Yi	Junshi Biosciences	2018/NMPA
	Sintilimab	DaBoshu	Innovent	2018/NMPA
	Camrelizumab	AiRuika	Hengrui Medicine	2020/NMPA
Anti-PD-L1	Tislelizumab	BaiZean	BeiGene	2019/NMPA
	Atezolizumab	Tecentriq	Roche/Genentech	2016/FDA
	Durvalumab	Imfinzi	AstraZeneca	2017/FDA
	Avelumab	Bavencio	EMD Serono/Pfizer	2017/FDA

ulators such as LINC00657 [136], MIR17HG [137], and lncRNA TCL6 [138] are also of importance in the regulation of the PD-1/PD-L1 axis.

circRNAs regulate immune checkpoints

The expression of circUHRF1 in human hepatocellular carcinoma (HCC) tissues is higher than that in matched paracancerous tissues. The increase of serum circUHRF1 level in patients indicates poor clinical prognosis and dysfunction of NK cells through upregulated TIM-3 expression. Zhang *et al.* [139] established a xenograft model and found that the implantation of circUHRF1-knockout cells led to an increase in sensitivity and overall survival against PD-1 therapy. The response of HCC to anti-PD-1 treatment may be hindered by enhanced expression of circUHRF1. So targeting circUHRF1 may be a promising and effective way to restore the sensitivity of HCC to anti-PD-1 treatment. circFGFR1, upregulated in NSCLC tissues, acts as miR-381-3p sponge to upregulate the expression of the C-X-C motif chemokine receptor 4 (CXCR4) and enhances NSCLC progression and resistance to anti-PD-1 treatment [140].

In the exosomes of serum from ovarian cancer (OC) patients, the expression of circ-0001068 is markedly upregulated compared with that in healthy people. Researchers confirmed that circ-0001068, secreted by OC cells, increases the expression of PD-1 through sponging miR-28-5p [141]. circRNA-002178, upregulated in LUAD tissues, could improve PD-L1 expression through sponging miR-34. Additionally, similar to the function of circ-0001068, circRNA-002178 could enhance PD-1 expression via sequestering miR-28-5p [142]. In colon cancer, circular RNA CDR1-AS increases PD-L1 level

via miR-7-independent principles [143].

Collectively, identification of the relationship between ncRNAs and PD-1/PD-L1 or CTLA-4 can provide a novel insight that enhances the efficacy of cancer immunotherapy through targeting these non-coding RNAs (Figure 2).

Immune Checkpoint Inhibitor Resistance

Immune checkpoint inhibitors (ICIs, such as PD-1, PD-L1, CTLA-4 inhibitors) have been clinically used in immunotherapy for different types of cancers. However, most patients can't benefit from it. The great challenge in the field of tumor immunotherapy comes from the complex drug resistance mechanism of ICIs and the overcoming strategies for different drug resistance mechanisms. According to the timing of the occurrence of ICI drug resistance, it can be divided into primary drug resistance and acquired drug resistance. The former refers to the situation that there is no remission after the use of ICIs, and the latter refers to the tumor progression after the initial remission [144,145]. Therefore, it is important to reveal the mechanism of drug resistance in immune checkpoints and strategies to overcome drug resistance.

New antigens and antigen presentation

Anti-PD-1 therapy depends on the recognition of tumor antigen-specific T cells in tumor tissue, and the loss of new tumor antigens means that T cells can not recognize the tumor, which may lead to the failure of PD-1/PD-L1 blocking therapy [146]. Human melanoma, renal cell carcinoma and NSCLC are the most sensitive to PD-1/PD-L1 therapy, mainly due to the high immunogenicity of their

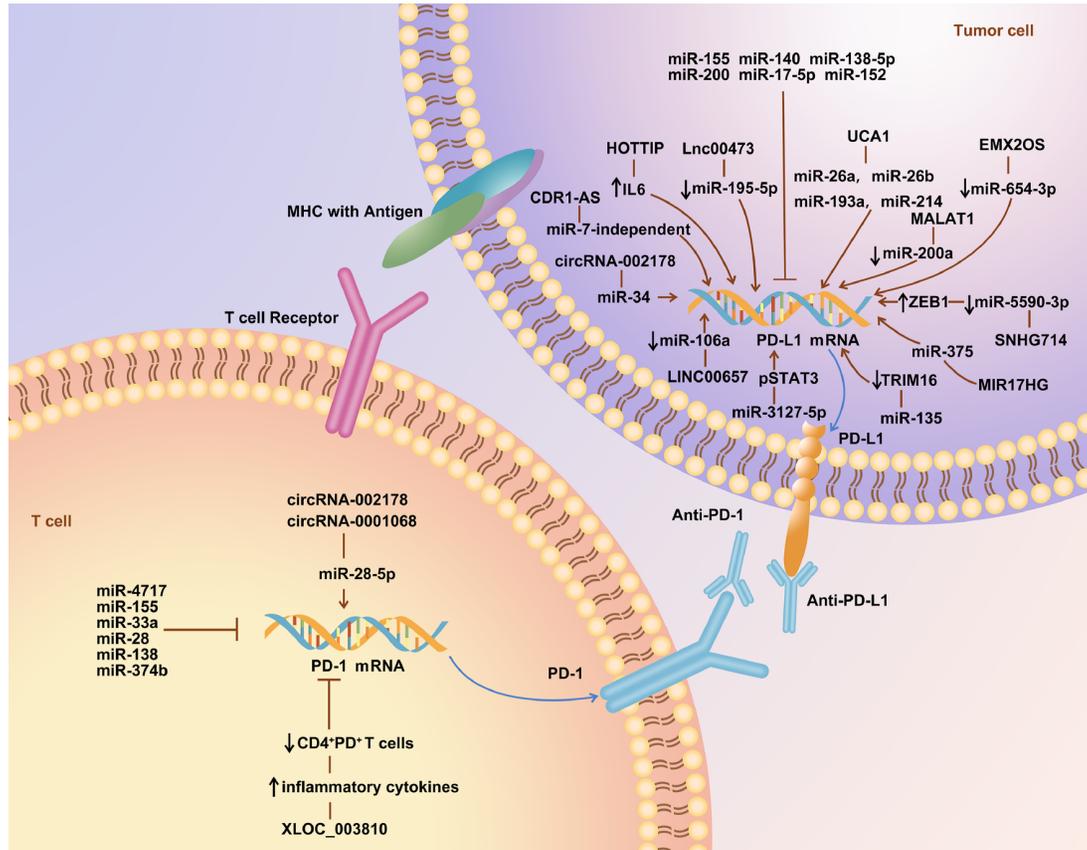


Figure 2. Non-coding RNAs involved in regulation of the PD-1/PD-L1 pathway in cancer Non-coding RNAs mainly regulate PD-1/PD-L1 pathway by directly targeting PD-1 mRNA and PD-L1 mRNA, and influence PD-1/PD-L1 expression.

tumors.

The absence of antigen presentation, such as β -2-microglobulin (β 2M) and HLA, is a mechanism for tumors to avoid antigen recognition and presentation. β 2M is necessary for the assembly of all HLA-I complexes and the presentation of tumor peptides by MHC to T cells. It has been shown that melanoma cells deficient in β 2M expression can restore the antigen presentation ability of cells and the tumor recognition ability of T cells by replacement of normal β 2M [147,148].

In triple-negative breast cancer (TNBC) patients, high expression of long intergenic non-coding RNA for kinase activation (LINK-A) was detected, while the infiltration of APC and activated CD8⁺ T cells was lower. It was suggested that LINK-A negatively regulates the recruitment of APC and CD8⁺ T cells. In addition, the expression of β 2M and MHC-I is decreased in patients with high expression of LINK-A. In terms of mechanism, LINK-A affects the loading and editing of MHC-I by degrading TPSN, TAP1, and CALR proteins of the peptide-loading complex (PLC). These findings suggested that LINK-A may be a potential prognostic indicator, and the use of LINK-A inhibitors can enhance the effect of ICIs [149]. In melanoma, MELOE-1, a translation product of lncRNA MELOE, can be recognized by tumor-infiltrating lymphocytes (TILs) with the highest immunogenicity. At present, it is considered as a targeted specific antigen that can enhance the efficacy of immunotherapy [149,150].

Cell signal transduction

Abnormal cell signal transduction is the main factor leading to drug resistance in immunotherapy, including PI3K/AKT pathway, WNT/ β -catenin pathway, JAK/STAT/IFN- γ and MAPK pathway [151]. PTEN is a tumor suppressor that inhibits the activity of PI3K. Increased expressions of immunosuppressive cytokines in tumor cells and decreased T cell infiltration in tumor areas are related to the loss of PTEN, and then the PI3K/AKT pathway is activated, which in turn leads to ICI resistance [152]. Similarly, the activation of the WNT/ β -catenin signaling pathway can lead to the excretion of T cells from the tumor microenvironment, which is related to anti-PD-1 acquired drug resistance in patients with melanoma [153].

The abnormal interferon- γ (IFN- γ) pathway is another factor of drug resistance in ICIs. T cells produce IFN- γ after recognizing tumor antigens. The effects of IFN- γ on JAK1 and JAK2 receptors, the signal transducer, and transcriptional activator (STAT) lead to the upregulation of anti-tumor response, antigen presentation and chemokine-related genes [154]. JAK1 and JAK2 are located in the downstream of IFN- γ signal pathway, which can regulate the expression of chemokine CXCL9, CXCL10 and CXCL11 to attract T cells to the tumor site, while functional deletion mutations of JAK1/2 may lead to reduced T cell infiltration and loss of IFN- γ signal, resulting in ICI resistance [155].

Tumor immune microenvironment

Tumor immune microenvironment (TIME) is the cellular environment around the tumor. The changes in the composition of tumor microenvironment may be related to the primary and acquired drug resistance of ICIs, including myeloid-derived suppressor cells (MDSCs) [156].

The presence of MDSCs in TIME can reduce the efficacy of ICIs [157]. MDSCs, derived from myeloid progenitor cells, are the precursor of dendritic cells, granulocytes or macrophages, and can

inhibit the function of T cells and NK cells. Activated MDSCs produce nitric oxide and upregulate the expression of Arginase-1, which can lead to L-arginine consumption in TIME and cell cycle arrest of T cells [158,159]. Meanwhile, the interaction between PD-L1 on MDSCs and PD-1 on T cells leads to T cell failure. MDSCs can also induce the expansion of Treg cells and decrease the anti-tumor activity of effector T cells [160,161]. Therefore, MDSCs may be a promising target for tumor immunotherapy. In melanoma patients, Huber and colleagues [162,163] found that a panel of eight miRNAs (miR-146a, miR-155, miR-125b, miR-100 and so on) derived from melanoma extracellular vesicles (EVs) are able to convert monocytes into MDSCs, which is relevant to ICIs. In addition, the basal level of these miRNAs in plasma is related to the efficacy of CTLA-4 or PD-1 blockers, suggesting that these miRNAs may be predictors of treatment response.

Conclusion and Perspective

At present, researches on the role of non-coding RNAs in EGFR and immune checkpoints is deepening, but the understanding of the mechanism of non-coding RNAs in drug resistance is still limited. We summarized the regulation of drug resistance of these two targeted drugs by non-coding RNAs in this review. Research indicates that a variety of non-coding RNAs play diverse roles in regulating EGFR-TKI resistance. These non-coding RNAs affect drug resistance by participating in some signaling pathways, such as PI3K/AKT, SHH and NF- κ B signaling. Apart from that, lncRNAs can influence drug resistance by serving as sponge of miRNAs and act on their target genes, thereby affecting the efficacy of EGFR-TKIs. Research on immune checkpoint inhibitor resistance regulated by non-coding RNAs only accounts for a small part, so it is necessary to explore the function of non-coding RNAs in the resistance to immune checkpoint inhibitors.

Non-coding RNAs have high predictive and prognostic value in various malignant tumors. Evidence is mounting that miRNAs can affect the anti-tumor immune response by affecting the expressions of immune regulatory molecules in tumors and immune cells. In addition to their important roles in tumor immune escape and changes in tumor-host interaction, immune-modulatory miRNAs usually have the characteristics of neoplastic, so they may become promising targets for combined immunotherapy in the future [164]. There are two main ways to use miRNAs to regulate immune checkpoints. One method is to use anti-miRNA antibodies to target mRNAs that block immune checkpoints in tumor microenvironment. Another is to use miRNA mimics to restore down-regulated miRNAs in tumor microenvironment and target mRNA molecules at immune checkpoints on the surface of tumor cells and T lymphocytes [165]. miRNA mimic molecules use nanoparticles to deliver double-stranded miRNAs, which can be coated with antibodies against tumor-specific antigens and directly target tumor sites. In the field of tumor therapy, the fastest-growing miRNA mimic is miR-34 (MRX34) [166] wrapped in a lipid carrier called NOV40. In 2013, MRX34 entered a multicenter phase I clinical trial for patients with primary liver cancer, small cell lung cancer, lymphoma, melanoma, multiple myeloma or renal cell carcinoma. After that, other microRNA-based drugs soon entered the stage of clinical trials. For example, miR-16 mimic entered into phase I clinical trial for patients with malignant pleural mesothelioma or non-small cell lung cancer. However, because of the negative events related to immunization, the development of these miRNA mimics as a drug is in a dilemma.

Now, more non-coding RNAs combined with targeted drugs have entered the clinical trials. With further studies of non-coding RNAs, some of these molecules may become potential therapeutic targets. Furthermore, a more comprehensive understanding of the tumor microenvironment may help more effectively select those patients who can benefit from immune checkpoint inhibitors, and in the future, the most appropriate treatment strategy for patients can be applied to achieve real precision medicine.

With the elucidation of the functions of non-coding RNAs in cancer treatment, non-coding RNAs are expected to be important therapeutic targets or ideal candidates for cancer precision medicine, especially for EGFR and immune checkpoints in the future.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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