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The potential of long noncoding RNAs for precision medicine in human cancer

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ABSTRACT

Precision medicine promises to better classify patients by individual clinical and biological biomarkers, which may provide an accurate assessment of disease risk, diagnosis, prognosis and treatment response. Cancer frequently displays substantial inter-tumor and intra-tumor heterogeneity and hence oncology is well suited for application of precision approaches. Recent studies have demonstrated that dysregulated lncRNAs play pivotal roles in tumor heterogeneity. In this review, attention is focused on the potential applications of lncRNAs as biomarker candidates for cancer risk evaluation, detection, surveillance and prognosis. LncRNAs are often stable in clinical samples and easily detected. The functional implications and therapeutic potential of targeting lncRNAs in human cancer are further discussed. Finally, existing deficiencies and future perspectives in translating fundamental lncRNA knowledge into clinical practice are highlighted.

1. Introduction

Precision medicine, which relies on individual differences in genetics, environments and lifestyle, classifies patients into precise groups that will potentially benefit from specific disease prevention and treatment protocols [1]. The rapid advancement of genome sequencing technology and bioinformatics algorithms have encouraged creative approaches to precision medicine. Powerful genomics, proteomics, metabolomics and diverse cellular assays enable scientists and clinicians to more precisely target specific diseases [2]. Importantly, precision medicine consists of not only precise treatment, but it also, by necessity, encompasses precise diagnoses [3]. Precision medicine therefore possesses the potential for broad application in a variety of medical specialties, including cardiology, endocrinology and oncology [4–7].

Oncology was one of the first fields proposed for the application of precision medicine. Cancer is a common disease and one of the leading causes of death globally [8]. Despite the extraordinary amount of money and effort expended to improve therapeutic efficacy in cancer, the survival outcome for many cancer patients has shown limited improvement. Although a much greater understanding of the molecular mechanisms of cancer progression has been put forward, little can be translated into clinical practice [9]. This may be partly due to the complexity of molecular and cellular heterogeneity of cancer cell clonal selection. Tumors exhibit molecular and cellular heterogeneity between different patients (inter-tumor heterogeneity) and even within each individual tumor (intra-tumor heterogeneity) [10]. Tumor heterogeneity has obvious consequences for cancer stem-like populations, resulting in treatment resistance, metastasis and recurrence [11–13]. Darwinian-like clonal evolution is presumably a major generator of tumor heterogeneity. The selective pressures of mutational diversity and adaptions to

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the microenvironment including therapeutic pressures drive the temporal evolution of cancer cell clonality [9]. Clonal evolution in cancer therefore provides both challenges and opportunities for successful treatment [14]. Consideration of the epigenetic and genetic heterogeneity in cancer may hold the key to more precise and efficacious diagnostic and therapeutic approaches [15].

The genomic characteristics of cancer form an important component of precision oncology. Whilst up to 70% of the genome is transcribed, the proportion of protein-coding elements in the genome is only approximately 1.5% [16]. However, non-coding RNAs (ncRNAs) are constitutively expressed and play critical roles in multiple biological functions [17]. Long non-coding RNAs (lncRNAs) belong to the ncRNA family and are defined as endogenous cellular RNAs of more than 200 nucleotides in length [18]. LncRNAs may be transcribed from several DNA elements such as enhancers, promoters, introns, and intergenic regions in eukaryotic genomes (Fig. 1). The transcribed lncRNAs may be further processed by different mechanisms, such as cleavage by RNase P to generate mature ends, formation of small nucleolar RNA and protein (snoRNA/snoRNP) complex caps at their ends, and formation of circular structures (Fig. 1) [19]. Genome-wide studies have revealed that more than 80% of cancer-associated genetic aberrance occurs in non-coding regions [20]. Accumulating evidence has indicated that lncRNAs are critical regulators of cellular processes implicated in cancer development and progression. Notably, aberrant expression of lncRNAs is associated with tumor cell genomic stability, proliferation, survival and motility [21]. Furthermore, lncRNAs may also perform important functions in angiogenesis, immune cell infiltration and immune surveillance [22,23]. Single-cell sequencing studies also suggest marked heterogeneity in lncRNA expression between individual cancer cells [24]. Hence, lncRNAs may be more cell-type specific than protein-coding genes [24], rendering them appropriate for use in precision oncology. However, clinical practice has to date mostly focused on protein-coding genes and there is currently a paucity of effort to translate lncRNAs to clinical utility. In this review, cancer-related lncRNAs have been grouped into five areas of utility in precision oncology, including cancer risk, detection, prognosis, targeted therapy and immunotherapy. The possible roles and potential applications of some important and well-characterized lncRNAs in precision oncology have been summarized. This review aims to expand the perspectives of the potential use of lncRNAs in precision oncology and facilitate directions for future research.

2. LncRNA in cancer risk evaluation

Disease prevention will presumably benefit the population more than attempted disease treatment. The risk of cancer development is contributed by both exogenous environmental influences and endogenous genetic composition [25]. One of the goals of precision oncology is to evaluate cancer predisposition and guide intervention for risk-reduction, which may effectively obviate cancer development. Genetic evaluation of specific cancer-risk has become clinically available over the last few decades. For example, people with mutations in *BRCA1/2* display remarkably increased risks in breast and ovarian cancer [26,27]. Furthermore, the risk for gastric cancer development is dramatically increased in E-cadherin (*CDH1*) mutation carriers [28].

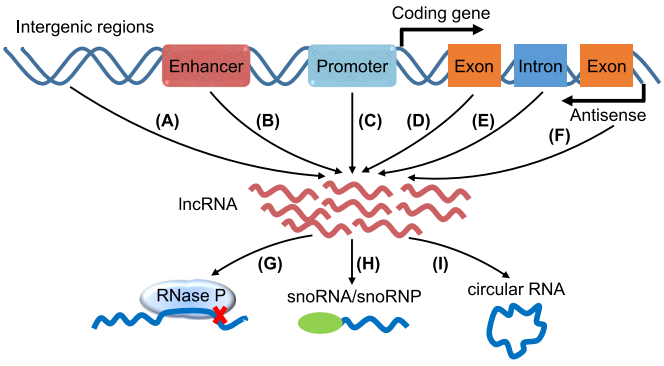

Fig. 1. The biogenesis of lncRNA in eukaryotic genomes. LncRNAs are pervasively interspersed in the eukaryotic genome in various locations. LncRNAs may be transcribed from (A) Intergenic regions, (B) Enhancer, (C) Promoter, (D) Exon, (E) Intron and (F) Antisense. LncRNAs may be further processed by (G) RNaseP cleavage, (H) small nucleolar RNA (snoRNA) and protein (snoRNP) complex caps and (I) formation of circular structures.

Genome-wide association studies have identified thousands of genetic polymorphisms (mainly composed of single nucleotide polymorphisms, SNPs) associated with susceptibility to disease. More than 90% of these SNPs are located outside of the protein-coding regions [29]. Characterizing cancer risk-associated SNPs provides an opportunity to develop methods of risk evaluation in precision oncology. Thus, genetic polymorphisms in lncRNAs may also be utilized for estimation of cancer susceptibility. For example, lncRNA HOX transcript antisense intergenic RNA (*HOTAIR*) was initially identified for possessing roles in the initiation and progression of various malignancies [30,31]. The tagging SNP (tagSNP) rs920778, rs1899663 and rs4759314 of lncRNA *HOTAIR* were identified to be significantly associated with the risk of esophageal squamous cell carcinoma (ESCC) [32]. Guo et al. further demonstrated that the tagSNP rs12826786 polymorphism in *HOTAIR* endowed a genotype-specific effect on *HOTAIR* expression and was associated with increased risk of adenocarcinoma of the gastric cardia [33]. Further studies also demonstrated a strong correlation between tagSNPs of *HOTAIR* and the susceptibility to develop colon and gastric cancers [34,35]. Additionally, genetic variants of *HOTAIR* are also associated with the risk of other cancers, including cervical, oral and breast cancers [36–38].

LncRNA *H19*, a maternally expressed imprinted gene, is located on chromosome 11 and involved in cancer progression [39]. Ariel et al. reported that patients with increased numbers of *H19*-positive cancer cells are at higher risk for early recurrence of bladder cancer [40]. The polymorphisms in lncRNA *H19* have also been reported to correlate with the susceptibility to develop various cancers. The polymorphism (SNP) rs2107425 has been identified to be significantly associated with breast cancer risk [41]. SNP rs2107425 is located approximately 2 kb upstream of the lncRNA *H19* locus. Other *H19* polymorphisms have also been reported including *H19* rs2839698 and rs217727. Encyclopedia of DNA Elements (ENCODE) DNase I hypersensitive site (DHS) sequencing and ChIP-Seq data analysis demonstrated that *H19* rs2839698 and rs217727 may affect the recruitment of transcription factors and subsequently modulate the expression of *H19* [42]. Whereas *H19* rs217727 exhibits no significant association with cancer susceptibility [42], *H19* rs2839698 was reported to be associated with increased risk of gastric and colorectal cancer in the Chinese population [43,44]. However, in Caucasians, the *H19* rs2839698 exhibits the opposite association with cancer risk [45]. A further meta-analysis using published data confirmed that *H19* rs2839698 may modify cancer susceptibility based on ethnicity [42].

LncRNA *PCAT1* was first identified as a prostate-specific lncRNA that may contribute to prostate cancer progression [46]. Several putative functional genomic polymorphisms of lncRNA *PCAT1*, such as rs2632159, rs1026411, rs1902432, rs710886 and rs16901904, have been identified to be associated with the risk of human cancer development. A case-control study was employed to determine the associations between these tagSNPs and prostate cancer risk, wherein *PCAT1* rs1902432 was identified to be significantly associated with increased risk of prostate cancer development [47]. A recent study systematically revealed that rs1026411 and rs710886 are also associated with susceptibility to NSCLC, while rs1026411 is associated specifically with the risk of lung adenocarcinoma [48]. The SNPs of lncRNA associated with cancer susceptibility are summarized in Table 1.

Genetic polymorphism of lncRNAs is therefore an important

Table 1
Selected lncRNAs and their tagSNPs in cancer susceptibility.

LncRNA	tagSNP	Cancer type	References
HOTAIR	rs920778, rs1899663, rs4759314	Esophageal squamous cell carcinoma, Cervical cancer	[32,36]
HOTAIR	rs12826786	Gastric cardia adenocarcinoma	[33]
HOTAIR	rs7958904	Colorectal cancer	[34]
HOTAIR	rs4759314	Gastric cancer	[35]
HOTAIR	rs920778	Oral squamous cell carcinoma	[37]
HOTAIR	rs920778, rs12826786, rs1899663	Breast cancer	[38]
H19	rs2107425	Breast cancer	[41]
H19	rs2839698	Gastric cancer, Colorectal cancer	[43,44]
PCAT1	rs1902432	Prostate cancer	[47]
PCAT1	rs1026411, rs710886	Lung cancer	[48]
PCGEM1	rs6434568, rs16834898	Prostate cancer	[107]
HOTTIP	rs17501292, rs2067087, rs17427960	Hepatocellular cancer	[108]
MALAT1	rs4102217, rs591291	Hepatocellular cancer	[108]
HULC	rs1041279, rs2038540	Hepatocellular cancer	[109]
POLR2E	rs3787016	Esophageal cancer	[110]
HULC	rs7763881	Esophageal cancer	[110]
CCAT2	rs6983267	Lung cancer	[111]
GAS5	rs145204276	Gastric cancer	[112]

contributor to cancer risk and evaluation thereof. Distinct genetic variants are associated with susceptibility to the development of different cancers. However, it is insufficient to simply determine the presence of specific lncRNA polymorphisms. The functional mechanisms and clinical utility of these genetic variants should be sufficiently understood to allow appropriate interpretation of these lncRNA polymorphisms for specific individuals.

3. LncRNAs in cancer detection

Cancer is a common disease and the leading cause of death worldwide. The high mortality rate of human cancer is partly due to the fact that a majority of cases are detected at advanced stages. There is an urgent need for convenient, rapid and highly specific early detection biomarkers for precision oncology. Accumulating evidence has suggested that various RNA molecules may serve as biomarkers for the detection of human cancer. In particular, extracellular RNAs in body fluids, such as serum, urine or saliva, may serve as non-invasive biomarkers for early detection of cancers [49]. mRNA determination has been previously employed in tumor prognosis. Previous studies have also demonstrated that multi-gene expression profiles may serve in cancer subtype classification. For example, a 50-gene panel, PAM50, has been successfully utilized in the classification of breast cancer [50]. Similarly, the expression of 31 genes involved in cell cycle progression has been applied to prostate cancer prognosis [51].

In addition to mRNAs, lncRNAs may also possess utility in the detection and prognosis of cancer. LncRNA *PCA3* is a prostate cancer specific lncRNA that is highly expressed in prostate tumors [52]. Furthermore, *PCA3* may also be detected in the urine of prostate cancer patients [53]. Hence, *PCA3* may serve as a potential biomarker for prostate cancer screening and detection. Although serum prostate-specific antigen (PSA) has been well applied as a prostate cancer biomarker, the specificity of PSA is low. Compared to PSA, *PCA3* exhibits higher specificity and easy accessibility with no biopsy required. Indeed, it has been reported that *PCA3* may serve as a first-line biomarker with improved specificity and sensitivity compared to PSA [54]. In addition, a *PCA3* score was strongly correlated with prostate tumor volume and may be able to improve active surveillance of the disease [55]. The transcription-mediated amplification (TMA)-based *PCA3* urine test was the first RNA-based cancer detection assay from body fluid that arrived to clinical practice [56]. Combining *PCA3* with other clinical biomarkers may provide more accurate detection of prostate cancer.

LncRNA *HULC* is another cancer-related lncRNA that can be found in the blood of hepatocellular carcinoma patients [57], indicating that *HULC* may serve as a potential non-invasive biomarker for cancer detection. Additionally, combined detection of *HULC* and *Linc00152* in serum achieves a more accurate prediction for the occurrence of hepatocellular carcinoma compared to *HULC* alone [58]. *HULC* may also serve as a serum biomarker for early detection of gastric cancer. Serum *HULC* levels are strongly correlated with *H. pylori* infection, tumor size and metastatic stage in gastric cancer patients. Both the sensitivity and specificity of *HULC* are higher than CEA and CA72-4 for gastric cancer detection [59]. A recent study also revealed higher *HULC* levels in cancer tissue and serum of pancreatic cancer patients. *HULC* was related to the size and grade of tumor and exhibits clinical utility for pancreatic cancer detection [60].

Compared with single lncRNA quantification, panels of multiple lncRNAs might be more appropriate for cancer detection and/or diagnosis. A panel containing 3 lncRNAs (*MEG3*, *SNHG16* and *MALAT1*) has been utilized for the detection of bladder cancer from serum samples [61]. In addition, a microarray followed by qRT-PCR analysis identified a combination of two lncRNAs (*uc004cox.4* and *GAS5*) in the urine with high accuracy for the detection of bladder cancer [62]. A panel of three lncRNAs (*PCAT-1*, *UBC1* and *SNHG16*) in exosomes has been determined by a multivariate logistic regression model to predict bladder cancer [63]. Panels of multiple lncRNAs have also been applied to the detection of hepatocellular and colorectal carcinomas [64,65]. Currently, several of these fundamental studies have been translated into the clinical setting for cancer detection. Clinical trials are underway in lung cancer diagnosis using serum exosomal lncRNAs (https://clinicaltrials.gov/) (NCT03830619). Furthermore, lncRNA *CCAT1* or *HOTAIR* is trailing for colorectal cancer (NCT04269746) or thyroid cancer (NCT03469544) detection, respectively.

Compared to protein biomarkers, lncRNAs are easy to detectable at a very low abundance. The PCR technique enables the lncRNA sequences to be amplified and thus detected with high sensitivity. Unlike protein biomarker detection, which requires specific antibodies, the cost of PCR used for lncRNA detection is much lower. Moreover, deep sequencing technology enables the quantification of lncRNA expression at the whole genomic level. Novel lncRNA biomarkers may potentially be identified from deep sequencing data and be developed to improve cancer detection.

4. LncRNAs in cancer prognosis

Determination of prognosis improves the understanding of the clinical outcomes and benefits clinicians to adopt effective intervention methods. Increasing studies have paid attention to comprehensively evaluate clinical prognosis using various biomarkers [66]. Several gene expression panels have been developed to classify cancer into different groups and refine prognosis estimation based on current guidelines. For example, the 70-gene signature (MammaPrint™) was developed to predict the risk of recurrence in breast cancer patients [67]. Emerging evidence has suggested that lncRNAs are also abnormally expressed and play critical roles in cancer progression. Thus, measurement of lncRNAs may be considered to improve the assessment of cancer prognosis.

In colorectal cancer, patients with similar histopathological characteristics may exhibit significantly different prognoses after surgery. Studies have identified oncogenic lncRNAs that are associated with prognosis in colorectal cancer. Colon cancer associated transcript-1 (*CCAT1*) was first described as a lncRNA that is highly expressed in colorectal cancer compared to normal tissues [68]. Elevated *CCAT1* levels were observed in the primary tumor, blood, and metastases of colorectal cancer patients. *CCAT1* has also been reported to correlate

with lymph node metastasis, clinical stage and survival in colorectal cancer [69]. Thus, *CCAT1* may serve as a valuable prognostic indicator for colorectal cancer. Nearly half of patients with advanced colon cancer tend to develop liver metastases. However, there are no effective biomarkers that can predict the susceptibility for liver metastatic. Cancer liver metastasis associated transcript-3 (*CLMAT3*) is a lncRNA that has been demonstrated as a prognostic biomarker for liver metastasis of colorectal cancer. *CLMAT3* is significantly upregulated in the primary tumor of colon cancer patients with liver metastasis and consequently predicts shorter overall survival time for these patients [70]. LncRNA *DANCR* (differentiation antagonizing non-protein coding RNA) has been identified to be involved in the maintenance of stemness of normal and liver cancer cells [71]. Furthermore, *DANCR* is upregulated in colon cancer tissue and correlates with tumor stage and poor survival outcomes in colon cancer patients [72]. Another promising prognostic marker for colon cancer is lncRNA *FTX*, which is conserved and encoded within the X-inactivation center. *FTX* is markedly upregulated in colon cancer tissue and predicts poor survival outcomes [73].

Mammary carcinoma is heterogeneous cancer that can be classified by various methods into molecular subtypes. A well-established molecular classification has been developed to classify patients into at least four subtypes including luminal A, luminal B, HER2-amplified and basal-like [74]. However, the prognosis of patients may differ even in the same subtype. Further prognostic markers are therefore needed to accurately predict prognosis and provide clinical guidance. A 4-lncRNA panel (*RP11-434D9.1*, *LINC00052*, *BC016831* and *IGKV*) has been identified enabling classification of triple negative breast cancer [75]. LncRNA *SPRY4-IT1* is increased in breast cancer tissue and is associated with tumor size and the pathological stage of breast cancer [76]. Additionally, lncRNA *H19* is increased in the plasma of breast cancer patients and *H19* levels are markedly decreased in postoperative compared to preoperatively drawn plasma [77]. An additional study utilizing an omics-based analysis identified a 12-lncRNA signature that is highly predictive of tumor recurrence and survival outcomes of breast cancer patients [78]. In clinical trials, the mRNA-lncRNA integrated signature has been developed to classify triple negative breast cancer patients and guide the therapeutic regimen (https://clinicaltrials.gov/) (NCT02641847).

In addition to colon and breast cancer, lncRNAs have also been developed as prognostic biomarkers in various other cancer types. In hepatocellular carcinoma, a comprehensive systematic review and meta-analysis identified a panel of 45 lncRNAs that could be potential non-invasive prognostic biomarkers [79]. LncRNA NEAT1 is upregulated in clear cell renal cell carcinoma and predicts poor prognosis [80]. Furthermore, lncRNA *Sox2ot* (Sox2 overlapping transcript) has been reported to predict poor prognosis in lung, liver and gastric cancer [81]. Further information of the association between lncRNAs and cancer prognosis is summarized in Table 2. These findings lead to potent possibilities for lncRNAs in precise evaluations of cancer prognosis.

Table 2
LncRNAs serve as prognostic biomarkers in human cancers.

LncRNA	Expression	Cancer type	Clinical features	References
CCAT1	Up	Colorectal cancer	Lymph node metastasis, Clinical stage, Survival	[69]
CLMAT3	Up	Colorectal cancer	Liver metastasis, Survival	[70]
DANCR	Up	Colorectal cancer	Tumor stage, Survival	[72]
FTX	Up	Colorectal cancer	Survival	[73]
SPRY4-IT1	Up	Breast cancer	Tumor size, Pathological stage	[76]
H19	Up	Breast cancer	Tumor size	[77]
NEAT1	Up	Clear cell renal cell carcinoma	Tumor size, Grade, Lymph node metastasis, Survival	[80]
Sox2ot	Up	Lung, liver and gastric cancer	Clinical stage, Survival	[81]
GAS5	Down	Cervical cancer	Lymph node metastasis, Survival, FIGO stage	[113]
ATB	Up	Colorectal cancer	pN stage, Survival	[114]
HULC	Up	Osteosarcoma	Clinical stage, Metastasis, Survival	[115]
SNHG16	Up	Bladder cancer	Survival	[116]
DGCR5	Down	Hepatocellular cancer	Survival	[117]
PVT1	Up	Pancreatic cancer	Clinical stage, N-classification, Survival	[118]
UCA1	Up	Osteosarcoma	Tumor size, Grade, Metastasis	[119]
AFAP-AS1	Up	Colorectal cancer	Survival	[120]
SHNG20	Up	Hepatocellular Carcinoma	Tumor size, Clinical stage, Survival	[121]

5. Targeted therapy potential of lncRNAs

Recent advances in the understanding of lncRNAs in cancer provide renewed therapeutic opportunities. Several lncRNA-targeting strategies have been proposed.

Post-transcriptional targeting is one approach for lncRNA targeted therapy, which provides a straightforward method to modulate lncRNA expression [82]. Antisense oligonucleotides (ASOs) and siRNAs are the most common means for post-transcriptional regulation. ASOs bind to RNA in a base-paired manner, triggering an RNaseH-mediated RNA degradation. The metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) is a highly conserved lncRNA that is involved in the metastasis of various cancers. Targeting *MALAT1* by ASOs markedly reduced the growth of primary breast tumors and lung metastasis in the MMTV–PyMT transgenic mouse model [83]. Another example is ASO targeting of the leukemia-induced non-coding activating RNA 1 (*LUNAR1*). Knockdown of lncRNA *LUNAR1* by ASOs was shown to inhibit cancer cell growth both *in vitro* and *in vivo* by repression of the IGF1R [84]. Mammary tumor-associated RNAs (MaTARs) is a superfamily of lncRNAs that is associated with human breast cancer. ASO-mediated knockdown of 20 MaTARs members significantly reduced the proliferation and invasion of mouse mammary cancer cells [85]. Additionally, ASO-mediated downregulation of lncRNA *SChLAP1* also significantly limited tumor formation and metastasis in prostate cancer [21].

siRNAs are double-stranded RNAs that specifically repress target RNAs in a RISC complex dependent manner. Targeting *MALAT1* using specific siRNAs significantly inhibited prostate cancer cell proliferation and invasion [86]. Furthermore, siRNAs directed against *HOTAIR* inhibited the invasion of breast cancer cells [30]. shRNA mediated *HOTAIR* depletion also inhibited the growth of gastric tumors *in vivo* [87].

The CRISPR/Cas9 system has also been developed to target the genomic DNA of lncRNAs. CRISPR/Cas9 interference has been used to knockout an array of lncRNAs in 7 human cell lines (six cancer cell lines and one iPSC line), wherein about 500 lncRNAs were identified to be required for cancer cell proliferation [88]. LncRNA *NEAT1* was reported to regulate the replication stress response of cancer cells. *NEAT1* deletion by the CRISPR/Cas9 system dramatically abrogated the metastatic ability of squamous cell carcinoma cells [89]. Gastric cancer metastasis-associated long non-coding RNA *GMAN* is upregulated in gastric cancer and associated with poor prognosis. Delivery of a CRISPR/Cas9 system targeting *GMAN* in a mouse model suppressed gastric cancer metastasis [90]. Additionally, the CRISPR/Cas13 system, which directly targets RNAs, has been developed and may be another promising approach to deplete lncRNAs in laboratory and clinic [91]. Furthermore, phase I/II clinical trials are underway in patients with pancreatic, ovarian and bladder cancer for lncRNA *H19* targeted therapy

based on intratumoral administration of the BC-819 plasmid [92]. The schematic of different approaches to target lncRNAs is summarized in Fig. 2.

A large proportion of protein targets in basic research are as yet undruggable. One of the main advantages of lncRNA targeting is that it can easily modulate the expression or activity of targeted proteins [93]. Another deficiency of protein targeted therapy is that many small molecule inhibitors possess poor specificity, especially in proteins possessing similar structural domains. Through careful design, the specificity of targeted lncRNA can be efficiently improved. Moreover, compared to protein-coding genes, lncRNAs are apparently more tissue-specific [94]. LncRNA targeted therapy may therefore exhibit less on-target and off-target toxicity compared to small molecule drugs. Therefore, consideration for lncRNA targeting in cancer is warranted and it may emerge as a promising therapeutic approach in oncology. The targeted strategy and therapeutic potential of lncRNAs in human cancer are listed in Table 3.

6. LncRNAs in immunotherapy

Tumor immunotherapy, particularly immune checkpoint inhibitors (ICIs), has improved the therapeutic outcomes in various cancers. Nevertheless, the response rate of immunotherapies is not optimal with only 15%–40% patients benefiting from tumor immunotherapy [95]. Whilst the majority of patients develop intrinsic or acquired resistance to immunotherapy, the mechanisms of immunotherapy resistance are not clear. Accumulating evidence has suggested that lncRNAs may play critical roles in immunological surveillance and resistance to immunotherapy. Therefore, understanding lncRNA regulated immunotherapy resistance may provide opportunities to both identify patients that may respond to immunotherapy and develop strategies to overcome immunotherapy resistance.

Aberrant expression of lncRNAs has been found both in cancer cells and immune cells in the tumor microenvironment. Cancer cell endogenous lncRNAs play critical roles in regulating immunotherapy resistance. Antigen presenting cell (APC) infiltration and the antigen presentation process have been reported to be affected by lncRNAs expressed in cancer cells. For example, elevated expression of lncRNA *LINK-A* in triple-negative breast cancer cells correlates with decreased APC infiltration, facilitating the escape of breast cancer cells from immune surveillance [96]. The expression of PD-L1 in tumor cells was also modulated by lncRNAs. In large B-cell lymphoma and pancreatic cancer, *MALAT1* has been observed to act as a miR-195 sponge to promote the

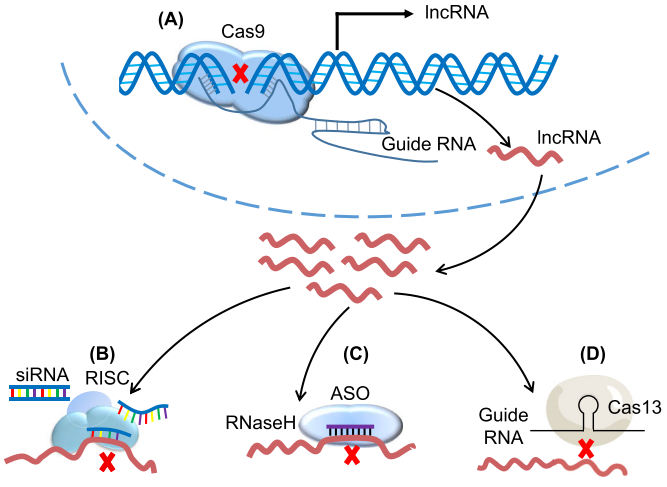

Fig. 2. Schematic summary of different approaches to target lncRNAs. (A) Transcriptional inhibition may be achieved through classical CRISPR/Cas9. (B–D) Post-transcriptional degradation may be achieved through siRNAs (B), ASOs (C) and CRISPR/Cas13 (D).

Table 3
Targeting strategies of lncRNAs in human cancer.

LncRNA	Cancer type	Therapy approach	References
MALAT1	Breast cancer	ASO	[83]
LUNAR1	Acute leukemia	ASO	[84]
MaTARs	Breast cancer	ASO	[85]
SChLAP1	Prostate cancer	ASO	[21]
MALAT1	Prostate cancer	siRNA	[86]
HOTAIR	Breast cancer	siRNA	[30]
HOTAIR	Gastric cancer	shRNA	[87]
NEAT1	Skin cancer	CRISPR/Cas9	[89]
GMAN	Gastric cancer	CRISPR/Cas9	[90]
USMycN	Neuroblastoma	ASO	[122]
MALAT1	Breast cancer	CRISPR/Cas9	[123]
BCAR4	Breast cancer	shRNA	[124]
PNUTS	Breast cancer	shRNA	[125]
XIST	Thyroid cancer	siRNA	[126]
SNHG16	Pancreatic cancer	shRNA	[127]
MALAT1	Ovarian cancer	shRNA	[128]
THOR	Renal cell carcinoma	CRISPR/Cas9	[129]
UCA1	Bladder cancer	CRISPR/Cas9	[130]

expression of PD-L1 [97]. In pancreatic cancer, it was demonstrated that the expression of PD-L1 was also regulated by lncRNA *LINC00473* [98]. T cells are the direct effector cells that recognize cancer cells and exert cytotoxic activity. LncRNAs also modulate T cell activation. *Lnc-sox5* was demonstrated to be upregulated in colorectal cancer, and *lnc-sox5* deletion results in enhanced cytotoxicity of $CD3^{+}CD8^{+}$ CTLs at the tumor site [99].

The aberrant expression of lncRNAs in the immune cells of the tumor microenvironment may also regulate the immunotherapeutic response. LncRNA *NEAT1* was demonstrated to be upregulated in the peripheral blood mononuclear cells of hepatocellular carcinoma patients. Depletion of *NEAT1* in $CD8^{+}$ T-cells significantly attenuated the apoptotic process in T-cells and enhanced cytotoxic activity [100]. The NF-κB interacting lncRNA *NKILA* is upregulated in tumor-specific CTLs and promotes their apoptosis process, resulting in shorter survival outcomes in patients with breast cancer and NSCLC [101]. LncRNAs also regulate the recruitment and activity of immunosuppressive cells. LncRNA *Olfr29-ps1* is highly expressed in MDSCs and promotes MDSCs to differentiate into monocytic MDSCs, which plays a key role in immune suppression [102]. *Lnc-chop* also regulated the differentiation of MDSCs [103]. Furthermore, lncRNA *PVT1* has been reported to regulate the granulocytic myeloid-derived suppressor cells (G-MDSCs). *PVT1* is transcriptionally regulated by HIF-1α in G-MDSCs, and upregulated *PVT1* promotes increased levels of Arg1 and ROS in these cells [104].

7. Conclusion and perspectives

With the advancement of genome sequencing technology, lncRNAs have been identified to play critical roles in the initiation and progression of cancers. We illustrate here that lncRNAs exhibit strong potential applications in all aspects of precision oncology. However, several limitations of lncRNAs in cancer studies should also be considered. Firstly, the majority of long lncRNAs are expressed at very low abundance, which leads to the concern of whether they are functionally relevant to clinical oncology [105]. Secondly, most of the downstream effector molecules of lncRNAs are proteins. Careful attention should be paid to determine whether a lncRNA or a more direct downstream protein is better as the therapeutic target. Thirdly, the ASOs or siRNAs in targeting lncRNA therapy exhibit poor membrane permeability. These targeting molecules are mainly enriched in the cytoplasm, which makes it difficult to target sub-nuclear lncRNAs [106]. Lipid-based or polymer-based nanoparticles that are capable of carrying ASOs or siRNAs may facilitate the application of lncRNA targeted therapy.

Although a considerable number of lncRNAs have been well studied, a large portion of the annotated lncRNAs have not yet been functionally characterized. Systematic studies on the identification and

characterization of lncRNAs in cancer will benefit the application of precision oncology. These efforts will be facilitated by large-scale RNA-Seq followed by loss-of-function studies. Additionally, while most reports are focused on the functional roles of a single lncRNA in cancer progression, a combination of multiple lncRNAs to form biomarker panels might improve the potential translation to clinical practice. Furthermore, precision oncology approaches should utilize all molecular classes of biomarkers. DNA, mRNA, lncRNAs and proteins all function in concert to drive the various biological processes required for cancer progression. Biomarker panels including all molecules of utility are therefore attractive to optimize risk prediction, detection, prognosis and treatment in precision oncology. Interdisciplinary technology should also be applied to precision oncology. For example, machine learning or other intelligent algorithms could be applied to improve the integration of information derived from various biomarkers in large scale cohort studies. The aim of precision oncology should be to translate molecular biomarkers to clinical application, providing improved predictive or therapeutic precision. However, studies with negative results are generally not well published, which may result in overestimation of the potential of the application of lncRNAs in precision oncology. Potent algorithms for evaluating patient risk, detection, prognosis and targeted therapy are essential to introduce and improve precise approaches to oncology.

Author contributions

MW, XZ, TZ and PEL conceived the idea for the review. MW, XZ, XH, and VP searched the literature and MW and XZ wrote the manuscript. MW generated the figure panels. TZ and PEL edited the final versions of the manuscript.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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