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Regulatory roles of long noncoding RNAs implicated in cancer hallmarks

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Cancer cells acquire numerous biological properties (designated "cancer hallmarks"), such as cell survival and energy metabolism, that facilitate tumor growth and metastatic dissemination during development. To date, eight hallmarks of cancer have been identified that provide a logical framework for understanding the remarkable diversity of neoplastic diseases, as proposed by Douglas Hanahan and Robert A. Weinberg. Long noncoding RNAs (lncRNAs), a category of transcripts widely demonstrated to exert significant regulatory effects on biological processes, have attracted considerable research attention due to their association with the occurrence and development of cancer. The mechanisms by which lncRNAs exert their functions require elucidation to optimize their potential utility as alternative biomarkers and therapeutic targets during tumor occurrence and progression. In this review, we have discussed recent research progress on lncRNAs involved in various cancer hallmarks and their related mechanisms of action, with a view to providing an updated picture of their immense therapeutic potential in the fight against cancer.

Mini Review

Key words: lncRNA, cancer hallmarks

Abbreviations: Akt: protein kinase B; ATG7: autophagy-related gene 7; ATP: adenosine triphosphate; Bax: Bcl-2 associated X; Bcl-2: B-cell lymphoma 2; CDK: cyclin-dependent kinases; CFIm: cleavage factor I; CRISPRi: CRISPR-mediated interference; CTL: cytotoxic lymphocyte; EGFR: epidermal growth factor receptor; EMT: epithelial-to-mesenchymal transition; ERK: extracellular signal-regulated kinase; EZH2: enhancer of zeste homolog 2; FGF: fibroblast growth factor; GAC: glutaminase isoform C; GLS: glutaminase; HCC: hepatocellular carcinoma; HIF: hypoxia-inducible factor; HK2: hexokinase 2; hnRNPK: heterogeneous nuclear ribonucleoprotein K; HUVECs: human umbilical vein endothelial cells; IFN: interferon; IGF: insulin-like growth factor; LDHA: lactate dehydrogenase A; LncRNA: long noncoding RNA; MAPK: mitogen-activated protein kinase; MMPs: matrix metalloproteinases; mTOR: mammalian target of rapamycin; PDGF: platelet-derived growth factor; PDK: pyruvate dehydrogenase kinase; PGK1: phosphoglycerate kinase 1; PHLPP: PH domain and leucine rich repeat protein phosphatases; PI3K: phosphoinositide 3-kinase; PKM: pyruvate kinase isozymes; PRC2: polycomb repressive complex 2; PTEN: phosphatase and tensin homolog; Rbm15: RNA binding motif protein 15; SMCHD1: structural maintenance of chromosomes flexible hinge domain containing 1; SNP: single nucleotide polymorphisms; STAT3: signal transducer and activator of transcription 3; TERC: telomerase RNA component; TGF-β: transforming growth factor beta; TIMPs: tissue inhibitors of metalloproteinases; Tregs: regulatory T cells; TSP: thrombospondin; ULK1: unc-51 like autophagy activating kinase 1; VEGFA: vascular endothelial growth factor A; VHL: von Hippel–Lindau; WTAP: Wilms' tumor 1-associating protein; YBX1: Y box binding protein 1; ZEB: zinc finger E-box binding homeobox

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Introduction

Long noncoding RNAs (lncRNAs), defined as >200 nt transcripts with low or no protein-coding potential, represent one of the most significant discoveries in recent decades. Several studies have demonstrated their roles in the initiation and development of disease.[1,2] Considering that lncRNAs participate in various biological processes (such as genomic imprinting, chromatin modeling and posttranscriptional regulation), it is presumed that dysregulation of lncRNA expression could hamper cellular homeostasis and lead to cancer initiation.[3] Genome-wide association and comparative analyses of cancer and normal cells have established differential expression patterns of lncRNAs as well as single nucleotide polymorphisms (SNPs) at their transcriptional loci.[4–6] Furthermore, cancer-specific lncRNA expression patterns appear more tissue- and stage-specific than those of protein-coding genes, supporting the potential development of lncRNAs as powerful alternative biomarkers and therapeutic targets.[7,8] However, the major problem confronted by researchers is the current dimension of the lncRNA transcriptome. Based on novel results obtained by the FANTOM consortium, 19,175 potentially functional lncRNAs in the human genome have been identified.[9] It is advisable to focus on lncRNAs with known functional roles or specific expression patterns in cancer cells and understand their modes of action in the search for translational opportunities. In this review, we have comprehensively summarized the details of experimentally verified lncRNAs involved in hallmarks of cancer, and discussed their correlation to different stages of cancer progression.

Expression Patterns and Action Modes of lncRNAs

Noncoding RNAs constitute an overwhelmingly high percentage (≥80%) of human transcripts.[10] Approximately 4–9% genomic sequences of mammals are transcribed into lncRNAs, representing a considerably higher proportion than protein-coding mRNA sequences (1%), albeit with low expression levels.[11] The ENCODE project and data from other comprehensive analyses of the transcriptome in mammals (FANTOM) have revealed the presence of a large number of lncRNAs on a genome-wide scale, which may overlap with protein-coding genes or show distribution within intergenic intervals.[12–14]

Theoretically, if noncoding RNAs are not under selection, expression diversity and divergence patterns would be similar among different tissues.[11] However, some are synergistically expressed with conserved mRNAs and have particular expression patterns in a tissue- or developmental stage-specific manner.[7,15,16] In cases where a sufficient number of normal samples are available for comparison, lncRNAs with cancer-specific expression in various organ systems could be identified.[17] Considering that the majority of lncRNAs do not encode proteins, their functions are closely associated with transcript abundance or expression levels. Over the past decade, multiple studies have identified alterations in lncRNA expression patterns in the context of cancers, potentially resulting from genetic and epigenetic changes including chromosomal translocations, copy number alterations, small insertions and deletions (INDELs) and SNPs,[1,6,18] or dysregulation by specific oncogenic and tumor-suppressor related signals and regulatory factors.[19–23] Overall, ~8,000 lineage and/or cancer-specific lncRNAs have been identified, representing a vast tumor-specific resource for cancer biomarkers and therapeutic targets,[24] which will be maintained and updated through continued research efforts on cancer-related lncRNAs. For instance, lncRNA-activated by transforming growth factor beta (TGF-β; lncRNA-*ATB*) levels are markedly increased in glioma, hepatocellular carcinoma and prostate cancer, and implicated in cancer cell proliferation and invasion.[25–27] Expression of lncRNA-*PVT1* in nonsmall cell lung cancer (NSCLC) is higher than that in normal cells, which is closely related to tumor invasion, metastasis and poor prognosis.[28]

To some extent, the genomic location of lncRNA transcripts can reveal, at least in part, their putative functions. Generally, lncRNAs exert their regulatory functions in two modes, specifically, *in-cis* whereby lncRNA loci act locally to regulate the expression of nearby genes or *in-trans* whereby lncRNA loci encode RNAs that act in a nonlocal manner.[29] For example, lncRNAs transcribed within the vicinity of a specific target gene can act as a *cis* element to recruit or impede transcription factors and thus modulate transcriptional productivity. Upon binding to complementary mRNA sequences, lncRNAs can act directly as effectors to interfere with transcriptional potency. LncRNAs are additionally reported to function as a scaffold of genomic structure to initiate the assembly of protein complex or as a sponge (or precursor) of small ncRNAs to regulate downstream gene expression. In addition, lncRNAs couple with proteins via formation of specific structures to alter localization of proteins or indirectly affect protein activities by altering configurational isomerism.[3] Accordingly, lncRNA targets vary from DNA to RNA to protein. Moreover, one lncRNA may not be confined to a single action mode. For example, lncRNA X-inactive specific transcript (lncRNA-*Xist*) can induce transcription silencing of chromatin by recruiting polycomb repressive complex 2 (PRC2),[30] the antisense transcript of Xist (*Tsix*) acts *in-cis* to repress transcription and negatively regulate *Xist* expression.[31] In addition, *Xist* has been shown to interact directly with numerous regulatory factors (heterogeneous nuclear ribonucleoprotein K [hnRNPK], Wilms' tumor 1-associating protein [WTAP], structural maintenance of chromosomes flexible hinge domain containing 1 [SMCHD1], and RNA binding motif protein 15 [Rbm15]), which play diverse roles in the initiation and spread of X-inactivation.[32]

Discovery of the diverse modes of action of lncRNAs in the context of cancer is complex owing to the high heterogeneity among different cancer types and elusive regulatory roles of lncRNA alone. Recent studies have demonstrated that lncRNAs are intricately implicated in cancer occurrence and development in a variety of ways.[2,33] For instance, lncRNA cancer susceptibility 2 (lncRNA *CASC2*) acts as a competing endogenous RNA by sponging miRNAs and negatively regulates pSTAT3 and c-Myc,[34] in turn, retarding cancer cell proliferation, migration, invasion and metastasis.[35,36] Yan and coworkers identified lncRNA, HOXB cluster antisense RNA 3 (*HOXB-AS3*), encoding

a small peptide that suppresses cancer growth instead of *HOXB-AS3* lncRNA. This peptide inhibits hnRNP A1-mediated regulation of pyruvate kinase isozyme (PKM) splicing and subsequent glucose metabolism reprogramming, consequently affecting colon cancer progression.[37] However, systematic elucidation of the functions of diverse lncRNAs has not been achieved yet, and further research is required to establish the functional mechanisms of action of lncRNAs in cancer.

Cancer Hallmarks

Carcinogenesis is a multifactor and multistage process, in which genetic alterations are accumulated, and many biological capabilities that act as hallmarks of cancer are acquired. Eight cancer hallmarks exist, as proposed by Douglas Hanahan and Robert A. Weinberg, specifically, sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, reprogramming energy metabolism and evading immune destruction.[38–40] We divided the eight known hallmarks into four groups according to the clinicopathological status of cancer cells: (*i*) *uncontrolled growth*: which includes sustaining proliferative signaling, evading growth suppressors and evading immune destruction; (*ii*) *increased cellular viability*: which includes resisting cell death, enabling replicative immortality; (*iii*) *increased motility*: which includes inducing angiogenesis, activating invasion and metastasis; (*iv*) *changed energy metabolism mode*: which includes reprogramming energy metabolism. In this review, we have systematically discussed the cancer-related lncRNAs reported in recent years (Table 1 and Supporting Information Table S1) and their roles in different cancer hallmarks during cellular transformation from normal to cancerous (Fig. 1).

LncRNAs Involved in Uncontrolled Cancer Growth

Normal cell growth comprises a deliberate strategy for regulating growth-promoting signals that instruct entry of cells and progression through the growth and division cycle, thereby ensuring proper control of cell number and maintenance of normal tissue architecture and function. However, cancer cells deregulate these signals, including intrinsic mitogenic signals (K-Ras, BRAF and mitogen-activated protein kinase [MAPK] pathways) and external components (ligands of cell surface growth factor receptors or cytokines secreted by cytotoxic lymphocytes [CTLs]), leading to eventual escape from cell cycle regulation.[4,39]

Recent studies have demonstrated that several lncRNAs play complex roles in coordinating tumor suppressor and growth arrest pathways. For example, RAS and its downstream cascades transmit cellular signals, resulting in increased transcription of genes involved in cell growth and division. Using a custom-designed lncRNA microarray, the lncRNA *Orilnc1* was identified as a genetic target of RAS critical for oncogenicity. *Orilnc1* was highly expressed in BRAF-mutated cancers, such as melanoma, and regulated by RAS–RAF–MEK–extracellular signal-regulated kinase (ERK) signaling via the transcription factor (activator protein 1 [AP1]). Silencing of *Orilnc1* blocked tumor cell proliferation and growth *in vitro* and *in vivo*.[41]

Some lncRNAs affect cancer cell proliferation by directly regulating cell cycle regulatory molecules. The lncRNA—antisense noncoding RNA in the INK4 locus (*ANRIL*) reported to be dysregulated in several human cancers[42–44]—is transcribed from the INK4b–ARF–INK4a gene cluster in the antisense strand and is believed to facilitate cancer cell proliferation.[45] Kyoko and coworkers showed the presence of higher levels of *ANRIL* in prostate cancer with involvement in repressing the p15/CDKN2B-p16/CDKN2Ap14/ARF gene cluster *in-cis* via direct binding of PRC.[137] Moreover, this lncRNA can regulate the CDK6/E2F1 pathway through epigenetic silencing of miR-99a/miR-449a via binding to PRC2 which could, in part, account for *ANRIL*-mediated cell growth regulation.[43]

Another well-characterized lncRNA, growth arrest specific 5 (*GAS5*), affects proliferation by influencing cell cycle progression. *GAS5* was originally identified by subtractive cDNA cloning of genes that are preferentially expressed in growth-arrested cells,[138] showing an evident decrease in expression in multiple cancer types.[48–50] *GAS5* induced growth arrest of gastric cancer cells through inhibition of G1–S phase translation, which was potentially mediated via upregulation of P21 and suppression of CDK6.[51]

On the other hand, excessive accumulation of cancer cells is derived not only from aberrant activation of the intrinsic mitogenic pathway but also attenuation of suppressor genes, RB and TP53 and immune surveillance. TP53 is the most extensively studied tumor-suppression factor activated during the stress response, including replicative stress, oxidative stress, hypoxia, DNA damage and nutrient deprivation, and plays critical roles in the maintenance of cellular number and function.[139–142] Recently, a number of lncRNAs have been shown to interact with the p53 pathway and form a complex regulatory network by acting as either the target (such as *MALAT1, MEG3, H19, LincRNA-RoR, 7SL, MT1JP, ZFAS1*) or regulator (such as *LincRNA-p21, PANDA, Pint, NORAD, TUG1, PVT1, LINP1, DDSR1*) of TP53.[143] For instance, TP53 target 1 (*TP53TG1*) has been identified as lncRNA critical for the correct response of p53 to DNA damage. The tumor growth suppressor features of *TP53TG1* are linked to its ability to block the tumorigenic activity of the RNA-binding protein, Y box binding protein 1 (YBX1). DNA methylation-associated silencing of *TP53TG1* produces aggressive tumors that are resistant to cellular death by DNA damage agents and small targeted molecules. This earlier study provides an example of a tumor-suppressor lncRNA undergoing epigenetic lesions in cancer located at the crossroads of DNA damage and oncogenic pathways.[56]

Immune defense reflects the whole-organism level of protection from abnormal cell growth via which the vast majority of incipient cancer cells are recognized and eliminated. However, cancers manage to evolve mechanisms to avoid recognition of the immune system, even facilitating tumor development. LncRNAs have been shown to mediate immune changes in cancer cells. The lncRNA epidermal growth factor receptor (*Lnc-EGFR*), upregulated in regulatory T cells (Treg), is correlated positively with tumor size and

Table 1. Summary of published well-studied lncRNAs involves in cancer hallmarks

LncRNA	Type	Molecular regulators	Hallmarks	References
Orilnc1	onco	RAS (+); RAF (+); MEK (+); ERK (+); AP1(+)	①	41
ANRIL	onco	p15 (–); p16 (–); MMP3 (+); TIMP2 (–); caspse-9 (+); caspase-3 (+); Bcl-2 (+); Bax (–); E2F1(+); c-Myc (+)	①②③⑥	42–47
GAS5	TS	CDK6 (–); PTEN (+); E2F1 (–); p21(+); cyclinD1 (–); CDK6 (–); vimentin (–); MMP2 (–)	①②⑥	48–55
TP53TG1	TS	p53 (+); YBX1 (–);	②	56
Lnc-EGFR	onco	NF-AT1(+)	⑧	57
IL7R	TS	E-selectin (–); VCAM-1(–); IL-6 (–); IL-8 (–)	⑧	58
PTENP1	TS	PTEN (+); PHLPP (+); ULK1 (+); ATG7 (+); p62 (+)	①③⑥	59
HOTAIRM1	onco	miR-20a (–); miR-106b (–); miR-125b (–); LC3B (+)	③	60
MEG3	TS	Cyclin D1 (–); cyclin B1 (–); CDK1 (–); p53 (+); caspase3 (+); procaspase-9 (+); cytochrome c (+); Bcl-2 (–); Bax (+)	①②③⑥	61–66
TERRA	TS	TRF2(–)	④	67
CARLo-5	onco	p27 (–); p21 (–); p16 (–); caspase-3 (–); Bax (–); Bcl-2 (+); Snail (+); Twist (+); c-Myc (+)	①②③⑥	68–72
UBE2CP3	onco	VEGFA (+); Ang2 (+); p-Erk (+); p-p70S6K (+); HIF-1α (+)	⑤	73
MVIH	onco	PGK1 (+)	⑤	74
HULC	onco	ZEB1 (+); ZO-1 (+); E-Cadherin (–); LC3-II/LC3-I (+); pmTOR (+); E2F1 (+); Snail (+)	①③⑥	75–79
ATB	onco	Cyclin E (+); cyclin D1 (+); miR-200 s (–); TGF-β2 (–); ZEB1 (+); ZEB2 (+); E-cadherin (–); ZO-1 (–); N-cadherin (+); vimentin (+); TGF-β (+)	①⑥	25–27,80
UCA1	onco	Cyclin D1(+); p27(–); ZEB1 (+); ZEB2 (+); E-cadherin (–); N-cadherin (+); Vimentin (+); Snail (+); β-catenin (+); MMP14 (–); MMP-7 (+); FGFR1 (+)	①②⑥	81–91
p21	onco	HIF1 (+)	⑦	92
IGFBP4-1	onco	HK2 (+); PDK1 (+); LDHA (+)	⑦	93
CCAT2	onco	GAC (+)	⑦	94
CRNDE	onco	GLUT4 (+); insulin (–); IGF-I (–); IGF-II (–)	⑦	95
SAMMSON	onco	P32 (+)	⑦	96
MALAT1	onco	CDK4 (+); BAX (–); ZEB2 (+); slug (+); E-cadherin (–); β-catenin (+); N-cadherin (+); vimentin (+);Twist (+); MMP13 (+); MMP19 (–); MMP-9 (+); TIMP-3 (–); VEGF (+); TGFA (+); miR-200s (–); TGF-β (+)	①③⑤⑥	97–109
H19	onco	RB (–); c-Myc (+); EGFR (–); cyclin A2 (+); CDK4 (+); cyclin B1 (+); cyclin D1 (+); cyclin E1 (+); P21 (–); IGF-II (–);	①②③⑤⑧	110–122
HOTAIR	onco	Cyclin D1 (+); cyclin E (+); CDK4 (+); CDK2 (+); E2F1 (+); p53 (–); p21 (–); p16 (–); P38 (+); PIK3R3 (–); Bcl-2 (+); caspase-9 (–); caspase-3 (–); NOTCH1 (+); β-catenin (+); N-cadherin (+); Vimentin (+); Snail (+); Twist (+); MMP9 (+); MMP2 (+); MMP3 (+); FGF1 (+); VEGFA (+); Ang2 (+); GLUT1 (+);	①②③⑤⑥⑦	88,123–131

Type: onco means the lncRNA promotes cancer progression; TS means the lncRNA inhibits cancer progression. *Molecular regulators*: + means the molecular has a positive correlation with the lncRNA; – means the molecular has a negative correlation with the lncRNA. *Hallmarks*: ①—sustaining proliferative signaling; ②—evading growth suppressors; ③—resisting cell death; ④—enabling replicative immortality; ⑤—inducing angiogenesis; ⑥—activating invasion and metastasis; ⑦—reprogramming energy metabolism; ⑧—evading immune destruction.

Abbreviations: Ang2, angiopoietin-2; AP1, activator protein 1; ATG7, autophagy-related gene 7; Bax, Bcl-2 associated X; Bcl-2, B-cell lymphoma 2; CDK, cyclin-dependent kinases; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; GAC, glutaminase isoform C; HIF, hypoxia-inducible factor; HK2, hexokinase 2; IGF, insulin-like growth factor; IL, interleukin; LDHA, lactate dehydrogenase A; MMP, matrix metalloproteinase; NF-AT1, nuclear factor of activated T-cells 1; PDK, pyruvate dehydrogenase kinase; PGK1, phosphoglycerate kinase 1; PHLPP, PH domain and leucine rich repeat protein phosphatases; PIK3R3, phosphatidylinositol 3-kinase, regulatory subunit 3; PTEN, phosphatase and tensin homolog; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloproteinase; TRF2, telomeric repeat-binding factor 2; ULK1, unc-51 like autophagy activating kinase 1; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; VEGFA, vascular endothelial growth factor A; YBX1, Y box binding protein 1; ZEB, zinc finger E-box binding homeobox; ZO-1, zona occludens-1.

EGFR/Foxp3 and negatively with interferon-gamma (IFN-γ) expression. This lncRNA stimulates Treg differentiation, suppresses CTL activity and promotes hepatocellular carcinoma immune evasion in an EGFR-dependent manner.[57] In addition, some lineage-specific lncRNAs are preferentially located adjacent to or intergenic with cytokine coding genes, such as lncRNA-*IL7R*,[58] lncRNA-*NeST*[144,145] and lncRNA-*Th2-LCR*,[146,147] and act downstream of lineage-specific transcription factors to regulate their expression.[148]

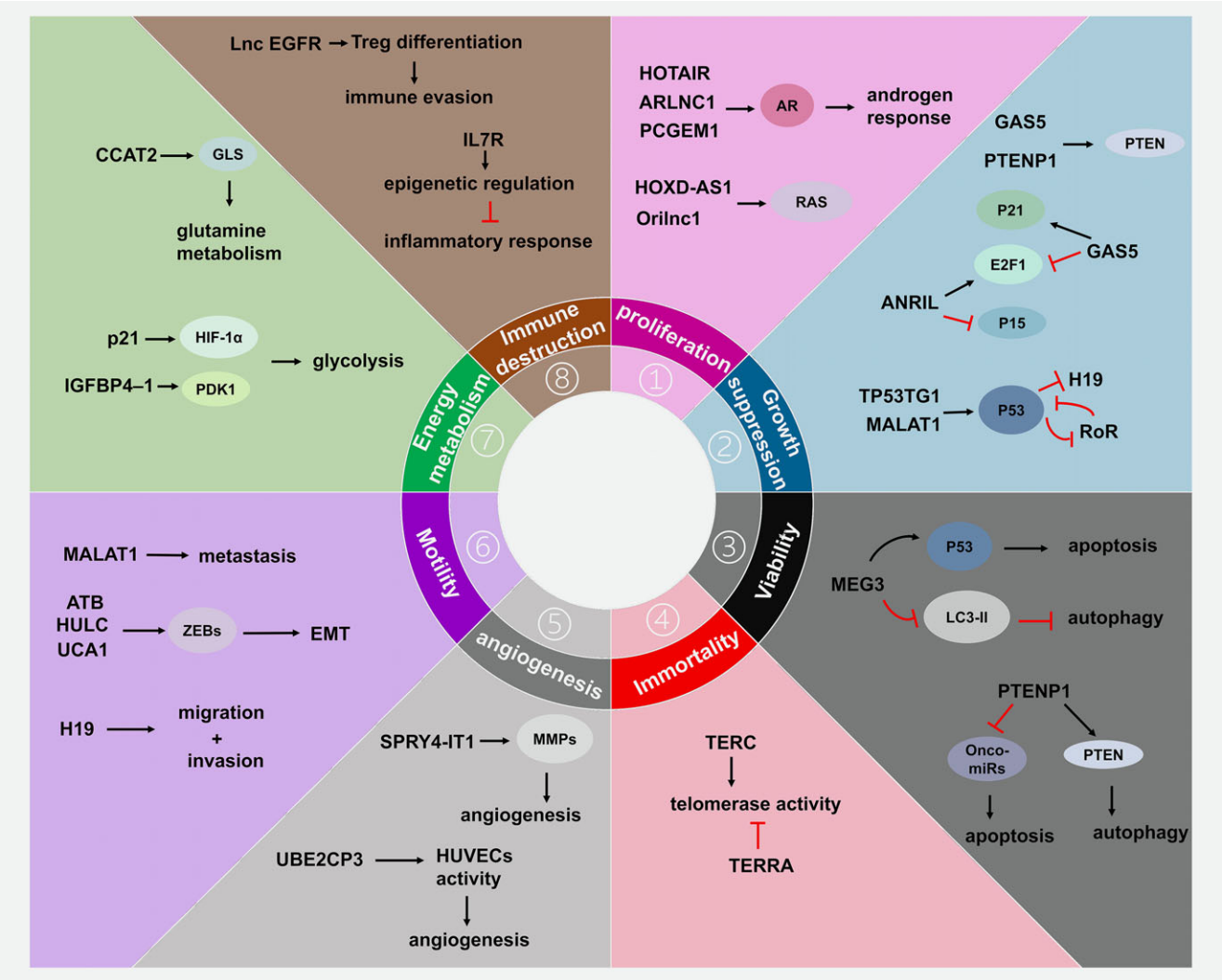

Figure 1. LncRNAs in Cancer Hallmarks. LncRNAs contribute to each of the eight hallmarks of cancer (diagram adapted from Hanahan and Weinberg, Cancer: Principles & Practice of Oncology, 2015, 28–57, ©Wolters Kluwer). Selected examples of lncRNAs and their molecular partners or genomic targets are shown for proliferation, growth suppression, immune destruction, immortality, motility, angiogenesis, viability and energy metabolism.[132–136] [Color figure can be viewed at wileyonlinelibrary.com]

LncRNAs Involved in Cancer Viability

Apart from disrupting growth signals, cancer also evolves from resistance to cell death and facilitation of replicative immortality. Various cell death processes, including autophagy and apoptosis are attributed to eliminating aberrant cells and maintaining organismic integrity under different states of stress stimuli. Cancer cells succeed in circumventing this barrier in the crisis phase and facilitate division into repeated cycles (resistance to senescence). Notably, progressive evidence indicates that specific lncRNAs regulate these processes, including inactivation and attenuation of death-inducing cascade signals, and extension of cell life via upregulating telomerase expression. For example, the lncRNA mentioned above, *GAS5*, has a strong positive correlation with apoptosis in prostate cancer cell lines, nonsmall cell lung cancer and breast cancer cells.[149–151]

Some tumor-suppressor lncRNA genes participate in apoptosis and autophagic regulation of cancer cells. The lncRNA phosphatase and tensin homolog pseudogene 1 (*PTENP1*) is a pseudogene of the tumor-suppressor gene, *PTEN*, capable of provoking autophagy initiation through repressing the oncogenic phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway.[59] Overexpression of PTENP1 in hepatocellular carcinoma (HCC) has been shown to significantly restore the expression of PTEN and decoy oncomiRs, miR-17, miR-19b and miR-20a, leading to increased expression of autophagic genes, such as unc-51 like autophagy activating kinase 1 (ULK1), autophagy-related gene 7 (ATG7) and p62/SQSTM1, in turn, triggering cell autophagy and suppressing HCC.[59,152]

In contrast to *PTENP1*, the lncRNA *HOTAIRM1* impedes autophagy by inhibiting all-trans retinoic acid (ATRA)-induced

cell autophagy of PML-RARA in promyelocytic leukemia (PML).[60,153,154] Interestingly, however, upon binding miR-20a/106b and miR-125b for enhancing ULK1, E2F1 and DNA damage regulated autophagy modulator 2 expression, HOTAIRM1 can additionally promote autophagy, contributing to autophagy-dependent degradation of PML-RARA.[60,155] Thus, overexpression of HOTAIRM1 may serve as a potential therapeutic measure for PML. The lncRNA, maternally expressed gene 3 (*MEG3*), a well-studied tumor suppressor, simultaneously affects cell apoptosis and autophagy in multiple cancers.[61–63] This lncRNA inhibits intrinsic cell survival pathways by reducing protein expression of B-cell lymphoma 2 (Bcl-2), enhancing Bcl-2 associated X (Bax) and activating the p53 downstream target, caspase-3.[64] Moreover, *MEG3* levels are negatively correlated with LC3-II, an autophagy marker, thus affecting cancer cell viability through suppression of cell autophagy.[156]

In the majority of immortalized cancer cells, the ability to maintain telomeric DNA length aids in avoiding replicative senescence, which is commonly achieved through upregulating telomerase or, less frequently, an alternative recombination-based telomere maintenance mechanism.[4,157] Telomerase RNA component (*TERC*) has been shown to have catalytic activity in the process of adding telomere repeats.[158] Moreover, the lncRNA telomeric repeat containing RNA (*TERRA*) is involved in the organization and maintenance of telomeric structure by regulating telomerase.[67,159,160]

In addition, genome instability, which facilitates mutational alterations of hallmark-enabling genes, could trigger growth immortality. Amplification of the 8q24 locus is a well-characterized oncogenic event in many human malignancies resulting in Myc amplification. Myc is a recognized oncogenic event in several human cancer types. Significant evidence implicates regulatory roles of lncRNA in Myc-driven cancers. Cancer-associated region lncRNA (*CARLo-5*, also designated colon cancer-associated transcript-1 (*CCAT1*)) located in the 8q24.21 gene desert region and initially characterized in colon cancer, also accelerates proliferation and suppresses apoptosis of cancer cells.[68] *CARLo-5* binds and positively regulates c-Myc,[68] promoting immortalization ability and, in turn, proliferation and viability of cancer cells.

LncRNAs Involved in Cancer Motility

Clinically, once tumor cells acquire the capability to migrate, cancer enters a stage of deterioration. Induction of angiogenesis and activation of invasion and metastasis mechanisms are responsible for this process. Tumor angiogenesis is a precondition for metastasis, which is driven by complex interplay between proangiogenic (VEGF/VEGFR, platelet-derived growth factor [PDGF]/PDGFR) and antiangiogenic factors (thrombospondin [TSP-1/TSP-2]) within the tumor microenvironment.[161] A number of lncRNAs are reported to participate in tumor angiogenesis. For example, *MALAT1*-deficient cells exhibited decreased vascular proliferation and vascular endothelial growth factor (VEGF) responsiveness leading to a reduced vascular network, compared to that in wild-type mice retina[162]; Similar to *MALAT1*, ubiquitin conjugating enzyme E2C pseudogene 3 (lncRNA *UBE2CP3*) is associated with increased levels of vascular endothelial growth factor A (VEGFA) in HCC cell supernatants and promotes angiogenesis *via* stimulating human umbilical vein endothelial cell (HUVEC) proliferation, migration and tube formation by activating ERK/HIF-1α/p70S6K/VEGFA signaling[73]; while microvascular invasion in liver cancer (*MVIH*) that is overexpressed in hepatocellular carcinoma suppresses angiogenesis by binding to phosphoglycerate kinase 1 (PGK1).[74]

In addition to angiogenesis, activation of epithelial-to-mesenchymal transition (EMT) is a crucial means by which carcinoma cells enhance invasive capacity.[163] Loss of E-cadherin is considered a fundamental event in EMT. Some lncRNAs, such as highly upregulated in liver cancer (*HULC*), *lncRNA-ATB* and urothelial cancer-associated 1 (*UCA1*), promote EMT through modulating the zinc finger E-box binding homeobox (ZEB) protein, which binds the E-cadherin promoter and suppresses its transcription.[26,75,76,81] Other than ZEB, Snail and Slug are important regulatory factors, which trigger the steps of desmosomal disruption, cell spreading, and partial separation at cell–cell borders, the first and necessary phase of the EMT process. LncRNAs, such as prostate cancer antigen 3 (*PCA3*) and translation regulatory lncRNA 1 (*TRERNA1*), promote cancer motility *via* acting as enhancers of Snail activity,[164,165] while lncRNA–small nucleolar RNA host gene 15 (*SNHG15*) promotes cancer progression by binding to and stabilizing Slug.[166] In addition, lncRNAs regulate cancer motility by activating (*H19*, *MALAT1*, *HOTAIR*) or inhibiting (*ROR*, *TCF7*, *TUG1*) multiple EMT-related pathways (such as TGF-β, fibroblast growth factor [FGF], Wnt/beta-catenin and Notch).[163,167]

LncRNAs Involved in Energy Metabolism

To maintain rapid proliferation and growth, cancer cells commonly reprogram metabolism to produce adenosine triphosphate (ATP) expeditiously for promoting macromolecular biosynthesis and cultivating an applicable homeostatic redox balance. Compared to normal cells, cancer cells have distinct metabolic characteristics, such as excessive glucose uptake, higher dependence on aerobic glycolysis, increased glutamine uptake and glutaminolysis and modified lipid metabolism.[168]

Glucose is the primary energy source for cells. Several lncRNAs modulate glucose metabolism in cancer cells through critical transcription factors that regulate expression of genes involved in glycolysis to facilitate the glycolytic process, such as hypoxia-inducible factor 1 (HIF-1). For instance, *lincRNA-P21*, a previously identified p53-inducible lncRNA,[169] is strongly induced by hypoxia and enhances glycolysis in a HIF-1α-dependent manner. *LincRNA-p21* stabilizes HIF-1α by alleviating von Hippel–Lindau (VHL)-mediated HIF-1α ubiquitination and subsequent degradation.[92] Other mechanisms by which lncRNAs modulate glycolysis have also been documented. For instance, the lncRNA *IGFBP4-1* influences ATP production and expression of specific enzymes, including hexokinase 2 (HK2), pyruvate dehydrogenase kinase

1 (PDK1) and lactate dehydrogenase A (LDHA), and the aerobic glycolysis rate in lung cancer.[93]

Glutamine, a growth-supporting metabolite, is the most plentiful amino acid in both cell culture medium and blood, serving as an essential supporting factor of cancer cell proliferation and growth.[170] Two types of glutaminases, GLS1 (glutaminase1) and GLS2 (glutaminase2), control the rate-limiting step in glutamine metabolism and are therefore subjected to fine adjustment.[170] LncRNA colon cancer associated transcript 2 (*CCAT2*) regulates glutamine metabolism of colon cancer cells in an allele-specific manner via binding the cleavage factor I (CFIm) complex, thus modulating the alternative splicing of GLS, with preferential induction of glutaminase isoform C (GAC) splicing through selection of the poly(A) site in intron 14 of precursor mRNA.[94]

LncRNAs additionally regulate cancer energy metabolism through various other mechanisms. The lncRNA colorectal neoplasia differentially expressed (*CRNDE)* regulated by insulin/insulin-like growth factors (IGFs) is a downstream target of PI3K/Akt/mTOR or Raf/MAPK pathways. Knockdown of a highly conserved sequence within intron 4 (gVC-In4) affects the expression of many genes that are correlated with insulin/IGF signaling pathway components and responses, including glucose and lipid metabolism.[95] The lncRNA, survival associated mitochondrial melanoma specific oncogenic noncoding RNA (*SAMMSON*), primarily localizes in the cytoplasm, and interacts with p32 to regulate mitochondrial homeostasis and metabolism.[96]

Complex Roles of lncRNAs Involved in Cancer Progression

Cancer development is a multifaceted process during which various hallmarks are acquired in an unexpected manner and the relative balance and significance of their contributions to malignant disease vary across the spectrum of human cancers.[39] Considering the versatile action modes and spatiotemporal expression patterns of lncRNAs, it is likely that these molecules play complex and diverse roles in cancer development without confinement to a single hallmark.

The lncRNA metastasis-associated lung adenocarcinoma transcript-1 (*MALAT1*) has been shown to participate in multiple cancer steps, such as proliferation, apoptosis, autophagy, angiogenesis, EMT and metastasis,[97–99] and is involved in tumorigenesis of several cancer types.[100,101] *MALAT1* can regulate signaling factors in both cell cycle and apoptotic pathways.[102] Autophagy is also conditioned by *MALAT1 via* modulation of pPI3K, p85α and Akt levels.[171] Furthermore, *MALAT1* facilitates cancer metastasis through inducing angiogenesis,[98] EMT,[103] and matrix metalloproteinase (MMP) and tissue inhibitor of metalloproteinase (TIMP) expression.[98] These collective findings support the utility of *MALAT1* as a potential biomarker of cancer progression.

LncRNA-*H19,* located on chromosome 11 in humans, is a maternally expressed imprinted gene shown to participate in multiple cancer hallmarks. *H19* has a highly conserved secondary structure and is a precursor of miR-675-5p/miR-675-3p, supporting its potential function as a reservoir of miR-675 that suppresses its targets or as a modulator of micro-RNAs or proteins via binding.[172,173] Current research suggests that *H19* exerts its activities mainly through these two mechanisms of action. For instance, *H19*-derived miR-675 downregulates the tumor suppressor RB in human colorectal cancer, causing increased tumor cell growth and soft agar colony formation.[110] Moreover, *H19*-derived miR-675 contributes to bladder cancer cell proliferation through inhibiting p53 and p53-dependent protein expression.[174] On the other hand, through interactions with miR-138 and miR-200a, *H19* promotes EMT by antagonizing their functions and leads to de-repression of their endogenous targets Vimentin, ZEB1 and ZEB2.[111] Additionally, in malignant melanoma, *H19* promotes glucose metabolism and cell growth via binding miR-106a-5p.[175]

Another well-characterized lncRNA, HOX Transcript Antisense RNA (*HOTAIR*), is involved in several processes associated with carcinogenesis, such as proliferation and mobility.[123–126] *HOTAIR* is a trans-acting lncRNA that serves as a scaffold for histone modification complexes.[176] Recent studies have shown that *HOTAIR* is overexpressed in many types of primary tumors and metastases, in turn, activating genomic relocalization of PRC2 and H3K27 trimethylation of various genes in different chromosomes, leading to increased cancer invasiveness and metastasis.[177–179] Battistelli *et al.*[180] showed that *HOTAIR* mediates physical interactions between Snail and enhancer of zeste homolog 2 (EZH2), an enzymatic subunit of the polycomb repressive complex 2, thus repressing Snail activity and ultimately promoting EMT. In addition to interacting with protein complexes as a scaffold, *HOTAIR* could also exert its functional effects by acting as miRNA sponge. For instance, through sequestering miR-206 at the posttranscriptional level, *HOTAIR* upregulates the prosurvival protein, Bcl-w, to enhance proliferation of breast cancer cells.[181]

Perspective

Cancer causes numerous deaths every year and requires long and arduous treatment courses. Elucidation of the specific mechanisms underlying cancer development provides significant benefits for cancer diagnosis and treatment. In this review, we have discussed the contributory roles of lncRNAs in cancer hallmarks. The occurrence and progression of cancer is clearly the result of a combination of multiple factors. Each hallmark interacts with another, and the modes of action of lncRNAs may be diverse. Interestingly, some lncRNAs, such as *H19* and *UCA1*, potentially participate in every cancer hallmark. These molecules not only influence cancer cell growth, invasion and metastasis but also alter energy metabolism and the immune system.[82,83,112–114,182] Researchers can take advantage of these findings to develop novel targets for cancer diagnosis and treatment. However, clinical application of lncRNAs is a considerable challenge due to the difficulties in function predictions owing to nonconserved primary sequences.

To resolve this issue, a number of factors need to be considered. First, information based on known findings should be assimilated. For example, by mining more dominant characters, we can develop constructive computational tools depending on machine-based

arithmetic to predict cancer-related lncRNAs. Second, integrated information (such as genomic location, neighborhoods, synergetic partners and coexpression networks) of lncRNAs should be utilized to predict their functions. Collecting and processing the available information on lncRNAs from a plethora of sources is tedious but extremely beneficial. So far, many integrated lncRNA databases had been developed, such as GENCODE, Noncode, lncRNAdb and LNCipedia. To accumulate valuable information on lncRNAs in cancer, our group recently developed a cancer-related lncRNA database designated "CRlncRNA"[183] accessible at http://crlnc.xtbg.ac.cn/, which integrates knowledge on clinicopathological and molecular features as well as hallmark characteristics of cancer-related human lncRNAs. The third challenge is how to improve the current technology to more effectively validate lncRNA functions. For example, by combining global run-on sequencing and RNA-seq data from ER-treated MCF7 cells, lncRNAs regulating cell cycle gene expression and proliferation in breast cancer cells have been identified.[184] In addition, using CRISPR-mediated interference (CRISPRi), Liu *et al.*[185] systematically determined 499 lncRNA loci required for robust cellular growth targeting from 16,401 loci in seven diverse cell lines. Notably, the biological traits of lncRNAs (conservation, action mode, secondary structure significance in function) are markedly different from those of mRNAs, resulting in diverse research strategies.

We believe that with the rapid advancements in technology and increasing knowledge on lncRNAs, elucidation of the specific roles of these molecules in distinct cancer types should further extend our understanding of the mechanisms underlying cancer occurrence and development and facilitate effective and timely diagnosis and treatment.

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