



Regulation Mechanism of Long Noncoding RNAs in Colon Cancer Development and Progression

Xiaohuan Tang, Xiaofang Qiao, Chao Chen, Yuanda Liu, Jiaming Zhu, and Jingjing Liu

Department of Gastrointestinal Nutrition and Hernia Surgery, The Second Hospital of Jilin University, Changchun, China.

Colorectal cancer (CRC) is the second most common cause of cancer-related death worldwide, and its high rates of relapse and metastasis are associated with a poor prognosis. Despite extensive research, the underlying regulatory mechanisms of CRC remain unclear. Long noncoding RNAs (lncRNAs) are a major type of noncoding RNAs that have received increasing attention in the past few years, and studies have shown that they play a role in many biological processes in CRC. Here, we summarize recent studies on lncRNAs associated with CRC and the signaling pathways and mechanisms underlying this association. We show that dysregulated lncRNAs may be new prognostic and diagnostic biomarkers or therapeutic targets for clinical application. This review contributes not only to our understanding of CRC, but also suggests novel signaling pathways associated with lncRNAs that can be targeted to block or eradicate CRC.

Key Words: Colorectal cancer, lncRNA, signaling pathway

INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies worldwide, and ranks the second most common cause of cancer-related death for both sexes.¹ The morbidity and mortality of CRC have increased in the past few years, especially in developing countries in Asia, such as China.² Despite advances in the prevention, diagnosis, and treatment of CRC, effective treatment strategies for this disease have yet to be developed.³ Metastasis and relapse are the main causes of failure in the treatment of CRC.⁴ Therefore, elucidating the molecular mechanisms underlying CRC progression and me-

tastasis is important. Recent evidence supports the involvement of various signaling pathways in the pathogenesis and development of CRC.⁵ Activation of the Wnt/ β -catenin cascade is a common phenomenon in CRC,⁶ and its downstream target genes can promote tumorigenesis by inducing cell cycle progression and abnormal proliferation.^{7,8} The Wnt/ β -catenin signaling pathway is involved in the regulation of epithelial-mesenchymal transition (EMT) and cell proliferation, invasion, and migration in CRC. This pathway also plays a vital role in regulating epithelial stem cell self-renewal, and the self-renewal ability of CRC stem cells is important for the initiation of CRC.⁹ Alterations in the Wnt/ β -catenin signaling pathway affect CRC, providing a potential target for treatment. The Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway, the PI3K/AKT signaling pathway, the MAPK cascade, the p53 pathway, Notch signaling, nuclear factor κ B (NF- κ B) signaling, and other pathways have also been shown to affect the development of CRC.

Increasing evidence indicates that noncoding RNAs (ncRNAs) play important regulatory roles in various biological processes, including cancer development.¹⁰ Long noncoding RNAs (lncRNAs) are ncRNAs longer than 200 nucleotides in length that are not translated into proteins.^{11,12} Recent studies have reported that various lncRNAs act as modulators of carcinogenesis and progression in human CRC.¹³ lncRNAs are required for CRC cell proliferation and migration,¹⁴ are associ-

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Co-corresponding authors: Jiaming Zhu, PhD, Department of Gastrointestinal Nutrition and Hernia Surgery, The Second Hospital of Jilin University, No. 218 Ziqiang Street, 130041 Changchun, China.

Tel: 86-431-81136210, Fax: 86-431-81136210, E-mail: Zhujiaming75@sina.com and Jingjing Liu, PhD, Department of Gastrointestinal Nutrition and Hernia Surgery, The Second Hospital of Jilin University, No. 218 Ziqiang Street, 130041 Changchun, China.

Tel: 86-431-81136210, Fax: 86-431-81136210, E-mail: jingjingstarone@163.com

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ated with a poor prognosis in CRC,¹⁵ and promote colon tumorigenesis.¹⁶ LncRNAs exert these effects by regulating various signaling pathways.¹⁷ For example, the lncRNA CCAL promotes CRC progression by regulating the Wnt/ β -catenin signaling pathway.¹⁸ These studies provide new insights with which to improve our understanding of the mechanisms underlying CRC development. Herein, we summarize the latest findings on lncRNAs associated with CRC and highlight associated regulatory mechanisms and signaling pathways that may lead to the development of lncRNA-based approaches in the treatment of CRC.

UNDERLYING MECHANISMS OF LNCRNAs IN THE REGULATION OF CRC

LncRNAs exert effects on gene expression at the transcriptional and post-transcriptional levels via various mechanisms. LncRNAs can bind to DNA, RNA, and proteins to influence transcriptional initiation, RNA stability, or the activity of signaling pathways. LncRNAs serve as a scaffold for the recruitment of transcriptional factors to the promoter region to affect gene expression. Several lncRNAs are involved and play critical roles in the development of cancers, such as malignant proliferation, metastasis, invasion, anti-apoptosis effects, and therapeutic resistance (Table 1). Recent studies have focused on the regulation of lncRNAs in CRC cells through signaling pathways. The underlying mechanisms are addressed in the following paragraphs.

LncRNAs regulate CRC cells through the Wnt/ β -catenin cascade

β -catenin affects both carcinogenesis and development. Overexpression of Wnt/ β -catenin pathway members is a common feature in CRC.^{6,19} Studies suggest that β -catenin plays a role as a transcription factor in concert with TCF1 and LEF1 to activate downstream target genes.²⁰ When Wnt ligands bind to the receptor FZD or LRPs, β -catenin is released from the β -catenin destructive complex, which consist of Axin, APC, and GSK3 β . The activation of the Wnt cascade may be induced by mutations of APC.²¹ Then, β -catenin accumulates and is translocated into the nucleus to activate the downstream genes of the Wnt/ β -catenin pathway through hcCF/LEF, and it may continue to induce the process of EMT through increasing the expression of key proteins.^{22,23} Over the past few years, an increasing number of studies have shown that EMT plays a vital role in cancer cell metastasis and invasion.²⁴ Some lncRNAs have proven to affect EMT by or not by Wnt/ β -catenin pathway.²³⁻²⁹ Several lncRNAs affect the Wnt/ β -catenin cascade to regulate CRC (Table 2), and the regulatory mechanisms are listed in Fig. 1.

Some lncRNAs, such as CCAL, CASC11, and CCAT2, can bind to proteins or microRNAs (miRNAs) to affect the Wnt/

β -catenin pathway indirectly. The lncRNA CCAL can bind to activator protein 2 α (AP-2 α), which can combine with β -catenin and APC to form a complex, thereby weakening β -catenin/TCF-4 interactions in CRC. The lncRNA CASC11 may activate the Wnt/ β -catenin cascade by binding to hnRNP-K, which can form a complex with GSK3 β , TCF4, β -catenin, and AXIN to inhibit the degradation of β -catenin. The physical interaction between TCF7L2 and the lncRNA CCAT2 can increase

Table 1. Signaling Pathways of LncRNAs Participating in the Regulation of Colorectal Cancer

LncRNA	Signaling pathway	Effect	Ref
CCAL	Wnt/ β -catenin	Oncogene	18
CASC11	Wnt/ β -catenin	Oncogene	30
CCAT2	Wnt/ β -catenin	Oncogene	31
MALAT1	Wnt/ β -catenin	Oncogene	32
SNHG1	Wnt/ β -catenin	Oncogene	33
CRNDE	Wnt/ β -catenin	Oncogene	27
ZEB1-AS1	Wnt/ β -catenin	Oncogene	34
H19	Wnt/ β -catenin	Oncogene	35
lincRNA-p21	Wnt/ β -catenin	Anti-oncogene	36
XIST	Wnt/ β -catenin	Oncogene	37
CTD903	Wnt/ β -catenin	Anti-oncogene	23
HNF1A-AS1	Wnt/ β -catenin	Oncogene	39
BCAT1	Wnt/ β -catenin	Anti-oncogene	40
AB073614	JAK/STAT	Oncogene	17
SBDSP1	JAK/STAT	Anti-oncogene	44
GACAT3	JAK/STAT	Oncogene	45
CASC2	JAK/STAT	Oncogene	46
AB073614	PI3K/PTEN/AKT/mTOR	Oncogene	51
DUXAP10	PI3K/PTEN/AKT/mTOR	Oncogene	52
RP11-708H21.4	PI3K/PTEN/AKT/mTOR	Anti-oncogene	53
lncRNA-422	PI3K/PTEN/AKT/mTOR	Anti-oncogene	54
PlncRNA-1	PI3K/PTEN/AKT/mTOR	Oncogene	50
CRNDE	MAPK	Oncogene	58
NNT-AS1	MAPK	Oncogene	59
PURPL	p53	Oncogene	62
lncRNA-ROR	p53	Oncogene	63
SNHG1	p53	Oncogene	64
ZFAS1	p53	Oncogene	65
HNF1A-AS1	p53	Oncogene	66
FAM83H-AS1	Notch	Oncogene	70
FOXO2-AS1	Notch	Oncogene	69
lnc-GNAT1-1	NF- κ B	Anti-oncogene	74
GAS5	NF- κ B	Oncogene	75
HOTAIR	NF- κ B	Oncogene	76
loc554202	Caspase cleavage	Anti-oncogene	77
MALAT1	Chemokine	Oncogene	79
DILC	IL	Anti-oncogene	82
GAS5	IL	Oncogene	75

lncRNA, long noncoding RNA; JAK, Janus kinase; STAT, signal transducers and activators of transcription; IL, interleukin; NF- κ B, nuclear factor κ B.

Table 2. The Regulation of LncRNAs in Wnt/ β -Catenin Cascade

LncRNA	Regulate	Target	Ref
CCAL	Up	AP-2 α	18
CASC11	Up	hn-RNP-K	30
CCAT2	Up	β -catenin/TCF	31
MALAT1	Up	β -catenin/C-Myc/MMP-7	32
SNHG1	Up	β -catenin/TCF-4/MMP-9 cyclin-D1	33
CRNDE	Up	miR-181a-5p	27
ZEB1-AS1	Up	miR-181a-5p	34
H19	Up	miR-200a	35
lincRNA-p21	Down	MRE/miR-451	36
XIST	Up	miR-34a	37
CTD903	Down	β -catenin/EMT	23
HNF1A-AS1	Up	β -catenin	39
BCAT1	Down	β -catenin/c-Myc/MMP-2 cyclin-D1	40

lncRNA, long noncoding RNA; AP-2 α , activator protein 2 α ; EMT, epithelial-mesenchymal transition.

Wnt/ β -catenin signaling pathway activity.^{18,30,31} Some lncRNAs promote the nuclear localization of β -catenin to upregulate the Wnt/ β -catenin cascade, such as MALAT1 and SNHG1.^{32,33}

MiRNAs are also important targets that help lncRNAs exert effects on signaling pathways by binding to a complex. For example, the lncRNAs CRNDE, ZEB1-AS1, H19, lincRNA-p21, and XIST affect the Wnt/ β -catenin signaling pathway by sponging or binding to miRNAs.³⁴⁻³⁸ In addition, lncRNAs can change the expression of certain vital proteins to affect the activation of the Wnt/ β -catenin cascade. The lncRNA CTD903 may downregulate Wnt/ β -catenin signaling and then decrease the expression of TCF, Snail, and Twist to suppress the EMT process, which is closely associated with the development of CRC. The lncRNA HNF1A-AS1 can induce CRC cell growth, invasion, and migration mediated by the Wnt/ β -catenin cascade by up-regulating the expression of β -catenin, cyclin D1, and c-Myc. LncRNA-BCAT1 overexpression inhibits β -catenin expression in CRC cells.^{23,39,40}

LncRNAs regulate CRC cells by affecting the JAK/STAT signaling pathway

JAKs and STATs are essential molecules in cytokine signal transduction pathways.⁴¹ Despite their long-recognized pivotal roles in immunological responses, recent studies have shown that JAKs and STATs play important roles in cancer initiation and progression.⁴² The activated JAK/STAT pathway can inhibit cell apoptosis and promote the proliferation and invasion of tumor cells.⁴³ Certain lncRNAs play a role in CRC by modulating the JAK/STAT pathway, acting as competing endogenous RNAs (ceRNAs) or by changing the expression of phosphorylated STAT3. The lncRNAs AB073614 and SBDSP1 contribute to the suppression of STAT3 phosphorylation,^{17,44}

whereas the lncRNAs GACAT3 and CASC2 act as ceRNAs for specific miRNAs to indirectly up-regulate SP1 and STAT3 expression.^{45,46}

LncRNAs regulate CRC cells by affecting the PI3K/PTEN/AKT/mTOR signaling pathway

The PI3K/PTEN/AKT/mTOR signaling pathway regulates various biological processes in cells, such as gene expression, metabolism, cell growth, and metastasis.⁴⁷ Although the effects of PTEN are frequently mediated by the negative regulation of the PI3K/PTEN/AKT/mTOR signaling pathway, it can also function as a suppressor independently.⁴⁸ Recent studies have demonstrated that lncRNAs regulate cancer progression through the PI3K/PTEN/AKT/mTOR cascade, which plays important roles in CRC cell proliferation and EMT.⁴⁹⁻⁵¹ Approximately 40% of malignant tumors are related to alterations of the PI3K/PTEN/AKT/mTOR cascade, which underscores the potential of the PI3K/PTEN/AKT/mTOR pathway as a target for clinical treatment. LncRNAs mainly affect the expression of related proteins to modulate signaling pathways, such as AB073614, DUXAP10, RP11-708H21.4, and lncRNA-422.⁵¹⁻⁵⁴ In addition, PlncRNA-1 regulates the phosphorylation of PI3K and AKT.⁵⁰

LncRNAs affect CRC cells through MAPK cascade

Studies have demonstrated that most human cancers are related to a biomolecular event, the activation of Ras/MAPK signaling.⁵⁵ Activation of the Ras/MAPK pathway promotes cell proliferation, migration, and differentiation.^{56,57} Conversely, inhibition of this pathway in CRC cells suppresses tumor development. The lncRNA CRNDE is important in the regulation of Ras/MAPK pathways. In addition, hnRNPUL2 can increase the stability of CRNDE to act as a vital mediator, thereby activating the Ras/MAPK cascade.⁵⁸ Wang, et al.⁵⁹ showed that the activity of the MAPK/Erk signaling pathway is regulated by the lncRNA NNT-AS1 and that activation of the MAPK/Erk signaling pathway can induce EMT in CRC cells, increasing CRC cell proliferation, invasion, and migration.

LncRNAs affect CRC cells through the p53 pathway

P53 is a well-known tumor suppressor that is associated with CRC. Overexpression of p53 promotes cell cycle arrest, apoptosis, and tumor suppression.^{60,61} LncRNAs are regulators and mediators of the p53 cascade, and the effect of many lncRNAs is mediated by regulating the expression of p53. For example, the lncRNAs PURPL, ROR, SNHG1, and ZFAS1 promote tumorigenicity in CRC by suppressing basal p53 levels.⁶²⁻⁶⁵ Furthermore, HNF1A-AS1 can repress the miR-34a/SIRT1/p53 feedback loop to down-regulate p53 and promote the metastasis of colon cancer.⁶⁶

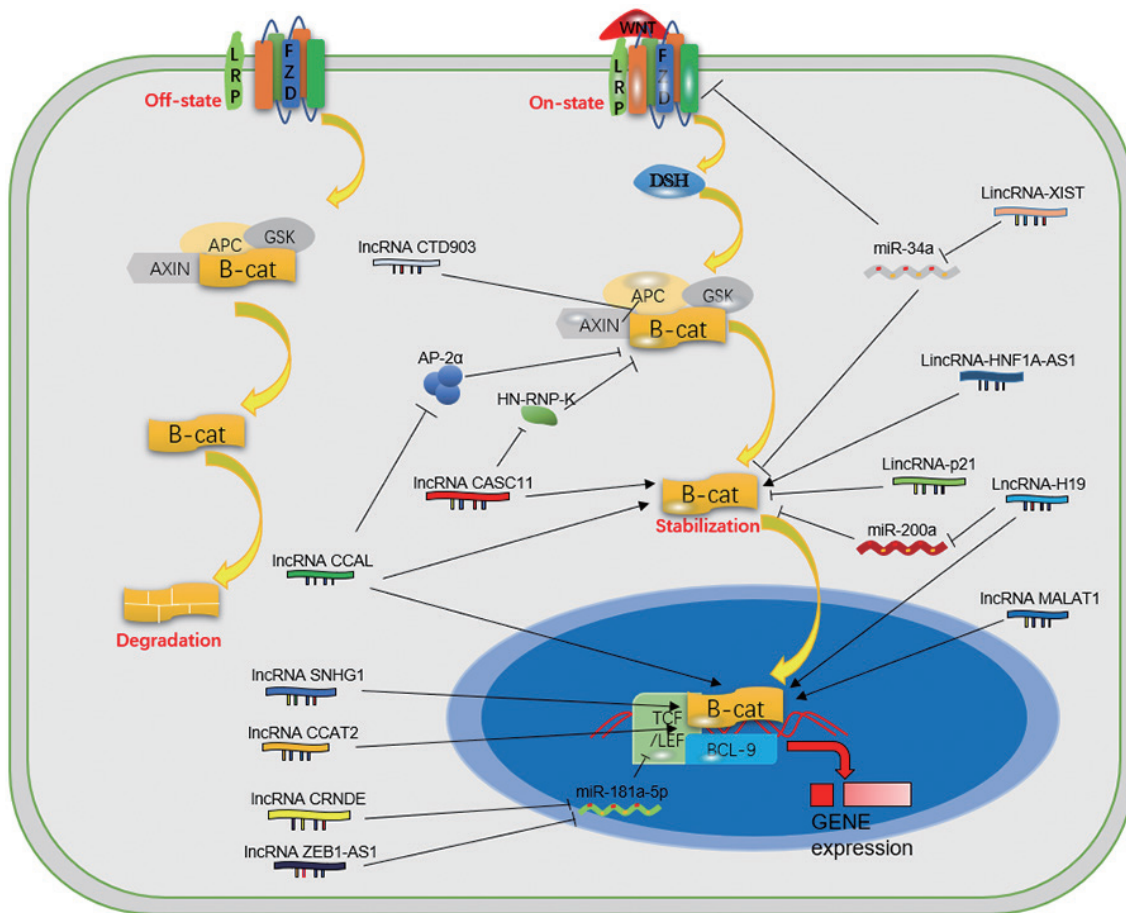


Fig. 1. The diverse regulatory mechanisms of lncRNAs on the Wnt signaling pathway. CCAL can activate Wnt/ β -catenin signaling pathway by down-regulating activator protein 2α (AP- 2α), which can attenuate β -catenin/TCF-4 interactions and increase β -catenin. CASC11 can interact with hnRNP-K to induce the degradation of β -catenin and activate the Wnt/ β -catenin signaling pathway. MALAT1 can increase the nuclear localization of β -catenin and activate the β -catenin pathway. SNHG1 can increase TCF-4 and β -catenin expression, leading to the nuclear accumulation of β -catenin and activation of the β -catenin pathway. CRNDE and ZEB1-AS1 can activate the Wnt/ β -catenin signaling pathway through sponging miR-181a-5p. LincRNA-p21 and CTD903 can reduce the levels of β -catenin in CRC cells. H19 competitively binds to miR-200a and indirectly increases β -catenin expression in CRC. CCAT2 over-expression inhibits β -catenin expression in CRC cells. HNF1A-AS1 can up-regulate the expression of β -catenin, cyclinD1, and c-Myc. LincRNA XIST binds to miR-34a, which can rescue the dysregulation of WNT1 and β -catenin. LncRNA, long noncoding RNA; CRC, colorectal cancer.

LncRNAs affect CRC cells by modulating the Notch signaling pathway

The Notch signaling pathway is involved in the tumorigenesis of various cancers including CRC.^{67,68} The cascade is observed in the processes of CRC cell proliferation, invasion, and metastasis. In addition, Notch signaling regulates EMT.⁶⁹ The lncRNA FAM83HAS1 is overexpressed in CRC cell lines and tissues concomitant with the up-regulation of two Notch signaling molecules, Notch1 and Hes1, thereby regulating the progression of CRC.⁷⁰ FOXD2-AS1 also regulates Notch signaling, acting as a tumor promoter in CRC.⁶⁹

LncRNAs affect CRC through the NF- κ B signaling pathway

The transcription factor NF- κ B was identified as a nuclear factor in 1986 and later shown to bind to enhancer elements to exert tumorigenic effects.^{71,72} Under physiological conditions, NF- κ B is inhibited by many proteins. When these proteins are phosphorylated, NF- κ B is activated and translocated to the

nucleus to promote the initiation and progression of CRC.⁷³ Most lncRNAs regulate this cascade by directly or indirectly modulating NF- κ B. For example, lnc-GNAT1-1 exerts suppressive functions in CRC through the RKIP-NF- κ B-Snail circuit, and lnc-GNAT1-1 knockdown downregulates PKIP and increases NF- κ B expression.⁷⁴ The lncRNA GAS5 can decrease the phosphorylation of NF- κ B to activate NF- κ B signaling.⁷⁵ In addition, the NF- κ B cascade is associated with 5-fluoropyrimidine resistance caused by lncRNA HOTAIR in CRC.⁷⁶

LncRNAs affect CRC cells by several other mechanisms

Caspase cleavage cascade

Apoptosis signaling can induce caspase expression, which may affect the progression of CRC. The overexpression of lncRNA loc554202 can promote G1 arrest and cause apoptosis to inhibit CRC cell proliferation, mainly via caspase cleavage cascade.⁷⁷

Chemokine signaling

Chemokines play an important role in promoting CRC invasion and metastasis.⁷⁸ The lncRNA MALAT1 promotes the progression of colon cancer through tumor-associated dendritic cells (TADCs), and using neutralizing antibodies or siRNA transfection to block chemokine ligand 5 could diminish the promotion of colon cancer induced by TADCs.⁷⁹

Interleukin pathway

Interleukins (ILs) are related to the development of cancer.^{80,81} The lncRNA DILC has been found to be negatively associated with the proliferation and metastasis of CRC via the IL-6/STAT3 cascade.⁸² IL-10 is associated with CRC cell proliferation and colony formation in relation to lncRNA GAS5.⁷⁵

PERSPECTIVES

lncRNAs account for more than 80% of ncRNAs and generally have a lower transcriptional level than that of chromosome modification, transcriptional regulation, post-transcriptional processing, epigenetic, and nuclear import.¹¹ Recent studies focusing on signaling pathways involved in cellular transformation have identified many cascades as potential treatment targets.⁴⁷ Several lncRNAs associated with the regulation of signaling pathways have been identified, and lncRNAs have become ideal biomarkers for early diagnosis, therapeutic evaluation, and prognostic prediction in cancer.⁸³ An extensive body of research has demonstrated that a number of cellular signaling pathways initiate and induce the progression of CRC, including the Wnt/ β -catenin pathway, the JAK/STAT pathway, the p53 pathway, the MAPK pathway, the PI3K/PTEN/AKT/mTOR pathway, the Notch signaling pathway, and the NF- κ B signaling pathway.⁸⁴ We investigated the effects of lncRNAs on signaling pathways and found that many lncRNAs control CRC properties by targeting different components thereof. Some components of signaling pathways have become attractive therapeutic targets because of their important functions in cancer. For instance, resveratrol can inhibit invasion and metastasis of CRC through MALAT1 because MALAT1 upregulates β -catenin and triggers its transfer to the nucleus.³² However, there are still no candidates for clinical application because of serious side effects, as proper signaling pathway activity is essential to sustaining normal cell survival. How to precisely regulate signaling pathways is challenging. Targeting these regulatory lncRNAs may be an alternative approach with which to achieve precise modulation of signaling pathways.

CONCLUSION

We summarized multiple functions and signaling pathways re-

lated to lncRNAs in CRC cells and highlighted their potential clinical applications as novel diagnostic and prognostic biomarkers and therapeutic targets. Our review provides new insights with which to better understand CRC and points toward the potential for lncRNA-based therapeutic strategies for CRC.

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AUTHOR CONTRIBUTIONS

Conceptualization: Jiaming Zhu. Data curation: Chao Chen. Formal analysis: Yuanda Liu. Funding acquisition: Jiaming Zhu. Investigation: Xiaohuan Tang. Methodology: Jingjing Liu. Project administration: Jiaming Zhu. Resources: Xiaofang Qiao. Software: Chao Chen. Supervision: Jingjing Liu. Validation: Xiaofang Qiao. Visualization: Xiaohuan Tang. Writing—original draft: Xiaohuan Tang. Writing—review & editing: Jingjing Liu.

ORCID iDs

Xiaohuan Tang	https://orcid.org/0000-0001-9526-6984
Xiaofang Qiao	https://orcid.org/0000-0001-6134-5270
Chao Chen	https://orcid.org/0000-0001-9092-2460
Yuanda Liu	https://orcid.org/0000-0002-5095-8466
Jiaming Zhu	https://orcid.org/0000-0002-8637-5406
Jingjing Liu	https://orcid.org/0000-0003-3112-0147

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