Name of journal: World Journal of Gastroenterology
Manuscript NO: 39416
Title: Long non-coding RNAs involved in metastasis of gastric cancer

Dear reviewer:
Thank you for providing us an opportunity to revise manuscript, we really appreciate editor and reviewers for your constructive comments and suggestions.
The responses to the comments are as follows:

Reviewer#1(03476648): We appreciate your thoughtful comments. We have supplemented newly searched lncRNAs and corrected imprecise statement. The detailed point-by-point responses for comments are listed below.

Comment 1. More updated data from studies published in 2018 could be included.

Answer: We updated our search results and supplemented several lncRNAs research articles about ”Yes-associated protein1(YAP1)”,” LINC00052”,” LncRNA BC005927”,” PTENP1”,” RP11-19P22.6-001” and ” DQ786243”.

Comment 2. Language editing is needed and also correction of typos throughout the manuscript.

Answer: We carefully read the article through and made the language editing and we find professionals to help us corrected mistakes.

Comment 3. “This review may provide a theoretical foundation for predicting metastasis and for intervening in metastatic GC.” This statement does not reflect the scopes of this review, please rephrase.

Answer:”This review summarizes in category the metastatic related lncRNAs, which may help to understand the mechanism map of mentioned lncRNAs, and may provide potential markers for prognostic prediction and monitoring relapse of GC. These mechanisms could be possible targets to intervene metastatic GC.”

Comment 4. ”Due to the unsatisfactory prognosis in advanced stage GC patients who have undergone surgery, chemotherapy or radiotherapy, measures should be taken to intensively monitor GC patients”. It would be helpful to describe here the state-of-the art regarding GC monitoring.

Answer:” The post-operative monitoring tools including endoscopic monitoring, CT, MRI, PET, serological monitoring(CA19-9,CA153,CA125,CA724), though the sensitivity did not match our expectation yet. Recently, circulating tumor DNA(ctDNA) are being considered as GC relapse predicting markers. Because of the unsatisfactory prognosis in advanced stage GC patients who have undergone surgery, chemotherapy or radiotherapy, measures should be taken to intensively monitor GC patients”

Comment 5. ”lncRNAs involved in degradation of the extracellular matrix (ECM)” should read “lncRNAs involved in regulation of degradation of the extracellular matrix (ECM)”

Answer: We made the modification as your comments.

Comment 6. Table 2: An idea would be to highlight the lncRNAs that have been validated in independent patient cohorts and also report Hazard Ratios and 95%CI

regarding OS and DFS.

Answer: We add “OS(HR&95%CI) “ and ” DFS(HR&95%CI)” to the Table 2, and collected lncRNAs that have been validated in cohorts and filled in their HR and 95%CI regarding OS and DFS.

lnc RNA ID	Dysregulation	Upstream regulators	Downstream targets	Metastasis processes	Clinical correlation	Univariate analysis(HR 95%CI) P＜0.05		Multivariate analysis(HR 95%CI) P＜0.05		Reference
						OS	DFS	OS	DFS	
MALAT1	up	JMJD1A	UPF1, Snail, N-cadherin, ZEB1 VE-cadherin /β-catenin complex, ERK/MMP, FAK/paxillin, EGFL7,miR122	EMT, Angiopoiesis, VM	Lymphatic metastasis, distant metastasis, TNM stage	1.38(1.03-1.85)	1.40(1.01-1.94)			[14,17,23,86,87]
HOTAIR	up		PCR2, miR34a, c-MET, SNAIL1, CDH1 miR-152, HLA-G	EMT, immune escape	Lymphatic metastasis, distant metastasis, TNM stage					[74-76,78,88-90]
FRLnC	up	FOXM1	Twist,TGFβ-1	EMT						[25]
UCA1	up		TGFβ-1 GRK2/ERK/MMP9	EMT, degradation of the ECM	Lymphatic metastasis, TNM stage	3.909(1.592-9.599)		2.917(1.069-7.962)		[30,74]
ATB	up	TGFβ-1	miR200s, ZEB1	EMT				3.50(1.73-7.44)		[26]
XIST	up		miR101	EMT	Lymphatic metastasis, distant metastasis, TNM stage					[27]
SNHG-6	up		miR101-3P,	EMT	Lymphatic					[28]

		ZEB1		metastasis, distant metastasis, TNM stage					
ZFAS1	up	ZEB1,SNAIL, Slug,Twist	EMT	Lymphatic metastasis, TNM stage					[29]
LINC00152	up		EMT	Lymphatic metastasis, TNM stage	2.162(1.327-3.524)		1.659(1.008-2.731)		[91]
HULC	up		EMT	Lymphatic metastasis, distant metastasis, TNM stage					[35]
Linc00978	up	TGFβ/SMAD ,Twist1, Slug	EMT	Lymphatic metastasis, TNM stage					[32]
YAP1	up	vimentin, β-catemin, E-cadherin	EMT	Lymphatic metastasis, distant metastasis, TNM stage					[33]
Linc00261	down	Slug, GSK3β	EMT	Lymphatic, metastasis		0.494(0.300-0.812)		0.551(0.323-0.940)	[36]
Linc00675	down	vimentin	EMT						[40]
SPRY4-IT1	down	vimentin	EMT, epigenetic regulation	Lymphatic metastasis, distant metastasis, TNM stage	1.247(1473-1.996)	2.223(1.806-2.59)	0.818(0.314-1.567)	1.741(1.324-2477)	[43,92]

LEIGC	down			EMT					[44]
GClnc1	up		WDR5/KAT2, H3K4,H3K9, SOD2	epigenetic regulation		2.21(1.46-3.33)		1.93(1.24-3.00)	[15]
LOC100130476	down	DNMT1		epigenetic regulation	Lymphatic metastasis, distant metastasis, TNM stage				[47]
AK058003	up		SNCG	epigenetic regulation, hypoxia	Lymphatic metastasis, TNM stage				[57]
BC005927	up	HIF-1α	BPHB4	hypoxia	Lymphatic metastasis, TNM stage				[58]
SNHG15	up		MMP2,MMP9	degradation of the ECM	Lymphatic metastasis, TNM stage				[93]
FENDRR	down		MMP2,MMP9	degradation of the ECM	Lymphatic metastasis	0.539(0.337-0.862)	0.563(0.370-0.856)	0.569(0.321-0.960)	0.555(0.344-0.897)	[16]
BM742401	down		MMP9	degradation of the ECM					[53]
C21orF96	up			Lymphangiogenesis, VM	Lymphatic metastasis, distant metastasis				[69]
LINC00052	up		Wnt/β-catenin pathway		TNM stage				
AA174084	down								[81]
RMRP	down				Lymphatic metastasis				[82]
SNHG1	up				Lymphatic metastasis				[94]

			, TNM stage	
SNHG5	down		TNM stage	[95]
MSTO2P	up	miR-335	Lymphatic metastasis , distant metastasis	[96]
ZEB1-AS1	up	miR-335-5p	Lymphatic metastasis , TNM stage	[97]
PTENP1	down	miR-106b, miR-93	Lymphatic metastasis , TNM stage	
RP11-19P22.6-001	down	nitric oxide synthase 2 (NOS2)	Lymphatic metastasis , TNM stage	
PCAT-1	up		distant metastasis	[98]
HOXD-AS1	up		Lymphatic metastasis , distant metastasis , TNM stage	[99]
CARLo-5	up		Lymphatic metastasis , distant metastasis	[100]
LINC00673	down		Lymphatic metastasis	[101]
LINC00982	down		Lymphatic metastasis , TNM stage	[102]
HMlincRNA717	down		distant metastasis	[103]
PVT1	up		Lymphatic	[104]

				metastasis					
GACAT3	up	IL-6/STAT3		distant metastasis, TNM stage					[105]
Sox2ot	down			distant metastasis	3.241(1.239-6.428)		3.844(1.873-7.332)		[106]
HOTTIP	up		HOXA13	Lymphatic metastasis, TNM stage					[107]
NEAT1	up			Lymphatic metastasis, distant metastasis					[108,109]
OTUB1-isoform2	up		N-cadherin, MMP2,MMP9, E-cadherin	Lymphatic metastasis, TNM stage	1,538(1.044-2.265)	1.615(1.111-2.348)		1.498(1.021-2.200)	[110]
PANDAR				Lymphatic metastasis, TNM stage	4.612(1.59-13.825)	3.113(1.591-6.093)	3.683(1.125-12.058)	2.359(1.153-4.830)	[111]
ZMAT1 transcript variant 2	down			Lymphatic metastasis, distant metastasis, TNM stage					[112]
JMJD1A	up		MALAT1,MAPK	Lymphatic metastasis, TNM stage	8.446(4.480-15.923)		3.988(1.948-8.167)		[113]
OR3A4	up		PDLIM2, MACC1,NTN4, GNB2L1	degradation of the ECM, angiopoiesis, VM	Lymphatic metastasis distant metastasis				[54]
HNF1A-AS1	down				Lymphatic metastasis				[114]

BANCR	up	Lymphatic metastasis, distant metastasis	2.457(1.715-3.521)		1.511(1.02-2.227)		[115]
DQ786243	up	Lymphatic metastasis, TNM stage					[116]
XLOC_010235	up	distant metastasis, TNM stage					[117]
CCAT2	up	Lymphatic metastasis, distant metastasis, TNM stage	2.631(1.348-5.672)	2.574(1.201-5.476)	2.405(1.194-5.417)	2.315(1.097-5.283)	[118,119]
Linc-UBC1	up	Lymphatic metastasis, TNM stage					[120]
HIF1A-AS2	up	Lymphatic metastasis, TNM stage	2.346(1.379-3.991)		1.724(1.002-2.964)		[121]
LET	down	Lymphatic metastasis, distant metastasis, TNM stage	2.513(1.414-5.847)		2.275(1.301-5.176)		[122]
LSINCT5	up	Lymphatic metastasis, TNM stage		2.501(1.326-4.719)		1.081(1.286-3.564)	[123]
AC130710	up	distant metastasis, TNM stage					[124]

FER1L4	down		Lymphatic metastasis , distant metastasis , TNM stage			[125]
RuPAR	down		Lymphatic metastasis , distant metastasis , TNM stage			[126]
H19	up	miR-675	Lymphatic metastasis , TNM stage	1.170(1.050-1.304)	1.137(1.005-1.287)	[127,128]
AC096655.1-002	down		Lymphatic metastasis , distant metastasis , TNM stage			[129]
SUMO1P3	up		Lymphatic metastasis			[130]
IGF2	up		Lymphatic metastasis			[131]
CCAT1	up		Lymphatic metastasis , TNM stage			[132]

Reviewer#2(02631746): Thank you very much for providing improvement suggestion. According to your suggestions, we have made revisions to our previous manuscript, the details are as follws.

Comment 1: The authors also need to outline briefly as to how this knowledge can be used in the treatment of the patient in addition to using it for prognosis.

Answer:" Silencing UCA1 inhibits resistance to adriamycin in GC, which suggests that UCA1 may be a novel therapeutic target";

"Furthermore, LEIGC overexpression enhances the GC cells sensitivity of 5-fluorouracil, and this characteristic enable LEIGC to be a potential therapeutic

target.”;
”lncRNAs involved specific mechanism of regulation of GC progression could be helpful in GC treatment. Those lncRNAs who are considered as independent prognostic factor by survival analysis such as MALAT1, Sox2ot, OTUB1-isoform 2, PANDAR, etc… and those lncRNAs dramatically altered in postoperative GC patients such as FERI4, may be utilized as prognosis evaluation markers. Some lncRNAs increased in metastatic tissue compared to primary focus may be beneficial in predicting metastasis.”

According to the reviewer’s comments, we have revised the manuscript.
Thank you!

Yours truly,
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