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METAANALYSIS

Relationship between ncRNAs and gastric cancer: meta-analysis

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ABSTRACT
OBJECTIVE: This study was designed to investigate the action and mechanism of cordyceps polysaccharide on rat acute liver failure (ALF).
METHODS: Sixty rats were randomly divided into five groups: normal group, model group, and cordyceps polysaccharide groups with high, middle and low doses (20, 10 and 5 mg/ml). Apoptosis was detected through TUNEL method. Protein expressions of caspase 1, IL-18, IL-10, VEGF, and SDF-1α in liver tissue are detected by Western Blot. PCNA and sIRPα1 contents were measured by PCR method. Rat ALF is modeled with a D-galactosamine induced by lipopolysaccharide (LPS).
RESULTS: The results after modelling showed tissue HE staining wiith typical manifestation of acute liver injury. Compared with the medicated group, serum ALT and AST, as well as hepatocyte apoptosis are significantly higher in the liver failure group, in a time-dependent way. This suggests that medication can effectively inhibit the expression of caspase 1, IL-18, and IL-10, while simultaneously increasing the expression of VEGF and SDF-1α, as well as of PCNA and sIRPα1. Cordyceps polysaccharide can alleviate the immune inflammatory response in acute liver failure, and may be specifically homing to the damaged liver, thus promoting the secretion of VEGF, proliferation of hepatocyte, regeneration of liver vessels, and repair of liver tissues.
CONCLUSION: Medication can reduce the IL-10 level, regulate the equilibrium of pro-inflammatory and anti-inflammatory factors, and decrease the level of caspase 1 and IL-18 *(Tab. 2, Fig. 1, Ref. 18)*. Text in PDF *www.elis.sk.*
KEY WORDS: non-coding RNAs, gastric cancer, meta-analysis.

Introduction

Non-coding RNAs (ncRNAs) are RNA molecules which cannot be translated into proteins and in most theriomas they play an important role in cell proliferation (1), migration (2), and differentiation (3). NcRNAs include microRNAs, long non-coding RNAs (lncRNAs), PIWI-interacting RNAs and so on (4). The relationships between abnormal expression of ncRNAs and gastric cancer (GC) have always been hot research topics (5). Currently the roles of different kinds of microRNAs and lncRNAs in clinical and pathological features, diagnosis and prognosis of GC have been studied (6), and various data have been shared. However, due to the limitation of sample sizes and methods, a single study does not necessarily have to reveal the relationships between ncRNAs and GC clearly, thus making meta-analysis a variable choice possibly offering a comprehensive understanding of the value of ncRNAs with disease. In this study, we were mainly focused on the relationships between ncRNAs and clinical and pathological features of GC.

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Materials and methods

Search strategy

Articles were searched from Pubmed published before august 14, 2016 with key words "gastric cancer", "microRNA", "miRNA", "non-coding RNA", "ncRNA" with limitation of English (language) and "not review".

Data extraction

To retrieve the data of articles, we built lists containing the number of article (during downloading), RNA studied, sample size, and other information that could be used for two-by-two tables and 95% confidence intervals (95% CIs).

Statistical analysis

The heterogeneity of data was assessed by I2 test (range 0 – 100 %). $p < 0.05$ was considered to be a statistically significant difference. Odd ratios (ORs) and 95% CIs were used to assess the associations between ncRNAs and GC. The significance of pooled ORs was determined by Z-test while $p < 0.05$ indicated significance. All the data were performed by Review Manager 5.3.

Results

Study characteristics

A total of 684 articles were downloaded from Pubmed. After

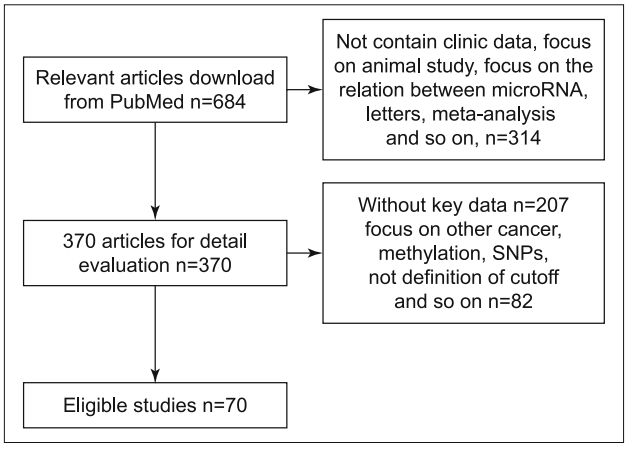

Fig. 1. Chart of study selection inclusion and exclusion criteria.

removing 314 irrelevant studied not containing clinical data, focusing on animal studies and relationships between microRNAs, letters, there were still 207 studies not including key data, 82 studies focusing on other cancers, methylation, and SNPs. Finally, 71 studies were left. The procedure of selecting the studies is shown in Figure 1.

ncRNA and clinical pathological features of gastric cancer

A total of 59 ncRNAs containing 45 miRNAs and 14 lncRNAs were included in the 71 studies. Among these 59 ncRNAs, 8 were detected in blood, 2 were detected in bone marrow, and the other 49 ncRNAs were detected in tissues. The sample sizes of each study were all more than 30. The following 11 ncRNAs were detected in more than two studies: H19 (n = 2), HOTAIR (n = 4), mir-199a-3p (n = 3), mir-19B (n = 2), mir-200B (n = 2), mir-200c (n = 3), mir-203 (n = 2), mir-21 (n = 3), mir-215 (n = 2), mir-301a (n = 2), mir-34a (n = 2), mir-370 (n = 2), mir-433 (n = 2), mir-9 (n = 2) (Tab. 1). Together, 8 data sets and 45 groups were combined. Heterogeneity was observed among 15 groups of data (I2 value from 50 % to 100 %) (Fig. 1), including 11 moderate and 4 severe (mir-200c and lymph node metastasis, I2 = 93 %; mir-200c and TNM stage, I2 = 96 %; mir-21 and liver metastasis, I2 = 90 %; mir-34a and lymph node metastasis, I2 = 91 %). By comparing the P values before and after these meta-analyses, we found that the statistical significances of 6 groups were changed (Tabs 1 and 2). Before combination, H19 ER outcome revealed that the H19 was significantly correlated with the depth of tumor invasion. Zhang revealed that mir-200c was significantly associated with cell grade (7, 8). However, the pooled P values did not support these associations. The P values of the associations between the expression of mir-200c with lymph node metastasis and TNM stage (9, 10), mir-34a with lymph node metastasis (11, 12), as well as mir-215 with tumor invasion depth (13, 14) changed from less than 0.05 to more than 0.05 (Tab. 2).

Discussion

Gastric cancer (GC) is the fourth most common cancer and the second leading fatal cancer in the world (15), and thus remains a major public health concern worldwide. Due to many methods of facilitating the early diagnosis (16), the mortality of GC has decreased considerably over the past 50 years (17). However, the improvement in GC patients' survival is still limited owing to the lack of early detection measures (18). There is still a need to develop new biomarkers of cancer.

Current studies of relationships between GC and ncRNAs are all mainly focused on microRNAs and lncRNAs. In our meta-analysis, two lncRNAs, H19 and HOTAIR, have been investigated in more than two articles with both increasing expression in GC. Expression of H19 was not correlated with gender (OR 1.02, 95% Cl: 0.48–2.18, p 0.96) and tumor invasion (OR 1.82, 95% Cl: 0.69–4.80, p 0.23) in our study; even the significant association between miR-200c expression and tumor invasion depth

Tab. 1. Summary of the comparison for the *P* values of the association between ncRNAs and clinicopathological features.

ncRNA	gender	age	lymph node metastasis	tumor invasion depth	vascular invasion	liver metastasis	TNM stage	cell grade	tumor site
H19 ER	0.82		0.002	0.04					
H19 TO	0.64		0.67	0.34					
Pooled *P* value	0.66		0.02	0.23					
HOTAIR WEI	0.63	1							
HOTAIR YOSHI	0.57		0.07		0.71	0.28			
HOTAIR Y-W	0.4	0.92			0.0005	0.49			
HOTAIR ZHIYUAN	0.7		0.002		0.17				
Pooled *P* value	0.26	0.95	0.002		0.005	0.2			
MIR-199a-3p CHEN	0.34		0.0001	<0.0001			<0.0001	0.32	
MIR-199a-3p ZHEN	0.78		0.01	0.03			0.007	0.04	
Pooled *P* value	0.82		<0.0001	<0.0001			<0.0001	0.05	
Mir-19b ouyang	0.59	0.91	0.03					0.05	0.04
mir19b yan li	0.03	0.46	0.12					0.03	0.01
Pooled P value	0.34	0.71	0.005					0.005	0.001

Tab. 2. Summary of the P values comparison of the association between ncRNAs and clinicopathological features.

ncRNA	gender	age	lymph node metastasis	tumor invasion depth	vascular invasion	liver metastasis	TNM stage	cell grade	tumor site
mir-200b hailin	0.56	0.61	0.04	0.01			0.0001	0.12	
mir-200b yunyun	0.25	0.29	<0.0001	0.9			0.05	0.99	
Pooled *P* value	0.75	0.29	<0.0001	0.03			<0.0001	0.23	
mir-200c Hirlin	0.22	0.09	0.03				0.0007	0.22	
mir-200c zhang	0.99	0.42	0.003				0.006	0.01	
Pooled *P* value	0.36	0.08	0.61				0.79	0.31	
mir-203 Hiroki	0.02				0.007				
mir-203 shao	0.51				0.48				
Pooled *P* value	0.03				0.01				
mir-21 Hiroki	0.9		1		0.81				
mir-21 Kazuo			0.1		0.83	0.27			
mir-21 yue juan	0.7		<0.0001			0.87			
Pooled *P* value	0.97		0.02		0.77	0.56			
MIR215 YJ	0.04		0.88	0.2					
MIR215 YU	0.36		0.23	0.17					
Pooled *P* value	0.03		0.35	0.05					
MIR301A ming	0.81		1	0.44			0.83	0.01	
MIR301A xiao	0.87		0.0003	<0.0001			0.0003	0.04	
Pooled *P* value	0.95		0.0007	0.0002			0.001	0.006	
MIR34A bairen	0.36		0.005						
MIR34A wen	0.58		0.06						
Pooled *P* value	0.88		0.54						

has been confirmed in Er-Bao Zhang article (OR 21.18, 95% Cl: 1.18–380, p 0.04); the pooled value (p 0.23) did not support this conclusion, neither that of the significant association between H19 and lymph node metastasis. As to HOTAIR, it was obviously associated with lymph node metastasis (OR 0.38, 95% Cl: 0.20–0.69, p 0.002), and vascular invasion (OR 0.47, 95% Cl: 0.28–0.80, p 0.005).

Speaking of microRNAs, we studied 9 kinds of microRNA in 40 groups of data. Among these data, 5 were significantly changed. P values of the associations between the expression of mir-200c and lymph node metastasis and TNM stage, as well as mir-34a and lymph node metastasis, and mir-215 and tumor invasion depth, changed from less than 0.05 to more than 0.05.

Besides, as to associations of mir-199a-3p with lymph node metastasis, tumor invasion depth, TNM stage and cell grade, mir-19b with lymph node metastasis, cell grade, tumor site; mir-200b with lymph node metastasis, tumor invasion depth, TNM stage; mir-203 with vascular invasion; mir-21 and lymph node metastasis; mir-301 with lymph node metastasis, tumor invasion depth, TNM stage, cell grade, P values were all less than 0.05, which indicated significant relationships with GC.

In conclusion, our meta-analysis demonstrated that some noncoding RNAs, such as H19 and mir-21 had strong associations with clinical and pathological features of gastric cancer.

Also, there are some limitations of this study. Firstly, several statistical heterogeneities had been observed, and some of them were even serious. Secondly, since most of the eligible articles came from China, the outcome cannot be applicable to other countries and regions.

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