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J Clin Immunol Exp Hematol

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分子诊断与治疗杂志

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973 2015CB

HCV

HCV

1

chylomicrons
CM very lowdensity lipopro
teins VLDL intermediate density
lipoproteins IDL low density li
poproteins LDL high density li
poproteins HDL CM VLDL
LDL HDL
CM HDL

Apo

Apo A Apo B
Apo C Apo D Apo E

Apo B100 LDL VLDL

Apo A Apo A HDL
Apo C CM VLDL
Lipoprotein lipase LPL
Apo C HCV LPL
CM VLDL HDL

1[3]

2 HCV

HCV

RNA HCV
HCV

E1 E2 HCV

HCV clau
din 1 B I scavenger receptor class
B type 1 SRB1 low density li
poprotein receptor VLDLR CD81 [4]

HCV
C E1 E2 p7 4
NS2 NS3 NS4A NS4B NS5A NS5B 6
HCV
HCV
[5] HCV
NS4B
[6] HCV NS4A NS4B

[6]

Lipid dr LDs HCV
7

[8]

4A HCV [9]

E1 E2

[10] NS2

E1/E2

[11]

VLDLs [12] LDs

Apo B100 Apo E APO C

Lipid Virus Particles LVPs

HCV VLDL Apo B100 HCV

LVPs Apo C Apo E

HCV LVPs

[13] HCV

VLDL

microsomal triglyceride trans

fer protein MTP VLDL

MTP [14]

GFP

Apo E [15]

HCV LVPs VLDL

Apo E VLDL

[16]

3 HCV

HCV

HCV 1.03~1.10 g/

mL [17]

VLDL LDL IDL HDL

Apo B

HCV

[18]

LVPs

[18]

HCV

HCV

HCV

[19] HCV

HCV

[20] HCV

HCV

1.07 g/mL LDL VLDL

73 nm VLDL [17]

HCV VLDL

HCV Apo E ApoC Apo C

VLDL [21]

HCV

[22]

40~140 nm

[23] HCV 3

[24]

HCV

[25] HCV

Apo B Apo A Apo C Apo C Apo C

Apo E [24]

HCV Apo E

HCV

Apo E Apo B

HCV [26] HCV

Apo E Apo B

Apo B HCV [26]

Apo E HCV

Apo E

[27] Apo E

Apo

E [28]

293t Apo E

[28] Apo

B/Apo E huh 7 LDs [26]

Apo E HCV

4 HCV

HCV

HCV

HCV

HCV
HCV
LDL
HCV [29 30]
λ3 Interferonλ3 IFNλ3
HCV rs12979860 CC
IFNλ3 HCV 1 G1
LDL HCV 3 G3
4 G4 LDL
[31] HCV
HCV
[32]
HCV
HCV
HCV [33]
HCV
HCV [34]
Chronic hepatitis B CHB
Chronic hepatitis C CHC
[35] CHC

Apo A HCV RNA
[36] Apo A HCV
C [37] Apo A HCV
HOMA IR
[38] Apo A HCV
HCV
G1b Apo A
[39] Apo A
HCV Apo
B 100 HCV
[40] Apo C

[41] Apo C HCV

Apo E HCV
Apo E 3 E2 E3 E4 E3
E2
HCV 3~5 [42] E4 HCV
[43] Apo
E3/E3
[44] Apo E
HCV
HCV
HCV HCV
HCV
HCV
[16]

HCV
CHC
HCV
HCV
HCV LVPs
HCV HCV

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YMDD

YMDD
DNA P
DNA
YMDD
229 Sanger YMDD
5 2
YMDD
229 2 74 74/229 32.31% YMDD
44 44/229 19.21% rtM204V 25 25/229 10.92% rtM204I 5
5/229 2.18% rtM204V/I Sanger 47 47/229 20.52% rtM204V 25
25/229 10.92% rtM204I 2 2/229 0.87% rtM204V/I 3
Sanger rtM204V/I Sanger
100% 95.95% 71/74 4.05% 3/74 2 κ
0.97 P<0.01 100%
YMDD
Sanger
Sanger YMDD HBV

YU Xuegao DENG Jiankai CHEN Yaoming CHEN Peisong HE Xiaohong ZHONG Liangying HUANG Bin
Department of Laboratory Medicine the First Affiliated Hospital Sun Yat sen University Guangzhou Guangdong China 510080

ABSTRACT Objective A next generation sequencing NGS was established for the detection of hepatitis B virus HBV YMDD mutations and its performance was also evaluated. Methods DNA was extracted from serum samples by centrifugation column and primers were designed to amplify the P gene region of HBV and the PCR products were captured by the target followed by NGS. The detection results were analyzed by using the bioinformatics software system to establish the NGS for the detection of HBV YMDD mutations. A total of 229 serum samples from patients with chronic HBV were collected. The NGS and Sanger sequencing were used to detect the YMDD gene mutations simultaneously and the detection performance for

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E mail hb906@163.com

NGS was evaluated. Five positive samples including different types of gene mutations and two negative samples were selected to detect repeatedly by NGS and the results were evaluated. Results Among 229 clinical samples 74 74/229 32.31% YMDD mutations were detected by two sequencing methods. Of which 44 44/229 19.21% were detected by NGS 25 25/229 10.92% were detected by rtm204i mutations and 5 5 / 229 2.18% rtm204v / I mixed mutations. 47 47 / 229 20.52% rtm204v mutations 25 25/229 10.92% rtm204i mutations and 2 2/229 0.87% rtm204v / I mixed mutations were detected by Sanger sequencing. Three cases of rtm204v/I mixed mutation missed by Sanger sequencing were detected by NGS. Compared with Sanger sequencing the sensitivity specificity and accuracy of NGS are100% . The complete coincidence rate was 95.95% 71/74 and the partial coincidence rate was 4.05% 3/74 . The consistency of the two methods was 0.97 P<0.01 . The repeatability coincidence rate between two methods is 100% . Conclusion The NGS for the detection of HBV YMDD mutations has been established. This method is more sensitive than Sanger sequencing and can detect more mixed mutations providing a new method for the detection of drug resistant genes of HBV.

KEY WORDS Next generation sequencing Sanger sequencing YMDD HBV resistance genes

hepatitis B virus HBV 3.6 HBV 100 HBV [1] HBV HBV 9 300 [1] lamivudine LAM [2 3]

1 16%~55% [4 5] LAM HBV tyrosine methionine aspartate aspartate YMDD 204 reverse transcriptase methionine 204 valine rtM204V reverse transcriptase methionine 204 isoleucine rtM204I [6 7] YMDD 2~28 12~31 [8 10] LAM YMDD

1

1.1

2017 1 12 LAM 3 5 mL 3 500 rpm 5 min HBV DNA PCR HBV DNA 100 IU/mL 229 182 47 17~77 46.1±13.63 Eppendort -80

1.2

ABI 9700 PCR LOT N8050200 LOT 4314 One Touch2 LOT 2457881 5247 ES LOT 74200 DA8600 LOT sn247560288 ABI 3500 DX LOT 4406019 Qubit 3.0 LOT 2321609904 Life Technology LOT #DA Z14648 SanPrep PCR LOT B518141 0100 Ion AmpliSeq™ Library Kit 2.0 LOT 4480441 Ion PI™ Hi Q™ OT2 Reagents 200 kit LOT A26434 Ion PI™ Hi Q™ Sequencing 200 kit LOT 4488315 Qubit® dsDNA HS Assay kit LOT 1788710 Life Technology

1.3

1.3.1 YMDD

1.3.1.1

DNA Qubit 3.0 DNA -20

1.3.1.2 DNA PCR
HBV P
HBV P 1 PCR
95 15 min 94 30 s
55 30 s 72 45 s 40
72 7 min
SanPrep PCR PCR
Qubit 3.0
DNA -20

1 PCR

Table 1 Primer sequence of target region for PCR amplification

1	5′ ACAACCAGCACGGGACC 3′
1	5′ GCGGGATAGGACAACAGAG 3′ P

1.3.1.3
PCR
Qubit
3.0
-20

1.3.1.4 DNA
Ion PI™ Hi Q™ OT2 Reagents
200 kit Life Technologies
One Touch2 ES Life Technologies

1.3.1.5 DA8600 Ion PI™ Hi
Q™ Sequencing 200 kit Life Technologies

1.3.1.6
variantCaller Allele Call
Absent No Call
YMDD Allele Call
Heterozygous Homozygous
YVDD
YIDD 2

2 YMDD

Table 2 Mutation category of YMDD

HBV	YVDD	739A>G
HBV	YIDD	741G>T

1.3.2 Sanger
PCR
2014 3401444

PCR PCR
PCR 50
2 min 95 15 min 94 30 s
55 30 s 72 45 s 40
72 7 min
PCR PCR
96 1 min 96 10 s
50 5 s 60 4 min 25
4 BigDye®
Terminator v3.1 Cycle Sequencing Kit
ABI 3500 DX
SeqScanner

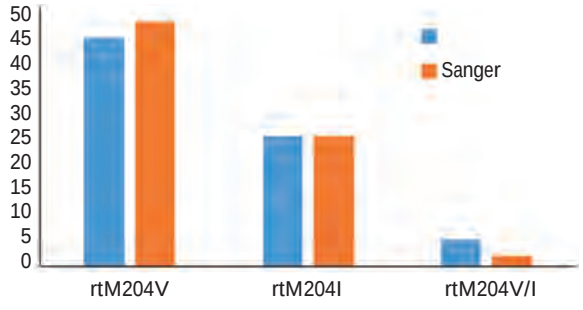
1.4
SPSS
Kappa
P<0.05

2

2.1 YMDD
229
44 rtM204V 25 rtM204I 5
rtM204V/I

2.2 YMDD
Sanger 229
74 YMDD Sanger
47 rtM204V 25 rtM204I
2 rtM204V/I
100% 100% 100% 2
95.95% 71/

74 4.05% 3/74
0/74 0% 1 3 100%
Sanger rtM204V/I



1 Sanger YMDD

Figure 1 The comparison of next generation sequencing method and Sanger sequencing method

2.4 Sanger
Sanger
3 2 YMDD
Kappa=0.97 P<0.01

2.5 3
Sanger 3
Sanger YVDD
YVDD/YIDD
3 2 1
HBV DNA 10^3~
10^5 IU/mL 4

2.3
Sanger 5
YIDD 2 YVDD
3 2
10

4 Sanger 3

Table 4 Analysis of inconsistent o ʁ V̈ ד ablh sistent o ʁ ᘔ 1

			Sanger	HBV DNA IU/mL
HBV 53	51	YVDD&YIDD	YVDD	1.16×10^4
HBV 71	66	YVDD&YIDD	YVDD	1.53×10^5
HBV 120	65	YVDD&YIDD	YVDD	2.14×10^3

HBV

PCR Sanger YMDD

PCR

Sanger

Sanger DNA

20%

PCR

[18 19]

DNA DNA

illumina Life

[20 21]

YMDD

229

YMDD 32.31% 74/229

[22] [23]

Sanger 47 rtM204V

25 rtM204I 2 rtM204V/I

44 rtM204V 25

rtM204I 5 rtM204V/I

100% 100%

100% 95.95% 71/74

4.05% 3/74 0/74 0%

100% 2 0.97 P<0.01

3 Sanger rtM204V

rtM204V/I

Sanger Sanger

Sanger 20%

3

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Snail TGFβ1 EMT

1 2 1 1 3 4 1 1
1 1 1

Snail β1 TGFβ1 EMT TGFβ1 PC3 DU145 EMT Western blot RT PCR EMT Marker EMT KDM4A Snail Gleason 60 Snail E cadherin Vimentin TGFβ1 PC3 Western blot RT PCR PC3 EMT E cadherin Snail1 Vimentin Snail1 E cadherin Vimentin Snail E cadherin Vimentin Snail KDM4A PC3 Snail1 *Snail*1 TGFβ1 TGFβ1 *Snail1* KDM4A

DU Yandan[1] NIU Yiqing[2] ZHENG Haijun[1] WANG Xiaoyan[1] JIANG Yuhai[3] CHEN Haiqiu[4] LI Yinyan[1] SUN Gang[1] LI Chunyu[1] LU Desheng[1] SUN Hui[1]

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ABSTRACT Objective To investigate the relationship between the methylation of *Snail* gene and the induction of epithelial mesenchymal transition EMT by TGFβ1 in prostate cancer cells. Methods PC3 and DU145 cells were induced by TGFβ1. The induced EMT phenotype was screened by cell

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2. 022150
3. 022150
4. ╠ K Q

morphology scratch and invasion experiments. Western blot and RT PCR were used to detect the expression of related markers in EMT cells and the decisive transcription factors in EMT were determined. The expression of histone demethylase kdm4a was silenced and the changes of cell morphology and transcription factor Snail were observed. The expression of snail E cadherin and vimentin were detected in 60 cases of benign prostatic hyperplasia control group and 60 cases of prostate cancer experimental group with Gleason grade 4 or above by immunohistochemistry. Results Cell morphology cell scratch and Transwell experiments demonstrated that the prostate cancer cell line PC3 had a significant migration and invasion ability after TGFβ1 induction. Western blot and RT PCR results showed that E cadherin expression was down regulated Snail1 and Vimentin expression were up regulated in the process of EMT occurrence especially Snail1. The control group showed Snail and Vimentin of cytoplasm were weakly positive E cadherin of membrane was strongly positive. Prostate cancer tissue showed that Snail and Vimentin were strongly positive E cadherin was weakly positive. Silenced histone demethylase KDM4A expression PC3 cells changed from mesenchymal to epithelial morphology Snail1 expression was down regulated. Conclusion The change of *Snail*1 methylated concentration is related to the TGF β1 induced epithelial stromal transformation of prostate cancer cells.

KEY WORDS Prostate cancer TGFβ1 Epithelial mesenchymal transition *Snail*1 KDM4A

Prostate cancer PCa PCa PCa 95% PCa [1] epithelial mesenchymal transition EMT [2 3] β1 transforming growth foctor β1 TGFβ1 SMAD EMT [4] Snail1 EMT Snail1 [5 6] Snail1 H3 [7] H3K9 KDM4A H3K9 KDM4A *Snail*1 PC3 Snail1 EMT

1

1.1

PC3 DU145 ATCC 1640 Gibco DMSO Sigma Trizol Invitrogen DNA Marker TakaRa BCA Thermo Cell Signaling McLean

1.2

1.2.1

90% 24 h 0.5% FBS 1640 10 20 ng/mL TGFβ1 24 48 h

1.2.2

80%

1.2.3 Transwell

Transwell 100 μL 500 μL 1640 100 μL 24 48 h

1.3 RT PCR EMT maker

1.2.1 Trizol RNA A260/A280 1.8~2.0 RNA 1 μg cDNA cDNA GAPDH

2 Ct=2 Ct Ct Ct Ct

1.4 Western Blot EMT maker

PBS

loading buffer 40 g β actin 12% SDS PAGE

β actin

1.5

Gleason 4 60

90% 75% 1 min PBS

1.6

$\bar{X} \pm s$

SPSS 22.0

$P<0.05$ $P<0.01$

2

2.1 TGFβ1 EMT Marker

PC3 DU145 TGFβ1

Western blot RT PCR EMT Marker

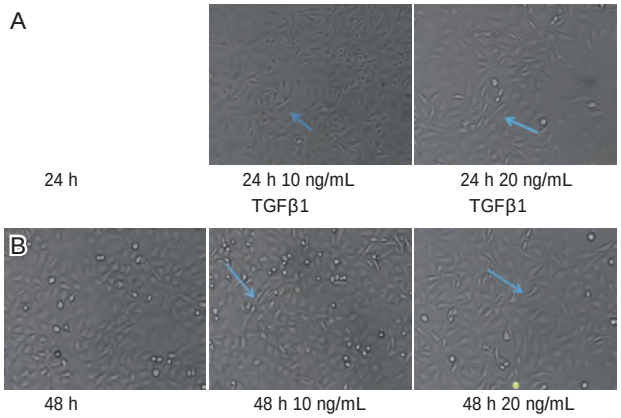
2.1.1 PC3

1.2.1

PC3 DU145 1 A B PC3 PC3 2A B Transwell TGFβ1 PC3 3 4

2.1.2 RT PCR Western blot PC3 EMT Marker

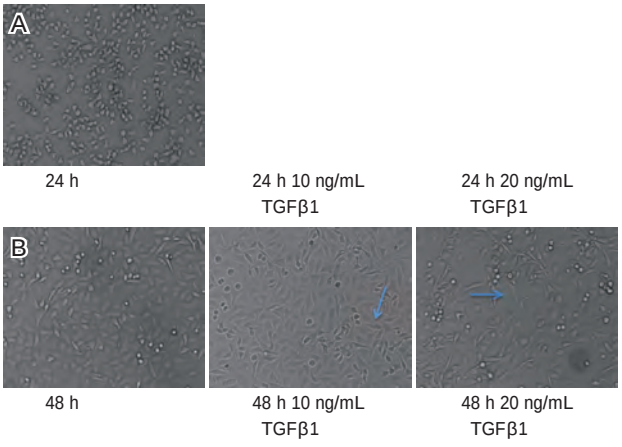
TGFβ1 PC3 EMT Marker E cadherin Snail1 Vimentin Snail1 5 Western blot Snail1 6 7



A DU145 10 20 ng/mL TGFβ1 24 h B 48 h ×40

1 DU145 TGFβ1 24 48 h

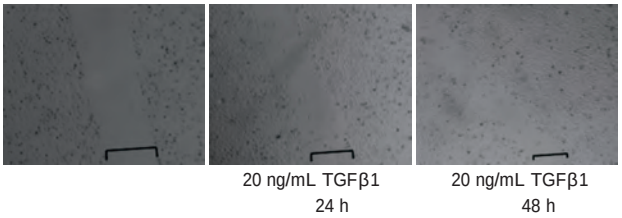
Figure 1 Morphological changes of DU145 cells induced by TGFβ1 for 24 and 48 hours under optical microscope



A PC3 10 20 ng/mL TGFβ1 24 h B 48 h ×40

2 PC3 TGFβ1 24 48 h

Figure 2 Morphological changes of PC3 cells induced by TGFβ1 for 24 and 48 hours under optical microscope



PC3 20 ng/mL TGFβ1 ×10

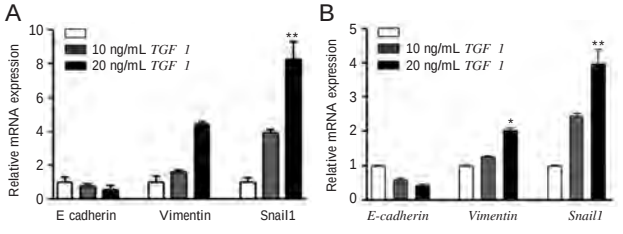
3 PC3 20 ng/mLTGFβ1 24 48 h

Figure 3 Scratch test results of PC3 cells treated with 20 ng/mL TGFβ1 for 24 and 48 hours

PC3 TGFβ1 ×10

4 PC3 Transwell

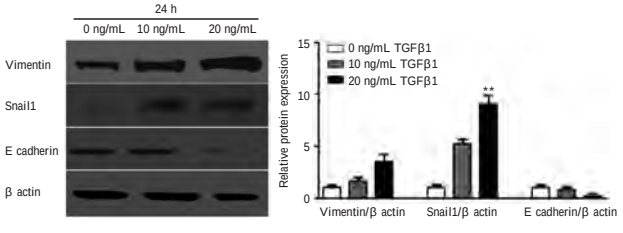
Figure 4 Transwell experiment results of PC3 cells



A 24 h EMT Marker mRNA B 48 h EMT Marker mRNA

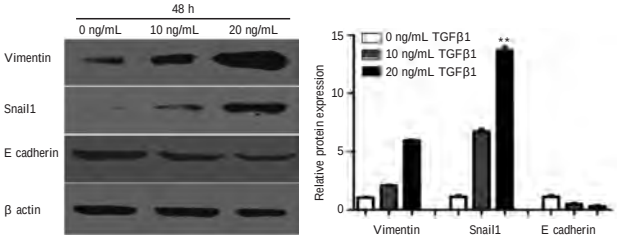
5 TGFβ1 PC3 EMT Marker mRNA

Figure 5 mRNA changes of EMT related Marker in PC3 cells induced by TGFβ1



6 TGFβ1 PC3 24 h

Figure 6 Expression of related proteins in PC3 cells induced by TGFβ1 for 24 hours



7 TGFβ1 PC3 48 h

Figure 7 Expression of related proteins in PC3 cells induced by TGFβ1 for 48 hours

2.2

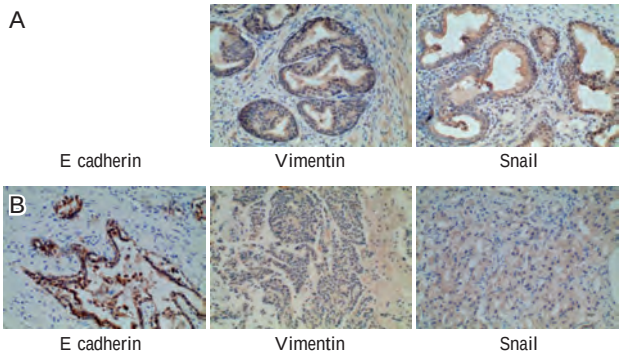
EMT Marker

E cadherin Vimentin Snail 8A

E cadherin Vimentin Snail 8B Snail

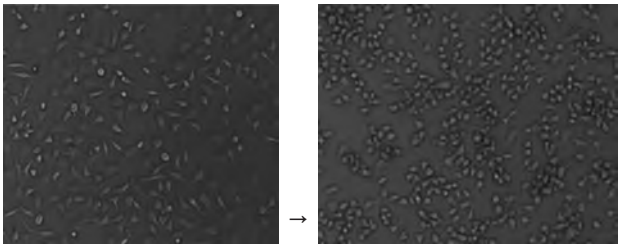
2.3 KDM4A PC3 Snail1

PC3 TGFβ1 TGFβ1+siKDM4A 20 ng/mL TGFβ1 KDM4A *Snail1* EMT PC3 9 marker Snail1 10



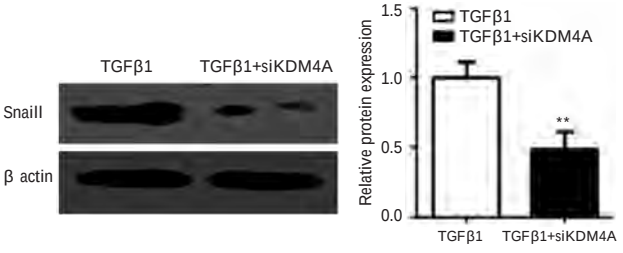
A B 8

Figure 8 Immunohistochemical results of benign prostatic hyperplasia and prostate cancer



9 KDM4A PC3 40×

Figure 9 Morphological changes of PC3 cells after silencing KDM4A



10 KDM4A Snail1

Figure 10 Changes of Snail1 expression after silencing KDM4A

3

[8] EMT *E-cadherin*

[9] E
EMT Snail Slug
[10] EMT
Snail ZEB1 ZEB2 HDAC
EMT E cadherin [11]

[12] H3
[13]
H3
H3

[14 15] H3 H3
K4 H3K36 H3K9

H3K9ME3
[16 17]

[18 19] KDM4 [20]
9 / 36

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HMGB1 TGFβ1 GP73

1 2 1

1 HMGB1 β1 TGFβ1
73 GP73 86
80 HMGB1 TGFβ1 GP73
HMGB1 TGFβ1 GP73
HMGB1 TGFβ1 GP73 P<0.05
HMGB1 TGFβ1 GP73 P<0.05 APACHE
HMGB1 TGFβ1 GP73 P<0.05
HMGB1 TGFβ1 GP73 ROC 0.805 0.827 0.855
HMGB1>33.44 μg/L TGFβ1>40.63 μg/L GP73>79.84 μg/L HMGB1 TGFβ1 GP73 AUC
0.917 72.7% P>0.05
95.3% P<0.05 HMGB1 TGFβ1 GP73

1 β1 73

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ABSTRACT Objective To investigate the prognostic value of serum high mobility group box 1 HMGB1 transforming growth factor β1 TGFβ1 and golgi glycoprotein 73 GP73 in patients with sepsis complicated with liver injury. Methods 86 patients with sepsis complicated with liver injury were selected as the observation group and 80 patients with sepsis alone as the control group. The differences of serum HMGB1 TGFβ1 and GP73 levels between the two groups were compared the risk factors affecting the prognosis of patients with sepsis complicated with liver injury were analyzed. The evaluation effect of serum HMGB1 TGFβ 1 and GP73 on the prognosis was discussed. Results The levels of HMGB1 TGFβ1 and GP73 in observation group were significantly higher than control group P<0.05 . With the aggravation of liver injury the levels of HMGB1 TGFβ1 and GP73 also showed significant increase P<0.05 . High APACHE score severe liver damage elevated of serum HMGB1 TGFβ1 and GP73 levels were risk factors for poor prognosis of sepsis patients combined liver damage P<0.05 . The area under ROC curve for prognostic evaluation of

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serum HMGB1 TGFβ1 and GP73 was 0.805 0.827 0.855. The optimal critical values were HMGB1>33.44 μg/L TGFβ1>40.63 μg/L GP73>79.84 μg/L respectively. The AUC of HMGB1 TGFβ1 and GP73 combined detection was 0.917. The sensitivity of combined detection was 72.7% which was not significantly different from that of single detection P>0.05 while the specificity of combined detection was 95.3% which was significantly higher than that of single detection P<0.05 . Conclusion The serum levels of HMGB1 TGF β 1 and GP73 are closely related to the liver injury of sepsis patients indicating that they can be used as reference indexes to evaluate the prognosis of sepsis patients with liver injury.

KEY WORDS Sepsis Liver injury High mobility group box 1 Transforming growth factor β1 Golgi glycoprotein 73

[1]

[2] [3]

30% 60%

[4] [5 6]

1 high mobility group box 1 HMGB1 β1 transforming growth factor β1 TGFβ1 73 golgi glycoprotein 73 GP73

HMGB1 TGFβ1 GP73

1

1.1

2017 1 2019 1 86 43 43 36~78 57.50±11.32 66 20 25 42 19 64 22 80 46 34 38~75 56.32±11.57 57 23 P>0.05 1

1 n %

Table 1 Comparison of basic data in 2 groups n %

	n	/					
	80	46/34	56.32±10.57	57	71.25	23	28.75
	86	43/43	57.50±11.32	66	76.74	20	23.26
t		1.115	0.199		0.936		
P		0.323	0.843		0.420		

1.2

[7]

2 38 36 20 /min 90 /min 12.0×10^9/L 4.0×10^9/L

total bilirubin TBIL ala nine transaminase ALT [8] TBIL> 34.1 μmol/L ALT> 80 U/L

ALT 1~3 TBIL 1~2 ALT 3~5 TBIL 2~3 ALT 5 TBIL 3

36~80

1.3

APACHE

28 d

5 mL 1 000 g 15 min

-80

HMGB1 TGFβ1 GP73

800

BIO RAD

1.4

SPSS19.0

$\bar{x}\pm s$ t

% ^{2}

Logistic

receiver operating characteristic curve ROC HMGB1 TGFβ1 GP73

P<0.05

2

2.1 HMGB1 TGFβ1 GP73

HMGB1 TGFβ1 GP73

P<0.05 2

2 HMGB1 TGFβ1 GP73

$\bar{x}\pm s$ μg/L

Table 2 Comparison of serum HMGB1 TGF β1 and GP73 levels between two groups $\bar{x}\pm s$ μg/L

	n	HMGB1	TGF β1	GP73
	80	21.12±5.82	26.49±4.69	44.48±18.05
	86	30.65±7.95	36.43±9.95	68.27±19.21
t		8.759	8.134	0.168
P		0.000	0.000	0.000

2.2 HMGB1 TGFβ1 GP73

HMGB1 TGFβ1 GP73

P<0.05

3

2.3

3 HMGB1 TGFβ1 GP73 $\bar{x}\pm s$,μg/L

Table 3 Comparison of HMGB1 TGFβ1 GP73 levels in patients with different degrees of liver injury $\bar{x}\pm s$,μg/L

	n	HMGB1	TGF β1	GP73
	25	26.48±5.40	30.16±6.39	57.46±14.95
	42	30.63±8.16	35.382±8.22	68.39±17.81
	19	36.17±7.09	46.99±8.86	82.24±19.57
F		9.648	24.817	11.046
P		0.000	0.000	0.000

P>0.05 APACHE

HMGB1 TGFβ1 GP73 P< 0.05

P<0.05 4

4

Table 4 Single factor analysis affecting prognosis of patients with sepsis and liver injury

	n=64	n=22	$t/^2$	P
	56.59±11.07	60.14±10.95	1.299	0.198
/	31/33	12/10	0.981	0.396
APACHE	17.47±6.15	26.14±6.83	5.542	0.000
d	4.38±2.17	5.14±2.11	1.395	0.167
(/ /)	24/36/4	1/6/15	151.592	0.000
HMGB1 μg/L	28.49±6.96	36.92±7.39	4.819	0.000
TGF β1 μg/L	33.30±7.85	45.53±9.94	5.881	0.000
GP73 μg/L	61.97±15.57	86.62±17.36	6.221	0.000

2.4 Logistic

APACHE

HMGB1 TGFβ1 GP73

Logistic

APACHE HMGB1 TGFβ1 GP73

P<0.05 5

5 Logistic

Table 5 Multivariate Logistic regression analysis

	B	*S.E.*	Wald	*P*	*OR*	95%*CI*
HMGB1	0.172	0.068	6.474	0.011	1.188	1.040~1.356
TGF β1	0.171	0.065	6.855	0.009	1.187	1.044~1.349
GP73	0.125	0.056	5.021	0.025	1.133	1.016~1.264
APACHE	0.375	0.167	5.008	0.025	1.454	1.048~2.019
	1.887	0.926	4.153	0.042	6.600	1.075~40.521

2.5 HMGB1 TGFβ1 GP73

ROC

HMGB1 TGFβ1 GP73 AUC 0.805 0.827 0.855

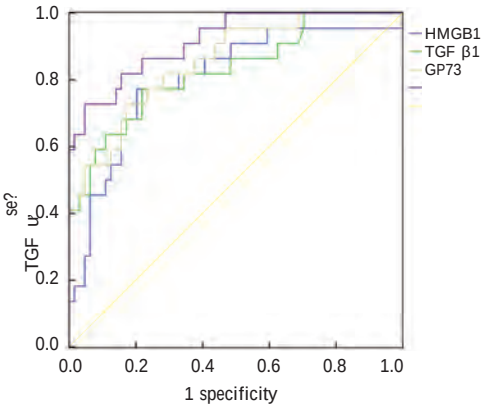
HMGB1>33.44 μg/L TGFβ1>40.63 μg/L GP73>79.84 μg/L HMGB1 TGFβ1 GP73

P>0.05 HMGB1 TGFβ1 GP73 AUC 0.917

P>0.05

P<0.05

6 1



1 HMGB1 TGFβ1 GP73 ROC

Figure 1 ROC curves of serum HMGB1 TGFβ1 and GP73 for prognosis

3

[9]

[10]

[11]

[12]

[13]

[14]

[15] [16]

[17]

[18]

HMGB1

HMGB1 6

TGFβ1

TGFβ1

TGFβ1

GP73

GP73

GP73

Xu GP73

ALT

HMGB1 TGFβ1 GP73

HMGB1 TGFβ1 GP73

HMGB1 TGFβ1 GP73

Logistic

APACHE

HMGB1 TGFβ1 GP73

APACHE

HMGB1 TGFβ1

GP73

ROC HMGB1 TGFβ1 GP73

HMGB1 TGFβ1 GP73

HMGB1 TGFβ1 GP73

HMGB1 TGFβ1 GP73

HMGB1 TGFβ1 GP73

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miR 137 SETD7

1 2 1

miR 137
H9C2 +miR con +miR 137 +miR 137+ pcDNA +miR 137+pcDNA SETD7 qPCR H9C2 miR 137 SETD7 mRNA Western blot SETD7 Cyclin D1 Cleaved Caspase 3 MTT LDH MDA TargetScan miR 137 SETD7 H9C2 miR 137 Cyclin D1 P<0.05 SETD7 mRNA LDH MDA Cleaved Caspase 3 P<0.05 miR 137 H9C2 miR 137 Cyclin D1 P<0.05 SETD7 LDH MDA Cleaved Caspase 3 P<0.05 miR 137 SETD7 SETD7 miR 137 H9C2 miR 137 SETD7

miR 137 SETD7

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ABSTRACT Objective To investigate the effects of miR 137 on cardiomyocyte injury induced by hypoxia reoxygenation and the underlying mechanism. Methods Cardiomyocytes H9C2 were divided into blank group hypoxia reoxygenation group hypoxia reoxygenation group+miR con hypoxia reoxygenation+ miR 137 group hypoxia reoxygenation+miR 137+pcDNA group and hypoxia reoxygenation + miR 137 + pcDNA SETD7 group. qRT PCR was used to detect the expression of miR 137 and SETD7 mRNA in H9C2 cells. The expression levels of SETD7 Cyclin D1 and Cleaved Caspase 3 protein were determined by Western blot. The cell proliferation was tested by MTT assay. The levels of LDH and MDA were detected by colorimetry. Targeted relationship between miR 137 and SETD7 was analyzed by Target Scan method in combination with dual luciferase assay. Results Hypoxia reoxygenation significantly decreased the expression of miR 137 Cyclin D1 and cell viability in H9C2 cells P<0.05 and greatly increased SETD7 mRNA and protein levels LDH activity MDA content Cleaved Caspase 3 protein levels and cells apoptosis rate P<0.05 . Up regulation of miR 137 promotes the Cyclin D1 expression and the cell viability in hypoxia reoxygenation treatment of H9C2 cells P<0.05 reduces SETD7 LDH MDA Cleaved Caspase 3 levels and inhibitscell apoptosis P<0.05 . MiR 137 targets to the expression of SETD7. Overexpression of SETD7

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partially reversed the protective effect of miR 137 on H9C2 cellsinduced by hypoxia reoxygenation. Conclusion miR 137 promotes hypoxia reoxygenation treated cardiomyocyte proliferation and inhibits apoptosis by targeting down regulation of SETD7 expression and protects the oxidative stress injury of cardiomyocytes induced by hypoxia reoxygenation.

KEY WORDS miR 137 Hypoxia reoxygenation SETD7 Cardiomyocytes Proliferation

Isch

emia reperfusion IR [1 2] IR

[3] IR

IR

IR

RNA MicroRNA miRNA/miR

RNA [4] miR

NA IR [5 6] miR 137

[7] IR [8]

miR 137 IR

H9C2

20 μL 5 mg/mL MTT 37
4 h 150 μL DMSO 37
10 min 490 nm
OD % = OD
/ OD ×100%

1.6 LDH MDA
H9C2 96 80%
LDH LDH PBS
H9C2 MDA
MDA

1.7
Annexin V FITC
H9C2 5 μL Annexin V FITC
10 μL PI
20 min

1.8
TargetScan http //www.targetscan.org/
miR 137 SETD7 3′ 3′untranslated region 3′UTR
SETD7 3′UTR WT SETD7
SETD7 3′UTR MUT SETD7
miR con miR 137 48 h

1.9
SPSS 22.0
$\bar{x}\pm s$ *t*
SNK *q* *P*<0.05

2

2.1 miR 137 SETD7

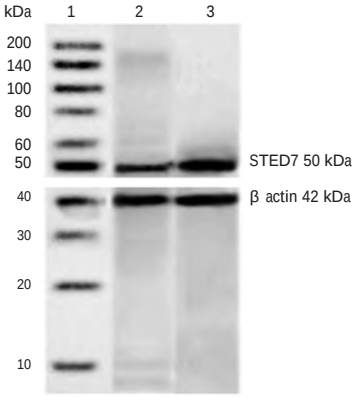
H9C2
miR 137 *P*<0.05 1
SETD7 mRNA *P*<0.05 1 1

1 miR 137 SETD7
$\bar{x}\pm s$ *n*=9

Table 1 Effects of hypoxia reoxygenation on the expression of miR 137 and SETD7 in cardiomyocytes $\bar{x}\pm s$ *n*=9

	miR 137	SETD7 mRNA	SETD7
	1.00±0.05	1.00±0.14	0.44±0.04
	0.29±0.06[a]	4.78±0.08[a]	0.76±0.08[a]
t	27.272	70.328	10.733
P	0.000	0.000	0.000

[a]*P*<0.05

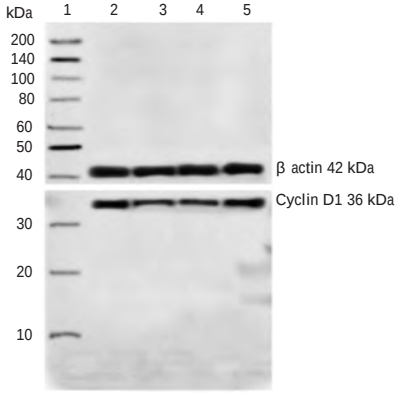


1. Maker 2. 3.
1 SETD7

Figure 1 SETD7 protein expression in cardiomyocytes

2.2 miR 137

H9C2
miR 137 Cyclin D1 *P*<
0.05 2 2 LDH MDA *P*<
0.05 2 +miR con
miR 137 H9C2 miR 137 Cyclin
D1 *P*<0.05 2 2
LDH MDA *P*<0.05 2



1. Maker 2. 3. 4. +miR con
5. +miR 137
2 Cyclin D1

Figure 2 Cyclin D1 protein expression in cardiomyocytes

2.3 miR 137

H9C2
Cleaved Caspase 3 *P*<
0.05 3 3 +miR con
miR 137 H9C2 Cleaved Caspase
3 *P*<0.05 3 3

+miR con

ƒ56” 0iApc!Sp W ` Â" …w C aprap0tqp W `Ga Pu0 ¡Â` Wpd6$ W `Ga

5 miR 137 SETD7 $\bar{x}\pm s$ n=9 P<0.05 6 5 H9C2

Table 5 miR 137 targeted SETD7 to regulate its expression $\bar{x}\pm s$ n=9

	SETD7
miR con	0.46±0.04
miR 137	0.18±0.03[a]
anti miR con	0.49±0.05
anti miR 137	0.78±0.06[b]
F	251.826
P	0.000

miR con [a]P<0.05 anti miR con [b]P<0.05

SETD7 miR 137

3

IR

9

IR

IR

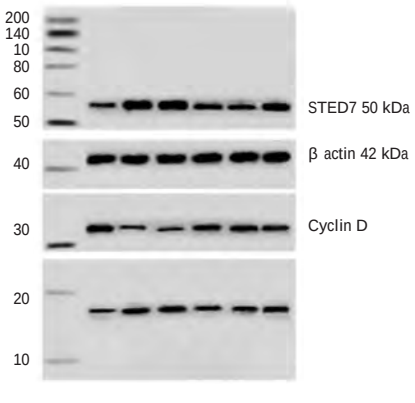
6 SETD7 miR 137 $\bar{x}\pm s$ n=9

Table 6 Overexpression of SETD7 partially reversed the protective effect of miR 137 on myocardial cells treated with hypoxia and reoxygenation $\bar{x}\pm s$ n=9

	SETD7	Cyclin D1	Cleaved Caspase 3	LDH U/L	MDA nmol/mL	%	%
	0.31±0.07	0.71±0.05	0.27±0.03	467.27±36.29	4.55±0.46	100.00±5.37	3.54±0.32
	1.24±0.09[a]	0.26±0.04[a]	0.61±0.06[a]	853.14±50.25[a]	14.21±1.33[a]	56.41±4.92[a]	21.46±4.86[a]
+miR con	1.14±0.11	0.19±0.03	0.71±0.07	877.02±61.47	15.19±2.83	59.35±5.44	23.72±5.16
+miR 137	0.64±0.07[b]	0.58±0.06[b]	0.47±0.06[b]	613.74±48.49[b]	7.62±1.15[b]	78.56±7.37[b]	9.69±7.08[b]
+miR 137+pcDNA	0.58±0.06	0.52±0.04	0.51±0.05	602.78±62.37	7.08±1.28	79.63±7.59	11.72±5.16
+miR 137+pcDNA SETD7	0.88±0.07[c]	0.38±0.04[c]	0.67±0.05[c]	751.58±49.61[c]	11.25±1.28[c]	63.75±6.74[c]	16.69±7.08[c]
t	176.638	180.671	77.640	84.893	66.712	60.796	17.625
P	0.000	0.000	0.000	0.000	0.000	0.000	0.000

[a]P<0.05 +miR con [b]P<0.05; +miR 137+pcDNA [c]P<0.05

1



ROS Keap1 Nrf2

[20]

SETD7 SETD7 miR 137

miR 137

SETD7

miR 137

SETD7

IR

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NSCLC ctDNA UMI
NGS ctDNA
163 2017 7 2019 7
NSCLC ctDNA NSCLC
11 98 NSCLC 37.8% 37
TP53 EGFR ERBB2 RET KRAS ALK PIK3CA BRAF MET ROS1 NRAS
33% 24% 10% 8% 7% 6% 4% 3% 3% 3% 1% 57 EGFR TKI
NSCLC 21 36.8% T790M 3 27.3% EGFR TKI
T790M T797S *KRAS* 2 *MET* 1
PIK3CA 8 29 ARMS PCR *EGFR*
ctDNA *EGFR* 13.8% NSCLC

NSCLC
DNA

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ABSTRACT Objective Next generation sequencing NGS based on unique molecular identifiers UMI was performed on circulating tumor DNA from non small cell lung cancer patients to investigate its clinical application value. Methods The blood samples of 163 NSCLC patients who visited the Affiliated Cancer Hospital of Sun Yat sen University from July 2017 to July 2019 were enrolled. A panel of 150 genes was used to detect the genetic mutations of the plasma samples the mutations of 11 driving genes related to NSCLC in plasma ctDNA of patients were detected by using the NGS based on UMI. Results Among 98 patients with TKI naïve patients including 73 lung adenocarcinomas 8 squamous carcinomas and 17 with unknown pathological types of NSCLC 37.8% 37 cases had no lung cancer driving gene mutation. The mutation frequencies of *TP53 EGFR erbB2 RET KRAS ALK PIK3CA BRAF MET ROS1* and NRAS were 33% 24% 10% 8% 7% 6% 4% 3% 3% 3% and 1% respectively. Among 57 NSCLC patients who developed after EGFR TKI targeted therapy T790M mutation was detected in 21 36.8% patients and

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T790M and t797s CIS resistant mutations were detected in 3 27.3% patients who developed after three generations of EGFR TKI treatment. Other resistant mutations included *KRAS* gene mutation 2 cases *MET* gene amplification 1 case and *PIK3CA* gene mutation 8 cases . Among 29 NSCLC patients with positive *EGFR* mutations in tissues only 4 matched plasma samples were detected positive and the consistency of *EGFR* detection rates between matched tissue and plasma samples were 13.8%. Conclusion This method can detect the sensitive mutations of targeted therapy in patients with primary NSCLC and monitor the drug resistant mutations after the progress of targeted therapy. Therefore the NGS based on molecular tags can provides valuable information about targeted treatment to guide the personalized medication of NSCLC patients.

KEY WORDS Non small Cell Lung Cancer Next Generation Sequencing Unique Molecular Identifiers Liquid Biopsy Circulating Tumor DNA Resistance Mutations

non small cell lung cancer NSCLC small cell lung cancer SCLC NSCLC 85% NSCLC NSCLC [1] NSCLC [2-4] [5,6] DNA cell free DNA cfDNA cfDNA DNA circulating tumor DNA ctDNA cfDNA DNA ctDNA DNA cfDNA [7,8] NSCLC *EGFR ALK ROS1 KRAS ERBB2 RET PIK3CA BRAF* [9] NSCLC ctDNA NSCLC ctDNA

1

1.1

163 2017 7 2019 7 NSCLC 97 59.5% 66 40.5% 28~88 60 90 55.2% 60 73 44.8% 57 35.0% 42 25.8% 64 39.2 % 130 79.8% 8 5.0% 25 15.2% ~ 33 20.2% ~ 101 62.0% 29 17.8 %

1.2 DNA

DNA 10 mL EDTA cfDNA DNA 4 2 h 2 10 mL 4 1 600 g 15 min 4 16 000 g 15 min 1.5 mL

QIAamp Circulating Nucleic Acid extract kit Qiagen cfDNA DNA QIAamp DNA FFPE Tissue Kits Qiagen ctDNA DNA Qubit dsDNA HS Assay Kit Thermo Fisher Scientific

1.3 ARMS PCR

ARMS PCR

EGFR

EGFR

DNA

>1% *EGFR*

18 19 21 36 EGFR TKI

20 T790M S768I

9

1.4

/ DNA

cfDNA

ctDNA

60 ng 30 ng

150 panel

/ DNA

DNA Illumina

NextSeq500 Illumina

75 bp ctDNA

10 000X

2 000X

1.5 ctDNA

Illumina NextSeq500 Illumina

bcl bcl2fastq Conver

sion Software Illumina bcl

fastq

BWA MEM [10]

hg19

fgbio

DNA reads

consensus reads BWA MEM

consensus reads

reads

95%

/

cfDNA

2

2.1 NSCLC ctDNA

98 NSCLC

73 8 17 98

NSCLC 11

2

4

11

98

98

11

98

37 37.8%

TP53 EGFR ERBB2 RET

KRAS ALK PIK3CA BRAF MET ROS1 NRAS

33% 24% 10% 8% 7% 6%

4% 3% 3% 3% 1% 2 *TP53*

NSCLC

1 23 24% *EGFR*

L858R 34.8% 8 19

26.1% 6 2 8.7%

20 1 4.3% *EGFR*

1 4.3% *EGFR* A864V

E746_A750del *EGFR* 3

K757R A613T A647T T678M

L833V+H835L 21.7% 5 *EGFR*

1 *EGFR* 7

7.0% *KRAS* 1 *KRAS*

6 2 5 G12V/C/

R 1 G13D *ALK* 3

ALK-EML4 3

ERBB2 Y772_A775dup 1

NRAS G12D

2.2 EGFR TKI

65 EGFR TKI

NSCLC 57

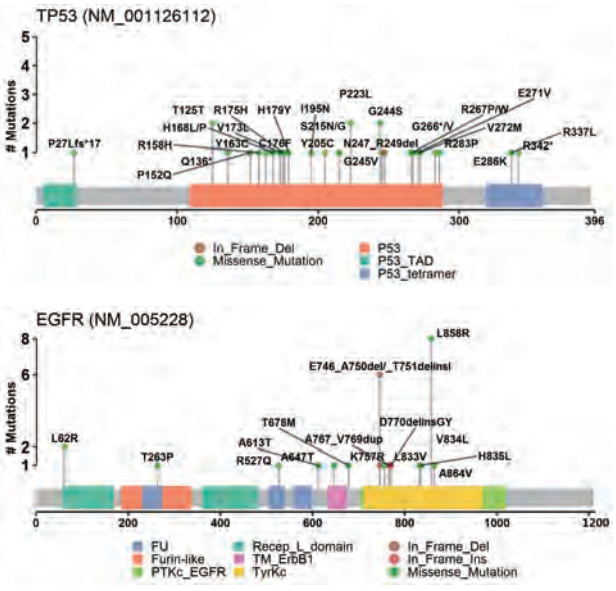
EGFR TKI 8

57

42 TKI 1 TKI

1 TKI 3 TKI

TKI 10 TKI



1 *TP53* *EGFR*

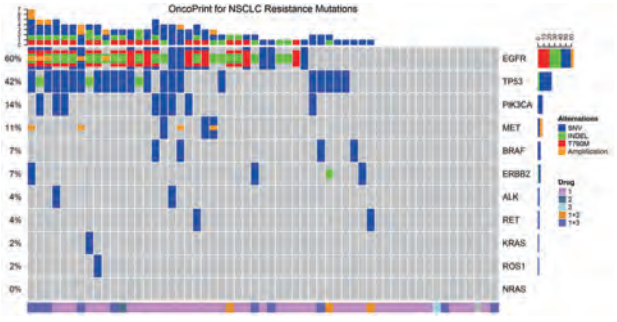
Figure 1 Mutation distribution in the functional domains of *TP53* and *EGFR*

SNV INDEL Fusion Amplification M F Unknown LUAD LUSC Y N

2 98 NSCLC

Figure 2 The mutation spectrum of 98 patients with tyrosine kinase inhibitor TKI naïve non small cell lung cancers

TKI 21 36.8% EGFR TKI T790M 11 TKI 3 27.3% T790M T797S *KRAS* 2 *MET* 1 *PIK3CA* 8 11 NSCLC EGFR TKI 3



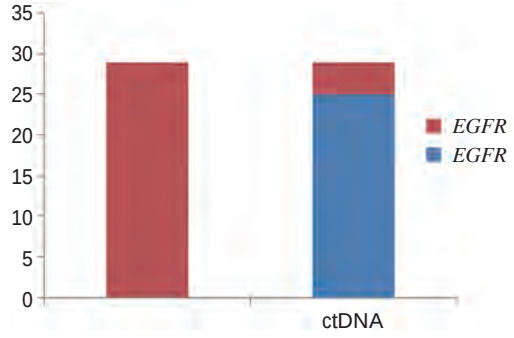
SNV INDEL T790M *EGFR* T790M Amplification 1 EGFR TKI 2 EGFR TKI 3 EGFR TKI 1+2 EGFR TKI EGFR TKI 1+3 EGFR TKI EGFR TKI 3 EGFR TKI

Figure 3 Resistance mutation distribution in 57 EGFR TKI relapsed patients

2.3 ARMS PCR *EGFR* NGS ctDNA *EGFR* 163 NSCLC 29 ARMS PCR 29 *EGFR* 13 *EGFR* 19 15 *EGFR* L858R 1 *EGFR* 20 29 NSCLC 18 ~ ~ 4 7 29 3 >5 cm 3 cm 4 ctDNA *EGFR* 1 K757R 1 L858R 1 E746_A750del 1 L858R V834L 4 ctDNA *EGFR* 4 3 >5 cm 3 ~ 1

3

NSCLC NSCLC *EGFR* NSCLC *EGFR* / / TKI / EGFR TKI



4 ARMS PCR *EGFR* NGS ctDNA EGFR

Figure 4 The comparison between *EGFR* mutations in tissues by ARMS PCR and in plasma by NGS

EGFR T790M

[11,12]

163 NSCLC

NSCLC 11

ctDNA NSCLC

NSCLC

ctDNA NSCLC

EGFR 24%

EGFR [13]

NSCLC 33

17 ctDNA

cfDNA

ctDNA 1% [14]

cfDNA ctDNA

ctDNA

ctDNA

EGFR T790M / EGFR TKI

50%

[15,16]

T790M 36.8%

ctDNA ctDNA

T790M

ctDNA

ctDNA

cfDNA

[17-20]

cfDNA

ctDNA

EGFR ctDNA *EGFR*

13.8% 29

4 ~

7 3

>3 cm 3 cm 3

cm

[21,22]

ctDNA

NSCLC

ctDNA

NSCLC

ctDNA

NSCLC

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PSCA

PSCA
688 1 442
PSCA 11 SNP ^{2} SNP
SNP rs2294008 *OR*=0.73 *P*=
4.78×10^{5} SNP T *P*<0.05
PSCA
PSCA

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ABSTACT Objective To explore the genetic relationship between PSCA gene polymorphism and gastric ulcer. Methods A total of 688 gastric ulcer patients and 1442 healthy control subjects from Chinese Han population were recruited. The potential association between gastric ulcer and 11 SNP loci covering *PSCA* gene was investigated by using the genetic association strategy of candidate genes. ^{2} test was used to analyze the correlation signals of single SNP locus. Results The results indicated that there was a significant correlation between the SNP locus rs2294008 and the disease status of gastric ulcer *OR*=0.73 *P*=4.78×10^{5} . The distribution frequency of the SNP T allele in the control group was significantly higher than that in the case group *P*<0.05 . Therefore it has a certain protective effect. Conclusion *PSCA* gene may be the susceptible gene of gastric ulcer.

KEY WORDS Gastric ulcers *PSCA* genetic polymorphisms Chinese Han population genetic association

ge
nome wide association study GWAS
PSCA single nucleotide
polymorphism SNP rs2294008
[7]

[1 3]

39% [3]

[4 6]

PSCA SNP

201750715046006

523110
E mail melodyjiaju@163.com

SNP

1

1.1

1 11 SNP

Table 1 Basic information including minor allele frequency and results of Hardy Weinberg equilibrium tests for 11 selected SNPs

		SNP	Allele1	Allele2	MAF	*P*	
8	142670446	rs2978974	A	G	0.304	0.493	5′
8	142670471	rs184389994	C	G	0.047	0.566	5′
8	142673587	rs117340570	C	T	0.037	0.461	
8	142674302	rs2978977	A	C	0.148	0.528	
8	142674428	rs146194718	G	A	0.097	0.172	
8	142676182	rs10956997	T	A	0.066	0.281	
8	142677319	rs587606222	C	G	0.037	0.461	
8	142677886	rs117919141	T	G	0.048	0.129	
8	142679754	rs13262164	T	C	0.084	1.000	
8	142680513	rs2294008	T	C	0.244	0.277	
8	142681306	rs2976391	A	C	0.364	0.333	

1 *PSCA* 11 SNPs

Figure 1 Linkage disequilibrium plot made from 11 selected SNPs of gene *PSCA*

OR

3

SNP rs2294008

3

PSCA

[10 12]

PSCA

RNA Small interfering RNA siRNA *PSCA*

[13 14]

PSCA

[15 16]

PSCA

T

PSCA

PSCA [14]

SNP rs2294008 C

PSCA CD4+ CD8+T

PSCA

rs2294008

T *PSCA*

[3]

rs2294008 T

OR 0.67

PSCA rs2294008

2

Table 2 results of single marker based genetic association analyses for 11 selected SNPs

	SNP	A1	A2				* ^{2}	*OR* 95%	*P*
8	rs2978974	A	G	A1A1/A1A2/A2A2	64/296/328	126/620/696	0.200	-	0.905
				A1/A2	424/952	872/2 012	0.147	1.03 0.89~1.18	0.701
8	rs184389994	C	G	A1A1/A1A2/A2A2	3/56/629	4/130/1 308	-	-	0.625
				A1/A2	62/1 314	138/2 746	0.162	0.94 0.69~1.28	0.687
8	rs117340570	C	T	A1A1/A1A2/A2A2	2/45/641	3/104/1 335	-	-	0.118
				A1/A2	49/1 327	110/2 774	0.166	0.93 0.66~1.31	0.684
8	rs2978977	A	C	A1A1/A1A2/A2A2	20/169/499	34/355/1 053	0.570	-	0.752
				A1/A2	209/1 167	423/2 461	0.201	1.04 0.87~1.25	0.654
8	rs146194718	G	A	A1A1/A1A2/A2A2	10/117/561	18/242/1 182	0.174	-	0.917
				A1/A2	137/1 239	278/2 606	0.107	1.04 0.84~1.29	0.744
8	rs10956997	T	A	A1A1/A1A2/A2A2	4/81/603	9/173/1 260	-	-	0.987
				A1/A2	89/1 287	191/2 693	0.036	0.98 0.75~1.27	0.849
8	rs587606222	C	G	A1A1/A1A2/A2A2	2/45/641	3/104/1 335	-	-	0.118
				A1/A2	49/1 327	110/2 774	0.166	0.93 0.66~1.31	0.684
8	rs117919141	T	G	A1A1/A1A2/A2A2	3/61/624	6/124/1 312	-	-	0.964
				A1/A2	67/1 309	136/2 748	0.048	1.03 0.77~1.40	0.826
8	rs13262164	T	C	A1A1/A1A2/A2A2	4/103/581	10/225/1 207	-	-	0.912
				A1/A2	111/1 265	245/2 639	0.223	0.95 0.75~1.19	0.637
8	rs2294008	T	C	A1A1/A1A2/A2A2	22/238/428	107/542/793	19.080	-	7.18×10^{-5}
				A1/A2	282/1 094	756/2 128	16.530	0.73 0.62~0.85	4.78×10^{-5}
8	rs2976391	A	C	A1A1/A1A2/A2A2	90/326/272	181/684/577	0.130	-	0.937
				A1/A2	506/870	1046/1 838	0.102	1.02 0.89~1.17	0.749

* SNP ^{2} Fisher

3 rs2294008

Table 3 Stratification analyses for SNP rs2294008

		/			^{2}	*OR* 95%	*P*
	T	372/783	0.21	0.26	7.855	0.74 0.60~0.91	0.005
	T	316/659	0.20	0.26	8.758	0.71 0.56~0.89	0.003
	T	72/150	0.22	0.28	1.921	0.72 0.45~1.15	0.166
	T	616/1 292	0.20	0.26	14.620	0.73 0.62~0.86	0.000
	T	156/328	0.20	0.26	4.860	0.69 0.50~0.96	0.027
	T	532/1 114	0.21	0.26	11.770	0.74 0.62~0.88	0.001
	T	492/560	0.20	0.25	6.687	0.76 0.62~0.94	0.010
	T	196/882	0.21	0.27	6.465	0.71 0.54~0.93	0.011

SNP rs2294008

PSCA [17]

SNP rs2294008 Sequenom MassARRAY SNP

DNA Matrix Assisted Laser Desorption/

3 Ionization Time of Flight Mass Spectrometry MAL

DI TOF MS SNP

[18]

[19]

SNP

11

11

PSCA

PSCA

PSCA rs2294008

SNP

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FBN1 c.2418A>G

c.2418A>G 1 *FBN1*
Life Tech Ion PGM 1
15 *FBN1* c.2418A>G
mRNA Minigene c.2418A>G
Hela RNA PCR qRT PCR Sanger
RNA qRT PCR mRNA
MUT Hela c.2418A>G mRNA *FBN1*
t=3.354 P<0.01 c.2418A>G
mRNA 3 t=4.979 P<0.01 t=3.243 P<0.05
t=5.017 P<0.01 mRNA c.2418A>G mRNA

FBN1 mRNA

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ABSTRACT Objective To investigate the effect of c.2418A>G mutation on the transcriptional process of fibrillin 1 *FBN1* gene and to explore its molecular pathogenesis. Methods Life Tech Ion PGM high throughput sequencing technology was used to detect 15 genes associated with hereditary aortic diseases in a patient with early onset thoracic aortic aneurysm without previous pathogenic factors. The *FBN1* gene was found to carry c.2418A>G heterozygous mutation. The software predicts that this mutation will lead to the occurrence of abnormal splicing of mRNA. The recombinant expression vector with c.2418A>G locus or normal locus was constructed by using Minigene technology. After transfecting Hela cells RNA was extracted and analyzed by real time quantitative PCR qRT PCR and Sanger sequencing. The RNA of lymphocytes in the blood of patient and healthy people was extracted and the effect of the mutation on mRNA splicing was confirmed by qRT PCR and sequencing. Results The mRNA containing c.2418A>G mutation was not detected in MUT Hela cells and the relative expression of *FBN1* gene was significantly lower than that in the normal control group t=3.354 P<0.01 . No mRNA containing c.2418A>G mutation was detected in the lymphocytes of patients and the relative expression of three different exon regions was significantly lower than that of healthy subjects t=4.979 P<0.01 t=3.243 P<0.05 t=5.017 P<0.01 indicating that abnormal mRNA is completely degraded. Conclusion The c.2418A>G mutation causes the degradation of mRNA suggesting the cause of the disease in this patient.

KEY WORDS Aortic aneurysm and dissection *FBN1* gene Heterozygous mutation mRNA degradation

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1 Fibrillin 1 *FBN1*
15 15q21.1 66
1 2 871
1
10~12 mm

[1] *FBN1* 1

[2]
Thoracic aortic aneurysm and dissection TAAD
TAAD 20%

[3]
FBN1 Marfan syndrome MFS 4%
TAAD *FBN1* [3 4]
1 15
FBN1 FBN2 TGFB2 TGFBR1 TGFBR2 SMAD3 SMAD4 MYH11 ACTA2 MYLK COL3A1 SLC2A10 NOTCH1 PRKG1 [5]

1

1.1
30 185 cm 90 kg 106/76 mmHg
58 mm 55 mm

1.2
Hela pcDNA3.1 - BI DMEM TRIzol™Reagent Lipofectamine 3000 Invitrogen PrimeSTAR® GXL DNA Polymerase PrimeScript™RT Master Mix T4 DNA EcoRI HindIII PCR TB Green™ Premix Ex Taq™ II QIAquick® Gel Extration Kit QIAGEN DH5α Solarbio Sanger

1.3
1.3.1
4 mL EDTA K2 DNA Qubit 2.0 DNA
ABI 9700 PCR ABI 2720 PCR Ion Chef™ System Ion Torrent PGM Ion Torrent 318 v2 Ion PGM™ Hi Q™
CoverageAnalysis VariantCaller hg19 GRCh37 Ion Reporter™ Sanger
[6]
Sanger

1.3.2
dbscSNV Mutation Taster Human Splicing Finder HSF

1.3.3 Minigene
1.3.3.1
DNA F EcoRI R HindIII Exon19 71 bp Intron19 1040 bp Exon20 126 bp Intron20 511 bp Exon21 53 bp 98 5 min 98 10 s 60 5 s 68 4 min 30 4 1 817 bp 5′ EcoRI 3′ HindIII pcD

NA3.1 - 16
DH5α
PCR
1

1 PCR
Table 1 PCR primers

	5′ 3′
F EcoRI	GGAATTCCCTTCGTGGGACCTATAAATGT
R HindIII	CCCAAGCTTGCTGTTCTTGCAGACTCCAT
GAPDH F	CCTGCACCACCAACTGCTTA
GAPDH R	GGCCATCCACAGTCTTCTGG
Exon4 6F	GGCTCCAGATCCATACAACACTGC
Exon4 6R	CACACCTTCCTCCATTGAGACAGC
Exon25 26F	CCTATGCCGAGGTGGTGTTT
Exon25 26R	TGTCGATACACGCGGAGATG
Exon55 56F	AGGAACCCCGTCACCAAATC
Exon55 56R	GGTCATGAATCCTCGGCCAT

1.3.3.2 Hela 15%
DMEM 37 5%CO_2
1 d Hela
2.5×10^5 /mL 6
24 h Lipofectamine 3000
48 h

1.3.3.3 qPCR Sanger TRIzol Hela
RNA cDNA
PCR F EcoRI
R HindIII qPCR 95 30 s
95 5 s 60 30 s 40 GAP
DH *FBN1* mRNA
Ct $2^{-\Delta\Delta Ct}$
1
3 PCR 1.5%

1.3.4 RNA
RNA
cDNA F EcoRI R HindIII
PCR 1.5%

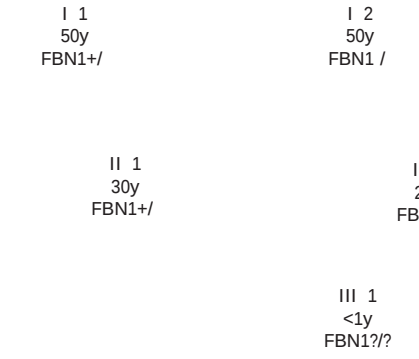
Exon 4~6 Exon 25~26 Exon 55~56
qPCR 3 mRNA
mRNA
1

1.4
GraphPad Prism 8.0
t *P*<0.05

2

2.1
Sanger *FBN1*
20 c.2418A>G
Sanger

1
1



1 TAAD
Figure 1 The family tree of TAAD

2 dbscSNV
Table 2 dbscSNV database prediction results

dbscSNV_ADA	dbscSNV_RF
0.999 2	0.994

dbscSNV_ADA dbscSNV_RF>0.6 dbscSNV
c.2418A>G FBN1

2.2 c.2418A>G FBN1
2.3 Minigene
2.3.1
WT
MUT PCR 2A Sanger 2B
2C MUT c.2418A>G

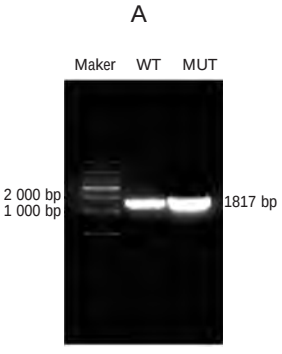
2.3.2 qPCR
qPCR 3A WT Hela

3 HSF Mutation Taster

Table 3 HSF and Mutation Taster prediction results

	HSF		Mutation Taster	
5′Motif	Donor decreased	Donor gained	Donor decreased	Donor gained
Ref Score	8.14	-2.29	0.98	-
Mut Score	4.45	5.25	0.86	0.48

HSF Mutation Taster



A PCR B WT C MUT

2 WT MUT

Figure 2 Identification results of WT and MUT

MUT Hela *FBN1* mRNA t=3.354 P<0.01 PCR 3B 266 bp Sanger 3C 3D 2

MUT Hela

2.4 RNA PCR 4A 266 bp PCR c.2418A>G 4B qPCR 4C *FBN1* mRNA 3 t=4.979 P<0.01 t=3.243 P<0.05 t=5.017 P<0.01 mRNA

3

TAAD

TAAD

TAAD [14 15]

20% MFS Loeys Dietz TAAD

Ehlers Dalos TAAD *FBN1*

TAAD [16]

11 [5] TAAD Yale

New Haven 598

[17] TAAD

[7] 56.8 MFS 24.8

50

MFS [8]

TAAD

15

Sanger

FBN1 20 c.2418A>G

RNA

[9]

mRNA *FBN1* 10

mRNA [10 11]

c.2418A>G *FBN1* 20 3

mRNA

ClinVar

c.2418A>G

mRNA mRNA

c.2418A>G mRNA

mRNA

mRNA

mRNA *FBN1*

[12 13]

FBN1

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450

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HMGN5

5 *HMGN5*
RT qPCR IOSE
4 *HMGN5* *HMGN5* shRNA
SKOV3 RT qPCR Western blot SKOV3 *HMGN5* mRNA MTT
HMGN5 *HMGN5* Tran
swell *HMGN5* Western blot SKOV3 PCNA MMP 9 Wnt1
β β catenin IOSE *HMGN5*
SKOV3 A2780 HO 8910 Caov3 *P*<0.05 Blank NC
sh HMGN5 SKOV3 *HMGN5* mRNA *P*<0.05 SKOV3
P<0.05 PCNA MMP 9 Wnt1 β catenin *P*<
0.05 *HMGN5* Wnt/β catenin SKOV3

HMGN5 Wnt/β catenin

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ABSTRACT Objective To investigate the effects of lentiviral mediated high mobility group nucleosome binding domain 5 *HMGN5* gene silencing on proliferation migration and invasion of ovarian cancer cells and to explore the mechanism. Methods RT qPCR was used to detect the expression of *HMGN5* in human ovarian epithelial cell line IOSE and four different ovarian cancer cells. *HMGN5* shRNA lentivirus vector was transfected into human ovarian cancer cell line SKOV3. RT qPCR and Western blot were used to detect the expression of *HMGN5* mRNA and protein in SKOV3 cells. MTT method was used to detect the effect of *HMGN5* gene silencing on cell proliferation scratch test was used to detect the effect of *HMGN5* gene silencing on cell migration and Transwell test was used to detect the invasion of *HMGN5* gene silencing on cell. Western blot was used to detect the expression of PCNA MMP 9 Wnt1 and β Catenin in SKOV3 cells. Results The expression of *HMGN5* in SKOV3 A2780 HO 8910 and CAOV3 was significantly higher than that in IOSE *P*<0.05 . Compared with blank group and NC group the expression level of *HMGN5* mRNA and protein in SKOV3 cells of sh HMGN5 group was significantly lower *P*<0.05 the proliferation migration and invasion ability of SKOV3 cells were significantly lower *P*<0.05 and the

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expression levels of PCNA MMP 9 Wnt1 and β Catenin cells were significantly lower $P<0.05$. Conclusion Silencing *HMGN5* may inhibit the proliferation migration and invasion of human ovarian cancer SKOV3 cells by blocking the activation of Wnt/β catenin signaling pathway.

KEY WORDS *HMGN5* gene ovarian cancer cells proliferation migration invasion Wnt/β catenin signaling pathway

[1]

[2]

5

<30 [3]

5 High mobility group nucleosome binding domain 5 *HMGN5* HMGNs Xq13.3 [4] *HMGN5* DNA DNA [5] *HMGN5* [6 9] Liu *HMGN5* *HMGN5* [10] Gan *HMGN5* 5637 [11] *HMGN5* *HMGN5*

1

1.1

IOSE SKOV3 A2780 HO 8910 Caov3 ATCC MTT Sigma RPMI 1640 Gibco *HMGN5* shRNA Amresco Trizol Invitrogen SYBR premix Ex Taq Kit TaKaRa Transwell Millipore Matri gel BD HMGN5 PCNA MMP 9 Cell Sigaling Technology Wnt1 β catenin Santa Cruz

1.2

IOSE SKOV3 A2780 HO 8910 Caov3 10 RPMI 1640 5 CO_2 37 80% 1 3

1.3 SKOV3 *HMGN5* shRNA

SKOV3 6 1×10^5/ 37 50% 1 1 RPMI 1640 2 mL 12 h *HMGN5* shRNA SKOV3 sh HMGN5 SKOV3 NC SKOV3 Blank SKOV3 37

1.4 RT qPCR

48 h SKOV3 Trizol RNA RNA cDNA cDNA SYBR premix Ex Taq Kit RT qPCR GAPDH RT qPCR 94 5 min 94 10 s 60 30 s 72 30 s 40

2 ^{CT} *HMGN5* mRNA ^{CT}= Ct Ct 3

1.5 Western blot 48 h SKOV3 RIPA 30 min BCA 40 μg 10% SDS 80 V 120 V 2 h HMGN5 1 800 PCNA 1 500 MMP 9 1 500 Wnt1 1 500 β catenin 1 500 4 TBST 1 3 000 1 h TBST ECL GAPDH Image J 3

1.6 MTT SKOV3 1×10^3/ 96 50% 1.3 24 48 72 h MTT 100 μL 37 4 h 150 μL 10 min 450 nm A SKOV3 4 3

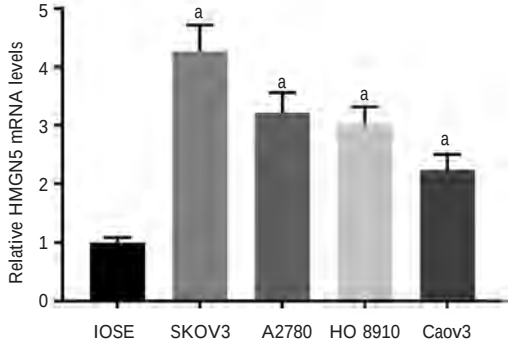
1.7 SKOV3 3×10^4/ 6 37 90% 0.5% PBS 0.5% 37 24 h 0 24 h = 0 h 24 h /0 h 3

1.8 Transwell Matrigel Matrigel Transwell SKOV3 1×10^5/mL 200 μL Transwell 600 μL 10% Transwell 37 48 h PBS 1 4% 10 min 0.1% 30 min PBS 5 3

1.9 SPSS 21.0 $\bar{x} \pm s$ SNK q P<0.05

2

2.1 HMGN5 RT qPCR IOSE 4 *HMGN5* 1 IOSE SKOV3 A2780 HO 8910 Caov3 *HMGN5* P<0.05 *HMGN5* SKOV3 SKOV3

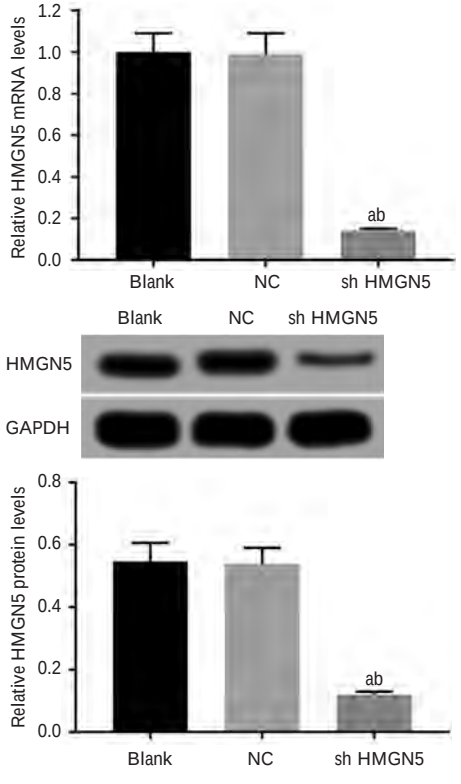


IOSE ^{a}P<0.05

1 RT qPCR 5 *HMGN5*

Figure 1 RT qPCR detection of *HMGN5* expression in five cells

2.2 *HMGN5* shRNA SKOV3 HMGN5 SKOV3 RT qPCR Western blot 2 Blank NC sh HMGN5 SKOV3 *HMGN5* mRNA



Blank [a] P<0.05 NC [b]P<0.05

2 SKOV3 *HMGN5* mRNA

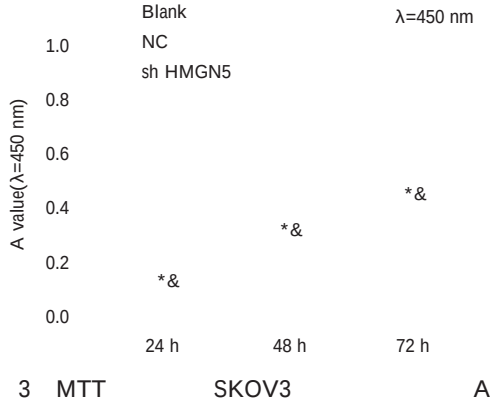
Figure 2 Comparison of *HMGN5* mRNA and protein expression levels in SKOV3 cells

P<0.05 Blank NC SKOV3 *HMGN5* mRNA

P>0.05 *HMGN5* SKOV3

2.3 *HMGN5* SKOV3

MTT 3 Blank NC sh HMGN5 SKOV3 24 48 72 h



3 MTT SKOV3 A

Figure 3 MTT detection of SKOV3 cells in each group at different time A value

A F 27.409 38.966 36.182 P<0.05 Blank NC SKOV3 24 48 72 h A P>0.05

HMGN5 SKOV3

2.4 *HMGN5* SKOV3

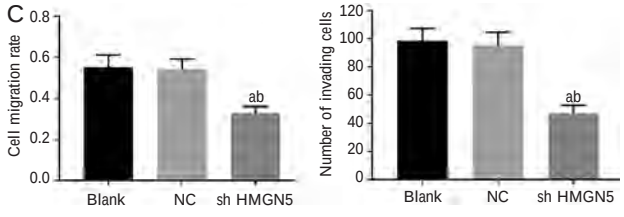
4A 4C Blank NC sh HMGN5 SKOV3 P<0.05 Blank NC SKOV3 P>0.05 Transwell 4B 4C Blank NC sh HMGN5 P< 0.05 Blank NC P>0.05 *HMGN5* SKOV3

A Blank NC sh HMGN5

0 h

24 h

B Blank NC sh HMGN5



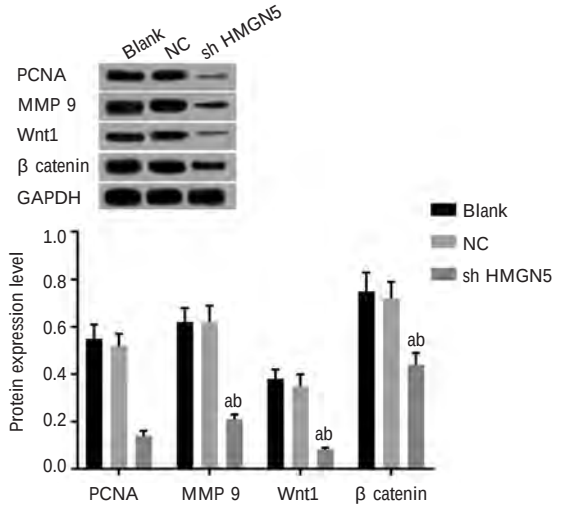
A B Transwell C Blank [a]P< 0.05 NC [b]P<0.05

4 Transwell

Figure 4 Scratch test and Transwell test to detect cell migration and invasion

2.5 *HMGN5* SKOV3

Western blot 5 Blank NC sh HMGN5 SKOV3 PCNA MMP 9 Wnt1 β catenin *P*<0.05 Blank NC SKOV3 PCNA MMP 9 Wnt1 β catenin *P*>0.05 *HMGN5* SKOV3 PCNA MMP 2 Wnt/β catenin



Blank [a]*P*<0.05 NC [b]*P*<0.05

5 Western blot SKOV3

Figure 5 Western blot analysis of protein expression in SKOV3 cells

3

HMGN5 *HMGN5* TNM [12] RT qPCR 4 *HMGN5* *HMGN5* *HMGN5* *HMGN5* [13 15] Wu *HMGN5* *HMGN5* [16] Xin *HMGN5* miR 488 [17] *HMGN5* *HMGN5* SKOV3 *HMGN5* siRNA *HMGN5* *HMGN5* SKOV3 *HMGN5* SKOV3 *HMGN5* siRNA SKOV3 RT qPCR Western blot *HMGN5* SKOV3 MTT *HMGN5* SKOV3 *HMGN5* SKOV3 Transwell *HMGN5* SKOV3 *HMGN5* PCNA DNA [18] MMP 9 MMP MMP 9 [19] Western blot *HMGN5* SKOV3 PCNA MMP 9 *HMGN5* MMP 9 Zhao [20] *HMGN5* *HMGN5* Wnt/β catenin Wnt1 Wnt [21] β catenin Wnt [22] Wnt/β catenin [23 25] Zhao SKOV3 *HMGN5* Wnt/β catenin Wnt1 β catenin *HMGN5* Wnt/β catenin *HMGN5* SKOV3 Wnt/β catenin

HMGN5 Wnt/β catenin

HMGN5

HMGN5

Wnt/β catenin SKOV3

HMGN5

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after gynecological laparoscopic surgery under general anesthesia. The combination of PTX 3 and PCT change rate is helpful for the early diagnosis of pulmonary infection.

KEY WORDS N pentamer 3 Procalcitonin general anesthesia Pulmonary infection Gynecological laparoscopy

5

1 2

1~4 5

3

Pentraxin 3 PTX 3 procalcitonin *n*=31 *n*=233 2

PCT

3 4

2~3 d

PTX 3 PCT

1

1.1

2016 6 2018 12

264

≥20

1.3 PTX 3 PCT

PTX 3 PCT

= 24 h - /

×100%

1.4

SPSS 11.5

% ^{2}

$\bar{X} \pm S$ t Pear

son

ROC P<0.05

2

2.1 PTX 3 PCT

2 PTX 3 PCT

P>0.05 24 h PTX 3

PCT P<0.05 PTX 3

PCT P<0.05 2

2 2 PTX 3 PCT n %

Table 2 Comparison of PTX 3 and PCT levels in 2 groups before and after operation n %

	n	PTX 3 ng/mL		PCT(μg/L)	
			24 h		24 h
	31	1.72±0.27	4.35±1.29[a]	0.21±0.05	1.32±0.26[a]
	233	1.68±0.25	2.76±0.74[a]	0.20±0.04	0.84±0.41[a]
t		0.829	10.110	1.268	6.408
P		0.408	0.000	0.206	0.000

[a] P<0.05

2.2 PTX 3 PCT

PTX 3 PCT 24 h

P<0.05 3

2.3 PTX 3 PCT

Pearson 24 h

PTX 3 PCT r=

0.546 P=0.000 1

3 2

	n	PTX 3	PCT
	31	162.23±59.78	532.52±192.77
	233	71.15±27.21	318.50±101.97
t		14.598	9.649
P		0.000	0.000

2.4 PTX 3 PCT

PTX 3 PCT

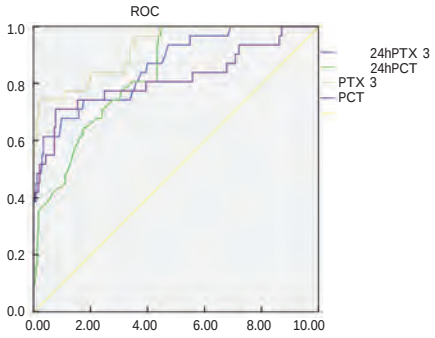
PTX AUC

0.924 PTX 3 0.871 PCT

0.923 4 2

3

6 7



1

2

ROC

Figure 2 ROC Curve of indicators in ppredicting pulmonary infection after gynecological laparoscopic surgery under general anesthesia

8 9

PCT PTX 3 PCT

C

10 11

PCT

12

PTX 3

13

14 15

24 h

PCT PTX 3

PCT PTX 3

PCT

PTX 3

ROC

PCT PTX 3

AUC>0.6 PCT PTX 3

PCT PTX 3

PCT

PTX 3

PTX 3

PXT 3

PCT PTX 3

24 h PCT PTX 3

1 .

J .

2017 27 19 4464 4467.

2 .

J . 2018 28

6 731 733.

3 . 3

J . 2019

28 3 370 373.

4 . CD64 PCT

NLR J .

2018 30 3 304 307.

5

J . 2003 15 7 460 465.

6 .

J . 2013 23

7 1582 1583.

7 .

J .

2009 19 7 2276 2277.

8 .

J . 2017 46 7 935 937.

• •

HBV HBV DNA PreS1 HBeAg

1 2 1 1 1

HBV

HBV HBV DNA PreS1 HBeAg

226 PCR

RT PCR HBV DNA

ELISA PreSl á' Â T•9 ³ »%ò%ÿ 4 –ó'H @ #0 • 0 @ 4 –ó'H @ 4 4 % / #@ 4 #gSsÐ @ 4

2011xkj092

1. 233001

2. 511400

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hepatitis B virus HBV HBV 8 A ~H [1] HBV [2] HBV HBV [3] HBV B C B Ba HBV C B [4] HBV

HBV DNA E hepatitis B e antigen HBeAg S1 Pre S1 antigen PreS1 HBV [5] 3 HBV

HBV DNA HBeAg PreS1 HBV

1

1.1

2017 1 8 226 153 73 17~73 2015 [6]

0.05 IU/mL

1.2

1.2.1

DNA PCR takara Pyrobest DNA polymerase 50 bp DNA 50 bp~400 bp HBV DNA PCR HBeAg Sl

1.2.2 HBV DNA s

DNA DNA PCR 1 PCR HBV 94 min72 2 min 94 30 s 58 30s 72 2.5 min

HBV HBV U1) 5′ TCA CCA TAT TCT TGG GAA CAA GA 3′
HBV U2 5′ ℃G 1 ẓ
HBV B Type B1
Type B2
HBV C Type C1
Type C2

3 B C PreS1

Table 3 Expression of PreS1 in genotype B C infected patients

	n	PrsS1 +	PrsS1 -	^{2}	*P*
B	131	63 48.1%	68 51.9%	0.002	0.965
C	93	45 48.4%	48 51.6%		

2 B C HBV DNA

Table 2 Expression of HBV DNA in genotype B C infected patients

	n	HBV DNA +	HBV DNA	^{2}	*P*
B	131	75 57.2	56 42.8%	0.867	0.352
C	93	59 63.4	34 36.6%		

10 12

HBV

PCR

HBV B 58.0%

C 41.1%

3

HBV DNA HBeAg PreS1

5

t r

1 776

2006 1 2016 1 1 776
G ISCN 2013
1 776 280 15.76%
26 1.46% 33 1.86% 140 7.88% 29
1.63% 39 2.20% 13 0.73% 806
108 13.40% 429 65 15.15%

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Department of Laboratory Medicine the First Affiliated Hospital of Nanjing Medical University Nanjing Jiangsu China 210029

ABSTRACT Objective To investigate the correlation between abnormal karyotypes and the distribution of chromosomal diseases in Nanjing. Methods 1 776) P Tf`

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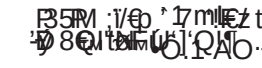
36.7% 652/1 176 12~45

1.2

1.2.1

e I €/ t` Ñ¸ ðgE æ3…à Òã R O2Ð/ Ñ³ ðgDà P ý Í w # R R 3-1Â ó7 8Sl"ø)!R ÍFý



2.2 21 73.68% 15 46 XX 40.00%
460 47 XXY 156 45 XO 12.18% 46 11.74% 46 XX 1.30% 45 XY rob 13 14 XY 5.13% 46 X i Xq 3.85% 0.65% / 312 128
47 XXY 6.73% 45 XY rob 13 14 131 45 XO 7.63% 1.28% 19 47 XY+ 14 46 XY 71.43%

2 n %

Table 2 Clinical manifestations karyotype classification and abnormal detection rate of common chromosomal karyotype abnormalities n %

%		*n*	%
460 25.90	47 XXY	54	11.74
	46 XX	6	1.30
	45 XY rob 13 14	3	0.65
/ 312 17.57	47 XXY	21	6.73
	45 XY rob 13 14	4	1.28
19 1.07	47 XY+21	14	73.68
15 0.84	46 XX	6	40.00
	45 XO	19	12.18
156 8.78	46 XY	8	5.13
	46 X i Xq	6	3.85
	46 XY	3	2.34
128 7.21	45 XO	1	0.78
	46 X i Xq	1	0.78
	45 XO	10	7.63
131 7.38	46 X i Xq	4	3.05
	46 XY	3	2.29
14 0.79	46 XY	10	71.43

3

50%

[1,2] 47 XXY
[3] 66.43% 93/140
[5] 47 XXY
[4] 460 312 /
75

45 XO
Turner syndrome Turner s
1 776 27.14% 38/140 Turner s
280 156
15.76% 5% [5] 19 12.18% 128
1 0.78% 131
[6] 2012 10 7.63%
6.37% [8]
[7] 46 XY
2019 11.9% 46 XX
39 2.20%

XY

[9] 33

1.86% 12 13 14

75% 9/12

[10]

[7]

3 / 4

0.73%

10 Mb

[11]

FISH CMA

DNA

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494

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17 . 3 D . 2008.

Chemerin 25 OH D3 visfatin

1 2 1 3

Chemerin 25 D3 25 OH D3 visfatin GDM IR 2017 2 2019 3 GDM 80 80 2 Chemerin 25 OH D3 visfatin HOMA IR Chemerin 25 OH D3 visfatin HOMA IR Chemerin 25 OH D3 visfatin GDM 25 OH D3 27.26±5.11 nmol/L 38.71±8.63 nmol/L Chemerin visfatin 273.92± 40.20 ng/mL 23.54±2.66 ng/mL 186.14±26.06 ng/mL 11.68±1.80 ng/mL t_1=10.211 t_2= 16.388 t_3=33.028 P <0.001 HOMA IR 3.89±1.38 1.62±0.46 t=13.958 P< 0.001 Spearman 25 OH D3 HOMA IR Chemerin visfatin HOMA IR r_1=-0.576 r_2=0.604 r_3=0.792 P <0.001 Chemerin 25 OH D3 visfa tin GDM 95.00% ^{2}=14.546 P=0.002 Chemerin 25 OH D3 visfatin GDM 3 GDM 25 D3

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ABSTRACT Objective To investigate the diagnostic value of serum chemoattractant Chemerin 25 hydroxyvitamin D3 25 OH D3 and visfatin levels in gestational diabetes mellitus GDM and insulin resistance in patients IR relevance. Methods 80 patients with GDM in our hospital from February 2017 to March 2019 were enrolled and 80 women with normal physical examination during the same period were recruited as the control group. Two groups of blood samples were collected after admission and serum Chemerin 25 OH D3 visfatin levels steady state model insulin resistance index HOMA IR were measured. The correlation between the levels of serum Chemerin 25 OH D3 visfatin and HOMA IR was statistically analyzed. The diagnostic efficacy of Chemerin 25 OH D3 visfatin alone and in combination was evaluated. Results The level of serum 25 OH D3 in the study group was 27.26 ± 5.11 nmol/L

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lower than that in the control group 38.71 ± 8.63 nmol/L and the levels of serum Chemerin and visfatin were 273.92 ± 40.20 ng/mL 23.54 ± 2.66 ng/mL higher than that in the control group 186.14 ± 26.06 ng/mL 11.68 ± 1.80 ng/mL t_1 = 10.211 t_2 = 16.388 t_3 = 33.028 respectively P<0.001 . The HOMA IR of the study group was 3.89 ± 1.38 higher than that of the control group 1.62±0.46 t=13.958 P< 0.001 . By Spearman correlation analysis the serum 25 OH D3 level was negatively correlated with HOMA IR the serum Chemerin and visfatin levels were positively correlated with HOMA IR r_1=-0.576 r_2= 0.604 r_3=0.792 P<0.001 . The sensitivity of chemorin 25 OH D3 and visfatin in the diagnosis of GDM was 95.00% higher than that of single index ^{2}=14.546 P=0.002 . Conclusion The levels of serum Chemerin 25 OH D3 and visfatin are closely related to insulin resistance in GDM patients and play an important role in the occurrence and progression of the disease. The combined detection of three can improve the diagnostic sensitivity of GDM.

KEY WORDS chemokine 25 hydroxyvitamin D3 visfatin gestational diabetes insulin resistance

Gestational diabetes mellitus GDM [1-3] 4.3%~5.1% GDM [4] Insulin resistance IR GDM 45%~80% [5,6] IR [7] Chemerin 2 IR [8,9] visfatin GDM [10,11] 25 D3 25 hydroxyvitamin D3 25 OH D3 D β [12,13] 80 GDM

Chemerin 25 OH D3 visfatin GDM IR Chemerin 25 OH D3 visfatin GDM

1

1.1 2017 2 2019 3 GDM 80 80 2 GDM P> 0.05 1

1.2 [14] GDM

1 2 $\bar{x}\pm s$ n %

Table 1 Comparison of 2 groups of general data $\bar{x}\pm s$ n %

		( )		kg	GDM	
	80	20~37 28.71±4.06	25~39 32.48±2.74	42~81 53.80±5.41	9 11.25	21 26.25 59 73.75
	80	21~38 29.02±3.59	26~38 32.70±2.52	43~83 54.46±5.25	3 3.75	23 28.75 57 71.25
$t/^2$		0.512	0.529	0.783	3.243	0.125
P		0.610	0.598	0.435	0.072	0.723

1.3

5 mL

3 000 r/min 10 min

Fasting blood glucose FBG

Fasting insulin FINS

Homeostasis model insulin resistance index HOMA IR HOMA IR=FBG× FINS/22.5 Chemerin 25 OH D3 visfatin

1.4

Chemerin 25 OH D3 visfatin HOMA IR

Chemerin 25 OH D3 visfatin HOMA IR Chemerin 25 OH D3 visfatin GDM

Chemerin 210 ng/mL 25 OH D3 28.2 nmol/L visfatin 25 ng/mL 4

1.5

SPSS 22.0 $\bar{x}\pm s$

t n % χ^2

Spearman $P<0.05$

2

2.1 Chemerin 25 OH D3 visfatin

25 OH D3

Chemerin visfatin $P<0.05$

2

2 Chemerin 25 OH D3 visfatin $\bar{x}\pm s$

Table 2 Comparison of serum levels of Chemerin 25 OH D3 and visfatin between the 2 groups $\bar{x}\pm s$

		Chemerin ng/mL	25(OH)D3 nmol/L	Visfatin ng/mL
	80	273.92±40.20	27.26±5.11	23.54±2.66
	80	186.14±26.06	38.71±8.63	11.68±1.80
t		16.388	10.211	33.028
P		<0.001	<0.001	<0.001

2.2 HOMA IR

HOMA IR 3.89±1.38 1.62±0.46 t=13.958 P<0.001

2.3 Chemerin 25 OH D3 visfatin IR

Spearman 25 OH D3 HOMA IR Chemerin visfatin HOMA IR $P<0.05$ 3

3 Chemerin 25 OH D3 visfatin IR n=80

Table 3 Analysis of correlation between serum levels of Chemerin 25 OH D3 and visfatin and IR n=80

		Chemerin	25 OH D3	visfatin
HOMA IR	r	0.604	-0.576	0.792
	P	<0.001	<0.001	<0.001

2.4 GDM

Chemerin 25 OH D3 visfatin $P<0.05$

Chemerin 25 OH D3 visfatin $P>0.05$ 4

4 GDM n %

Table 4 The Value of Serum Indicators in the Diagnosis of GDM Individually and Jointly n %

25(OH)D3	72.50	58/80	82.50	66/80	77.50	124/160
Chemerin	80.00	64/80	86.25	69/80	83.13	133/160
Visfatin	82.50	66/80	87.50	70/80	85.00	136/160
	95.00	76/80	81.25	65/80	88.13	141/160
χ^2	14.546		1.612		6.920	
P	0.002		0.657		0.075	

3

IR GDM IR GDM [15] HOMA IR GDM IR IR GDM IR

IR

GDM [16 17]

IR

[18 19]

9 .
4
J . 2018 10 7 76 79.
10 .
J .
2017 46 10 1402 1404.
11 .
Visfatin J . 2017 57
46 55 57.
12 .
25 D3
J . 2017 34 5 993 995.
13 .
D
TNF α J .
2017 23 2 228 231.
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J . 2016 47 5 31 33.
17 .

J . 65 85 J .. 17 J . 3117

CEA NSE SCCA miR 21

1 1 2

CEA NSE SCCA miR 21 87 CEA NSE SCCA PCR miR 21 CEA NSE SCCA miR 21 TNM CEA NSE SCCA miR 21 P<0.05 CEA SCCA miR 21 P>0.05 NSE TNM P< 0.05 CEA NSE SCCA miR 21 P<0.05 CEA NSE SCCA miR 21 P<0.05 4 P<0.05 CEA NSE SCCA miR 21

miR 21

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ABSTRACT Objective To investigate the relationship between CEA NSE SCCA combined with miR 21 and clinicopathological features curative effect and prognosis in patients with lung cancer. Methods 87 patients with lung cancer were selected as the experimental group and 87 healthy people in the same period of physical examination as the control group. The expression levels of CEA NSE and SCCA in serum were detected by electrochemiluminescence immunoassay and miR 21 was detected by real time PCR. The correlation of tumor markers CEA NSE SCCA and miR 21 with sex age pathological type and clinicopathological characteristics of TNM stage in patients with lung cancer was analyzed before treatment and the correlation with curative effect and prognosis was analyzed after treatment. Results compared with the control group the expression levels of CEA NSE SCCA and miR 21 in the experimental group were significantly higher than those in the control group P<0.05 . The expression levels of CEA SCCA

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and miR 21 were not correlated with clinicopathological features of lung cancer P>0.05 . NSE was correlated with TNM stage of lung cancer P<0.05 . The expression levels of CEA NSE SCCA and miR 21 were correlated with the curative effect P<0.05 . The survival curve showed that the expression levels of CEA NSE SCCA and miR 21 were correlated with the survival prognosis of the patients P<0.05 . The sensitivity of the combination of the four indexes in the diagnosis of lung cancer were significantly better than those of single index and the difference was statistically significant P<0.05 . Conclusion the expression levels of CEA NSE and SCCA in serum of patients with lung cancer are significantly higher than those of normal controls and the expression level of miR 21 is significantly lower than that of normal controls which could be used as indicators of diagnosis curative effect and prognosis of lung cancer.

KEY WORDS Carcinoembryonic antigen neuron specific enolase squamous cell carcinoma antigen miR 21 lung cancer

lung cancer

25% [1] 90%~95%

[2]

[3]

Carcinoembryonic antigen CEA neuron specific enolase NSE squamous cell carcinoma antigen SCCA [4] mRNA 21

miRNA

miR 21 $P<0.05$

2

2.1 CEA NSE SCCA miR 21

CEA NSE SCCA $P<0.05$

miR 21 $P<0.05$ 1

1 CEA NSE SCCA miR 21 $\bar{x}\pm s$

Table 1 Expression of CEA NSE SCCA and miR 21 in each group $\bar{x}\pm s$

	CEA μg/L	NSE μg/L	SCCA μg/L	miR 21
	2.35±0.26	6.14±0.79	1.41±0.11	0.92±0.14
	11.65±1.75	14.51±1.62	2.94±0.16	2.13±1.13
P	0.032	0.027	0.029	0.041

2.2 CEA NSE SCCA miR 21

CEA SCCA miR 21 TNM $P>0.05$

NSE $P>0.05$ $P<0.05$ ~ NSE 12.37 14.98 15.76 2

2.3 CEA NSE SCCA miR 21

PR 26.4% ^{2}=5.78 CEA NSE SCCA miR 21 $P<0.05$ SD 40.2% ^{2}=8.26 CEA NSE SCCA miR 21 $P<0.05$ PD 33.3% ^{2}=4.91 CEA NSE SCCA miR 21 $P<0.05$ 3

%

PR 26.4%
SD 40.2%
PD 33.3%

2.4 CEA NSE SCCA miR 21 [7]

[8]

Kaplan Meier CEA NSE SCCA

CEA NSE SCCA CT miR 21 [9] CT 3

CEA NSE SCCA miR 21 1

2.5

CEA NSE SCCA miR 21 51.7% 37.9% 52.9% 63.2% 90.8% 82.7% 85.1% 81.6% 85.1% 70.1% 4

3

CEA NSE SCCA

CEA SCCA

NSE TNM

3

CEA NSE SCCA miR 21

CEA NSE SCCA miR 21

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miR 21 125

RNA 21 miR 21 125 CA125
80 50 50
miR 21 CA125 miR 21 CA125
miR 21 CA125
miR 21 CA125 P<0.05 miR 21 CA125
AUC 0.959 P<0.05
P>0.05 miR
21 CA125 P<0.05 1
miR 21 CA125 P<0.05 miR 21 CA125

RNA 21 125

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Department of obstetrics and gynecology Rugao people s hospital Rugao Jiangsu China 226500

ABSTRACT Objective To investigate the changes of serum microRNA21 miR 21 and carbohydrate antigen 125 CA125 in ovarian cancer patients and its clinical significance. Methods Peripheral blood samples

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[1]

60%~70%

[2]

125 Carbohydrate antigen 125 CA125

[3]

RNA microRNA miRNA

RNA

[4 5] RNA 21 microRNA

21 miR 21

80 miR 21 CA125

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1.1

2016 1 2018 1

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65 53.68±6.32

2 miR 21 CA125 $\bar{x}\pm s$

Table 2 Comparison of expression levels of serum miR 21 and CA125 in each group $\bar{x}\pm s$

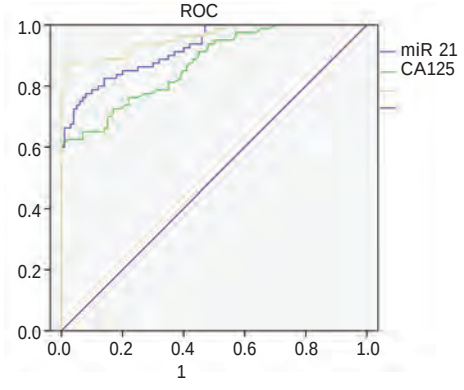
	n	miR 21	CA125 U/mL
	50	1.02±0.36	19.34±4.85
	50	1.55±0.42	29.91±6.23
	80	2.39±0.72	52.66±18.83
F		87.123	107.454
P		0.000	0.000

ROC miR 21 CA125 AUC 0.925 0.872 miR 21<2.13 CA125<35.50 U/mL miR 21 CA125 78.8% 62.5% 92.0% 98.0% AUC 0.959 91.3% miR 21 CA125 P<0.05 92.0% P>0.05 3 1

3 miR 21 CA125 U/mL %

Table 3 Diagnostic value of serum miR 21 and CA125 in ovarian cancer U/mL %

				Youden	AUC	95%
miR 21	2.13	78.8	92.0	0.708	0.925	0.888~0.961
CA125	35.50	62.5	98.0	0.605	0.872	0.822~0.922
		91.3	92.0	0.833	0.959	0.931~0.986



1 miR 21 CA125 ROC

P<0.05 5 3

7

90%

40% [8,9]

Figure 1 ROC curve of serum miR 21 and CA125 detection for the diagnosis of ovarian cancer

2.3 miR 21 [10] CA125 CA125 ROC miR 21 CA125 [11] ~ CA125 CA125 miR 21 CA125 ~ CA125 P<0.05 4 1 CA125

2.4 miR 21 CA125 CA125 1 miR 21 CA125 miRNA RNA 3′

4 miR 21 CA125 *n* %

Table 4 comparison of serum miR 21 and CA125 expression in patients with different clinical and pathological characteristics *n* %

		miR 21				CA125			
				^{2}	*P*			^{2}	*P*
~	*n*=45	30 66.67	15 33.33	23.220	0.000	23 51.11	22 48.89	14.670	0.000
~	*n*=35	33 94.29	2 5.71			27 77.14	8 22.86		
	n=47	31 65.96	16 34.04	31.869	0.000	22 46.81	25 53.19	32.175	0.000
	n=33	32 96.97	1 3.03			28 84.85	5 15.15		
	n=52	35 67.31	17 32.69	39.521	0.000	29 55.77	23 44.23	7.988	0.007
	n=28	28 100.00	0 0.00			21 75.00	7 25.00		

5 miR 21 CA125 $\bar{x}\pm s$

Table 5 Comparison of serum mir 21 and CA125 expression levels in ovarian cancer patients before and after surgery $\bar{x}\pm s$

	n	miR 21	CA125 U/mL
	80	2.39±0.72	52.66±18.83
1	80	1.87±0.53	38.52±9.57
t		5.465	5.787
P		0.000	0.000

mRNA

[12] [13 14] miRNA

miR 21 miRNA

TPM1 PTEN SPRY2

[15 17] miR 21

miR 21

miR 21

ROC miR 21 CA125

miR 21 CA125

AUC 0.8

miR 21

AUC CA125

miR 21

miR 21 CA125 AUC

miR 21 CA125

miR 21 CA125

miR 21 CA125

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H_2O_2 PC12

PC12 H_2O_2 PC12

SOD qRT PCR miR 422a

miR 422a miR 422a H_2O_2 PC12 SOD Western blot

Bcl 2 Bax H_2O_2 PC12 $P<$, 2

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[1 2]

[3 4]

[5]

1

1.1

PC12

RPMI 1640 Gibco

Annexin V FITC/PI

30%

H_2O_2 PBS

Bcl 2 Bax

Sigma

HRP IgG

miR 422a mimics

miR NC miR 422a anti miR 422a

anti miR NC

Trizol PCR qRT

PCR TaKaRa

SOD

Lipofectamine2000

1.2

1.2.1

100 200 300 nmol/L H_2O_2

PC12 PC12

H_2O_2 PC12

H_2O_2 300 nmol/L

10 20 40 60 mg/L PC12 10%

RPMI 1640 37

5%CO_2 24 h PC12 H_2O_2

12 h

PC12 H_2O_2

12 h

ECL

Quantityone

= /

1.2.5 qRT PCR miR 422a

Trizol PC12 RNA

RNA

RNA cDNA qRT PCR

SYBR Pre mix Ex Taq 2× 10 μL cDNA 2 μL

0.8 μL ROX Reference Dye 50× 0.4 μL

ddH_2O_2 6 μL 95 5 min 1

95 15 qs 60 60 s 72 30 s

40 ABI 7500 PCR

miR 422a

1.3

SPSS 21.0

$\bar{x} \pm s$

t

P<0.05

2

2.1 H_2O_2 PC12

PC12 PC12 + H_2O_2 100 nmol/L

PC12 + H_2O_2 200 nmol/L PC12 + H_2O_2 300 nmol/L

PC12 P<0.05 SOD

P<0.05 1

1 PC12 + H_2O_2 300 nmol/L PC12

H_2O_2 300 nmol/L

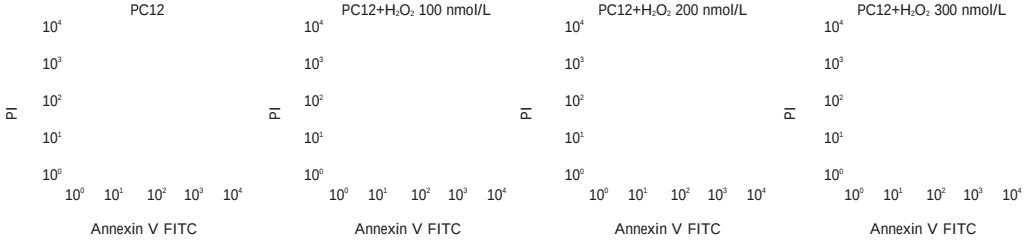
1 H_2O_2 PC12 $\bar{x} \pm s$ n=6

Table 1 Hydrogen peroxide induces PC12 damage in neurons

$\bar{x} \pm s$ n=6

	SOD(U/mL)	%
PC12	17.72±1.68	7.58±0.52
PC12+H_2O_2 100 nmol/L	14.95±1.34[a]	11.23±1.20[a]
PC12+H_2O_2 200 nmol/L	10.02±1.00[a]	17.21±1.76[a]
PC12+ $H_2O_2$300 nmol/L	6.72±0.58[a]	55.78±4.33[a]
F	97.706	504.091
P	0.000	0.000

PC12 [a]P<0.05



1 H_2O_2 PC12

Figure1 Effects of different concentrations of hydrogen peroxide on apoptosis of PC12 neurons

2.2 H_2O_2 PC12

SOD

PC12

H_2O_2 300 nmol/L

PC12 P<0.05 SOD

P<0.05 Bcl 2

P<0.05 Bax P<

0.05 P<0.05

2 2 H_2O_2

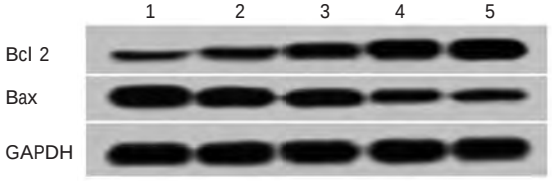
PC12

40 mg/L

2.3 H_2O_2 PC12 miR

422a

qRT PCR PC12



1. 2. 10 mg/L 3. 20 mg/L 4. 40 mg/L

5. 60 mg/L

2 H2O2 PC12

Figure 2 Effects of Pulsatilla chinensis on apoptotic protein expression of PC12 induced by hydrogen peroxide in nerve cells

PC12+H_2O_2 300 nmol/L PC12 miR 422a

P<0.05 PC12+

H_2O_2 300 nmol/L PC12+H_2O_2 300 nmol/L+

2 H_2O_2 PC12 SOD

$\bar{x}\pm s$ n=6

Table 2 Effects of Herba Anemoniae on Apoptosis and SOD Expression of PC12 Neurons Induced by H_2O_2 $\bar{x}\pm s$ n=6

mg/L	SOD U/mL	Bcl 2	Bax	%
	6.71±0.54	0.26±0.03	1.23±0.12	52.58±4.52
10	9.66±0.84[a]	0.45±0.04[a]	0.94±0.09[a]	33.93±3.24[a]
20	12.01±1.12[ab]	0.58±0.06[ab]	0.71±0.07[ab]	24.81±2.56[ab]
40	15.62±1.37[abc]	0.76±0.08[abc]	0.43±0.04[abc]	12.26±1.13[abc]
60	16.23±1.41[abc]	0.82±0.08[abc]	0.37±0.04[abc]	10.25±1.01[abc]
F	79.023	82.984	125.961	227.141
P	0.000	0.000	0.000	0.000

[a]*P*<0.05 10 mg/L [b]*P*<0.05 20 mg/L [c]*P*<0.05

40 mg/L PC12 miR 422a *P*<0.05 3

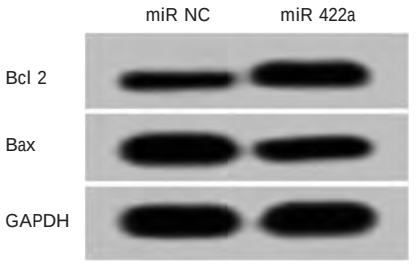
2

miR 422a PC12 1.12±0.10 PC12+H_2O_2 300 nmol/L PC12+H_2O_2 300 nmol/L+ 40 mg/L *F* *P*

2.4 miR 422a H_2O_2 PC12 SOD

miR NC miR 422a PC12 *P*<0.05 SOD *P*<0.05 Bcl 2 *P*<0.05 Bax *P*<0.05 3 4

2.5 miR 422a H_2O_2 PC12 SOD 40 mg/L+ anti miR NC 40 mg/L+ anti miR 422a PC12 *P*<0.05 SOD Bcl 2 *P*<0.05 Bax *P*<0.05 4 5 miR 422a H_2O_2 PC12 SOD



3 miR 422a H2O2 PC12

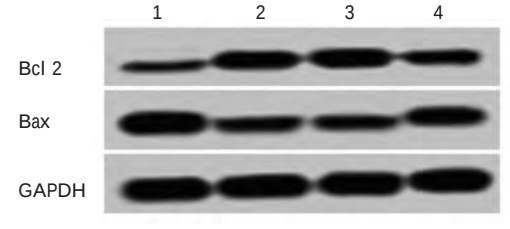
Figure 3 Effects of overexpression of microRNA 422a on apoptotic protein expression of PC12 induced by hydrogen peroxide in nerve cells

4 miR 422a H2O2 PC12 SOD $\bar{x}\pm s$ n=6

Table 4 Effect of over expression of microRNA 422a in on apoptosis and SOD activity of PC12 neurons induced by hydrogen peroxide $\bar{x}\pm s$ n=6

	SOD U/mL	Bcl 2	Bax	%
miR NC	6.71±0.54	0.26±0.03	1.23±0.12	52.58±4.52
miR 422a	14.37±1.28[a]	0.65±0.06[a]	0.53±0.05[a]	19.71±1.58[a]
t	13.506	14.241	13.190	16.815
P	0.000	0.000	0.000	0.000

miR NC [a]*P*<0.05



1. 2. 40 mg/L 3. 40 mg/L+anti miR NC 4. 40 mg/L+anti miR 422a

4 miR 422a H_2O_2 PC12

Figure 4 Inhibiting the expression of miR 422a reverses the effect of Saussurea chinensis on apoptotic protein expression of PC12 induced by hydrogen peroxide in nerve cells

3

PC12

H_2O_2 PC12

O

	miR 422a
	0.12±0.01
40 mg/L	0.83±0.08
40 mg/L+anti miR NC	
40 mg/L+anti miR 422a	
F	
P	

• •

miR 192 miR 29c 2

RNA 192 miR 192 RNA 29c miR 29c 2

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with urinary NGAL r=-0.338 P=0.002 and miR 29c was positively correlated with urinary NGAL r=0.516 P<0.001 . The sensitivity of miR 192 for diagnosis of DN was 52.50% and the specificity was 75.58%. The sensitivity of miR 29c for diagnosis of DN was 50.00% and the specificity was 86.05%. The combined diagnostic sensitivity was 97.50% the specificity was 95.34% and the accuracy was 96.39%. The sensitivity and accuracy of the joint detection were higher than the single test P<0.05 . Conclusion The abnormal expression of miR 192 and miR 29c in plasma is closely related to the occurrence and development of type 2 diabetic nephropathy. The combined detection of the two can improve the diagnostic efficiency of type 2 diabetic nephropathy.

KEY WORDS miR 192 miR 29c type 2 diabetic nephropathy

diabetes mellitus DM

2

diabetic nephropathy DN 2

DN

1 3 2

RNA microRNA miRNA

RNA

miRNA 2

4 miRNA 2

miRNA

2

RNA 192 microRNA 192 miR 192 DN

DN

5 NJDSP3/"4

GATT 3′ 5′ GGAACGCTTCAC GAATTTG 3′ miR 192 5′ GGGGCT GACCTATGAATTGA 3′ 5′ CAGTG CAGGGTCCGAGGT 3′ miR 29c 5′ GTAGCACCATTTGAAATCAG 3′ 5′ TTGGCACTAGCACATT 3′ cDNA 2.0 μL Primer 1.0 μL RNase H_2O 7 μL SYBR Primix Ex Taq™ 10 μL 95 2 min 95 15 s 60 30 s 72 30 s 40 $2^{-\Delta\Delta Ct}$ miR 192 miR 29c

1.2.4

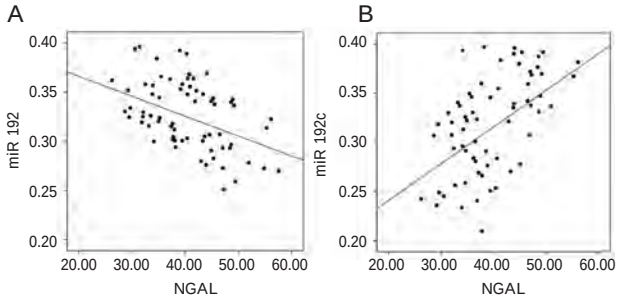
5 mL 3 000 r/min 10 min EP -80 enzyme linked immunosorbent assay ELISA NGAL

1.2.5

2 DM 86 DN 80 receiver operating characteristic ROC miR 192 miR 29c 2 miR 192 miR 29c 2

1.3

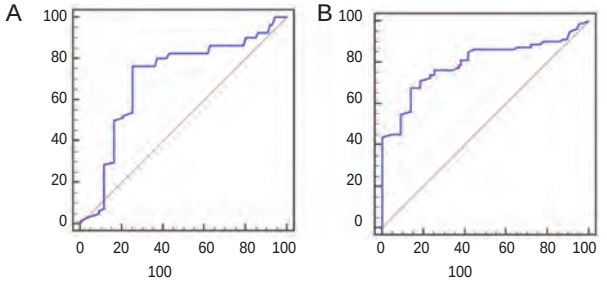
SPSS 21.0 ± x ± s *t* Pearson ROC miR 192 miR 29c 2



1 miR 192 miR 29c DN NGAL

Figure 1 Correlation analysis between plasma miR 192 and miR 29c expression and NGAL in patients with DN

miR 192 2
52.50% 75.58% AUC
0.679 95%*CI* 0.602~0.749 0.40 2A
ROC miR 29c
miR 29c 2
50.00% 86.05% AUC 0.796
95%*CI* 0.726~0.854 2.94 2B



2 ROC miR 192 miR 29c

Figure 2 ROC analysis of the value of plasma miR 192 and miR 29c in the diagnosis of type 2 diabetic nephropathy

2.5 2
97.50%
95.34% 96.39% 3 miR 29c 2
miR 192
P<0.05 3 4

3

2

[12]

3 miR 29c miR 192

Table 3 Diagnostic value of combined detection of miR 29c and miR 192 in type 2 diabetic nephropathy

	78	2	80
	4	82	86
	82	84	166

4 miR 29c miR 192

Table 4 Diagnostic value of combined detection and single detection of miR 29c and miR 192 in type 2 diabetic nephropathy

miR 192	52.50%	42/80 *	75.58%	65/86	64.46%	107/166 *
miR 29c	50.00%	40/80 *	86.05%	74/86	72.29%	114/166 *
	97.50%	78/80	95.34%	82/86	96.39%	160/166
^{2}	9.578		1.064		7.070	
P	0.008		0.587		0.029	

NC *P<0.05 DM #P<0.05

[13]
2
miRNA
[14]
2 miRNA
2
miR 192
[15] miR 192 2
UACR miR 192
[16] miR 192
1 Egr1 DN [17]
2 miR
192 miR 192
2
2 NGAL
2 NGAL
DM 2
miR 192 NGAL
NGAL 2
miR 192
miR 192
miR 29c

6

6 IL 6 PCT
80 *n*=38
n=22 *n*=20 40 IL 6 PCT ROC
IL 6 PCT Logistic IL 6 PCT
IL 6 PCT
P<0.05 *P*<
0.05 IL 6 PCT > > ROC
IL 6 PCT AUC 0.806 95%*CI* 0.96~10.61 *P*=0.008 0.892 95%*CI* 1.28~9.16 *P*=0.000
IL 6 PCT 89.61% 86.76%

2017 Se1201710

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Sepsis Systemic inflammatory response syndrome SIRS [1] [2] 2 000~3 000 / 1 400 1%~2% ICU 25% ICU [3] ICU [4] 200 [5] 6 interleukin 6 IL 6 procalcitonin PCT IL 6 PCT IL 6 PCT IL 6 PCT

1

1.1

2015 6 2017 6 80 2012 ACCP American College of Chest Physicians SCCM Society of Critical Care Medicine ESICM European Society of Intensive Care Medicine ATS American Thoracic Society [6] 24 h multiple organ dysfunction syndrome MODS

38 SIRS MODS 18 20 56~89 75.51±12.37 22 SIRS MODS 12 10 59~88 74.38±10.64 20 MODS 9 11 66 90 76.73±13.65 40 20 20 54~90 74.38±10.52 P>0.05

1.2 IL 6 PCT

Cobas E601

1.4

SPSS 22.0 $\bar{x}\pm s$ one way ANOVA SNK q Youden ROC IL 6 PCT Logistic IL 6 PCT P<0.05

2

2.1 IL 6 PCT

IL 6 PCT P<0.05 P<0.05 IL 6 PCT < < 1

1 IL 6 PCT n $\bar{x}\pm s$

Table 1 Comparison of IL 6 and PCT levels in different study groups and control groups n $\bar{x}\pm s$

	n	PCT ng/L	IL 6 pg/mL
	40	0.01±0.35	9.163±2.647
	38	0.85±0.95*	40.16±16.23*
	22	2.28±2.74*#	98.62±36.49*#
	20	4.267±3.769*#	106.294±42.135*#

* *vs* P<0.05 # *vs* P<0.05 *vs* P<0.05

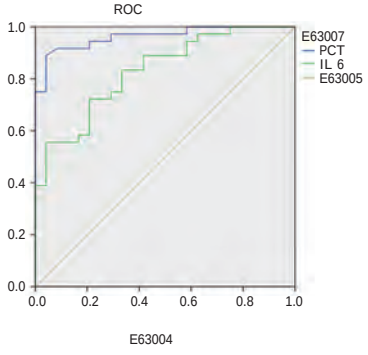
2.2 IL 6 PCT

IL 6 PCT IL 6 PCT AUC 0.806 0.892 IL 6 PCT Youden 2 1

2 IL 6 PCT ng/mL,%

Tab. 2 Analysis of the diagnostic value of IL 6 and PCT for sepsisz ng/mL,%

					Youden		AUC	
PCT	90.35	87.26	6.38	0.16	72.68	94.26	0.892	1.110
IL 6	89.61	86.76	5.12	0.29	69.21	92.37	0.806	56.127



1 IL 6 PCT ROC

Figure 1 ROC diagram of IL 6 and PCT for diagnosis of sepsis

2.3 IL 6 PCT Logis tic

80 15 65

IL 6 PCT

2.2 PCT>1.110 ng/ mL PCT≤1.110 ng/mL

^{2}=4.20 P= 0.041 IL 6>56.12 pg/mL IL 6≤56.12 pg/mL

^{2}=7.49 P=0.006 3

3 IL 6 PCT

Table 3 Single factor analysis of prognosis in patients with IL 6 PCT and sepsis

	n=65	n=15	^{2}	P
PCT				
≤1.110 ng/mL	27 41.54	2 13.33	4.20	0.041
>1.110 ng/mL	38 58.46	13 86.67		
IL 6				
≤56.127 pg/mL	29 44.62	1 6.67	7.49	0.006
>56.127 pg/mL	36 55.38	14 93.33		

PCT>1.110 ng/mL IL 6>56.127 pg/mL logistic PCT>1.110 ng/ mL IL 6>56.127 pg/mL

OR 9.35 98%CI 1.96~ 8.92 12.98 95%CI 0.89~12.39 4

4 IL 6 PCT Logistic

Table 4 Logistic analysis of prognosis in patients with sepsis predicted by IL 6 and PCT

		SE	OR	P	95%CI
PCT>1.10 ng/mL	1.86	0.06	9.35	0.001	1.96~8.92
IL 6>56.12 pg/mL	2.83	0.15	12.98	0.001	0.89~12.39

3

IL 6

CRP PCT

2~3 h

IL 6

[7] [8]

IL 6

[9] Srisangthong IL 6

IL 6

[10] IL 6

IL 6

Srisangthong

IL 6>56.12 pg/mL

OR

9.35 98%CI 1.96~8.92 IL 6

IL 6

IL 6 IL 6

[11]

IL 6

PCT

4 h

[12] 6~24 h [13]

PCT

PCT

PCT

[14] PCT>0.5 ng/L

PCT>1.0 μg/L

D

D PCT
BM VM
TM D PCT C CRP
ROC D PCT
D PCT CRP BM VM
u=110.0 100.5 95.5 185.0 177.5 150.0 80.5 P<0.05 BM TM D
PCT CRP u=51.5 45.0 60.0 54.5 P<0.05 ROC D
AUC 0.907 PCT AUC 0.878 D 91.7% 89.9%
PCT 85.6% 98.6% D

D ROC

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ABSTRACT Objective To investigate the expression of D lactic acid combined with procalcitonin PCT in bacterial meningitis viral meningitis and tuberculous meningitis and its diagnostic value. Methods The levels of D lactate PCT CRP red leukocyte count glucose chloride ion and total cerebrospinal fluid protein in patients with bacterial meningitis BM viral meningitis VM and tuberculous meningitis TM were measured. The diagnostic value of D lactic acid and PCT in bacterial meningitis was analyzed by receiver operator characteristic curve ROC sensitivity and specificity. Results There were significant differences in D lactate PCT CRP RBC count CSF total protein and glucose between BM group and VM group u=110.0 100.5 95.5 185.0 177.5 150.0 80.5 P<0.05 . The difference of D lactate PCT CRP and leukocyte count between BM group and TM group was statistically significant u= 51.5 45.0 60.0 54.5 P<0.05 . ROC curve analysis showed that area under the curve AUC of D lactate was 0.907 and AUC area of PCT was 0.878. The sensitivity of D lactate was 91.7% the specificity was 89.9% the sensitivity of PCT was 85.6% the specificity was 98.6%. Conclusion D lactate combined with PCT is necessary for the early diagnosis of bacterial meningitis.

KEY WORDS D lactate Procalcitonin Bacterial meningitis Receiver operator characteristic curve

1 2

010050
E mail fanghuei@yeah.net

D pro calcitonin PCT [3,4] D

D

1

1.1

2016 3 2017 6 68

>18

3 viral meningitis VM 17 tuberculosis meningitis TM 20 bacterial meningitis BM 31

28

20160113

1.2

1.2.1

C

D

Sigma AU640

1.2.2

3 000 r/min 15 min AU640 2 h

[5]

[5] [6] C C reactive protein CRP C [7] PCT CRP PCT D [5]

[8]

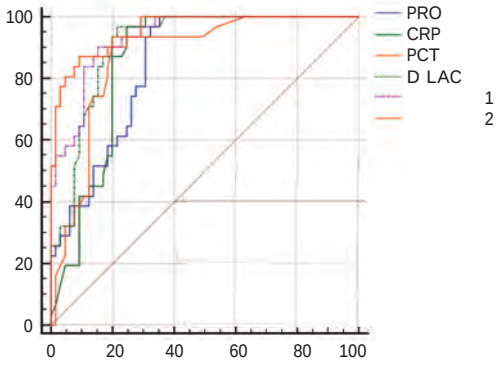
1.3

SPSS 16.0 F $\bar{x} \pm s$ t Kruskal Wallis

1 $\bar{x}\pm s$

Table 1 Clinical data and laboratory examination results of cerebrospinal fluid related indexes in experimental groups $\bar{x}\pm s$

		VM	TM	BM	*F*	*P*
	42.5±10.6	44.6±8.9	38.5±8.7	45.8±11.3		
/	16/12	8/9	12/8	17/14		
mmol/L	4.1±1.3	3.3±1.2	2.9±1.0	2.66±0.9	9.6	0.006
mmol/L	119.8±8.9	113.7±7.3	115.3±6.9	111.1±7.2	15.3	0.002
mg/L	294.9±31.6	367.9±42.5	2035.3±837.6	2465.6±1021	68.3	<0.001
(/μL)	2±1.8	10.3±7.6	685.6±427.6	812.9±471.3	85.9	<0.001
(/μL)	7±5.8	136.3±98.6	191.6±133.3	211.2±173.2	12.3	<0.001
CRP mg/ L	0.239±0.092	0.411±0.185	0.627±0.312	0.678±0.252	42.6	<0.001
PCT μg/ L	0.048±0.075	0.052±0.024	0.057±0.033	0.165±0.183	52.6	<0.001
D mmol/L	3.77±1.97	10.23±5.26	32.59±14.3	43.58±14.3	62.7	<0.001



D LAC D PCT CRP C PRO 1 D PCT 2 D PCT CRP 1 ROC

Figure 1 ROC curve of diagnostic index related to bacterial meningitis

2 AUC

Table 2 AUC of cerebrospinal fluid diagnostic indexes

	AUC	*P*	95%
mmol/L	0.630	0.007	0.625~0.726
mg/L	0.845	<0.001	0.761~0.914
mmol/L	0.644	0.005	0.540~0.739
(/μL)	0.836	<0.001	0.770~0.919
(/μL)	0.788	<0.001	0.698~0.824
CRP mg/ L	0.826	<0.001	0.746~0.899
PCT(μg/L)	0.878	<0.001	0.769~0.919
D mmol/ L	0.907	<0.001	0.794~0.935
1	0.933	<0.001	0.905~0.998
2	0.957	<0.001	0.924~1.024

1 AUC 0.933 8 2 AUC 0.957

2.3

3 D cutoff 37.9 mmol/L 91.7% PCT cutoff 0.168 μg/L 85.6% 98.6% D PCT Logis tic 1 85.1% 99.5% 8 2 83.9% 100%

3 cutoff

Table 3 Cutoff value sensitivity and specificity of cerebrospinal fluid diagnostic indicators

	cutoff	%	%
mmol/L	2.6	62.3	86.5
mg/L	1983.5	85.3	90.3
mmol/L	113.6	65.3	80.3
(/μL)	552.6	85.5	91.6
(/μL)	175.3	72.7	88.7
CRP mg/L	0.586	87.3	85.7
PCT(μg/L)	0.168	85.6	98.6
D mmol/L	37.9	91.7	89.9
1		85.1	99.5
2		83.9	100.0

3

[10]

70% 3 d [11]

BM D PCT
3 D PCT
[12]
D PCT

[13]

C

PCT
PCT

D

ROC
D ROC
0.907
AUC 0.878
Li [14]
D
[15]

1 2
AUC 0.933 0.957

D 91.7% 89.9%
PCT
85.6% 98.6%

99.5% 100% [16]

D L

L [17 18]
D
D D
C A [19]

PCT
PCT

D
ROC
D

1 Taskin E Turgut M Kilic M et al. Serum procalcitonin and celebrospinal fluid dytokines level in children with meningitis inflame J . Mediators Inflamm 2004 13 4 269 273.
2 Oberhoffer M Stonans I Russwurm S et al. Procalcitonin expression in human peripheral blood mononuclear cells and its modulation by lipopolysaccharides and sepsis related cytokines in vitro J . J lab Clin Med ń 26 273 ʎ 1 eq %ps ɖ

GATA3 CK20

GATA3 CK20 BUC
89 BUC 16 GATA 3 GATA3
20 CK20 BUC BUC GATA3
85.4% 100.0% CK20 BUC 62%
CK20 BUC
BUC P<0.05
GATA3 CK20
GATA3 CK20

ZENG Yumei DU Juan CHEN Yingzhi CHU Bing
Department Pathology of Zhongshan City People s Hospital Guangdong Province Affiliated Zhongshan Hospital of Sun Yat Sen University Zhognshan Guangdong China 528400

ABSTRACT Objective To investigate the expression and significance of GATA3 and CK20 in bladder urothelial carcinoma BUC . Methods The levels of GATA binding protein 3 GATA3 and cytokeratin 20 CK20 were detected by immunohistochemical assay from 89 cases of BUC and 16 cases of benign lesions. The correlation between the expressions and the pathological parameters was analyzed Results The positive rate of GATA3 was 85.4% in BUC 100.0% in benign lesions 62% in BUC and 62% in benign lesions. The positive rate of CK20 in BUC with high grade lesions myometrial infiltration and lymph node metastasis was significantly higher than that in BUC with low grade lesions and non myometrial infiltration and BUC without lymph node metastasis P<0.05 . Conclusion GATA3 and CK20 may be used as independent prognostic factors to predict tumor progression.

KEY WORDS Bladder urothelial carcinoma GATA3 CK20

9 [1]
bladder urothelial carcinoma [3] 20 cytokeratin 20
BUC 6 [2] CK20

[4]
BUC GATA3 CK20
GATA 3 GATA binding protein 3 GATA3 BUC

528400
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1

1.1

2015 1 2016 7
105 BUC 89
16 BUC 66
23 34~79 57
World Health Organize
WHO [5] 25
64
52
37 16 12
4

1.2

10%
3 μm
120 8 min 10 min
3% H_2O_2 10 min
GATA3 CK20
37
1 h phosphate buffer solution PBS
pH 7.4 3 3 min Envision
37 15 min PBS pH 7.4 3
3 min DAB 2 min Mayer
PBS

1.3

GATA3
CK20
5 >10%~25%
1+ >25%~50% 2+ >50%
3+ GATA3 ≤
10% CK20

1.4

SPSS 15.0
[2] P<0.05

2

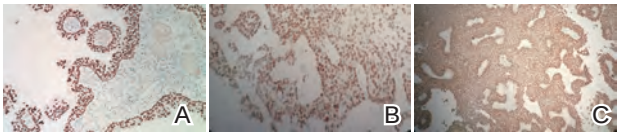
2.1 GATA3

GATA3
100% 85.4%
GATA3
P<0.05 1 1

1 GATA3

Table 1 Relationship between GATA3 expression and clinicopathological parameters of bladder tumor

	n	GATA3					P
		0	1+	2+	3+	%	
							0.365
	16	0	1	4	11	100.0	
	89	13	9	32	35	85.4	
							0.395
	66	1	2	19	38	89.4	
	23	4	1	6	12	82.6	
							0.021
	25	0	1	6	18	100.0	
	64	12	8	18	26	81.2	
							0.020
	52	15	1	13	27	78.8	
	37	2	8	11	16	94.6	
							0.021
	35	11	6	10	9	71.4	
	13	0	1	3	6	100.0	



A EnVision ×200 B
EnVision ×400 C EnVision ×200
1
GATA3

Figure 1 Positive expression of GATA3 in benign lesions of urinary tract low grade and high grade BUC

2.2 CK20

CK20
100%
40.0% 71.9%
86.5% 51.9%
92.3% 62.9% P<
0.05 2 2

3

GATA3
[6 7]

GATA3 GATA3

Wilson

[13] Nandi [14]

GATA3

20 CK20 Cytokeratin

CK

[8 9] [15] [9] CK20

[10 11]

105 GATA3 BUC

100.0% GATA3 [16] CK20

85.4% GATA3

1 Hiroshi [12]

GATA3

98% GATA3 CK20 16

14% CK20

GATA3 BUC 61.7%

CK20 BUC

GATA3

40.0% 71.9%

GATA3

CK20

GATA3 CK20

BUC

BUC

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15 . miRNA 21 TPM1

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DNA

DNA
ctDNA ctDNA
ctDNA
DNA cfDNA cfDNA ctDNA
ctDNA ctDNA
ctDNA ctDNA

DNA PCR

CHENG Xiaowen
Department of Clinical Laboratory The First Affiliated Hospital of Anhui Medical University Hefei Anhui China 230022

ABSTRACT With the rapid development of various new molecular methods and the improvements in genomic the analysis of circulating tumor DNA ctDNA is gradually shifting from basic research to clinical application. Numerous studies have shown that ctDNA has a broad prospect for prediction monitoring and prognostication of tumors. ctDNA is an abnormal cell free DNA cfDNA present in the blood of tumor patients. Although the biological mechanism of cfDNA is not clear ctDNA analysis has begun to be applied in clinical practice which is helpful to promote the development of accurate tumor treatment. In this paper the detection methods of ctDNA the application of ctDNA in cancer precision medicine and the challenges of ctDNA detection and analysis are reviewed in order to further explore the practical clinical application of ctDNA.

KEY WORDS Circulating tumor DNA Quantitative PCR Next generation sequencing precision medicine of tumor

1948 Mandel cfDNA
cell free DNA DNA
cfDNA 1977 Leon [1] circulating tumor DNA ctDNA ctDNA
cfDNA DNA
[2 4] Vogelstein [5] 1999 PCR digital
KRAS PCR dPCR
KRAS
KRAS DNA 2012

81302150 2014jyxm761
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E mail windy135@sina.com

Forshew [6] cfDNA

cfDNA
whole genome sequencing WGS

[7 8] 2013
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ctDNA

100 [19] ctDNA

ctDNA [6 32] ctDNA

ctDNA

ctDNA CA125 [20]

1 6 [33]

[20] ctDNA ctDNA

ctDNA

ctDNA

ctDNA ctDNA

[21 22] ctDNA NSCLC

2 48% ctDNA epidermal growth factor receptor EGER

100% [23] ctDNA

ctDNA

ctDNA [34] T

ctDNA 2 000 cfDNA ctDNA

copies/mL [24] [35]

2.2 ctDNA ctDNA

ctDNA

[25 26] 82% minimal residual disease MRD

ctDNA 47% [19] 50% [36]

non small cell lung cancer NSCLC 2.5 ctDNA

ctDNA [27] dPCR

93.3% [28] ctDNA

noninvasive prenatal testing

NIPT shallow ctDNA

whole genome sequencing sWGS

16

6 37.5% [29] ctDNA ctDNA

[37]

2.3 ctDNA ctDNA

cfDNA 70 ctDNA

2 human epidermal growth

cfDNA factor recepter HER2

30 ctDNA

ctDNA 5

ctDNA

[30 31] ctDNA HER2

91.4% Kappa =0.784 $P<$

2.4 ctDNA 0.001 ctDNA

ctDNA

HER2

[38]

[39 40]

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2016 Food and Drug Administration FDA

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249

HBV DNA 343

441

CYP2C19 6

ORMDL3 11

miR 34 17

MTHFR C677T 22

MTHFR *MTRR* 28

B NF κB/p65 Bcl 2 Bax 33

MMP 9 28 39

NT proBNP 44

49

54

3 58

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ASAP1 *GSTM3* 96

101

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2 VEGF

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miR 122 miR 150 418
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Snail TGFβ1 EMT 451
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FBN1	c.2418A>G	479
	HMGN5	

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