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文献综述 REVIEW

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■背景资料
原发性肝癌是我国最常见的恶性肿瘤之一, 我国每年新发病例约占全球的45%, 已成为世界上肝癌发病最集中的地区. 经过近半个世纪的努力, 我国医务工作者在肝癌的防治上已取得了举世瞩目的成绩. 但肝癌发生发展迅猛 复发率和转移率很高, 要提高肝癌患者生存率应加强肝癌的基础研究, 促进肝癌早期诊断技术和生物治疗的发展.

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摘要
在肝细胞癌(HCC)发生发展过程中, 伴随着原癌基因和抑癌基因的突变, 各种参与调控的细胞因子表达也发生异常并最终影响疾病的进程和转归. 目前对肝细胞癌的分子病理学研究已经集中在这些细胞因子的异常表达及其相互关系网络上, HBx蛋白 SAM TGF等细胞因子的研究已经十分深入, 而且, 随着各种新技术的应用, 更多的低丰度调控蛋白也逐渐被发现, 其在肝细胞癌细胞增殖调控 异常分化 衰老和凋亡调节以及肿瘤演进等方面起着重要作用.

关键词: 肝细胞癌; 癌基因; 抑癌基因; 突变; 细胞因子

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0 引言

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(SELDI) ,
fmol ,
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1 细胞增殖的调控

, .
, (HBV)
(HCV) B1
,
.
,
. ,
.
HBV , X
HBV (S)
[1]. X HBV
, p53
FAK Src [2-3] DNA
. ,
HBx p53 E-box
, p53 , p53
, PTEN
, AKT ,
. , p53 HBV
. , p53
HBx HBV
.
, Zhu *et al*[4] , HBx
,
. C57-TgN(HBx)
C57BL/6
(DEN) , DEN
C57BL/6
,
.

HCV
, 2 a , 1 a
, IFN
[5]. HCV
, 5A(NS5A)
[6]. NS5A
3 (STAT3) D1 (>2.5 cm)
, . (-) ,
, STAT3 HCV E
NS5A . , . ,
, NS5A STAT3 D1 E
Bcl-xL p21 . , NS5A p53 . , G_1
Jak1 STAT3, p53
. -γ- (DCP) ,
Met Janus 1 .
STAT3 [7], DCP
Myc ,
3- /Akt . ,
, , p53 ,
249 (p53mt249), . (
AAG AGT[8]. p53) .
, , , DNA
(IGF- receptor, IGF-IR) , S- (SAM) ;
(insulin-like growth factor , IGF-)P3 6 moSAM ,
, . IGF- . , SAM
IGF-IR , , [16]: (1) SAM
. p53mt249 SAM
IGF- IGF-IR ; (2) , DNA
, [9], G_0 SAM/SAH(S-) ;
G_1 . Kong *et al*[10] , (3)DNA 5- SAM
, (RZ) p53 , DNA ; (4)c-Ha-ras
42%, p53, c-Ki-ras c-myc
, , SAM/SAH ;
. (5)SAM DNA .
IGF- “
, ”, ,
, IGF- .
, (PCNA) , ,
(HCC) , “ ” . ,
[11-12].
Alexia *et al* $HepG_2$ Huh-7 . Oh *et al*[17] (CH)
, (LGDNs)
IGF- , IGF- / (HGDNs) HCC
/ HCC , (TRFL) (TA) ,
[13]. , , IGF- TRFL TA LGDNs HGDNs
IR h7C10 . LGDNs TRFL TA CH,

■研发前沿
肝癌研究热点主要集中在肝炎病毒感染 细胞凋亡 癌基因和抑癌基因与肝癌的关系 肝癌演进的分子机制 细胞因子在肝癌发生发展中的作用等方面.

■同行评价
本文介绍了肝细胞癌发生发展过程中一些细胞因子的异常表达及其相互关系, 内容丰富, 新颖, 能反映涉及到的肝细胞癌基础研究的前沿进展,具有先进性,文字流畅,可读性强.

HGDNs , LGDNs TRFL 17%, 7%LGDNs TA, HGDNs TRFL TA HCC . , , , LGDNs HGDNs . , HGDNs HCCs. , HBV X (hTERT) mRNA , HBV [18]. (IFN) , [19], , JAK/STAT S MEK/ERKt [20] , , , IFN-β IFN-α, S [21]. [22] α Con1(IFN-α Con1) KIM-1 HAK-1B , IFN-α Con1 , , IFN-α Con1 . , , α [23]: , IFN-α 8 , IFN-α2, -α5 -α10 , IFN-α1 . , , 2',5'- (2'5'-OAS) , HAK-3 , KYN-3 2'5'-OAS.

2 癌细胞的去分化

: . , . Nakano *et al*[24] 41 P- (P-gp) P53 , P-gp ; , . , P-gp ; , P-gp . , P-gp 87%, . , p53 12.5%, 52%, 82.5%, , , P-gp p53 ; , : P-gp , p53 [25]. , p53 HCC [26], , . , , , (DHEA-ST) , DHEA-ST . , DHEA-ST . EBAG9 , , RCAS1 , RCAS1, T , (TILs) [27]. EBAG9/RCAS1 [28], , EBAG9/RCAS1 , ; , EBAG9/RCAS1 . , EBAG9/RCAS1 , . . [29]: RCAS1 , - , RCAS1 . A_2(PLA_2) , . , , PLA_2 , . , Ohshima *et al* [30] PLA_2 ,

PLA_2 ,
,
PLA_2 ,
, ,
.
HCC
(CD-Ks), cyclin D
; cyclin-CDK
(cyclin-dependent kinasein-hibitors, CKIs) .
7 CKIs,
: Ink4 (inhibitor of cdk4) ,
p15 p16 p18 p19,
cdk4/cdk6-cyclin D ;
Cip/Kip(CDK-interacting protein/kinase inhibitor protein) , $P21^{cip1}$, $P27^{kip1}$ P57,
cyclin-CDK . HCC ,
cyclin D1 . p16
CKIs ,
, HCC
,
HCC CKIs. *et al*[31]
38 P16 P21
, P16 ,
(58%) ; Edmondson
- Edmondson -
HCC, >3 cm HCC ≤3 cm
HCC,
. P21 ,
.
. , P16 HCC
.
(MT) ,
,
. 1957
, [32], MT
,
,
. , MT
p53
. MT
,
,
MT
.
, : ,
MT MT1 MT2 [33].
, MT Zn-MT ,
HCC(<40 mm) , MT Cu ;
HCC(> =40 mm) , MT Cu Zn
, SOD Cu Zn [34].

3 癌细胞衰老及凋亡调节

,
, ,
caspase *bcl*-2 p53
,
, [35].
. ,
HCC 1p, 4q, 6q, 8p, 13q 16p
(loss of heterozygosity, LOH)[36-38],
(MSI) , LOH
[39]. ,
, HCC
[40]. *et al*[41]
DNA , 56 HCC 1p36
10 .
, LOH 69%, LOH RIZ ,
D1S199. LOH AFP HBsAg
Edmondson
; D1S2893 D1S507 ,
HBsAg LOH HBsAg
; D1S199 , AFP LOH
AFP ; D1S468 ,
LOH .
HCC lp36 LOH, HCC
,
LOH .
p53 ,
, .
P53 , p21
bax , , p53
CD95 ,
Fas [42].
et al[43]
(PCNA) p53 Fas

, (AI)
PCNA (LI) p53 Fas HCC
; AI P53
Fas HCC ;
LI HCC :
; Edmondson TNM
, AI , LI p53
, Fas . HCC
, PCNA
.

, (TGF)-β1
. TGF-β1
, TGF-βⅡ (TGR2)
. Park *et al*[44]
, , , ,
TGF-β1 , TGR2
. TGF-β1
TGR2 ,
, TGR2 TGF-β1
,
. NF-kappaB c-Src β1
MAP TGF-β1
, [45-47].
, [48]
(PBR)
, PBR
caspase-3
, , PBR Bcl -2
Bcl-xl , . PBR
G_1/S G_2/M .
PBR
, .
, Yu *et al*[49]
MK , MK
. E1A MK
(AdMK) ,
. ,
, AdMK
. , , AdMK
.
AdMK ,
. ,
MK

,
. SJ-8026 ,
[50], , SJ-8026
.
, HCC Hsp-70
(DCs),
HCC T [51].

4 肝细胞癌的演进

, ,
, , ,
,
.
,
.
,
α5 CD44
uPA
KAI 1 nm23 -H1
syndecan-1 p27 galectin-3
HCC . ,
-1 ,
(MMP)-1 MMP-7 ,
;
, MMP-3 MMP-9
. HCC ,
2 -3 .
MMPs
HCC [52].
, .
, ,
.
Torimura *et al*[53]
: a1, a2, a3, a6
b1 . :
,
,

MMPs , . , . Zhang *et al*[54] , β1 MAP β1 , . , . Frachon *et al*[55] CD31, CD34 BNH9 , , , 29% 47% , 75% 100% . , 3 . , CD31, CD34 BNH9 . , *et al*[56] Angiopoietin 21 (Ang21) Angiopoietin 22(Ang22) : Ang21 mRNA , . Ang22mRNA , . Ang22 . . Ang22 . , , , Ang22 . (VEGF) , [57], , , . *et al*[58] VEGF flk1 flt1 , . VEGF flk1 flt1 ; VEGF , , VEGF flk1/flt1 . (bFGF) , Poon *et al*[59] bFGF , bFGF 0.22 71.2 ng/L , bFGF TNM , . bFGF >10.8 ng/L >5 cm . adiponectin , , HCC , , FGF adiponectin , [60]. [61]: (MDR) , MDR , , Ets-1 c-Met HGF iNOS MDR . , 27(HSP27) , S 2 β-1 [62], HCC [63]. Yasuda *et al*[64] HSP27 (Ser-15, Ser-78, and Ser-82)HSP27 , HSP27 . , HSP27 TNM . , , HSP27 . , HSP27 C , HSP27 . [65], HCC , 70(HSP70) HSP27, Ki-67 , HCC . HCC LOH [66], APC, OGG1 DCC LOH , p53 RB1 LOH . 8p12 HTPAP . 826 bp, NH2 175 , HCC , HTPAP HCC , 8p , [67].

. , , LCM(
,)
,
,
. Endo *et al*[68] [74]. ,
α-, β-, γ- , ,
13
, , , (13 752 kDa
, α-, β-, γ- 11 472 kDa) ,
,
. , γ- . ,
β- .

. , Endo *et al* ,
α-
β-
;
, sLeX
. Zhang *et al*[69]
sLeX
,
,
AFP
. , CK19[70],
osteopontin[71],
COX-2 .
MMPs
, Ozaki *et al*[72]
RT-PCR MMPs
, HGF c-Met
Ets , mRNA
, MMP-1, -3, -7
, MMP-2, -9 .
MMPs HGF Ets-1 ,
,
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, ,
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[73].
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