热休克蛋白90在肝细胞癌中的研究进展

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摘要 肝细胞癌中蛋白质稳态是其生长和转移的基础, Hsp90作为分子伴侣可维持多种促癌分子的稳定性, 并抑制抑癌分子的活性, 使蛋白质合成和降解之间保持平衡, 致使癌细胞在恶劣微环境的持续刺激下依旧可以生存。然而, Hsp90抑制剂因在临床试验中表现出严重的不良反应, 故迄今没有一种抑制剂获得FDA的批准。该篇文章阐述了Hsp90的结构、表达调控、伴侣循环以及Hsp90过表达与肝细胞癌之间的联系, 旨在阐明Hsp90在肝细胞癌发生发展中的作用, 为临床用药提供理论依据。

关键词 Hsp90; Hsp90循环; Hsp90抑制剂; 肝细胞癌

Research Progress of Heat Shock Protein 90 in Hepatocellular Carcinoma

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Abstract In hepatocellular carcinoma, protein homeostasis is the basis of its growth and metastasis. Hsp90, as a molecular chaperone, maintains the stability of various cancer-promoting molecules and inhibits the activity of cancer-inhibiting molecules to maintain a balance between protein synthesis and degradation, so that cancer cells can still survive under the continuous stimulation of harsh microenvironment. However, severe adverse reactions to Hsp90 inhibitors in clinical trials resulted in none of the inhibitors being approved by the FDA. This paper describes the structure, expression regulation, chaperone circulation of Hsp90 and the relationship between Hsp90 overexpression and hepatocellular carcinoma, in order to clarify the role of Hsp90 in the occurrence and development of hepatocellular carcinoma and provide theoretical basis for clinical drug use.

Keywords Hsp90; Hsp90 chaperone cycle; Hsp90 inhibitor; hepatocellular carcinoma

肝细胞癌(hepatocellular carcinoma, HCC)是多个基因组和表观基因组表达失调累积的结果, 由此产生一些过表达信号与异常表达蛋白质[1]。蛋白质合成时, 新生肽链有许多疏水基团暴露在外, 有分子间或分子内聚集的倾向, 蛋白质容易发生错误的折叠[2]。肝细胞癌的蛋白质稳态(proteostasis)是其许多恶性表型的基础, 蛋白质个体的稳定性(protein stability)决定肝细胞癌总体蛋白质稳态[3-4]。分子伴侣(molecular chaperone)可以帮助蛋白质正确折叠、修复或降解错误折叠的蛋白质, 维持蛋白质的稳定性[5]。在肝细胞癌中, 一些伴侣分子经常过表达, 降低错误折叠蛋白质的比例并解聚已经聚集的蛋白质, 使它们免受泛素–蛋白酶体系统的降解, 维持促癌分子的稳定性。

热休克反应首次被发现是在果蝇染色体中, 在

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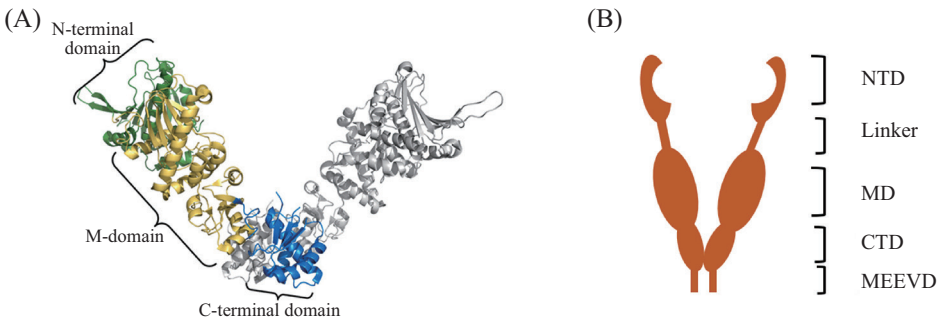
高温环境下热休克蛋白(heat-shock proteins, Hsp)表达增加会导致果蝇染色体特征性膨化。随后发现热休克蛋白几乎存在于所有生物体中, 并作为伴侣分子指导新生肽链按特定的方式正确折叠[6]。而肿瘤细胞在应对热、营养缺乏和氧缺乏等应激反应时, 热休克蛋白会反应性增高, 使恶性肿瘤的蛋白质合成和降解之间保持平衡, 致使肿瘤细胞在恶劣微环境持续刺激下依旧可以生存。热休克蛋白根据其单体分子量从10~100 kDa进行分类, 主要的热休克蛋白家族成员是Hsp100、Hsp90、Hsp70、Hsp60和小Hsp(sHsp)[7]。Hsp90是研究最广泛的热休克蛋白家族成员之一, 有四种亚型, 分别是Hsp90α、Hsp90β、GRP94、TRAP-1, 前两种存在于细胞质中, 后两种分别存在于内质网与线粒体中。应激诱导表达的Hsp90α和组成性表达的Hsp90β是哺乳动物两种主要的亚型, 两者有86%的氨基酸序列相同, 具有高度的同源性[8]。Hsp90在肝细胞癌组织和细胞系中高表达, 维持多种促癌分子的稳定性, 并抑制抑癌分子的活性[9], 最终促进肝细胞的生长和转移。因此, 本篇文章阐述Hsp90的结构、表达调控、伴侣循环以及Hsp90过表达与肝细胞癌之间的联系, 旨在阐明Hsp90在肝细胞癌中的作用, 为临床用药提供理论依据。

1 Hsp90的结构

Hsp90由两个结构相同亚基组成的同二聚体, 每个亚基结构包括三个主要的保守结构域, 即氨基端结构域(amino-terminal domain, NTD)、羧基端结构域(carboxy-terminal domain, CTD)和中间结构域(middle domain, MD)[10](图1)。NTD和MD通过一个长、灵活、带电的连接结构域连接(linker), 该结构域可以调节NTD-MD接触并影响Hsp90的功能。Hsp90的C-端还包含一段MEEVD(Met-Glu-Glu-Val-Asp)结构模体, 该模体可结合含有TPR结构域(tetratricopeptide repeat domains)的共伴侣蛋白。NTD介导Hsp90与ATP的结合; MD主要负责Hsp90与分子伴侣及客户蛋白的结合; CTD则主要参与Hsp90亚基的同源二聚化[11-13]。NTD结合ATP是Hsp90折叠新生肽链所必需的, 当MD没有与底物结合时, Hsp90具有固有的低酶活性, 因此MD具有调节Hsp90 ATP酶的活性作用[14]。

2 Hsp90的表达调控

肿瘤细胞在应对热、营养缺乏和氧缺乏等应激反应时, 热休克因子1(heat shock factor 1, HSF1)会从与Hsp90、共伴侣蛋白p23和含有TPR结构域的免疫亲和素(immunophilin, IMM)形成的抑制复合物中释放出来, 并且会三聚化迁移入核与Hsp90上游的热休克元件(heat shock element, HSE)结合, 诱导Hsp90的表达[15](图2)。到目前为止, 细胞如何感知外界压力情况并将其传递给HSF1的作用机制还不完全清楚[16]。HSF1作为热休克反应最主要的转录调控因子可以受到多种信号分子和通路的调控, 例如, 谷氨酰胺转移酶2通过其蛋白二硫异构酶活性促进HSF1上Cys36和Cys103分子间二硫键的形成, 从而促进HSF1三聚体的形成; MEK1/2可以磷酸化HSF1上的Ser326, 以增强HSF1的核易位; 相反, AMPK介导的Ser121位点磷酸化抑制HSF1核易位[17]。由mTOR介导的HSF1磷酸化会触发HSF1驱动的转录, 而转录产物Hsp90又可以正反馈激活mTOR通路, 最终促进肿瘤进展和转移[18]。



A: Hsp90的结构[10]; B: Hsp90的示意图。

A: the structure of Hsp90[10]; B: schematic representation of the Hsp90 structure.

图1 Hsp90蛋白质结构

Fig.1 Protein structure of Hsp90

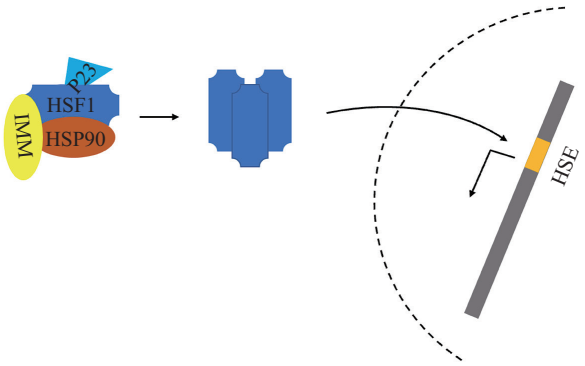


图2 HSF1从抑制复合物中释放出来并三聚化迁移入核的示意图

Fig.2 Schematic diagram of HSF1 releasing from the inhibitory complex and trimeric migration into the nucleus

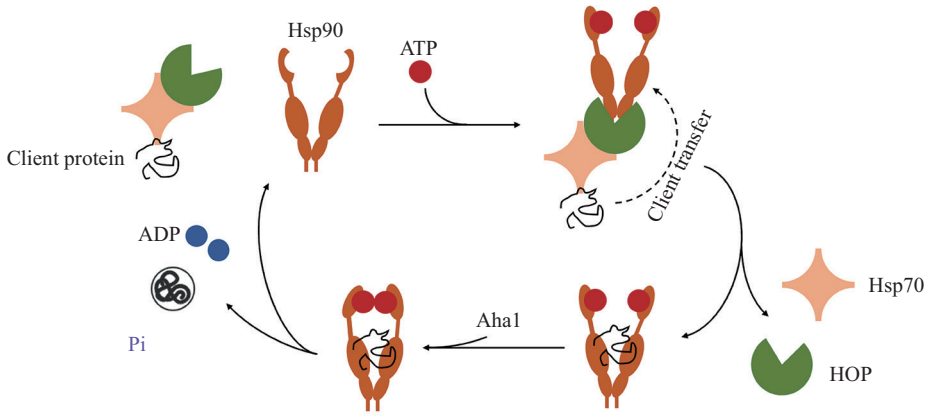


图3 Hsp90伴侣循环的示意图

Fig.3 Schematic representation of the Hsp90 chaperone cycle

3 Hsp90伴侣循环

热休克蛋白Hsp90的主要功能是帮助新生多肽正确折叠、修复或降解错误折叠的蛋白质，促进数百种蛋白质底物的成熟，依赖Hsp90的客户蛋白通过Hsp90伴侣循环被正确地折叠和成熟[19]。大量共伴侣蛋白(Co-Chaperones)通过蛋白质–蛋白质相互作用来调节Hsp90二聚体的构象变化，这些共伴侣蛋白包括Hsp70、Hsp40、HOP(Hsp70/Hsp90 organizing protein)、Cdc37(cell division cycle 37)、Aha1(activator of Hsp90 ATPase homolog 1)与P23，它们招募特定的客户蛋白至Hsp90同二聚体，从而介导蛋白质底物的成熟与Hsp90的构象循环[20]。

Hsp90伴侣循环由三个关键步骤组成：①由ATP/ADP结合控制的Hsp90同二聚体的构象循环；②客户蛋白、伴侣分子与共同伴侣蛋白形成超级复合物；③成熟客户蛋白的释放(图3)。起初，Hsp90同二聚体以开放构象“V”形存在，未折叠的客户蛋白、Hsp70和Sti1/Hop形成了一个与开放构象Hsp90结合的三元复合物。Hsp90的羧基端与HOP相互作用，客户蛋白转移到中间结构域，等待Hsp90的氨基端结构域处于关闭状态。而Hsp90构象循环是由ATP/ADP循环驱动的，ATP与氨基端结合后，Aha1作为唯一能强烈刺激Hsp90的ATP酶活性的共同伴侣，促进Hsp90 ATP酶活性并使氨基端发生二聚化，形成一个紧密封闭的构象。当处于封闭状态时，Hsp90将客户蛋白限制在其中。当ATP水解释放能量时，客户蛋白同时折叠成活性立体结构。与Hsp90结合的ADP又使Hsp90氨基端重新回到开放构象进入下一个客户蛋白折叠周期，与此同时成熟的客户蛋白被释放出来，并且与伴侣分子分离[21-27]。

在此期间，一些共同伴侣，如Cdc37与Hsp90氨基端结合，抑制ATP酶的活性，影响ATP结合时间；P23与Hsp90氨基端相互作用，形成超异质蛋白复合物，稳定闭合构象，调节反应周期的进程[22]。另外有研究表明，肿瘤细胞Hsp90存在于多伴侣复合体中，并且具有更强的ATP酶活性[28]。

4 Hsp90在肝细胞癌中的作用

Hsp90作为伴侣蛋白维持肝癌细胞中异常表达客户蛋白的稳定性, 从而促进肝细胞癌的进展(表1和图4)。Hsp90在肝癌组织中表达上调并且Hsp90的高表达与较差的临床病理特征, 包括静脉浸润、晚期TNM分期和高病理分级相关[29]。Hsp90可以通过囊泡运输和外泌体介导的分泌被释放到细胞外, 分泌到细胞外的Hsp90被称为胞外热休克蛋白90(extracellular heat shock protein-90, eHsp90)。eHsp90在肝细胞癌细胞系BEL-7404(P53突变体)和Huh7(P53突变体)细胞中显著上调[30], P53突变体增强了Hsp90α囊泡运输和外泌体介导的分泌[31]。eHsp90α又可以通过与细胞外基质蛋白或细胞表面受体的相互作用来增强细胞的运动性, 并支持癌症转移。血浆Hsp90α在区分AFP阴性和限制性肝癌患者方面具有极高的准确性, 并且甲胎蛋白与血浆Hsp90α联合辅助诊断肝细胞癌, 提高了诊断的敏感性和特异性[32-33]。

4.1 对肝癌细胞迁移、入侵和转移的影响

肝细胞癌是一种高血管性的侵袭性肿瘤, 经常发生肝外和肝内转移, 预后较差, 特别是血管侵犯门静脉是肝细胞癌肝内转移的一个特殊特征[34-36]。阐明HCC转移的机制将影响HCC患者的生存率和预后。在有血管侵犯的肝细胞癌中, Hsp90家族蛋白及其共同伴侣在肿瘤组织中的表达明显高于相应的癌旁组织, 但在无血管侵犯的肝细胞癌中, 这种差异不显著[37]。又有研究表明, Hsp90β与EMT诱导转录因子Twist1相互作用, 促进Twist1去泛素化和核易位, 导致肝细胞癌中内皮细胞依赖性的血管生成[38]。而Hsp90高表达也可以促进上皮–间充质转化, 促进间质标志物Vimentin表达, 降低上皮标志物E-cadherin表达, 抑制肿瘤干细胞凋亡, 从而促进肝癌细胞的侵袭[39]。

肝细胞癌的细胞迁移受到肌动蛋白细胞骨架重排和细胞黏附协调变化的调节[40]。肌动蛋白可以通过聚合和解聚的状态, 形成丝状肌动蛋白(F-actin)和球状肌动蛋白(G-actin)两种形式, F-actin的分布对于细胞迁移非常重要[41-42]。在乙型肝炎病毒(HBV)感染的高侵袭性肝癌中, HBV X蛋白与钙调蛋白相互作用, 将Hsp90从钙调蛋白中释放出来, 接着Hsp90与LIMK1结合, 诱导其二聚化以增强LIMK1的活性和稳定性, 导致F-actin的积累, 促进肝细胞癌细胞的迁移[43]。Hsp90去乙酰化修饰也可以调节肌动蛋白的聚合, 去乙酰化酶Sirt2诱导Hsp90泛素化降解, 通过LIMK1/cofilin通路, 抑制肌动蛋白聚合[44]。DIAPH3是肌动蛋白细胞骨架的主要调节因子, 其与Hsp90相互作用, 正向调控HCC细胞的生长、迁移、集落形成、上皮–间充质转化[45]。由此可见, Hsp90通过调控肝癌的上皮–间充质转化、血管生成以及肌动蛋白细胞骨架重排, 最终促进肝癌细胞的侵袭转移。

4.2 对肝癌细胞活力的影响

在肝细胞癌中, 一些与增殖相关的信号蛋白经常异常表达, Hsp90通常与这些异常表达信号分子直接作用, 使其免受蛋白酶体的降解, 进而影响肝细胞癌细胞活力。例如, Bclaf1是一种转录因子, 在肝细胞癌中经常上调并可促进肝细胞癌细胞系HepG2和Huh7细胞增殖; Hsp90α的羧基端结构域与Bclaf1相互作用, 维持Bclaf1的稳定性, 使Bclaf1在肝癌中发挥增殖作用[46]。有研究表明, 单独使用Hsp90特异性抑制剂处理HepG2细胞就会导致细胞增殖减少[47]。

自噬在肝细胞癌中抑癌或促癌作用一直是研究的热门领域。肝细胞癌快速增殖使其能量需求不断增加, 因此分子伴侣介导的自噬(chaperone-mediated autophagy, CMA)作为应对长期刺激的反应而被激活, 并且CMA从起始的抑癌作用会转变为促癌作用, 从而帮助癌细胞在营养匮乏的微环境中生存[48]。正如前言所述, Hsp90的表达也会随着肿瘤细胞的应激而升高。在自噬中发挥重要作用的分子(例如Akt、Beclin1、Ulk1、LAMP-2A)也被报道是Hsp90的客户蛋白[49]。这表明在肝癌晚期, Hsp90的高表达可促进自噬发生并且发挥促癌作用。但有趣的是, Hsp90又可以与客户蛋白相互作用, 使其客户蛋白免受自噬途径的降解, 进而增强肝癌细胞的活力、迁移和侵袭能力[50]。

肝细胞癌的代谢重编程目的是维持癌细胞增殖和长期存活, 有研究指出, Hsp90在调节糖酵解和氧化磷酸化之间的微妙平衡中发挥着重要作用, 以应对肿瘤微环境的变化, 促进肿瘤进展[51]。Hsp90可以通过Hsp90依赖的信号通路来间接调节代谢重组, 或者直接控制某些代谢酶的稳定性、构象和功能活性。例如, M2-型丙酮酸激酶(pyruvate kinase M2, PKM2)是有氧糖降解的关键酶, 可以促进肿瘤细胞的增殖和合成代谢; Hsp90和PKM2可以形成蛋白复合物, 直接介导Hsp90诱导PKM2的thr328磷酸化, 促进肝癌细胞的有氧糖酵解和增殖, 并抑制肝癌细胞

表1 Hsp90在肝细胞癌中的作用

Table 1 The role of Hsp90 in hepatocellular carcinoma

肝癌细胞系 Cell lines of HCC	功能机制 Mechanism of action	生物学功能 Biological function	参考文献 References
HepG2	The expression levels of PCNA and Bcl-2 are increased	Hsp90 induced cell proliferation	[47]
HepG2, Huh7	Bclaf1 interacts with the C-terminal domain of Hsp90α to protect it from proteasomal degradation	Promote cell proliferation	[46]
MHCC97-L, MHCC97-H	A20, a dominant-negative regulator of NF-κB, forms a complex with Hsp90 and causes the disassociation of the A20/Hsp90 complex via downregulation of HSP90	Hsp90 increased the resistance of HCC cells to sorafenib	[9]
Hep3B, Huh7	Hsp90 can bind to PKM2 and subsequently increased PKM2 abundance	Hsp90 potentiates the glycolysis and proliferation, reduces the apoptosis and thus enhances the growth of HCC cells	[52]
HEL-7404, Huh-7, Hep3B, QGY-7701, MHCC97	Hsp90 interacts with HMGCR and up-regulates its protein expression by inhibiting protein degradation	Hsp90 promotes the growth, migration and metastasis of HCC cells	[30]
HepG2, Huh7	The stability of DNA-PKcs depends on Hsp90α N-terminal nucleotide binding domain (NBD) in HCC cells	Promote the growth of HCC cells	[53]
HepG2	HBx interferes with the interaction between CaM and Hsp90 to facilitate the interaction between Hsp90 and LIMK1	Enhances liver cancer cell migration	[43]
HepG2, Huh7	Hsp90 inhibits the autophagic degradation of the DDX5 protein	Increases cellular viability, migration, and invasion in HCC cells	[50]
Hep3B, HepG2	Hsp90 inhibits the ubiquitination and proteasomal degradation of HIF-1α	Hsp90 induces the proliferation and inhibits the apoptosis of HCC cells	[29]
PLCPRF-5, MHCC-97L, SMMC-7721, MHCC-97H	Hsp90β interacts with Twist1 and promotes its deubiquitination and stabilization to nuclear translocation and enhances the VE-cadherin promoter activity	Hsp90β promotes aggressive vasculogenic mimicry via epithelial-mesenchymal transition	[38]
HEL-7404, Hep3B, HepG2, QGY-7701	DIAPH3 activates the β-catenin/TCF signaling by binding Hsp90 and disrupting the interaction between GSK3β and Hsp90	Promotes the growth, migration and metastasis of HCC cells	[45]

PCNA: proliferating cell nuclear antigen; Bcl-2: B-cell lymphoma 2; Bclaf1: B-celllymphoma 2-associated transcription factor 1; PKM2: pyruvate kinase M2; HMGCR: 3-hydroxy-3-methylglutaryl-CoA reductase; DNA-PKcs: DNA-dependent protein kinase catalytic subunit; CaM: calmodulin; LIMK: cofilin-LIM kinase; HIF1: hypoxia-inducible factor 1; DIAPH3: diaphanous-related formin 3; GSK3β: glycogen synthase kinase 3β.

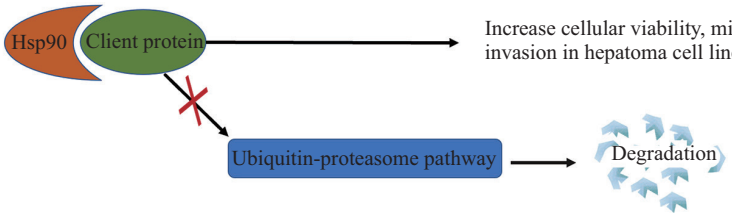


图4 Hsp90在肝癌中的作用机制示意图

Fig.4 Schematic representation of the mechanism of Hsp90 in hepatocellular carcinoma

的凋亡[52]。

总的来说, 随着肝细胞癌进展, Hsp90会应激性表达增加并协调肝癌的各种生物学行为(比如自噬、代谢重构等), 最终使肝癌细胞能在缺氧、营养缺乏等恶劣的微环境中生长。

5 热休克蛋白抑制剂在肝细胞中的作用

Hsp90的一些客户蛋白是肝细胞癌中许多信号通路的关键蛋白, 所以Hsp90抑制剂可以同时靶向多个肝细胞癌相关的通路。理论上与单靶点的治疗药物相比, Hsp90抑制剂对肝细胞癌有更好的抗肿瘤作

用。其中多数抑制剂靶向Hsp90氨基端结构域的ATP结合位点, 包括格尔德霉素及其衍生物17-AAG、17-DMAG、IPI-493、IPI-504与WK88-1, 根赤壳菌素及其衍生物VER-22296、AT13387、STA-9090与NVP-AUY922[23]。但由于严重的不良反应, 比如肝毒性和抑制Hsp90 ATP酶功能反馈性触发HSF1的释放, 使抑制剂的治疗效果差, 因此到目前为止还没有获得FDA批准的氨基端抑制剂。与此同时许多研究小组开始开发羧基端抑制剂, 其中最具代表的化合物是新生霉素, 其第一期临床试验已在非癌症的患者中进行[54]。Hsp90伴侣循环机制的功能解剖突出了破坏Hsp90伴侣循环是寻找治疗靶点的思路。例如通过靶向共伴侣蛋白, 如HOP、Cdc37、p23等; 靶向客户蛋白与共伴侣蛋白的结合; 靶向Hsp90与共伴侣蛋白的结合[55], 其中靶向Hsp90-共伴侣的PPI抑制剂已经取得了很大的成功[56]。关于靶向Hsp90-共伴侣蛋白–客户蛋白作为癌症治疗靶点的有效性, 还有待进行更多的探索[57]。

6 结语和展望

Hsp90会随着肝癌的进展而表达增加, 最终促进肝细胞癌的生长和转移, 其是诊断、治疗和监测肝细胞癌非常有前景的分子靶点。对Hsp90生物功能机制的深入研究, 可能会有望在临床中改善肝癌患者的预后。但Hsp90抑制剂严重的毒副作用, 限制了其在临床中的应用。因此寻找Hsp90抑制剂的替代疗法变得尤为重要。然而Hsp90在正常的细胞中大量存在, 占细胞总蛋白的1%~3%[28], 区分致瘤性Hsp90和正常功能的Hsp90也是目前我们应对的难题。总之探究Hsp90与肝细胞癌发生发展之间的联系, 对于改善肝癌患者的预后具有重要的意义。

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