

Dysregulation of apoptosis in hepatocellular carcinoma cells

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Abstract

Hepatocellular carcinoma (HCC) is a major health problem, being the sixth most common cancer world-wide. Dysregulation of the balance between proliferation and cell death represents a pro-tumorigenic principle in human hepatocarcinogenesis. This review updates the recent relevant contributions reporting molecular alterations for HCC that induce an imbalance in the regulation of apoptosis. Alterations in the expression and/or activation of p53 are frequent in HCC cells, which confer on them resistance to chemotherapeutic drugs. Many HCCs are also insensitive to apoptosis induced either by death receptor ligands, such as FasL or TRAIL, or by transforming growth factor-beta (TGF- β). Although the expression of some pro-apoptotic genes is decreased, the balance between death and survival is dysregulated in HCC mainly due to overactivation of anti-apoptotic pathways. Indeed, some molecules involved in counteracting apoptosis, such as Bcl-X_L, Mcl-1, c-IAP1, XIAP or survivin are over-expressed in HCC cells. Furthermore, some growth factors that mediate cell survival are up-regulated in HCC, as well as the molecules involved in the machinery responsible for cleavage of their pro-forms to an active peptide. The expression and/or activation of the JAK/STAT, PI3K/AKT and RAS/ERKs pathways are enhanced in many HCC cells, conferring on them resistance to apoptotic stimuli. Finally, recent evidence indicates that inflammatory processes, as well as the epithelial-mesenchymal transitions that occur in HCC cells to facilitate their dissemination, are related to cell survival. Therefore, therapeutic strategies to selectively inhibit anti-apoptotic signals in liver tumor cells have the potential to provide powerful tools to treat HCC.

INTRODUCTION

Apoptosis represents a physiological way to eliminate excess cells during both liver development and regeneration^[1]. Indeed, insufficient apoptosis has been associated with development and progression of tumors of the liver and the biliary tree^[1,2]. Hepatocellular carcinoma (HCC) is a major health problem, being the sixth most common cancer world-wide^[3]. It is a heterogeneous tumor commonly associated with chronic liver diseases which frequently culminate in cirrhosis, such as alcoholic cirrhosis and chronic hepatitis B and C infections. During recent years, major advancements in the knowledge of this complex disease have been reported^[3]. This review is an effort to update the recent relevant contributions reporting molecular alterations for HCC that induce an imbalance in the regulation of apoptosis.

THE P53 PATHWAY

Among the most common alterations observed in HCC are mutations in the p53 tumor suppressor gene (*TP53*)^[4]. Different chemotherapeutic agents require p53 to induce apoptosis. Indeed, tumors with a disruption in the p53 pathway are generally resistant to chemotherapy. The presence of specific mutational hotspots in *TP53* in different types of human cancer implicates environmental carcinogens and endogenous processes. In this sense, somatic mutations at the third base in codon 249 of *TP53* in HCC have been related to exposure to aflatoxin B1 (AFB1), in association with HBV infection^[4]. Chronic infection with HBV and HCV viruses and exposure to oxidative stress, including hemochromatosis or inflammation, induce damage in the DNA and mutations in cancer-related genes, including *TP53*. Thus, it would

seem plausible that p53 mutation might operate in either HCC initiation or progression, depending on the context. However, adenoviral delivery of p53 recombinant DNA into mice models bearing hepatocellular carcinomas did not apparently suppress tumor growth^[5]. De-Pinho *et al* in a recent work^[6] have helped to clarify this point. They have demonstrated that the effect of p53 loss in hepatocellular carcinoma that is associated with chronic liver disease is dependent on cellular context, in particular intact or dysfunctional telomeres, and they have hypothesized that a decreased p53 function might contribute to hepatocyte survival in the presence of telomere-induced chromosomal instability.

THE TGF- β PATHWAY

The transforming growth factor-beta (TGF- β) family of cytokines plays a physiological role during embryonic development and its misregulation can result in tumorigenesis^[7]. TGF- β -1 is an important regulatory suppressor factor in hepatocytes, inhibiting proliferation^[8] and inducing cell death^[9]. Paradoxically, TGF- β may also modulate other pro-tumorigenic processes, such as cell invasion, immune regulation or microenvironment modification^[7]. Blocking TGF- β up-regulates E-cadherin and reduces migration and invasion of hepatocellular carcinoma cells^[10]. Furthermore, liver tumors expressing late TGF- β -responsive genes (anti-apoptotic and metastatic) display a higher invasive phenotype and increased tumor recurrence when compared to those that show an early TGF- β signature (suppressor genes)^[11]. Indeed, the escape from the anti-proliferative and pro-apoptotic actions of TGF- β might be a prerequisite for hepatocarcinoma progression^[12].

Disruption of the TGF- β pathway occurs in HCC^[13] and might cause dysregulation of apoptosis. In favour of this hypothesis, recent studies have demonstrated that overexpression of SMAD3 reduces susceptibility to develop hepatocarcinoma, by sensitizing hepatocytes to apoptosis through down-regulation of Bcl-2^[12]. However, perturbations at receptor or SMAD levels do not appear to be as frequent as they are in colon or pancreatic cancer^[13] and expression of TGF- β is up-regulated in a great percentage of HCC patients^[11,13]. Thus, other possible ways to disrupt TGF- β signalling might exist and they remain to be explored. Interestingly, Mishra *et al* have recently demonstrated that HCC might arise from loss of TGF- β signalling adaptor protein embryonic liver foldrin (ELF), a crucial Smad3/4 adaptor^[14,15]. HCC cells might also overexpress a specific set of microRNAs (miRNAs) that would allow the escape from TGF- β -induced apoptosis^[16,17]. Furthermore, recent results have indicated that TGF- β might play a dual role in controlling apoptosis in hepatocytes and hepatoma cells. On one hand, it induces cell death, but on the other it could activate anti-apoptotic signals, the epidermal growth factor receptor (EGFR) being required for this effect^[18-20]. Indeed, EGF is an important survival signal for TGF- β -induced apoptosis in hepatocytes^[21]. The enzyme phosphatidylinositol 3-kinase (PI3K) mediates the effect of EGF on TGF- β -induced death by acting upstream from the mitochondrial

changes, probably counteracting TGF- β -induced oxidative stress^[22]. The autocrine loop of EGFR activated by TGF- β in hepatoma cells would require a high activity of TACE/ADAM17^[20], the metalloprotease responsible for shedding of the pro-tumor necrosis factor (proTNF- α) that it is also necessary for shedding of the EGF family of growth factors^[23]. Although the possible role of an increased expression of TACE/ADAM17 in the development of human hepatocellular carcinoma (HCC) has been barely studied, a recent report indicates that the quantities of ADAM17 mRNA vary among different pathological types of HCC, but are significantly higher in poorly differentiated HCC than in well or moderately differentiated HCC^[24]. Overexpression of TACE/ADAM17 might confer an advantage on HCC cells by impairing TGF- β -induced apoptosis through transactivation of the EGFR. Concluding, HCC cells might impair the suppressor arm in TGF- β -signalling, with enhancement of the response to this factor in terms of tumor progression and invasion (Figure 1).

THE DEATH RECEPTOR PATHWAYS

HCCs show resistance to apoptosis mediated by several death receptors. The majority of the HCCs show one or more alterations in the Fas pathway molecules, which inhibit Fas-mediated apoptosis^[25]. The status of Fas and Fas ligand (FasL) expression can predict HCC recurrence^[26]. Loss of response to Fas in HCC cells may be produced either by down-regulation of *Fas* expression^[25,27], concomitant with decreased expression of downstream molecules, such as FADD or FLICE^[27], or by up-regulation or over-activation of molecules that counteract its pro-apoptotic effect, including nuclear factor-kappaB (NF- κ B), Bcl-2 or Bcl-Xl^[28-30]. The cellular FLICE/caspase-8-inhibitory protein (cFLIP), an intracellular inhibitor of caspase-8 activation, is constitutively expressed in human HCC cell lines and displays higher levels in HCC tissues than in nontumor liver tissues^[31]. It has also been described that HCC tissues show overexpression of BRE, an antiapoptotic protein that binds to the cytoplasmic domains of tumour necrosis factor (TNF) receptor-1 and Fas, attenuating death-receptor initiated apoptosis^[32]. Furthermore, it has been suggested that extracellular factors might counteract Fas-induced apoptosis in HCC cells. Indeed, hepatocyte growth factor (HGF), through activation of the PI3K/AKT pathway, suppresses Fas-mediated cell death in human HCC cell lines, by inhibiting Fas-death-inducing signalling complex (DISC) formation, especially FADD and caspase 8 interaction^[33] (Figure 2).

TNF-related apoptosis-inducing ligand (TRAIL) selectively induces apoptosis in various transformed cell lines but not in almost normal tissues^[34]. HCC cells constitutively express TRAIL mRNA and protein, but there are contradictory and confusing data about the expression of the different TRAIL receptors in HCC cells and tissues^[35-37]. Certain evidence indicates that most HCC cells are insensitive towards TRAIL-mediated apoptosis, suggesting that the presence of mediators can inhibit the

TRAIL cell-death-inducing pathway in HCC^[36,37]. It has been reported that hepatitis B virus core protein inhibits TRAIL-induced apoptosis by blocking the expression of the TRAIL receptor 2 (TRAIL-R2/DR5)^[38]. Overactivation of NF- κ B and Bcl-X_L in HCC cells might also restrain the TRAIL-mediated apoptosis^[39]. After an initial debate about the potential liver toxicity of TRAIL in freshly isolated human hepatocytes^[37], there is a recent interest in the development of new therapeutic approaches that can sensitize HCC cells to TRAIL-induced apoptosis. Indeed, it has been proposed that TRAIL, in combination with chemotherapeutic agents, may have potential in the treatment of HCC^[40]. Of clinical relevance, proteasome inhibitors and histone deacetylase (HDAC) inhibitors might sensitize HCC cells but not primary human hepatocytes for TRAIL-induced apoptosis^[41,42].

ALTERATIONS IN THE EXPRESSION OR FUNCTION OF APOPTOSIS REGULATORY PROTEINS

It is worthy of note that many of the genetic alterations observed in HCC lead to an imbalance in the pro- and anti-apoptotic members of the Bcl-2 family^[43]. Bcl-X_L is overexpressed in a great percentage of HCCs^[44], and so is Mcl-1^[45]. In contrast, pro-apoptotic members of the family, such as Bax or Bcl-X_s are down-regulated in HCC with dysfunction in the p53 pathway^[46]. Furthermore, recent results have indicated that some pro-apoptotic members of the BH-3-only family, such as Bid, show decreased expression in HCC related to hepatitis B or C infection^[47].

Recent investigations have revealed that nearly 90% of clinical tumors from advanced HCC patients express high levels of X-linked inhibitor-of-apoptosis protein (XIAP), a well known inhibitor of caspases. Studies in established HCC cell lines with different metastatic capabilities indicated a correlation of metastasis with resistance to apoptosis and increased expression of XIAP^[48]. Interestingly, it had previously been suggested that XIAP might also function as a cofactor in TGF- β signalling^[49]. Thus, overexpression of XIAP might confer resistance to the apoptotic effects of TGF- β , allowing HCC cells to respond to this cytokine in terms of migration and invasion. Genome-wide analyses of tumors in a mouse model of liver cancer and in HCC tissue have recently revealed a recurrent amplification in a region of human chromosome 11q22, delineating *LAP1*, the known inhibitor of apoptosis, as one of the candidate oncogenes in the amplicon^[50]. Survivin, another member of the family of inhibitor of apoptosis proteins, is also overexpressed in HCC cell lines and tissues^[51,52] and it has been suggested that it might play a pivotal role in metastasis^[53]. Survivin might play an important role in progression of HCC not only by inhibiting apoptosis^[54], but also by promoting cell proliferation^[51] and may be positively correlated with high risk of disease recurrence and poor prognosis^[55]. Concluding, HCC cells show an imbalance

in the expression of pro- and anti-apoptotic proteins, which favours cell survival (Figure 2).

OVERACTIVATION OF SURVIVAL SIGNALS IN HCC CELLS

Some autocrine signal activators, such as EGF receptor (EGFR) ligands, might protect liver tumor cells from apoptosis induced by stress, physiological factors or pro-apoptotic drugs^[56]. Dysregulation of growth factor signalling, including EGF and IGF-1 pathways, has been well established in human HCCs^[57,58]. Viral hepatitis infections might contribute to the enhancement of the expression of EGFR ligands^[59]. The tyrosine kinase p60^{c-src} is also overactivated in hepatoma cells^[56,60] that protect themselves from death stimuli^[61], and it accounts in a large part for the desensitization of liver tumor cells to TRAIL and CD95. Interestingly, blockade of EGFR or c-Src in primary hepatocytes only marginally increases cell death^[56,61], which indicates that both tyrosine kinases are critical effectors that specifically protect liver cancer cells from death stimuli, providing a weak point in cancer cells for a potential therapeutic approach.

Signal transducer and activator of transcription (STAT) proteins become activated by tyrosine kinases in response to cytokines and growth factors. It has been reported that suppressor of cytokine signalling (SOCS)-1 and (SOCS)-3, negative regulators of the JAK2-STAT signalling pathway, are silenced by methylation in human hepatoma cell lines and HCC tissues, which leads to constitutive activation of STAT3 in these cells^[62,63]. Deletion of the (*SOCS*)-3 gene in hepatocytes promotes the activation of STAT3, resistance to apoptosis and accelerated proliferation, resulting in enhanced hepatitis-induced hepatocarcinogenesis^[64]. In addition, hepatitis C virus (HCV) core protein exerts an inhibitory effect on (*SOCS*)-1 gene expression^[65]. Hepatitis viruses also activate STAT-3 *via* oxidative stress^[66-68], which might contribute to cellular transformation^[69]. Abrogation of constitutive STAT3 activity sensitizes human hepatoma cells to apoptosis induced by TRAIL or drugs^[70,71].

The PI3K/Akt pathway is also altered in HCC. The expression of the *PTEN* gene product is reduced or absent in almost half of HCCs and hepatocyte-specific abrogation of *PTEN* expression in mice results in the development of HCCs^[72]. Recent results have indicated that the expression of a negative regulator of PI3K (phosphatidylinositol-3-kinase interacting protein I: PIK3IP1) is reduced in most cases of human HCC, pointing to a tumor suppressor-like function for this protein^[73]. Interestingly, hepatic overexpression of PIK3IP1 negatively regulates PI3K activity in the tissue and suppresses the development of HCC^[73].

Overexpression of Ras proteins is frequently observed in HCC^[74], at least in part due to epigenetic silencing of inhibitors of the Ras pathway^[75]. Furthermore, it has been reported that the expression of different ERK inhibitors, such as the Spred family of Ras/ERK inhibitors or the dual-specificity phosphatase-1 (DUSP1), is dysregulated in

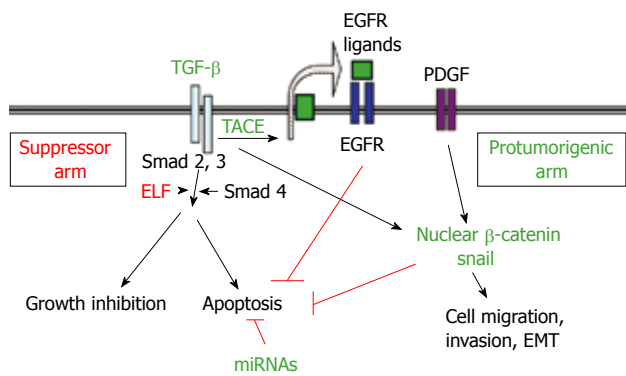


Figure 1 Dysregulation of the TGF- β pathways in HCC cells favours its pro-tumorigenic activities. In red, molecules whose expression is down-regulated; in green, molecules either up-regulated or overactivated. See text for details.

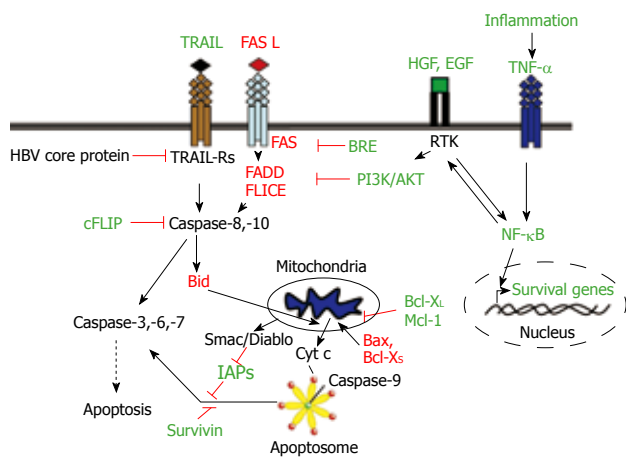


Figure 2 Alterations in the expression or functions of death receptor pathways and apoptosis regulatory proteins in HCC cells. In red, proteins either down-regulated or inactivated; in green, proteins either up-regulated or overactivated. See text for details.

HCC^[76,77]. Activated *RAS* oncogene collaborates with the hepatitis B virus HBx protein to transform cells by suppressing HBx-mediated apoptosis^[78]. Thus, dysregulation of the Ras pathway might also be playing a role in balancing pre-neoplastic hepatocytes towards survival in HBV- or HCV-mediated HCC.

In summary, different molecular alterations may contribute to an enhancement of anti-apoptotic signals in HCC cells that allow them to survive pro-apoptotic stimuli (Figure 3).

LIVER INFLAMMATION AND RESISTANCE TO APOPTOSIS

A link between inflammation and liver cancer was suspected some years ago, but the precise mechanisms are just beginning to be understood^[79]. Recent experimental data support the hypothesis that inflammation promotes carcinogenesis and that NF- κ B signalling is at the heart of such inflammation^[79]. Different studies have implicated members of the NF- κ B/Rel family in both HBV- and HCV-induced neoplastic development of the liver^[80].

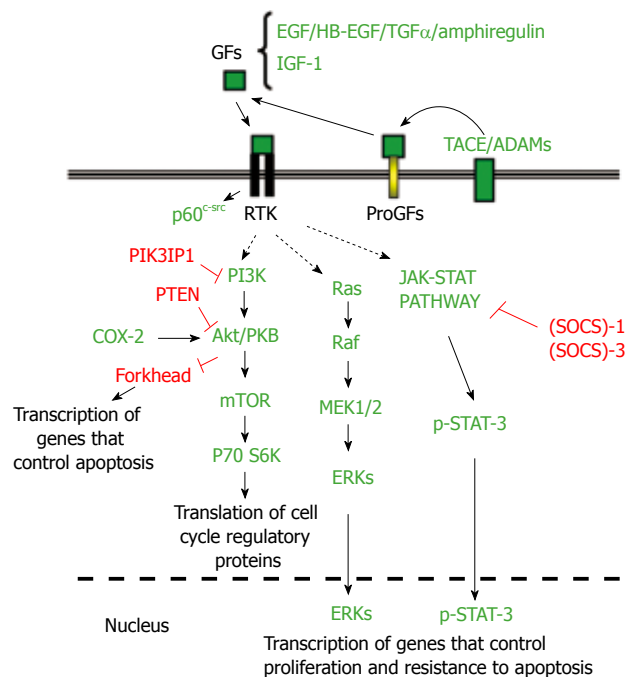


Figure 3 Overactivation of survival signals in HCC cells. In red, proteins either down-regulated or inactivated; in green, proteins either up-regulated or overactivated. See text for details.

Several mechanisms have been proposed for activation of NF- κ B by the hepatitis virus. Overall, inflammatory hepatitis might activate NF- κ B by the concerted action of cytokines, such as TNF- α , chemokines or interleukins, and viral proteins, which likely will promote cell survival of pre-cancerous hepatocytes^[80]. Furthermore, a correlation between EGFR ligands and NF- κ B activity has been provided by studies in transforming growth factor-alpha (TGF- α)/c-Myc mice. Indeed, an important role for NF- κ B in inhibiting c-Myc-induced apoptosis was found essential for hepatocarcinogenesis^[81]. Two pro-survival NF- κ B targets are an antiapoptotic member of the Bcl-2 family, Bcl-X_L, and a member of the caspase inhibitors, XIAP, which are frequently overexpressed in human HCCs, as commented above^[44,48]. Interestingly, the NF- κ B/Bcl-X_L/XIAP axis potentially counteracts the TGF- β -induced apoptosis^[82] and exerts a general cytoprotective role on preneoplastic hepatocytes^[83]. Recent results also link NF- κ B to the increase in the autocrine expression of EGF receptor ligands, such as TGF- α , in hepatocytes and hepatoma cells^[84,85]. In summary, overactivation of the NF- κ B pathway might generate resistance to apoptosis, through different mechanisms, in HCC cells (Figure 2).

Many epidemiological studies demonstrate that treatment with non-steroidal anti-inflammatory drugs (NSAIDs) reduces the incidence and mortality of certain malignancies, especially gastrointestinal cancer^[86]. The cyclooxygenase (COX) enzymes are well known targets of NSAIDs. Overexpression of COX-2 in HCC cells increases proliferation and survival through Akt activation^[87]. Accordingly, recent evidence indicates that selective inhibition of COX-2 in HCC cells leads to a marked induction of apoptosis and inhibition of proliferation and, thus, may offer therapeutic and preventive poten-

tial in human hepatocarcinogenesis^[88]. COX-2 inhibitors might induce apoptosis signalling in HCC cells via death receptors and mitochondria^[89]. Recent data have demonstrated that simultaneous inhibition of PI3K/Akt/mTOR and COX-2 activity in *in vitro* models causes massive apoptosis of neoplastic hepatocytes^[90].

EPITHELIAL-MESENCHYMAL TRANSITIONS AND APOPTOSIS RESISTANCE

During later stages in the development of liver tumors, a loss in cell-cell contacts and the acquisition of fibroblast-like phenotype is observed. This phenomenon, known as epithelial-to-mesenchymal transition (EMT), might contribute to increasing the migratory and metastatic capabilities of the cells^[91]. Cytokines, such as TGF- β and extracellular matrix molecules are thought to fundamentally contribute to the microenvironmental interaction between stromal and malignant cells, and provide the basis for a broad repertoire of epithelial transdifferentiation. Interestingly, EMT of liver cells also results in enhanced resistance to apoptosis^[92,93], probably due to up-regulation of *SNAIL*, the gene that codifies for Snail, a repressor of E-cadherin expression that also has effects on cell homeostasis, inhibiting the cell cycle and preventing cell death^[94] (Figure 1).

A high percentage of human HCCs show high levels of β -catenin^[95,96], either through stabilizing mutations of the β -catenin or overexpression of *FZD*, therefore favouring the intracellular accumulation of the protein^[95]. Furthermore, certain evidence indicates that TGF- β might induce nuclear β -catenin accumulation, through induction of PDGF signalling^[97] (Figure 1). β -catenin expression leads to elevated EGFR levels in hepatocytes and immunohistological analysis shows high correlation between the expression of nuclear/cytoplasmic β -catenin and EGFR in most hepatoblastomas^[57]. β -catenin also participates in homotypic cell-cell interactions through its association with E-cadherin. Thus, β -catenin accumulation in HCC cells might contribute to impairing E-cadherin expression, mediating the EMT process, migration and survival. Indeed, there is evidence suggesting that up-regulation of *CTNNB1*, the gene encoding for β -catenin, also contributes to the enhancement of hepatocellular carcinoma cell survival^[98].

In summary, a significant number of relevant molecular mechanisms altered in HCC initiation and progression are compromising the balance between survival and apoptotic signals in the pre-neoplastic hepatocytes. Some physiological pro-apoptotic molecules are down-regulated or inactivated in HCC, but the balance between death and survival is mainly disrupted due to overactivation of anti-apoptotic signals. Therefore, liver cancer cells might show stronger requirements of these intracellular pathways to survive. The absence of standard systemic therapy for advanced cases of HCC has changed with the recent positive randomized trial testing the multikinase sorafenib, which represents a breakthrough in the management of this neoplasm^[3,58]. Interestingly, sorafenib induces tumor

cell apoptosis in HCC cells, through, at the least, inhibiting the RAF/MEK/ERK pathway^[99]. Similar situations might be found with other multikinase inhibitor drugs that are on the way towards approval for HCC therapy^[58,100]. Of relevance here is certain evidence indicating that erlotinib-induced growth inhibition in HCC cells correlates with overexpression of pro-apoptotic factors like caspase and gadd5, as well as down-regulation of anti-apoptotic factors, such as Bcl-XL^[101]. Another receptor tyrosine kinase inhibitor, sunitinib, which has also shown intriguing outcomes in advanced HCC^[100], is a strong apoptosis inducer in different tumor cells, an effect that is enhanced in the presence of inhibitors of the PI3-K/Akt/mTOR pathway^[102]. Bevacizumab, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody, has been proven to be efficient in inhibiting the growth of nonmetastatic HCC^[103]. Interestingly, recent evidence indicates that VEGF signalling inhibitors might be effective in inhibiting tumorigenesis more through their pro-apoptotic than their anti-angiogenic properties^[104]. Therefore, therapeutic strategies to selectively inhibit anti-apoptotic signals in HCC cells might have the potential to provide powerful tools in the future to treat liver cancer.

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