The Role of Src-Phosphorylation at the α1-Na/K-ATPase at Caveola in the Pathogenesis and Treatment of NASH Related Hepatocellular Carcinoma: Overview of Published Literature

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Abstract

The incidence of Hepatocellular Carcinoma (HCC) and its related mortality is increasing, becoming the 2nd and fastest-growing cause of cancer related mortality worldwide. In particular, the rise of HCC can be attributed to the cellular metabolic disturbances promoted by the epidemic of obesity and the lack of markers for its early detection. With few treatment options and a 50% to 70% recurrence rate after resection or loco-regional treatment, HCC has become a major and steadily increasing global health challenge. This review focuses on the current knowledge related to the pathogenesis of NASH-related HCC in order to provide a novel pathway for theoretical treatment options. For instance, regulation of Src-phosphorylation by the α1-subunit of the Na/K-ATPase may initiate protein interactions, beginning at the anchoring-Caveolin-1 in the plasma membrane, that promote disturbances in the intrinsic apoptotic pathway. This apoptotic cascade is activated and regulated by the mitochondria during energy distress, as often observed in NASH-related HCC. As part of this pathway, the Smac/DIABLO-survivin signaling equilibrium may play a pivotal role in regulating the pathogenic ‘apoptotic switch’ in NASH related malignancy. Additionally, we propose inhibition of Src phosphorylation at the α1-Na/K-ATPase as a putative target for the treatment of HCC.

Keywords: Hepatocellular carcinoma; NASH, Na/K-ATPase-α1-Caveolin-1; Survivin; Smac/DIABLO; Hedgehog; Apoptosis

Abbreviations

ESLD: End-Stage Liver Disease; GSH: Glutathione Reduced; GSSG: Glutathione Oxidized; HAV, HBV, and HCV: Hepatitis A, B, and C Viral Infection, respectively; FA: Fatty Acid; HCC: Hepatocellular Carcinoma; HFD: High-Fat Diet; HTN: Hypertension; NAFLD: Non-Alcoholic Fatty Liver Disease; NASH: Non-Alcoholic Steatohepatitis; NKA: Na/K-ATPase

Introduction

Cancer is the second leading cause of death worldwide, accounting for 1 in every six deaths [1]. Hepatocellular Carcinoma (HCC) is the second and fastest-growing cause of malignancy-related mortality with an estimate of 840,000 new cases every year, contributing to 9.1% of all cancer deaths [2-4]. HCC is a highly lethal malignancy that primarily originates from a background of end-stage organ disease (ESLD or cirrhosis). ESLD develops from multiple etiologies, such as infectious (hepatitis B and C virus infection), genetically inherited (hemochromatosis, primarily biliary cirrhosis, α-1 antitrypsin deficiency, Wilson’s disease), toxic (alcohol, drugs, aflatoxins), and metabolic (Non-Alcoholic Steatohepatitis - NASH) [2]. The most significant risk factor for HCC is advanced liver fibrosis (stage IV or cirrhosis). The only treatment currently available to intervene in the concomitant organ dysfunction, portal hypertension, and early-stage malignancy is liver transplantation. Although transplantation is a highly successful form of therapy with overall survival rates of >65% at five years, this form of therapy is limited due to the scarcity of graft donors.
Moreover, the majority of patients with HCC at presentation are already in the late stages of the disease, thereby precluding resection or transplantation. Most loco-regional therapies, i.e., TACE, Y90, and ablation, are performed as a bridge for transplantation. In brief, with poor prognosis, few treatment options, and up to a 70% recurrence rate, HCC has become a prominent and increasing global health challenge [2,5].

Obesity is increasing in the Western world, with one in three to four adults being either overweight or obese, and with a total projection of 2.2 billion individuals by 2030. The epidemic of obesity and its metabolic consequences (HTN, hyperlipidemia, and insulin resistance) have led to Non-Alcoholic Fatty Liver Disease (NAFLD) and its progressed inflammatory form, NASH, in becoming significant causes of ESLD and HCC [2-5,8]. Therefore, NASH-related HCC is predicted to rise exponentially in the next ten years with an estimated increase in cases of 21% for NAFLD, 63% for NASH, and 137% for HCC in the US by 2030 [2,9]. We aim in this review to enunciate novel molecular mechanisms that underpin the genesis and progression of NASH to cirrhosis and HCC in order to uncover targets for the prevention, early diagnosis, and treatment of HCC.

Epidemiology

The global geographical variation in the incidence of HCC is due, at least in part, to the multiplicity of risk factors involved in its genesis and progression. The majority (80%) of HCC cases occur in sub-Saharan Africa and eastern Asia (Figure 1), where the main etiological factors are Hepatitis B (HBV) and aflatoxin poisoning [3,10,11]. Although HCV is the primary risk factor in the western countries, including USA, Europe, and Japan, [3,10,12] this trend is fast changing due to the decline in HCV infection as a result of effective treatment and the upsurge in the incidence of obesity, diabetes and HTN (the metabolic syndrome). Along these lines, NAFLD/NASH has already risen to the top etiological factor for HCC in developed countries, including the US [6,13]. Accumulated data demonstrates that NAFLD affects well above 80 million in the US, making it the most common cause of liver disease in the United States [6]. It is estimated by the year 2030, 2.2 billion people around the world will be overweight and 1.1 billion will be obese [14-16]. Over the last 40 years, the incidence of HCC in the US has tripled, increasing from a burden of 14 million in 2012 to a predicted burden of 22 million by 2032 [3]. Gender difference in the occurrence of HCC has been reported with men having more cases than women in ratio of 2.4: 1. [3,11] Comitantly, the age-adjusted incidence of HCC has increased from 1.6 to 4.6 per 100,000 individuals among Native Americans and Alaskan Natives, followed by African Americans, Caucasians, and Hispanics, with an average five-year survival of <15% [3,12,17]. Additionally, while the prevalence of NAFLD, including NASH, is assumed to be prominent among Hispanics and Caucasians, the distribution of cases among NAFLD/NASH-related HCC patients regarding their ethnic groups is yet to be elucidated [6,18,19].

Metabolic Mechanisms for NASH-Related HCC

The hallmark of NASH is inflammation, hepatocellular damage, and fibrosis, which can proceed to HCC with or without cirrhosis [20,21]. The molecular pathogenesis of NASH-related HCC is complex and involves the interplay of multiple mechanisms; a few examples include the genetic, metabolic, immunologic, and endocrine pathways, as well as gut microbiota, which together result in the activation of oncogenic responses [20,22]. Various hypotheses have been enunciated to explain the detailed cellular mechanisms involved in the progression from NAFLD to NASH and subsequently to HCC. One such theory entails that steatosis and insulin resistance is the underlying, initiating factors that set the stage for the progression of NASH from metabolic, oxidative stress (Figure 2) [20,23,24].
progression of NASH to HCC, [20] we would like to propose a novel pathway that involves the phosphorylation of Src. The Src protein is encoded by the proto-oncogene that is highly similar to the v-src gene of Rous sarcoma virus. Src may play a role in the regulation of embryonic development and cell growth that upon phosphorylation at the α1 subunit of the Na/K-ATPase-CAV-1 complex may promote a signaling pathway for the ‘apoptotic switch’ of a cell experiencing energy distress. Initially, we will discuss the context of the Caveolin-1, SMAC, and Survivin proteins, followed by the functioning of α1-Na/K-ATPase-CAV-1-Src signaling complex, in the hopes of providing an insight into the possible role of the Na/K-ATPase-α1-caveolin-1/SMAC/Survivin pathway in the pathogenesis of NASH related HCC.

Caveolin-1 (CAV-1) is a 21- to 24-KDa protein with 178 amino acid residues. It belongs to the caveolin family of proteins, which is comprised of Caveolin-1, Caveolin-2, and Caveolin-3. It is the main structural component of the 50 nm to 100 nm small flask-shaped invaginations of the plasma membrane, known as caveolae [54–58]. Caveolin-1 is also found in the Golgi apparatus, in Golgi-derived transport vesicles, as well as the cytoplasm. Depending on the cell type, it is expressed either as a soluble cytosolic form or as a secreted form [57,58]. Caveolin-1 is a scaffolding protein that plays a crucial role in caveola formation, signal transduction, vesicular trafficking, lipid transport, and cholesterol homeostasis. Its configuration, structure, and intracellular travel are summarized in Figures 3 and 4, respectively [55,56,58,161].

Caveolin-1 interacts with and inhibits a variety of proteins that are involved in cell signaling, cell proliferation and survival, such as G-protein, Neu-receptors, Src-family kinases, Epidermal Growth Factor Receptor (EFG-R), endothelial Nitric Oxide Synthase (eNOS), and protein kinase C [54–56,59,60]. CAV-1 functions as a tumor suppressor and is down-regulated in several human cancer types such as ovarian, lung and breast cancers, sarcomas and colon cancer [56,60–63]. CAV-1 also enhances tumor progression and metastasis.

Figure 3: Caveolin-1 structure and caveolae morphology. A) Schematic diagram showing the different domains present in caveolin-1 that permit interaction with other proteins and membranes. B) Caveolin-1 anchorage via the membrane insertion domain into regions enriched in sphingolipids and cholesterol. C) Caveolin-1 oligomerizes to generate the proteinaceous coat of caveolae, small invaginations (50 nm to 100 nm) of the plasma membrane.

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In particular, caveolin-1 is a tumor promoter in prostate cancer, with its expression correlating positively with tumor formation in prostate carcinoma cell lines [55,64-66]. Similar results have also been reported for bladder and esophageal cancers [55,64,67,68]. Currently, it is accepted that CAV-1 can act both as a tumor suppressor and a tumor promoter and that its role in carcinogenesis depends on the cancer type and stage [55,69]. In contrast, CAV-1 is over expressed in Hepatocellular Carcinoma (HCC). The increased expression of CAV-1 drives cell progression, growth, invasion, metastasis, metabolism, and survival, and is a poor prognosis for HCC patients [69-74]. Wang et al. [55,75] demonstrated that CAV-1 expression protected Hepa 1-6 cells from ActD induced apoptosis and enhanced their transformation potential both in vitro and in vivo via the upregulation of the survivin-mediated survival pathway. Similarly, Yu et al. [69,76,77] showed that CAV-1 was over expressed in HCC cell lines, as well as in tissues, and promotes HCC cell invasiveness. Furthermore, it enhances tumor formation, progression, and metastasis in vivo via the activation of the Wnt/β-catenin-Tcf/Lef pathway at the transcriptional level. Interestingly, CAV-1 knockdown inhibited tumor growth and metastasis [69]. In concordance with the presented evidence, there is an increase in the expression of CAV-1 both at the protein and mRNA levels in human cirrhotic livers with hepatocellular carcinoma. This evidence suggests CAV-1 is an oncogenic protein and a possible biological marker of malignant activity [72,73,78]. Furthermore, immunohistochemical staining of human HCC exhibited an upregulation of CAV-1 that positively correlated with tumor differentiation, intrahepatic metastasis, vascular invasion, recurrence, and death. Additionally, increase CAV-1 expression significantly protects HepG2 cells from apoptosis involving the anti-apoptotic protein survivin [71,74].

Survivin is a member of the Inhibitor of Apoptosis Proteins (IAPs) family. It is a 142 - amino acid, 16.5 kDa protein that is encoded by a single-copy gene that resides on the human 17q25 chromosome [79-83]. Survivin is unique in comparison to other members of the IAP family, not only because it is the smallest member, but because survivin has a single Baculoviral IAP Repeat (BIR) domain lacking both the Really Interesting New Gene (RING)-finger domain and the Caspase–Associated Recruiting Domain (CARD), that are present in other members of the IAP family [79,80,84-86]. Moreover, survivin plays a key role in the regulation of apoptosis (programmed cell death) and cell cycle progression (mitosis) [81,83,87]. It is highly expressed in embryonic and fetal tissues, but undetectable in normal adult differentiated tissues, except for the placenta, CD34+ stem cells, basal colonic epithelial cells, testis, and thymus [80,81,83,87-95]. Additionally, survivin is over expressed in most human cancer types, such as breast, pancreatic, lung, brain tumors, neuroblastomas, melanoma, soft tissue sarcomas, colon cancers, lymphoma, prostate, acute myeloid leukemia, as well as hepatocellular carcinoma [79-83,85,87-91,94]. To date, survivin is the most potent apoptosis-inhibiting protein, and its deed is mediated through caspase-9 inactivation. This action results in the dissociation of the Apaf-1-caspase-9 complex, with a resultant inactivation of caspase-3, the chief executioner protein of the apoptotic pathway [80,84,87,96]. Survivin inhibits caspase-9 in the presence of a cofactor, the Hepatitis B X-Interacting Protein (HBXIP), and in association with X-linked IAP [80,95,97,98]. Conversely, survivin is inhibited by the mitochondrial released pro-apoptotic protein, Smac/DIABLO (second mitochondrial-derived activator of caspase), to be discussed later in the review. In summary, survivin plays a critical role in the cellular interplay between apoptosis and cell division (Figure 5) [79,80,99].

In the cell, survivin is localized in the cytosol, mitochondria, and nucleus. Its subcellular localization correlates positively with its various cellular functions. Nuclear survivin mediates its role in mitosis, while the cytosolic and mitochondrial pools serve its anti-apoptotic function [79,99,100]. Survivin translocation from its nuclear pool to the cytoplasm is regulated by an evolutionarily conserved exportin-1 (Crm-1) Nuclear Export Signal (NES). NES is critical for the survivin nuclear-to-cytoplasm movement because its mutation results in the trapping of survivin in the nucleus, leading to improper cell division and the loss of protein anti-apoptotic function [79,101-103]. Furthermore, following cell death stimulation in tumor cells, mitochondrial survivin is rapidly released into the cytosol to inhibit apoptosis and promote tumorigenesis [79,99,104].

The promotion of HCC proliferation by survivin is driven by its role in mitosis, as earlier discussed. During the G2/M phase of the cell cycle, survivin is highly expressed and binds to the microtubules that make up the mitotic spindles. This binding stabilizes the structure of the microtubules and prevents the hydrolysis of the spindles, resulting in the protection of the integrity of mitotic organelles, evasion of checkpoint growth arrest, and continuous cell division [95,104,105]. Besides, the fibroblast growth upregulates survivin expression in HCC. This upregulation results in increased cancer cell proliferation via the activation of the Phosphatidylinositol 3-Kinase (PI3K) pathway [95,106] and promotes tumor angiogenesis through the Vascular Endothelial Growth Factor (VEGF) [107,108]. Elevated survivin expression also leads to an increase in β-catenin protein levels, which results in the enhancement of the transcriptional activity of the β-catenin/T cell factor (Tcf)/Lymphoid Enhancer-Binding Factor (LEF). Additionally, these heightened β-catenin levels promote the
expression of Vascular Endothelial Growth Factor (VEGF), resulting in tumor stromal angiogenesis [95,109].

In carcinogenesis, increased survivin expression drives tumor growth, progression, metastasis, and resistance to anticancer therapy, in various types of cancer due to its ability to promote a cellular switch from apoptosis to mitosis [80,81,87,104,110-112]. Survivin is highly upregulated in both HCC tissues and cancer cell lines when compared to non-cancerous tissues and cells [81,95,113,114]. The inhibition of apoptosis in HCC cells by survivin is mediated via several molecular mechanisms, including the binding/inhibition caspase -9. Caspase -9 is a key apoptotic protein in the intrinsic pathway of apoptosis. This process involves the interaction of survivin and Smac, which leads to the release of the Inhibitor of Apoptosis Proteins (IAPs) from the Smac/IAP complexes and results in apoptotic inhibition (Figure 6) [95,115,116]. Additionally, survivin can inhibit apoptosis by binding to Hepatitis B X-Interacting Protein (HBIXP), which results in inhibition of Caspase-9 [79,95,98,117]. It is worth noting that HBIXP is a ubiquitous cytoplasmic protein in human tissues and can bind to Hepatitis B virus X (HBX). The binding of survivin to HBIXP forms a complex that is known as the survivin-HBIXP complex. This complex inhibits the intrinsic pathway of apoptosis via blockage of the binding of pro-caspase-9 to its apoptotic ligand protease, known as activating factor 1 (Aparf1). Intriguingly, the expression of HBX following hepatitis B virus infection results in its binding to survivin HBIXP complex. Such binding inhibits caspase driven apoptotic mechanisms and controls the apoptosis of HCC in a survivin-favored direction. Thus, survivin mediated apoptosis process plays a key role in the development and progression of hepatitis-B-related hepatocellular carcinoma [79,95,98,117,118]. Furthermore, the inhibition of apoptosis by survivin in HCC and other forms of cancer can also occur through molecular mechanisms that involve the Bax pathway [95,119].

In contrast to survivin, Smac/DIABLO (Second mitochondria-derived activator of caspases/direct inhibitor of apoptosis-binding protein or Smac), is a pro-apoptotic protein that is released from the mitochondria into the cytosol in response to programmed cell death stimuli [120-122]. Such apoptotic stimuli include UVB-irradiation, antineoplastic drugs (e.g., etoposide), hypoxia, growth factor withdrawal, glucocorticoids, and heat shock [115,120]. Upon exposure to these stimuli, the outer mitochondrial membrane becomes more permeable, which leads to the release of proteins (cytochrome C, Smac, and Omi/HtrA2) from the intermembrane space into the cytosol [120]. Following the onset of apoptosis, the N-terminus (which serves as the mitochondrial targeting signal, MTS) of the precursor Smac/DIABLO is cleaved by limited proteolysis to generate the mature 26 kDa protein [115,121,122]. In the cytosol, the matured Smac protein binds and neutralizes the inhibitory effects of the Inhibitors of Apoptosis Proteins (IAPs) on caspases, thereby promoting caspases activation and initiating apoptosis (Figure 6) [115,120-124]. Members of the IAPs family include X-Linked Inhibitor of Apoptosis (XIAP), Cellular IAP-1 (c-IAP1), Cellular IAP-2 (c-IAP2), Testis specific IAP (Ts-IAP), survivin, livin, and BRUCE/Apollon [120,125]. These proteins all share the unique characteristic of having one or more copies of the Baculovirus IAP Repeat (BIR) domain [115,126]. Smac interacts with the BIR2 and BIR3 domains of the XIAP (the most studied member of the IAPs), leading to the release of caspase-3 and caspase-9 from its inhibition, resulting in apoptosis [115,120,127,128]. The N-terminus of the mature Smac is required for this interaction, [115,127] which also interacts directly with survivin. Mutational analysis revealed that the amino acid Asp-71 in survivin is critical for this interaction, and the binding process occurs via the C-terminal coiled-coil domain of survivin [115]. Upon initiation of apoptosis, survivin binds to Smac, which is released from
the mitochondria, and this leads to the reduction of the antagonistic effect of Smac on XIAP [115,129]. Survivin is unable to inhibit caspases directly, but its interaction with Smac allows endogenous IAPs (XIAP) to block caspases and thereby inhibit apoptosis [80,115].

Smac can also inhibit survivin, thereby placing both proteins in a central position concerning the regulation of apoptosis [79,80]. In HCC, the Smac mRNA and protein expressions are reduced in comparison to normal liver tissue. The decrease in Smac levels in HCC has also been shown to correlate positively with tumor progression and increase in survivin expression [120,130].

α1-Na/K-ATPase-CAV-1-Src signaling plays a role in the regulation of embryonic development and cell growth. Early work by our group pioneered by Dr. Xie, identified a novel signaling complex composed of the α1 isoform of Na/K-ATPase, CAV-1, and the sarcoma related kinase (Src), which plays a critical role regulating the signaling from membrane micro-domains named caveolae. Na/K-ATPase (NKA) is not only an ion pumping protein but also acts as an important scaffolding protein that integrates signaling from various membrane receptors at caveolae. The NKA translates these signals into changes in cellular fate, such as cell growth and differentiation [131-134]. The importance of this signaling mechanism was demonstrated in the pathogenesis of the metabolic syndrome, as well as in aging and embryonic development [135,136]. In support of this hypothesis, genetic deletion of a Caveolin Binding Motif (CBM) at the α1-NKA resulted in a lethal embryonic phenotype in homozygous mice, despite normal NKA protein expression and ion pumping function. This observation indicates that α1-NKA-CAV-1 interaction is required for the proper execution of developmental signaling pathways. Conversely, chronic activation of the NKA-CAV-1-Src signaling complex promotes pro-inflammatory pathways and tissue fibrosis through the amplification of ROI. This pathway embraces a vicious feed-forward mechanism, as evident in several disease phenotypes, including renal fibrosis, uremic cardiomyopathy, and metabolic disorders such as obesity [135,137,138]. Although a balanced signaling mechanism through NKA-CAV-Src is essential for normal physiological function, chronic activation of this signaling mechanism under pathophysiological conditions can further promote or aggravate disease conditions. This hypothesis was tested by blocking the Src-phosphorylation signaling at the NKA-CAV-1 complex by pNaKtide; a peptide developed from the N domain (nucleotide-binding domain) of the α1 isoform [139]. The former ROI amplification loop plays an important role in the pathophysiological progression of NALFD to NASH and HCC (submitted for publication), and elevated Src kinase activity has been associated with poor prognosis in HCC [140,141]. We propose that the α1-NKA-CAV-1-Src signaling complex can be therapeutically targeted in the pathogenesis of NASH related HCC, a malignancy driven by metabolic disturbances. Also, another dysfunctional NKA-CAV- Src signaling has been found in tumor genesis, as shown in the Warburg phenotype and in tumor progression to metastases [142,143]. Significantly, metabolic dysfunction and cancer progression were mitigated by pNaKtide [143,144].

The α1-NKA-CAV-1-Src signaling pathway has been challenged in terms of studying its interaction and complex composition...
A careful juxtaposition of the preceding literature indicates a link between Caveolin-1, Survivin, and Smac/DIABLO in the pathogenesis of HCC. Interestingly, the Hedgehog (Hh) signaling pathway is also involved in early embryonic development, as well as tissue regeneration in various models of injury. This pathway features several essential proteins for regulation, as well as a set of transcriptional factors that become activated in the nucleus (Figure 7). In the "off" configuration, in the absence of a Hh ligand, a transmembrane protein at the plasma membrane, Patched (Ptc), inhibits another transmembrane protein called Smoothened (SMO). SMO is involved in the activation of a signaling cascade that leads to the activation of a family of GLI transcription factors. During activation of this pathway, a Hh ligand, there are several depending on the organism species, binds to Ptc, allowing for SMO activation. SMO activation leads to a series of intracellular signaling/protein transport those results in the nuclear translocation of the GLI transcription factors [155,156].

The Ptc receptor at the cell membrane has been shown to form a complex with the Smo protein, and this complex has been indicated to be located in caveolin-enriched microdomains of the plasma membrane. Specifically, the Ptc protein has been shown to contain a binding domain for interaction with CAV-1 [157]. CAV-1 quantity at the cell membrane is regulated by the NKA, specifically by the association between CAV-1 and a CAV-1 binding motif in the α-1 subunit of the Na/K-ATPase [131]. Additionally, studies have demonstrated that although in healthy liver cells, the Hh signaling pathway is believed to be inactive, in cancerous and non-healthy liver cells, this signaling pathway becomes activated [158]. Therefore, it is likely that a CAV-1 stabilized Ptc-Smo transmembrane receptor complex interacts with upregulated Hh ligands, causing activation of the Hh signaling pathway, and enhances nuclear expression of the GLI transcription factors. GLI transcription factors are essential, as they have been implicated in a multitude of tumorigenesis studies involving Hh signaling pathways [159]. One such study has implicated the GLI2 transcription factor as having a direct correlation with the expression of the inhibitory of apoptosis protein survivin. This study analyzed the binding sites in the survivin promoter region for GLI transcription factors, and the application of a GLI2 inhibitor decreased survivin protein and mRNA expression in both tumor cell lines and cancerous tissue in a nude mouse model. Furthermore, increased expression of survivin was induced in human fibroblast cell lines that were transfected with vectors of Gli1, Gli2, and ΔNGLI2, an active form of Gli2 [160].

Summary

The incidence of HCC and its related mortality is increasing becoming nowadays the most common cause for liver transplantation in the Western. In particular, the rise of HCC can be attributed to the cellular metabolic disturbances promoted by the epidemic of obesity and the lack of markers for its early detection. This review offered current knowledge related to the pathogenesis of NASH-related HCC and provided a novel pathway for treatment options. Regulation of Src-phosphorylation at the α1-subunit of the Na/K-ATPase in caveolae may abrogate disturbances in the intrinsic apoptotic cascade regulated by the mitochondria during energy distress. Furthermore, Smac/DIABLO-survivin signaling plays a pivotal role in the pathogenic 'apoptotic switch' of NASH related malignancy. Two signaling pathways have been implicated in the perpetuation of this described mechanism; the CAV-1/B-catenin and the CAV-1/Hh pathways. Finally, we propose inhibition of Src phosphorylation at the α1-Na/K-ATPase as a putative target for the treatment of HCC.

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