A Specific Splicing Variant of SVH, a Novel Human Armadillo Repeat Protein, Is Up-Regulated in Hepatocellular Carcinomas

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors with poor prognosis. By representational difference analysis (RDA), a novel human gene designated SVH, up-regulated in the clinical HCC sample, was identified. The deduced SVH protein consisted of 343 amino acids with a transmembrane domain and an armadillo repeat. Northern blot revealed that SVH was expressed in most human adult tissues. Four variants of SVH, SVH-A, -B, -C, and -D, resulting from alternative splicing in the coding region of the SVH transcript, were observed and were all localized in endoplasmic reticulum (ER). Up-regulation of SVH-B, but not the other variants, was evident in about 60% (28 of 46) of HCC samples, detected by quantitative real-time PCR. Human liver cell line QSG-7701, transfected with SVH-B, acquired an accelerated growth rate and tumorigenicity in nude mice, whereas inhibition of SVH-B in hepatoma cell line BEL-7404, using antisense oligodeoxynucleotides, induced apoptosis. It is suggested that the splicing variants of SVH have distinct biological functions, and SVH-B may play an important role in hepatocarcinogenesis.

ABSTRACT

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors with poor prognosis. By representational difference analysis (RDA), a novel human gene designated SVH, up-regulated in the clinical HCC sample, was identified. The deduced SVH protein consisted of 343 amino acids with a transmembrane domain and an armadillo repeat. Northern blot revealed that SVH was expressed in most human adult tissues. Four variants of SVH, SVH-A, -B, -C, and -D, resulting from alternative splicing in the coding region of the SVH transcript, were observed and were all localized in endoplasmic reticulum (ER). Up-regulation of SVH-B, but not the other variants, was evident in about 60% (28 of 46) of HCC samples, detected by quantitative real-time PCR. Human liver cell line QSG-7701, transfected with SVH-B, acquired an accelerated growth rate and tumorigenicity in nude mice, whereas inhibition of SVH-B in hepatoma cell line BEL-7404, using antisense oligodeoxynucleotides, induced apoptosis. It is suggested that the splicing variants of SVH have distinct biological functions, and SVH-B may play an important role in hepatocarcinogenesis.

MATERIALS AND METHODS

Clinical Samples. Clinical HCC samples were collected from Zhongshan Hospital immediately after surgery and were diagnosed to stage II-III by pathological examination. The paired nontumorous liver samples were 3 cm away from the edge of HCC lesions from the same patients. These constructs were verified by DNA sequencing (Sangon, Shanghai, China).

Molecular Cloning of SVH Gene. The cDNA sequence of SVH was obtained by aligning the ESTs from the NCBI database, and was confirmed by reverse transcription-PCR in the cDNA from the hepatoma cell line BEL-7404. Four spliced variants were found, and the coding sequence of each variant was amplified by LA Taq polymerase (TaKaRa, Dalian, China) and was cloned directly into pEGFP-N1 (Clontech, Palo Alto, CA) and pcDNA3.1A (Invitrogen, Carlsbad, CA), respectively. Primers used in this procedure were listed in Table 1. The different products were cloned into the pgEM-SZ(+) (Promega, Madison, WI) and were confirmed by DNA sequencing (Sangon, Shanghai, China).

Northern Blot Analysis. To analyze SVH expression in various normal adult human tissues, the Multiple Tissue Northern blot (Clontech) was purchased. The blotting membrane was incubated in prehybridization solution of 5× SSC, 5× Denhardt’s solution, 0.1% SDS, and 50 μg/ml salmon sperm DNA at 68°C for 3 h, and then hybridization was performed using an 850-bp cDNA fragment of SVH-A (493–1342 bp) labeled with [α-32P]dCTP by random priming (Promega) at 68°C for 12 h. The mem-

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4 The abbreviations used are: HCC, hepatocellular carcinoma; RDA, representational difference analysis; ER, endoplasmic reticulum; PCNA, proliferating cell nuclear antigen; EGFR, epidermal growth factor receptor; GTP, guanine triphosphate; EGFP, enhanced green fluorescent protein; GTP, guanosine triphosphate; PARP, poly(ADP-ribose) polymerase; PI, phosphatidylinositol; A5, antisense; SE, sense; MI, missense; HRP, horseradish peroxidase; EST, expression sequence tag; NCBI, National Center for Biotechnology Information; aa, amino acid(s).
brane was washed in 0.1× SSC containing 0.5% SDS at 65°C for 1 h, exposed to a phosphor screen, and visualized by an FLA-3000A Plate/Fluorescent Image Analyzer (Fuji Photo Film, Tokyo, Japan). After stripping, the same membrane was similarly hybridized to the β-actin probe.

Quantitative Real-Time PCR Analysis. Total RNA was extracted from the paired HCC samples with TRIZOL Reagent (Invitrogen), and then was treated with amplification grade Dnase I (Invitrogen) before cdNA synthesis. The mRNA for SVH and β-actin were designed to span exon junctions to prevent the amplification of other variants. The specific PCR products were confirmed by DNA sequencing and were used as templates to generate standard curves. Each assay included a no-template control, cdNA samples in triplicate to avoid the individual differences in the nude mice.

Phosphorothioate ODNs for AS Assay. Two groups of phosphorothioate ODNs were designed as shown in Table 2 and were synthesized by Sangon. The ODNs were freshly dissolved in 0.1 M PBS before use and were transfected with 20 μg/ml LipofectAMINE Reagent (Invitrogen).

Apoptosis Assay. Annexin V binding, PARP activity, and Bcl-2 expression were investigated to determine whether cell death was occurring by apoptosis. Annexin V-FITC binding and PI staining were performed according to the manufacturer’s protocol (Roche, Indianapolis, IN) and were analyzed by flow cytometry (Becton Dickinson, San Jose, CA; Ref. 20). To detect the PARP activity or Bcl-2 expression, 20 μg of total cellular proteins were run on 8 or 15% SDS-PAGE, electrophoretically transferred to a nitrocellulose membrane (Schleicher and Schuell, Dassel, Germany), and blotted with mouse anti-PARP monoclonal antibody (PharMingen, San Diego, CA: 1:1000) or with rabbit anti-Bcl-2 polyclonal antibody (Santa Cruz Biotechnology, 1:200). After binding a HRP-conjugated antimouse/rabbit antibody (1:3000; Amersham Little Chalfont, England), it was developed using the ECL luminescent system (Amersham). The membrane was reprobed by goat anti-actin polyclonal antibody (Santa Cruz Biotechnology; 1:2000) and then HRP-conjugated antigen antibody (1:5000; Promega) as the loading control.

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**Table 1** Primers for cDNA confirmation, plasmid construction, alternative splicing detection, and quantitative real-time PCR

<table>
<thead>
<tr>
<th>Primer set</th>
<th>Name</th>
<th>Sequence</th>
<th>Target variant</th>
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<tr>
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<td>P5-1</td>
<td>5'-GCT CGG TCA TGG GTT GC-3'</td>
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<td>P3-1</td>
<td>5'-TGA TTT TTC TCC CCT TTA TTA-3'</td>
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<td>Plasmid construction</td>
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<td>Splicing detection</td>
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<td>P3-3</td>
<td>5'-CCA CTT GGG CAC GGA GAA-3'</td>
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<tr>
<td>Quantitative real-time PCR</td>
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<td>P5-5</td>
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<td></td>
<td>P5-6</td>
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<td>P3-4</td>
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<td>5'-AAC TTG CAC CCT TAT CCT GA-3'</td>
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<tr>
<td></td>
<td>Probe1</td>
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<td>Probe2</td>
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<td>P5-Actin</td>
<td>5'-TCA CCC ACA CTG TGC CCA TCT AC-3'</td>
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<td></td>
<td>P3-Actin</td>
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<tr>
<td></td>
<td>Probe-Actin</td>
<td>5'-TAM) ATG CCC CAC ATG CCA TCC TGC G (TAMRA)-3'</td>
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**Table 2** Phosphorothioate ODNs for AS Assay

<table>
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<th>Sequence</th>
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<tr>
<td>SE-1</td>
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<td>MI-1</td>
<td>5'-GTC AGC GTG TAA ATC GAG TA-3'</td>
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<td>5'-ACA ACT GAC CCT CTG ACG TCC C-3'</td>
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<td>SE-2</td>
<td>5'-GGG AGC TCA GAG GGT CAG TGT T3-3'</td>
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<td>MI-2</td>
<td>5'-AGA ACT GAC CTT CTC TGG ACG TCG C-3'</td>
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<td>AS-3</td>
<td>5'-AGA AGA GAA GAC ATC TCA TCC AC-3'</td>
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<td>SE-3</td>
<td>5'-GTA TGT GAG GAT GTC TCT TGT GCT-3'</td>
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<tr>
<td>MI-3</td>
<td>5'-ACC AGA ACA GAC ATC TCA TCGA A TCG-3'</td>
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<tr>
<td>Group 2</td>
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<tr>
<td>AS-12</td>
<td>5'-GCT GCA GTC AAC GGA GAA G-3'</td>
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<tr>
<td>SE-12</td>
<td>5'-TCC TCC GTG AAC CAC AGC-3'</td>
</tr>
<tr>
<td>MI-12</td>
<td>5'-GCT CGA GTC AAC CGA CCA-3'</td>
</tr>
<tr>
<td>AS-22</td>
<td>5'-GTC CAA GAC CTC GCA GGC TG-3'</td>
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<tr>
<td>SE-22</td>
<td>5'-AGA CAG CGG AAG GGT TCC AG-3'</td>
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<tr>
<td>MI-22</td>
<td>5'-GTC GCA CAC CTC GCA GGG TG-3'</td>
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<tr>
<td>AS-32</td>
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<tr>
<td>SE-32</td>
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<td>MI-32</td>
<td>5'-GGA AAT CCA ACG AAG GT-3'</td>
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RESULTS

Molecular Cloning and Characterization of the SVH Gene. A modified cDNA RDA method was used to identify genes differentially expressed in HCC tissues (20). A 116-bp cDNA fragment up-regulated in the HCC sample was thus identified. The ESTs from NCBI database homology to this fragment were aligned into a 2647-bp cDNA cluster (GenBank accession no. AY150854) with an open reading frame encoding a putative protein of 343 amino acids (Fig. 1A). The complete sequence of the putative gene, designated SVH (specific Splicing Variant involved in Hepatocarcinogenesis), was confirmed by reverse transcription-PCR and was verified by DNA sequencing (Fig. 1B). The predicted mRNA had a typical Kozak consensus sequence preceding the ATG initiation codon, and a polyadenylation signal located 13 bp upstream of the polyadenylation site. The PROSITE analysis5 indicated that there was a possible armadillo repeat and a cell attachment sequence RGD from aa 33 to 35 (Fig. 1A). Potential phosphorylation sites present in SVH included three protein kinase C sites and six casein kinase II sites. The SOSUI algorithm6 predicted a transmembrane domain at the NH2 terminus of the protein (aa 7–29; Fig. 1A).

5 Internet address: http://www.expasy.ch/prosite/.
6 Internet address: http://sosui.proteome.bio.tuat.ac.jp/sosuimenu0.html.
were estimated in a Northern blot (Fig. 1C). The predicted length of 2647 bp was in good agreement with the major transcript size of ~2.6 kb. It was also found that SVH was expressed in all of the tissues tested, with high levels in placenta, liver, kidney, heart, and brain.

Fig. 2. Alignment of the human SVH, ALEX1, ALEX2, and ALEX3 proteins. The amino acid sequences were aligned by ClustalW.\(^7\) Among the four amino acid sequences: residues in black shadow were 100% identical; residues in dark gray were 75% identical; residues in French gray were 50% identical.

Fig. 3. Genomic structure and alternative splicing pattern of the SVH gene. A, genomic structure of SVH relative to the sequence contig of genomic clones. Structures were oriented centromeric to left and telomeric to right. AC073117, AC108167, AC007683, accession numbers of the clones. Boxes on the contig, the locations of exons of SVH. Boxes on the right, the locations of exons of SVH. Boxes on the left, expression of SVH in human liver and hepatoma cell lines by reverse transcription-PCR. Labels above each panel, the names of the cell lines. Bottom panel, expression of \(/H9252\)-actin used as the control.

Fig. 4. Subcellular localization of SVH proteins in QSG-7701 cells. A, Western blot of total protein from cells transfected with SVH-GFP fusion protein or with GFP, and parental QSG-7701 cells using rabbit anti-GFP antibody. Protein weight marker was the BENCHMARK prestained protein ladder (Life Technologies, Inc.); \(kD, M_r\) in thousands. Labels above each panel, N, parental QSG-7701 cells; V, GFP-transfected cells; A, B, C, D, E, H, K, N, O, QSG-7701 cells transiently transfected with SVH-A, -B, -C, -D, or -T fused with GFP and vector, respectively. C, F, I, L, immunofluorescence staining of anti-calnexin antibody in the QSG-7701 cells transiently transfected with SVH-A, -B, -C or -D fused with GFP, respectively. D, G, J, M, the overlay of the two images (B and C, E and F, H and I, K and L, respectively) acquired with different filter sets was computer-mediated.

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\(^7\) Internet address: http://bioweb.pasteur.fr/seqanal.interfaces/clustalw.html.
sequences, the gene structure of SVH was assembled. It was shown that comparing cDNA sequence of the SVH gene with the human genome sequences, the gene structure of SVH was assembled. It was shown that SVH gene was located on chromosome 7q11.22 and was composed of seven exons spanning a genomic sequence of 25 kb (Fig. 3A). On the basis of their molecular weight, the four splicing variants of SVH were defined as SVH-A, -B, -C, and -D (Fig. 3C). These four sequences were submitted to GenBank with the accession numbers of AY150854, AY150853, AY150852, and AY150851, respectively. It was also found that expression level of SVH-B was lower in the liver cell lines L-02 and QSG-7701 than in the hepatoma cell lines BEL-7402, BEL-7404, SMMC-7721, and QGY-7703 (the last was from the hepatoma tissue of the same donor as was QSG-7701; Refs. 22 and 23).

Subcellular Localization of SVH. Human liver cell line QSG-7701 was used to characterize the subcellular localization of SVH proteins. Because variant-specific antibodies against SVH were not available, the four SVH variants, fused with EGFP in their COOH termini, were used in the localization assay (Fig. 4A). Under a confocal microscopy, it was shown that the four variants shared the same localization characterization over the cytoplasm and nuclear envelope and that no apparent signals were detected in the plasma membrane (Fig. 4, B, E, H, and K). Immunofluorescence analysis with organellar-specific dyes was also performed (Fig. 4, C, F, I, and L). The majority of SVH signals codistributed with the signals of calnexin (Fig. 4, D, G, J, and M), known as an ER transmembrane protein (24).

To further analyze the effect of the transmembrane domain on the subcellular localization, we constructed SVH-T, a truncated SVH-A lacking the integrated NH2-terminal transmembrane domain (deletion from aa 9 to 19). We observed that the SVH-T-EGFP fusion protein had the same distribution pattern as did EGFP (Fig. 4, N and O). These findings indicated that SVH was expressed predominately in the ER and that the NH2-terminal sequence was necessary to the subcellular localization characterization of SVH.

Up-Regulation of SVH-B in HCC. Because the SVH gene was originally identified for its up-regulation in clinical HCC samples, the expression levels of the four SVH variants were measured by quantitative real-time PCR in independent HCC samples and their paired normal liver tissues, calibrated by the expression level of β-actin. It was observed that the SVH-B was up-regulated by at least 1.5-fold in 28 of 46 HCC samples, whereas in the remaining 18 HCC samples, SVH-B was expressed at almost similar levels as in the paired liver tissues (Fig. 5B). Moreover, the expression levels of other variants did not exhibit consistent association with HCC tissues (Fig. 5, A, C, and D), indicating that up-regulation of SVH in HCC was splicing-format-specific (P < 0.05, Pearson’s χ2 test). Only SVH-B, not any of the other three formats, was up-regulated in clinical HCC.

Pathological information from the HCC samples was analyzed to detect whether they associated with an up-regulation of SVH-B. The results of using Fisher’s test suggested that the status of sex, age, and pathological stage and the expression levels of AFP, HBsAg, HBcAg, HCV, PCNA, VEGF, CD34, cytokteratin 7, cytokteratin 8, and EGFR were not significantly associated with the SVH-B mRNA level (data not shown).

Overexpression of SVH-B Accelerated Cell Growth and Assigned Cell Tumorigenicity in Nude Mice. To determine the effect of SVH-B overexpression on cell growth, the SVH-B expression construct was introduced into the normal liver cell line QSG-7701; SVH-A, -C, -D, and -T were used as controls. As shown in Fig. 6A, the overexpression of SVH-A, -B, -C, -D, or -T in the transfected cells

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SVH-B, A SPlicing VARIANT OF SVH, UP-REGULATED IN HCC

Emerging data highlight the importance of alternatively spliced transcripts involved in tumorigenesis. Normal and neoplastic tissues showed differences both in the pattern of altered splicing and in the amounts of altered products. Splicing alteration may change the ligand

observed at sites into which control cells had been injected (Fig. 6C). These results indicated that cells overexpressing SVH-B acquired accelerated cell growth rate and tumorigenicity in nude mice.

Inhibition of SVH-B Induced Cell Apoptosis. To examine the effect of down-regulation of SVH-B expression on hepatoma cells, we designed two groups of AS ODNs targeted to the specific exons (Table 2; Fig. 3C). The inhibition of specific transcript expression could be achieved by a combination of these AS ODNs (Table 3). Control ODNs were also used, including SE ODNs that were complementary to AS sequences, and MI ODNs that were similar to the AS ODNs except for three or four mismatch nucleotides. For each transcript, two groups of AS ODNs were applied to inhibit the expression of each transcript to ensure the specificity of ODN treatment. A conclusion was drawn only when both AS ODNs against the same transcript had identical effects on the treated cells. The results of AS ODNs from Group 1 are shown in Fig. 7.

The AS and control ODNs were applied to hepatoma cell line BEL-7404 at the concentration of 5 μM. Measured by quantitative real-time PCR, the expression of each variant was specifically inhibited in AS ODN-treated cells but not in control ODN-treated cells (data for SVH-B are shown in Fig. 7A, and data for SVH-A, -B, -C, and -D are represented in Table 3.). It was indicated that AS ODNs was a specific and effective approach to inhibit the expression of the spliced variants at the mRNA level.

The growth rate of BEL-7404 cells was examined at indicated times after AS ODNs treatment (Fig. 7B). Specific inhibition of the expression of SVH-B decreased the cell numbers and then caused cell death. To investigate the mechanism of cell death induced by the inhibition of SVH-B, we measured annexin V binding (25), PARP cleavage (26), and Bcl-2 expression (27). We observed via flow cytometry that when the expression of SVH-B was inhibited, the binding percentage of FITC-labeled annexin V increased from 10% to 40% 24 h after the treatment; moreover, PI staining indicated that 20–30% of these cells became apoptotic (Fig. 7C). We also isolated the total protein from the ODN-treated BEL-7404 cells 72 h after the ODN treatment. Western blotting showed that PARP, a Mr 116,000 nuclear chromatin-associated enzyme that was usually cleaved into Mr 85,000 and 25,000 fragments in apoptotic cells (26), was cleaved in the SVH-B-inhibited cells. Furthermore, Bcl-2 expression level was decreased in these cells (Fig. 7D). These evidences suggested that the inhibition of SVH-B-induced apoptosis and continuous SVH-B expression was required for cell survival and growth.

DISCUSSION

Table 3 Inhibitory effects of AS ODNs on the four variants of SVH

<table>
<thead>
<tr>
<th>Name</th>
<th>SVH-A</th>
<th>SVH-B</th>
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</table>

a The ODN could inhibit the expression level of the corresponding variant from the SVH transcript.
b The ODN had no inhibitory effect on the expression level of the corresponding variant from the SVH transcript.

Emerging data highlight the importance of alternatively spliced transcripts involved in tumorigenesis. Normal and neoplastic tissues showed differences both in the pattern of altered splicing and in the amounts of altered products. Splicing alteration may change the ligand

was confirmed by Western blotting using anti-His_n tag antibody. The growth of SVH-B transfectants was significantly enhanced compared with that of control cells (Fig. 6B), although the morphological appearance and the cell cycle distribution of the transfectants were indistinguishable from that of the control cells (data not shown). In addition, we examined whether overexpression of SVH-B would affect the tumorigenicity of QSG-7701 cells in nude mice. At 2 months after injection, tumors were visually identified at sites into which SVH-B transfectants had been injected, but no tumor was
binding of growth factor receptors (28) and cell adhesion molecules (14) and may alter the activation domains of transcriptional factors (16), the subcellular localization of the encoded protein (29), and even the phosphorylation activity of protein kinase (30).

The detail mechanism of altered splicing pattern in tumorigenesis is still unknown. Mutation at the original splice site or changes in the splicing machinery or splicing efficiency might contribute to this change in tumor development. Mutations around the intron and exon boundary would influence the possibility of splicing at the corresponding sites (31). It has also been suggested that illegitimate alternative splicing is a result of the abnormal stoichiometry of splicesome components (32). For example, down-regulation of splicing factor U2AF35 was critically involved in the misspliced form of the CCK-B receptor gene in pancreatic cancer cells (33). Furthermore, specific cellular environment plays a role in determining the nature of alternative splicing. The high temperature and low pH in the tumor tissue environment may exert an effect on the structure of the pre-mRNA and may lead to a reduced recognition by the splice machinery (34).

In our case, one of the specific splicing variant SVH-B, which lost exon 2 and exon 2 only, was up-regulated in 60% of clinical HCC samples, whereas, other splicing variants, including SVH-A, SVH-C, and SVH-D, did not exhibit the association with HCC. It was predicted that inclusion/exclusion of exon 2/5 would neither lead to a frame shift nor interfere with the integrated NH2-terminal transmembrane domains and the COOH-terminal armadillo repeat of the four variants. It was also predicted that the exclusion of exon 2 from SVH-A might result in the loss of one protein kinase C phosphorylation site, three N-myristoylation sites, and one casein kinase II site; in addition, the inclusion of exon 5 in SVH-B generated a potential N-myristoylation site compared with SVH-D. It is speculated that these additional posttranslational modifications might determine differential activity of the corresponding proteins. Additional studies on the differences among the four spliced variants in their functional domains, protein structure, binding protein partners, and biological functions are warranted.

It was also observed that the four splicing variants of SVH were present in all of the samples examined, suggesting that multiple alternative splicing of SVH is frequent in both tumor and normal tissue. Alternative splicing may be relevant for the fine tuning of SVH actions, and balance among the different variants may modulate the overall SVH function. Molecular mechanisms on how splicing machineries are involved in carcinogenesis should be studied.

The significance of SVH-B in HCC was demonstrated by the overexpression of SVH-B gaining a fast growth rate and high tumorigenicity in nude mice, as well as by the inhibition of SVH-B causing cell apoptosis. It is suggested that the vast catalogue of cancer cell genotypes is a manifestation of six essential alterations in cell physiology that collectively dictate malignant growth: self-sufficiency in growth signals; insensitivity to growth-inhibitory signals; evasion of programmed cell death; limitless replicative potential; sustained angiogenesis; and tissue invasion and metastasis (35). Our data imply that SVH-B may be positively related to cell growth and tumorigenesis and may be involved in cell resistance toward apoptosis.

SVH encoded a novel human armadillo repeat protein, with significant similarities to the ALEX1, ALEX2, and ALEX3 genes. All of the four proteins had the NH2-terminal transmembrane domains and the COOH-terminal armadillo repeat. Similar to the ALEX genes, SVH carried the armadillo repeat less than six times; thus, it was not a classical member of the armadillo-repeat family (36). However, the SVH gene was located on chromosome 7q11.22, and all three ALEX genes were located on the same chromosomal interval Xq21.33-q22.2. Moreover, alternative splicing was detected in the coding sequence of SVH, although the entire coding regions of ALEX genes resided in a single exon (21).

Notably, it was reported that expression of ALEX1 and ALEX2 was lost or significantly reduced in human lung, prostate, colon, pancreas, and ovarian carcinomas and also in the cell lines established from different human carcinomas. However, the involvement of the genes in HCC was not tested. Kurochkin et al. speculated that ALEX genes might play a role in suppression of tumors originating from epithelial tissues (21). It is very interesting that SVH and ALEX proteins are both related to carcinogenesis, although SVH-B is in positive correlation in HCC, whereas ALEX proteins are in negative correlation in various carcinomas. We noticed that SVH was highly expressed in...
human liver, whereas ALEX transcripts were barely detectable in liver (21). The armadillo repeat domain is thought to be involved in protein-protein interaction (37–39). Armadillo family members have revealed diverse cellular locations and have been implicated in a variety of processes including tumorigenesis (36). Functionally, the armadillo family members may play different roles in carcinogenesis. For example, β-catenin (40), δ-catenin (41, 42), and p120 (43) possess oncogenic activities, yet APC is a tumor suppressor gene (37). The different roles of SVH and ALEX genes may be related to their cellular specificities and the protein partners interacting with specific armadillo family members. Seeking proteins that interact with the SVH-B variant but not with other transcription variants, thus, becomes a preferable approach in revealing the molecular mechanism related to the role of SVH-B in hepatocarcinogenesis.

REFERENCES


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A Specific Splicing Variant of SVH, a Novel Human Armadillo Repeat Protein, Is Up-Regulated in Hepatocellular Carcinomas

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