Annals of Diagnostic Pathology 39 (2019) 86–91

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

journal homepage: www.elsevier.com/locate/anndiagpath

Original Contribution

Utilization of spectrins βI and βIII in diagnosis of hepatocellular carcinoma☆

Shaomin Hu[1], Deborah Jue[1], Joseph Albanese, Yanhua Wang*, Qiang Liu*

Department of Pathology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY 10467, United States of America

ARTICLE INFO

Keywords:
Spectrin βI
Spectrin βIII
Hepatocellular carcinoma
Focal nodular hyperplasia
Hepatic adenoma
Cholangiocarcinoma

ABSTRACT

Spectrins are a group of cytoskeletal proteins which participate in many important cellular functions. It has been suggested that loss of spectrin isoforms may be associated with tumorigenesis of lymphoma, leukemia, gastric cancer and hepatocellular carcinoma (HCC). We recently reported that βI spectrin expression was present in normal hepatocytes but lost in HCC cells, which suggested that spectrins may be helpful markers in diagnosis of HCC. In this study, using immunohistochemical staining, we further investigated the expression pattern of four spectrin isoforms (αII, βI-III) on different benign and malignant liver tumors including focal nodular hyperplasia (FNH), hepatic adenoma (HA), HCC, and cholangiocarcinoma (CC). The results revealed that βI spectrin was moderately to strongly positive in FNH and HA tissues, but was only weakly positive or lost in HCC cases and was weakly positive in all CC cases. In addition, the βIII spectrin, majority of which was moderately positive in both FNH and HA tissues, was mostly lost in poorly differentiated HCC but remained at least moderately positive in most CC cases. These results suggest that spectrins βI and βIII may be used to differentiate well differentiated HCC from FNH or HA, and poorly differentiated HCC from CC, respectively.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the major leading causes of cancer deaths worldwide, with over 600,000 deaths annually [1]. Early diagnosis of HCC is critical for effective and efficient care for patients. Although there are various stains widely available, it can still be difficult to diagnose HCC in liver biopsies at both ends of the spectrum: well differentiated HCC versus a benign lesion, and poorly differentiated HCC versus cholangiocarcinoma (CC).

Spectrins are a group of cytoskeletal proteins which are important in maintaining plasma membrane integrity and cytoskeletal structure, sorting proteins, regulating cell proliferation, and involving in calcium-mediated and tyrosine kinase-phosphatase signal transduction [2,3]. Spectrin comprises α- and β-subunits that form an antiparallel dimer. They were originally identified in erythrocyte plasma membranes, with the first spectrin subunits identified as αI and βI [3,4]. Isoforms αII and βII–V have now been described, along with various splicing isoforms [2].

Spectrins have been extensively studied in hematology, but only very few studies explored their roles in HCC. Molecular studies have revealed βII spectrin to be a tumor-suppressor protein in the tumorigenesis of HCC [5]. Loss of βII spectrin expression was demonstrated in human HCC specimens and cell lines [5-8]. We recently studied the expressional profile of spectrins in various benign tissues and corresponding carcinoma specimens, and revealed that βI spectrin expression was present in normal hepatocytes but lost in HCC cells [9]. These findings suggest that detection of spectrin expression may be helpful in diagnosis of HCC. The goal of the present study is to see if spectrin immunostain can aid in the differentiation of HCC from benign liver lesions and CC.

2. Materials and methods

2.1. Case selection

This retrospective study was approved by the Institutional Review Board of our medical school. Archives at Department of Pathology of our institution were searched for cases of focal nodular hyperplasia (FNH, n = 5), hepatic adenoma (HA, n = 5), well to moderately differentiated HCC (n = 8), poorly differentiated HCC (n = 4, including one undifferentiated HCC) and intrahepatic CC (n = 5). The clinical information of the cases was summarized in Table 1, and representative

☆ The authors declare no conflict of interest.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

* Corresponding authors at: Montefiore Medical Center, Albert Einstein College of Medicine, 111 E 210th St, Bronx, NY 10467, United States of America.
E-mail addresses: ywang@Montefiore.org (Y. Wang), qliu@Montefiore.org (Q. Liu).

[1] Both authors contributed equally to this manuscript.

https://doi.org/10.1016/j.anndiagpath.2019.02.009

Table 1
Summary of clinical information of the cases.

Age at diagnosis (years)	Gender	Relevant clinical history[a]	Relevant clinical presentation	Tumor size (cm)	Procedure done
Focal nodular hyperplasia					
26	F	N/A	Heartburn, liver mass shown on ultrasound	8	Partial hepatectomy
10	F	Obesity	elevated liver function tests, liver mass shown on ultrasound	13	Left hepatectomy
36	F	Oral contraceptive pills use	Asymptomatic, incidental finding	6.5	Segment 6 partial hepatectomy
23	F	Nonalcoholic steatohepatitis	Elevated liver function tests, mass shown on ultrasound	3.7	Caudate lobe partial hepatectomy
26	F	N/A	Abdominal pain, liver mass found on CT	8	Segment 7 wedge resection
Hepatic adenoma					
39	F	Oral contraceptive pills use	Elevated alkaline phosphatase, liver mass shown on imaging	4.5 and 14.0	Partial hepatectomy
46	F	N/A	Elevated liver function tests, liver mass shown on ultrasound	5	Segment 6 partial hepatectomy
31	F	N/A	Abdominal pain, liver mass found on CT	1.5	Left lateral partial hepatectomy
53	F	History of superficial high grade papillary urothelial carcinoma	Found incidentally on imaging	4	Partial hepatectomy
48	F	Obesity	Found incidentally on CT	3	Segment 6 partial hepatectomy
Well to moderately differentiated hepatocellular carcinoma					
64	M	Heptitis C, cirrhosis	Found incidentally on MRI	2	Left hepatectomy
69	M	Heptitis C, alcohol abuse, laryngeal cancer	Fever, abdominal pain, liver lesion found on CT	3	Left hepatectomy
63	M	Heptitis C for 35 years, cirrhosis	Liver mass found on screening imaging	1.5	Partial hepatectomy
22	F	N/A	Abdominal pain	7	Right hepatectomy
66	M	Heptitis C, alcohol abuse, cirhosis	Liver mass shown on ultrasound	4.6	Partial hepatectomy and omentectomy
66	M	Hepatitis C	Chest pain, liver mass found on MRI	3.2	Segments 4, 5 partial hepatectomy
55	F	N/A	Decreased appetite, weight loss, abdominal pain	6	Partial hepatectomy
72	M	Hepatitis C	Jaundice, liver mass found on ultrasounds	6	Right hepatectomy
Poorly differentiated hepatocellular carcinoma					
63	F	Hepatitis C, alcohol abuse, cirrhosis	Abdominal pain, liver mass found on CT	1.1	Right hepatectomy
66	M	Hepatitis C, cirrhosis	Liver mass found on screening imaging	2.5	Right lobe partial hepatectomy
54	F	N/A	Presented with right upper abdominal pain, elevated alpha-fetoprotein, CT showed right lobe/mass	16	Partial hepatectomy of segments 5, 6, 7
64	M	Hepatitis C, alcoholic abuse, cirrhosis	Liver mass found by imaging, admitted for nausea and weakness	4.6	Hepatectomy
Cholangiocarcinoma					
39	M	Hepatitis B	Liver mass shown on ultrasound	13.7	Partial hepatectomy
72	F	N/A	Subjective fever, loss of appetite, weight loss	7.8	Left lobe partial hepatectomy
79	M	N/A	Found incidentally on CT during workup for hematuria	6.5	Segment 7 partial hepatectomy
66	M	N/A	Jaundice and pruritis for 1 month	4.5	Right hepatectomy
72	F	Hepatitis C	Liver mass found on screening MRI	2.3	Partial hepatectomy

[a] N/A: not available.

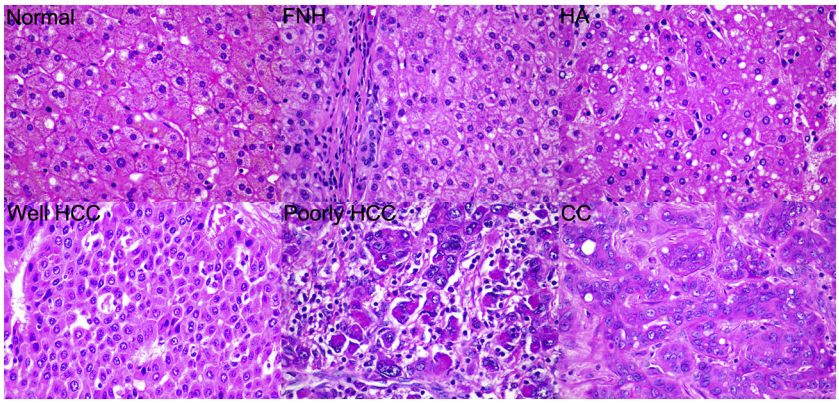

Fig. 1. Representative histomorphology of normal liver parenchyma (normal), focal nodular hyperplasia (FNH), hepatic adenoma (HA), well differentiated hepatocellular carcinoma (well HCC), poorly differentiated hepatocellular carcinoma (poorly HCC) and cholangiocarcinoma (CC) cases (H&E, original magnification 400×).

histomorphology of each type of neoplasm was shown in Fig. 1. The cases were independently reviewed by three pathologists (D.J., Q.L. and Y.W.), and a representative block of each case was selected for immunohistochemical stain of αII, βI, βII, and βIII spectrins. αI spectrin is not included in this study, as its expression is mostly limited to the bone marrow tissue (restricted to erythrocytes), placenta and testis [10].

2.2. Immunohistochemical studies

The primary antibodies used in this study are: monoclonal anti-αII antibody (Becton-Dickinson Biosciences, San Jose, CA; clone 35, 1:50 dilution), monoclonal anti-βI antibody (Affinity Bioreagents, Golden, CO; clone 4C3, 1:100 dilution), monoclonal anti-βII antibody (Becton-Dickinson Biosciences, San Jose, CA; clone 42, 1:4000 dilution), and polyclonal anti-βIII antibody (Santa Cruz Biotech, Santa Cruz, CA; rabbit polyclonal, 1:100 dilution). Representative formalin-fixed, paraffin-embedded tissue sections were antigen-retrieved and immunostained as described before [11,12]. A stain was considered positive if it was expressed by at least 20% of the neoplastic cells [11,12]. The intensity of a positive staining was further interpreted as weak, intermediate or strong (Fig. 2). The subcellular localization was recorded as membranous, cytoplasmic, or nuclear. Staining of tumor/lesion-adjacent normal hepatocyte was used as internal normal control. The immunostain slides were reviewed and scored by three pathologists (D.J., Q.L. and Y.W.).

3. Results

Moderate to strong cytoplasmic staining of βI spectrin was found in normal liver parenchyma and all FNH (n = 5) and HA (n = 5) cases. However, the staining was negative (n = 5, 62.5%) or weak (n = 3, 37.5%) in all 8 well to moderately differentiated HCC cases (in both well and moderately differentiated areas), negative (n = 2, 50%) or weak (n = 2, 50%) in all four poorly differentiated HCC cases, and was weak in all CC (n = 5) cases (Table 2, Fig. 3). The tumor adjacent normal liver parenchyma of all HCC and CC cases showed moderate to strong cytoplasmic βI spectrin staining (Fig. 3).

Variable membranous and cytoplasmic staining (from weak to moderate) of βIII spectrin was present in normal liver parenchyma, all FNH and HA cases, and some of the well to moderately differentiated

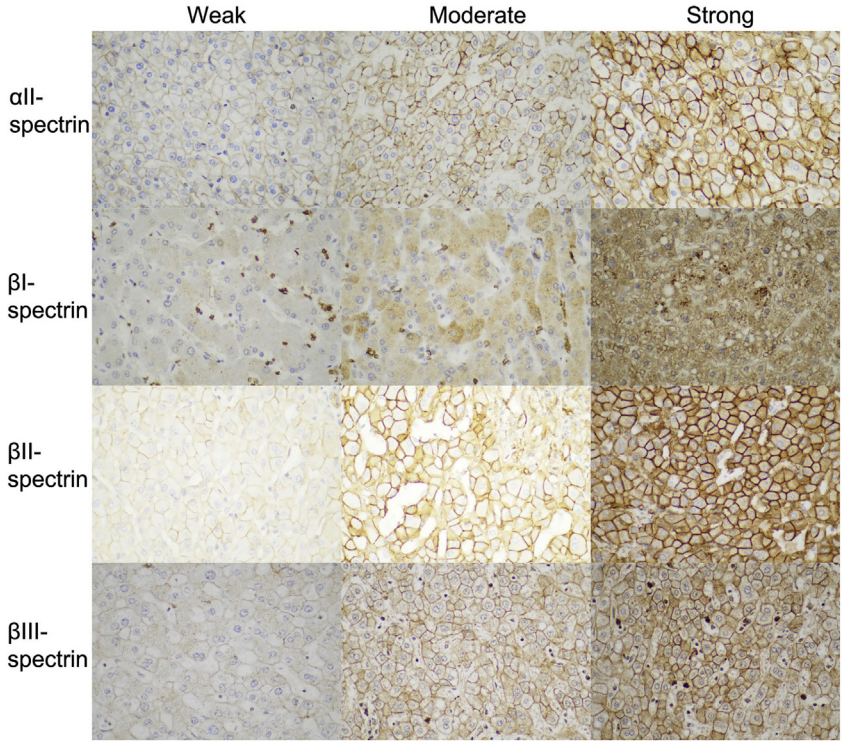

Fig. 2. Representative weak, moderate and strong immunostain of αII, βI, βII and βIII spectrins (original magnification 400×).

Table 2
Summary of immunohistochemical stain.

Daignosis[a]	αII-Spectrin (membranous[b])	βI-Spectrin (cytoplasmic)	βII-Spectrin (membranous[b])	βIII-Spectrin (membranous + cytoplasmic)
FNH (n = 5)	Modrate (n = 5)	Strong (n = 3) moderate (n = 2)	Strong (n = 2) moderate (n = 3)	Moderate (n = 4) weak (n = 1)
HA (n = 5)	Moderate(n = 4) Weak (n = 1)	Strong (n = 3) moderate (n = 2)	Strong (n = 3) moderate (n = 2)	Moderate (n = 4) weak (n = 1)
Well to moderately differentiated HCC (n = 8)	Strong (n = 3) moderate (n = 5)	Weak (n = 3) negative (n = 5)	Strong (n = 4) moderate (n = 4)	Moderate (n = 4) weak (n = 1) negative (n = 3)
Poor differentiated HCC (n = 4 including one undifferentiated)	Strong (n = 1) moderate (n = 3)	Weak (n = 2) negative (n = 2)	Strong (n = 4)	Only cytoplasmic: weak (n = 1) moderate (n = 1) negative (n = 2)
CC (n = 5)	Strong (n = 3) moderate (n = 2)	Weak (n = 5)	Strong (n = 5)	Only cytoplasmic: moderate (n = 3) strong (n = 1) weak (n = 1)

[a] FNH, focal nodular hyperplasia; HA, hepatic adenoma; HCC, hepatocellular carcinoma; CC, cholangiocarcinoma.
[b] Predominantly membranous, with mild cytoplasmic staining.

HCC cases (Table 2, Fig. 4). In contrast, the staining of βIII spectrin in all poorly-differentiated HCC and CC cases was limited to cytoplasm. Three of the four poorly differentiated HCC cases showed negative (n = 2) or weak (n = 1) cytoplasmic staining of βIII spectrin, and only one displayed moderate cytoplasmic staining (Table 2, Fig. 4). The staining of the CC cases revealed moderate to strong cytoplasmic staining in four cases and weak cytoplasmic staining in only one case (Table 2, Fig. 4).

Moderate to strong membranous with mild cytoplasmic expression of βII spectrin was present in normal liver parenchyma and all FNH, HA, HCC and CC cases (Table 2). Various membranous expression (moderate to strong) along with mild cytoplasmic staining of αII was present in all FNH, HA, HCC and CC cases, and the adjacent normal liver parenchyma (Table 2).

4. Discussion

βI spectrin was the first identified β subunit of human spectrin [13]. It was originally identified in erythrocytes as the major component of the membrane cytoskeleton. In human, βI spectrin is encoded by *SPTB* gene, the mutation of which has been associated with red cell membrane disorders [14]. Besides erythrocytes, the RNA level of *SPTB* has been reported to be predominantly present in bone marrow, heart, brain, placenta, and prostate tissue, while very low in liver tissues [10]. In our study, we detected moderate to strong staining of βI spectrin in normal hepatocytes using a monoclonal antibody generated using purified human erythrocyte βI spectrin as immunogen. Strongly positive staining of RBCs in the same section served as an internal positive control. Similar moderate to strong staining pattern was also observed in all FNH and HA cases. Interestingly, all HCC cases were stained negatively or only weakly for βI spectrin. More specifically, βI spectrin staining was absent in 5/8 (62.5%) of well to moderately differentiated HCC cases (in both well and moderately differentiated areas), and was weakly stained in the remaining 3/8 cases (37.5%). These results are consistent with our previous finding that βI spectrin staining was lost in HCC [9], and suggests that βI spectrin is a potential marker for diagnosing well differentiated HCC from the benign mimics. All the CC cases showed weakly positive βI spectrin staining.

βIII spectrin was identified to be a major component of the Golgi and vesicular membrane skeletons [15]. The βIII spectrin protein is widely expressed in various human tissues. It is highly expressed in brain and moderately presents in major organs including liver [10]. In brain, mutation of βIII spectrin has been shown to cause spinocerebellar ataxia type 5 and seizure disorders [16,17]. So far, the role of βIII spectrin in the liver remains unknown. We previously revealed that βIII spectrin is positively stained in both normal liver (n = 3) and HCC tissue (n = 3) using a polyclonal anti-βIII spectrin antibody [9]. In this study, we revealed that weak to moderate membranous and cytoplasmic βIII spectrin stain was observed in all FNH and HA cases and half (4/8, 50%) of the well to moderately differentiated HCC cases. Majority of the poorly differentiated HCC cases (3/4, 75%) were negative to weak for βIII spectrin stain. In contrast, most of CC cases (4/5, 80%) showed moderate to strong βIII spectrin stain. These results suggest that βIII spectrin stain could have some value in differentiating poorly differentiated HCC from CC, while its value in diagnosing well to moderately differentiated HCC versus HA or FNH is limited.

βII spectrin is the most common member of non-erythrocytic spectrins. It is a cytoskeletal protein that has critical role in posttranslational

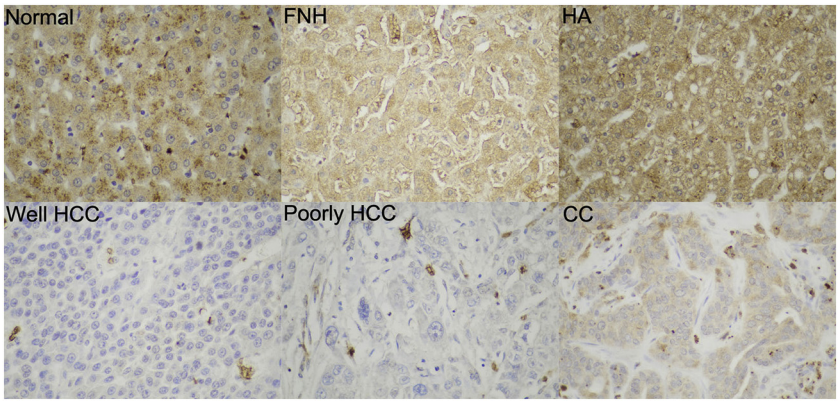

Fig. 3. Representative βI spectrin immunostain of normal liver parenchyma (normal), focal nodular hyperplasia (FNH), hepatic adenoma (HA), well differentiated hepatocellular carcinoma (well HCC), poorly differentiated hepatocellular carcinoma (poorly HCC) and cholangiocarcinoma (CC) cases (original magnification 400×).

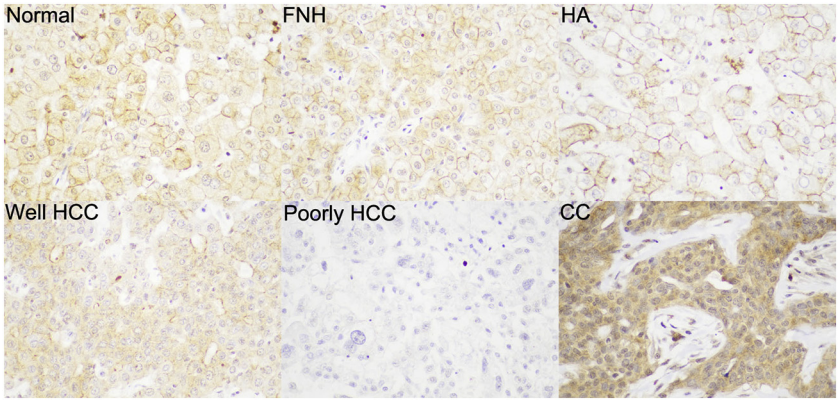

Fig. 4. Representative βIII spectrin immunostain of normal liver parenchyma (normal), focal nodular hyperplasia (FNH), hepatic adenoma (HA), well differentiated hepatocellular carcinoma (well HCC), poorly differentiated hepatocellular carcinoma (poorly HCC) and cholangiocarcinoma (CC) cases (original magnification 400×).

targeting and localization of essential membrane proteins and in signal transduction [18]. Ubiquitous expression of βII spectrin has been detected in most of the human tissues including heart and liver [10]. Many studies have revealed βII spectrin is an important protein in maintaining normal cardiac membrane excitability, mechanical function and embryogenesis [18,19]. An alternatively spliced short variant of βII spectrin called embryonic liver b-fodrin 3 (ELF3) was identified to be an essential adaptor protein of the TGF-β pathway [8,20]. ELF3 is a tumor suppressor and plays an important role in liver development and hepatocyte differentiation. Mice with heterozygous deletion of ELF3 spontaneously developed HCC [5]. The expression of ELF3 was located at the basolateral membrane, cytoplasmic and nuclear compartments of hepatocytes [5]. Nuclear ELF3 expression was demonstrated to be significantly reduced in human HCC specimens and cell lines using an anti-ELF antibody against its residuals 2–14 [5-7]. Interestingly, in our study, using a monoclonal antibody generated against Human βII spectrin amino acid 2101–2189, we detected moderate to strong βII spectrin staining in normal hepatocytes and FNH and HA cases, which was limited mostly to membrane. The nuclear stain of βII spectrin was negative. Furthermore, no significant difference in the staining pattern or density of βII spectrin was observed in HCC cases, as compared to those of FNH, HA or CC cases. Therefore, it indicates that human βII spectrin functions differently from EFT3 isoform in hepatocytes. Further investigating the role of EFT3 in the diagnosis of HCC would be of interest when commercial anti-EFT3 antibody becomes available.

αII spectrin is a 285 kDa scaffolding protein encoded by *SPTAN1* which is abundantly expressed in most eukaryotic cells [10]. Studies in animal models revealed that αII spectrin deficiency is embryonically lethal. Mice with homozygous deletion of αII spectrin died at embryonic day 12.5 due to malformations of the neural tube and cardiac systems [21]. αII-spectrin was also reported to be involved in immunological synapse formation and stability during T-cell activation [22], in invadosome stability and extracellular matrix degradation [23], and in DNA repair and cell cycle regulation [24]. In humans, point mutations or in-frame deletions and duplications of *SPTAN1* have been linked to severe neurodevelopmental impairment such as west syndrome, infantile epileptic encephalopathy and childhood onset epilepsy syndromes [25]. So far, the role of αII spectrin in liver development or function has not been reported. We detected variable αII spectrin staining (weak to strong) in normal liver, FNH and HA tissue. Although αII spectrin is the only α spectrin in hepatocytes that forms heterodimer with βI spectrin (which was lost in HCC cases as mentioned above) and βIII spectrin (which was lost in poorly differentiated HCC cases as mentioned above), we didn't observe significant changes in αII spectrin staining pattern between HCC and normal hepatocytes or benign liver tumors.

5. Conclusion

In conclusion, in this study, we found that βI spectrin was only weakly stained or lost in HCC and CC cases while at least moderately stained in normal hepatocytes and all FNH and HA cases. We also revealed that βIII spectrin was weakly stained or lost in most poorly differentiated HCC cases but retained moderate to strong stain in most CC cases. These findings suggest, for the first time, that βI and βIII spectrins could be helpful in differentiating HCC from FNH or HA and in differentiating poorly differentiated HCC from CC, respectively. Of note, this is a pilot study with limited numbers of cases investigated. Large-scale studies are necessary to further evaluate the usefulness of these two markers for clinical diagnosis of HCC.

References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394–424.
[2] Liem RK. Cytoskeletal integrators: the spectrin superfamily. Cold Spring Harb Perspect Biol 2016;8(10).
[3] Machnicka B, Czogalla A, Hryniewicz-Jankowska A, Boguslawska DM, Grochowalska R, Heger E, et al. Spectrins: a structural platform for stabilization and activation of membrane channels, receptors and transporters. Biochim Biophys Acta 2014;1838(2):620–34.
[4] Marchesi VT, Steers Jr. E. Selective solubilization of a protein component of the red cell membrane. Science 1968;159(3811):203–4.
[5] Kitisin K, Ganesan N, Tang Y, Jogunoori W, Volpe EA, Kim SS, et al. Disruption of transforming growth factor-beta signaling through beta-spectrin ELF leads to hepatocellular cancer through cyclin D1 activation. Oncogene 2007;26(50):7103–10.
[6] Baek HJ, Lim SC, Kitisin K, Jogunoori W, Tang Y, Marshall MB, et al. Hepatocellular cancer arises from loss of transforming growth factor beta signaling adaptor protein embryonic liver fodrin through abnormal angiogenesis. Hepatology 2008;48(4):1128–37.
[7] Zhi X, Lin L, Yang S, Bhuvaneshwar K, Wang H, Gusev Y, et al. betaII-Spectrin (SPTBN1) suppresses progression of hepatocellular carcinoma and Wnt signaling by regulation of Wnt inhibitor kallistatin. Hepatology 2015;61(2):598–612.
[8] Tang Y, Katuri V, Dillner A, Mishra B, Deng CX, Mishra L. Disruption of transforming growth factor-beta signaling in ELF beta-spectrin-deficient mice. Science 2003;299(5606):574–7.
[9] Wang Y, Khader S, Mehlman M, Albanese J, Ratech H. Loss of αII and βIII spectrin isoforms in body fluids is associated with metastasis. Adv Cytol Pathol 2017;2(1):00007.
[10] Fagerberg L, Hallstrom BM, Oksvold P, Kampf C, Djureinovic D, Odeberg J, et al. Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics. Mol Cell Proteomics 2014;13(2):397–406.
[11] Gorman EB, Chen L, Albanese J, Ratech H. Patterns of spectrin expression in B-cell lymphomas: loss of spectrin isoforms is associated with nodule-forming and germinal center-related lymphomas. Mod Pathol 2007;20(12):1245–52.
[12] Wolgast LR, Cannizzarro LA, Ramesh KH, Xue X, Wang D, Bhattacharyya PK, et al. Spectrin isoforms: differential expression in normal hematopoiesis and alterations in neoplastic bone marrow disorders. Am J Clin Pathol 2011;136(2):300–8.
[13] Winkelmann JC, Chang JG, Tse WT, Scarpa AL, Marchesi VT, Forget BG. Full-length sequence of the cDNA for human erythroid beta-spectrin. J Biol Chem 1990;265(20):11827–32.
[14] Da Costa L, Galimand J, Fenneteau O, Mohandas N. Hereditary spherocytosis, elliptocytosis, and other red cell membrane disorders. Blood Rev 2013;27(4):167–78.
[15] Stankewich MC, Tse WT, Peters LL, Ch'ng Y, John KM, Stabach PR, et al. A widely expressed betaIII spectrin associated with Golgi and cytoplasmic vesicles. Proc Natl

Acad Sci U S A 1998;95(24):14158–63.
[16] Stankewich MC, Gwynn B, Ardito T, Ji L, Kim J, Robledo RF, et al. Targeted deletion of betaIII spectrin impairs synaptogenesis and generates ataxic and seizure phenotypes. Proc Natl Acad Sci U S A 2010;107(13):6022–7.
[17] Ikeda Y, Dick KA, Weatherspoon MR, Gincel D, Armbrust KR, Dalton JC, et al. Spectrin mutations cause spinocerebellar ataxia type 5. Nat Genet 2006;38(2):184–90.
[18] Derbala MH, Guo AS, Mohler PJ, Smith SA. The role of betaII spectrin in cardiac health and disease. Life Sci 2018;192:278–85.
[19] Smith SA, Hughes LD, Kline CF, Kempton AN, Dorn LE, Curran J, et al. Dysfunction of the beta2-spectrin-based pathway in human heart failure. Am J Physiol Heart Circ Physiol 2016;310(11):H1583–91.
[20] Mishra L, Cai T, Yu P, Monga SP, Mishra B. Elf3 encodes a novel 200-kD beta-spectrin: role in liver development. Oncogene 1999;18(2):353–64.
[21] Stankewich MC, Cianci CD, Stabach PR, Ji L, Nath A, Morrow JS. Cell organization, growth, and neural and cardiac development require alphaII-spectrin. J Cell Sci 2011;124(Pt 23):3956–66.
[22] Meissner JM, Sikorski AF, Nawara T, Grzesiak J, Marycz K, Boguslawska DM, et al. alphaII-spectrin in T cells is involved in the regulation of cell-cell contact leading to immunological synapse formation? PLoS One 2017;12(12):e0189545.
[23] Ponceau A, Albiges-Rizo C, Colin-Aronovicz Y, Destaing O, Lecomte MC. alphaII-spectrin regulates invadosome stability and extracellular matrix degradation. PLoS One 2015;10(4):e0120781.
[24] Mjelle R, Hegre SA, Aas PA, Slupphaug G, Drablos F, Saetrom P, et al. Cell cycle regulation of human DNA repair and chromatin remodeling genes. DNA Repair (Amst) 2015;30:53–67.
[25] Syrbe S, Harms FL, Parrini E, Montomoli M, Mutze U, Helbig KL, et al. Delineating SPTAN1 associated phenotypes: from isolated epilepsy to encephalopathy with progressive brain atrophy. Brain 2017;140(9):2322–36.