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Original contribution

Synemin expression is widespread in liver fibrosis and is induced in proliferating and malignant biliary epithelial cells☆

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Summary The expression profile of intermediate filament proteins provides valuable information on the differentiation of specific cell populations and their contributions to disease. Synemin is one of the few intermediate filament proteins whose expression pattern during pathological situations is poorly characterized. We conducted a systematic immunohistochemical investigation of synemin expression in human liver diseases. In normal liver and in the early prefibrotic phase of chronic viral hepatitis or steatohepatitis, synemin was localized in hepatic stellate cells (HSCs) and vascular cells. Fibrotic or cirrhotic liver disease promoted intense synemin staining of HSCs in parenchymal and fibrous zones. In portal tract fibroblasts, synemin expression was rare under normal conditions but was widespread in severe inflammatory diseases associated with portal expansion, consistent with the notion that some fibrotic reactions involve HSCs, whereas others involve both HSCs and portal fibroblasts. Most sinusoidal endothelial cells were synemin negative in normal liver but were positive in hepatocellular carcinomas. Synemin was also expressed in the epithelial component of the ductular reaction in various liver diseases and in cholangiocarcinoma cells but not in hepatocellular carcinoma cells. Myofibroblasts in stromal reaction to carcinomas were synemin positive. Thus, synemin helps delineate different types of liver fibrotic reactions and provides a marker for sinusoidal capillarization and for proliferating biliary epithelial and cholangiocarcinoma cells.

1. Introduction

Cytoskeletal proteins are valuable markers for identifying liver cell types and analyzing their contributions to disease [1-3]. Of particular interest are intermediate filament (IF)

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proteins, whose expression patterns are highly cell-type specific [1,2]. Hepatocytes, for example, express keratins 8 and 18, whereas biliary epithelial cells express keratins 7 and 19 in addition to keratins 8 and 18 [1]. Keratins are not found in hepatic stellate cells (HSCs), which instead express (at least in rats) glial fibrillary acid protein (GFAP), desmin, and vimentin [1]. In a rat model of fibrosis, HSCs synthesized nestin, a type IV IF protein expressed mainly during astrocyte and muscle development [4].

Synemin is a type IV IF protein whose C-terminal domain is 3 to 4 times larger than that of most other IF proteins [5,6] and, uniquely, contains binding sites for microfilament-associated proteins (eg, α-actinin, vinculin, and dystrobrevin) [5,7,8], suggesting that synemin functions in linking IFs to microfilaments. In birds and mammals, synemin is present in most contractile cells of ectodermal or mesodermal origin, including myoepithelial, skeletal, cardiac, and smooth muscle cells [6,9-11]. Synemin is also expressed in noncontractile cells derived from the mesoderm, such as avian erythrocytes [12], or from the ectoderm, such as lens [13] and glial cells [11,13,14]. Glial cells expressing synemin include Schwann cells [11], Muller cells [13], and developing, but not mature, cerebral astrocytes [14]. In the optic nerve, however, mature astrocytes express synemin [11], as do malignant and reactive astrocytes [15].

Little is known about synemin expression in disease outside the nervous system. The liver contains mesenchymal and epithelial cell types whose phenotypes are affected by various pathologic conditions. For instance, during liver fibrogenesis, HSCs and portal fibroblasts acquire a myofibroblastic phenotype and actively deposit extracellular matrix proteins [16]. Like other cell types that express synemin, normal and fibrotic HSCs are characterized by GFAP expression (at least in rats) [17-19] and contractile features [3]. In this study, we systematically investigated synemin expression profiles in normal and diseased human liver. The results revealed that synemin is abundant in HSCs of normal and fibrotic livers and that its expression is induced in portal tract fibroblasts with the progression of portal fibrosis. Interestingly, synemin expression was also upregulated in proliferating and malignant biliary epithelial cells. Our results on synemin distribution in the normal rat and human liver are in agreement with those recently published by Uyama et al [20]. These authors also demonstrated that, in cultured rat HSCs, synemin is present in a subset of focal adhesion sites.

2. Materials and methods

2.1. Human tissue selection and classification

Formalin-fixed, paraffin-embedded human liver tissues were obtained from archived material. A well-defined homogeneous cohort of cases was selected (Table 1).

Table 1 Immunohistochemical localization of synemin in mesenchymal cells in normal and diseased human liver

Disease/condition	Immunolabeling score			
	No. of cases	Perisinusoidal	Portal	Fibrous septa/desmoplasia
Normal	7	1+	−/+	N/A
Alcoholic steatohepatitis	8	3+	−/+	N/A
With fibrosis/cirrhosis	9	4+	2+	4+
Nonalcoholic steatohepatitis	7	3+	−/+	N/A
With fibrosis/cirrhosis	6	4+	2+	4+
Chronic hepatitis B				
Stage 0	3	1+	1+	N/A
Stage 1	6	2+	2+	1+
Stage 2	6	2+	3+	2+
Stage 3	5	3+	4+	4+
Stage 4	4	3+	4+	4+
Chronic hepatitis C				
Stage 0	4	2+	1+	N/A
Stage 1	8	2+	2+	1+
Stage 2	5	2+	3+	2+
Stage 3	12	3+	4+	4+
Stage 4	11	3+	4+	4+
Autoimmune hepatitis, stage 2	3	3+	4+	3+
Primary biliary cirrhosis, stage 3	4	2+	3+	4+
Primary sclerosing cholangitis	4	2+	4+	4+
Secondary biliary fibrosis	6	1+	4+	4+
Intrahepatic cholangiocarcinoma	8	0	0	4+
Hepatocellular carcinoma	11	3+	N/A	3+
Metastatic tumors	12	N/A	N/A	4+

Abbreviation: N/A, not applicable.