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Inositol trisphosphate receptor, type 3 (InsP3R3) is regulated by microRNA-506 (miR-506) which is upregulated in primary biliary cirrhosis (PBC)

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The type III isoform of the inositol 1,4,5-trisphosphate receptor (InsP3R3) is apically localized and triggers Ca2+ waves and secretion in a number of polarized epithelia. However, nothing is known about epigenetic regulation of this InsP3R isoform. We investigated miRNA regulation of $InsP_3R_3$ in primary bile duct epithelia (cholangiocytes) and in the H69 cholangiocyte cell line, because the role of InsP3R3 in cholangiocyte Ca2+ signaling and secretion is well established and because loss of InsP3R3 from cholangiocytes is responsible for the impairment in bile secretion that occurs in a number of liver diseases. Analysis of the 3'-UTR of human InsP3R3 mRNA revealed two highly conserved binding sites for miR-506. Transfection of miR-506 mimics into cell lines expressing InsP3R3-3'UTR-luciferase led to decreased reporter activity, while co-transfection with miR-506 inhibitors led to enhanced activity. Reporter activity was abrogated in isolated mutant proximal or distal miR-506 constructs in miR-506 transfected HEK293 cells. $InsP_3R_3$ protein levels were decreased by miR-506 mimics and increased by inhibitors, and $InsP_3R_3$ expression was markedly decreased in H69 cells stably transfected with miR506 relative to control cells. miR506-H69 cells exhibited a fibrotic signature. *In situ* hybridization revealed elevated miR506 expression *in vivo* in human diseased cholangiocytes. Histamine-induced, InsP3-mediated Ca2+ signals were decreased by 50% in stable-miR-506 cells compared to controls. Finally, InsP3R3-mediated fluid secretion was significantly decreased in isolated bile duct units (IBDU) transfected with miR-506, relative to control IBDU. Together, these data identify miR-506 as a regulator of InsP3R3 expression and of $InsP_3R_3$-mediated Ca2+ signaling and secretion.

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Liver transplantation in a patient with primary Antiphospholipid syndrome and Budd-Chiari syndrome

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The Antiphospholipid Syndrome (APS) is an acquired thrombophilic disorder in which auto antibodies are produced to a variety of phospholipids determinants of cell membranes or phospholipid binding proteins. APS is characterized by a hypercoagulable state potentially resulting in thrombosis of all segments of the vascular bed. Venous thrombosis typically presents with deep vein thrombosis (DVT) in the lower extremities. Other thrombotic presentations include osteonecrosis and venous occlusion of solid organs such as the liver (Budd-Chiari Syndrome (BCS)), kidneys and the adrenal glands with resulting in adrenal insufficiency. There are few reports about association between antiphospholipid antibodies (aPL) and development of BCS. We report the case of BCS development in young Russian male with primary APS. His disease began at the age of 15 with ileofemoral thrombosis of the left leg. Due to irregular taking of anticoagulants, the development of ileofemoral thrombosis on the right side was noted. An ascites and an evident hepatic insufficiency were noted after 5 years from the onset. In January 2011 an ascites gradually appeared and then because of the accumulation of large quantity of liquid, a laparocentesis was performed resulting in evacuation of 11 liters of liquid; gradual rising of liver failure was noted. Inferior vena cava thrombosis-a stenosis of its infrarenal part and BCS were diagnosed by CT angiography. BCS led to the development of liver cirrhosis with its evident functional deficiency and the development of multiple organ failure. An additional thrombosis risk factor was heterozygous prothrombin gene (G20210A) mutation. Besides that, the patient showed polymorphism in PAI-1 gene (4G/4G genotypes of PAI-1). The patient underwent orthotopic liver transplantation on 26.08.2012. At present time his state is good, the blood flow in the liver restored and its function is not impaired.

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