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**PROAPOPTOTIC PROTEIN BIM AND ITS UPSTREAM ACTIVATOR FOXO3A ARE OVEREXPRESSED IN PRIMARY BILIARY CIRRHOSIS BUT NOT IN PRIMARY SCLEROSING CHOLANGITIS**

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**Introduction** Apoptosis, with subsequent aberrant expression of pyruvate dehydrogenase complex (PDC-E2) on cell surface has been postulated to play an important role in the pathogenesis of Primary Biliary Cirrhosis (PBC). More recently, a particular feature of cholangiocytes that leads to prolonged exposure of an intact immunoreactive PDC-E2 to the immune system within apoptotic blebs has been described. Whether this effect is related to specific for PBC, impaired regulation of apoptotic pathways remains to be established. The transcription factor FoxO3a is known to be an upstream activator of Bim (Bcl-2-interacting mediator of cell death) protein which is involved in cellular apoptosis. The aim of the study was to analyse gene expression of transcription factor FoxO3a and Bim in livers of patients with early PBC, end-stage PBC, end-stage Primary Sclerosing Cholangitis (PSC) and control liver tissue.

**Methods** Total RNA was isolated from liver tissues obtained either during routine percutaneous liver biopsies (early PBC n=21) or from explanted livers from end-stage diseases (PBC n=19; PSC n=8). Liver tissues from large margin resections of HCC were used as controls (n=19). Gene expressions were evaluated using Quantitative Taq Man real time PCR analysis. Protein levels (not measured in early PBC) were assessed with Western Blot.

**Results** As compared to controls, expression of FoxO3a mRNA showed statistically significant increase in both early PBC (2.2-fold increase; p=0.006) and end-stage PBC (4.3-fold increase; p=0.003). Expression of FoxO3a was significantly higher in patients with more advanced fibrosis (F0-2 vs F3-4, p=0.042). Also, a substantial upregulation of Bim mRNA was observed both in early PBC (eightfold increase vs controls; p=0.045). and end-stage PBC (8.2-fold increase vs controls; p=0.003). Correspondingly, levels of Foxo3a and Bim proteins were significantly enhanced in end-stage PBC. Levels of FoxO3a and Bim mRNAs in PSC were not significantly different from controls.

**Conclusion** Upregulation of FoxO3a and Bim observed in PBC but not in PSC may support an involvement of apoptotic pathways in the pathogenesis of this condition.

**Competing interests** None.

**Keywords** apoptosis, Bim, FoxO3a, PBC, PSC.