Editorial

MicroRNAs link inflammation and primary biliary cholangitis

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Primary biliary cholangitis (PBC) is an autoimmune slowly progressive liver disease characterized by the destruction of intrahepatic bile ducts, which gradually evolves into cirrhosis and liver failure (1). Ursodeoxycholic acid (UDCA) is the first choice for the treatment of PBC patients and has shown to significantly reduce the need for liver transplantation (2). The precise aetiology of PBC is not known, but is considered to be related to a combination of genetic, epigenetic and environmental factors. Selected HLA single nucleotide polymorphisms have been associated to PBC (1); however, they are not sufficient to explain the pathogenesis of the disease. Genome-wide association studies showed the existence of additional risk loci that are linked to inflammatory mediators such as interleukins (IL) and members of the tumour necrosis factor (TNF) family (3-5). Genetic alterations account for no more than 20% of PBC, and growing evidence supports the role of epigenetic modifications in the pathogenesis of PBC. Derangement of non coding RNAs (ncRNA) has been associated to PBC. MicroRNAs (miRNA, miR) are small ncRNAs that act at the post transcriptional level and regulate gene expression (6). MiRNAs are involved in a large variety of physiological processes playing crucial roles in maintaining cell homeostasis and finely regulating cellular phenotypes. miRNA profiling of untreated or refractory human PBC tissues showed deregulation of a number of miRNAs that control expression of transcripts involved in cell proliferation, apoptosis, oxidative stress, inflammation, and metabolism (7). More recently, miRNAs were shown to induce a pro-inflammatory cytokine storm that contributes to the development of liver autoimmune cholangitis in a murine model of PBC (8). miR-506 was previously found to be over-expressed in human liver tissues of PBC patients in comparison to healthy donors (7,9). Furthermore, miR-506 is located on the X chromosome in line with the predominant prevalence of PBC in women (10). Banales *et al.* have previously shown that miR-506 can directly target the Cl^-/HCO_3^- anion exchanger 2 (AE2), which controls the intracellular pH homeostasis by stimulating the hepatobiliary secretion of bicarbonate (9). AE2 also mediates the restoration of the secretin response observed following treatment with UDCA (11,12), confirming a central role for AE2 in the pathogenesis of PBC. Despite the beneficial effects of UCDA, novel treatments are urgently needed as around 40% of PBC patients are refractory to UCDA treatment (13). Thus, a better understanding of the mechanisms involved in the pathogenesis of PBC could provide additional opportunities for therapeutics development. In this work, Erice *et al.* investigated the mechanisms responsible for miR-506 upregulation and explored the effect of this miRNA in the inflammatory reaction associated to PBC. Using recombinant luciferase reported vectors the authors identified the region of miR-506 promoter that regulates its expression. miRNAs were shown to be regulated by a variety of mechanisms that include genetic alterations (14), promoter methylation (15), and transduction signalling (16). Recent evidence points to a regulation of miR-506 by long non coding RNAs that act as competing endogenous RNAs (17). Here, authors show that miR-506 expression is regulated by a number of proinflammatory cytokines, which are known to be involved in PBC such as IL-12, IL18, and TNF. Overexpression of miR-506 in human cholangiocytes determined changes of the proteomic profile, in particular

the downregulation of OPA1 and ATP5H and the up-regulation of CAPN1, involved in mitochondrial metabolic processes. Interestingly, miR-506 was able to induce cellular proliferation, and changes in the cholangiocyte phenotype with loss of epithelial markers and increase of mesenchymal, profibrotic and inflammatory markers. Enforced expression of miR-506 could increase DNA damage and primed cholangiocytes to the toxic effect of bile acids. An increase in mitochondrial metabolism and oxidative stress was also observed after stable expression of miR-506 in cholangiocytes.

Recent evidence suggests that the peripheral blood mononuclear cells (PBMC) of PBC patients hold a deranged profile of miRNAs that can induce an aberrant immune and inflammatory response (18). In this work, Erice *et al.* showed that PBMC proliferation and function is educated by cholangiocytes with over-expression of miR-506 towards an inflammatory status. These data add significant insights into the pathogenesis of PBC and provide the bases for the exploration of miR-506 as a target of therapy given the inhibition of its expression could not only control the aberrant phenotype of cholangiocytes, but could also reduce the host aberrant immune response that contributes to the poor prognosis of the disease.

Of note, miR-506 was found to be downregulated in a variety of solid tumours (19). However, miR-506 was never described as a driving miRNA in primary liver cancers (20-22). Indeed, hepatic tumours are a rare evolution of PBC and only sporadic cases have been described (23). Interestingly, Erice *et al.* noticed that neither IL-6 nor TGF-b, which are known to be pro-tumorigenic in cholangiocytes (24), can induce expression of miR-506, and miR-506 can in turn stimulates a cytokine storm that does not include pro-tumorigenic cytokines. It could be speculated that the over-expression of miR-506 in PBC acts as a limiting factor for the malignant transformation of cholangiocytes, even though more data are warranted to support this hypothesis.

In conclusion this study provides useful insights into the mechanisms of regulation and the biological effect of miR-506 in human cholangiocytes. It defines a central role for miR-506 in the pathogenesis and inflammatory response of PBC and paves the way for the development of novel therapies for this disease.

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