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Commentary

Looking Into the Crystal Ball: Predicting Non-response to Ursodeoxycholic Acid in Primary Biliary Cholangitis

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Primary biliary cholangitis, formerly designated primary biliary cirrhosis, represents a model cholestatic liver disease characterized by chronic, progressive immune-mediated bile duct destruction mainly affecting middle-aged women. Though its distinct pathogenesis remains to be fully defined, complex environmental-host immunogenic interactions have been highlighted by large-scale genome-wide association studies (GWAS) identifying a total of at least 27 disease-associated human leukocyte antigen (HLA) and non-HLA risk loci (Gulamhusein et al., 2015). The diagnosis can be firmly assumed in the presence of at least two of three criteria including biochemical evidence of chronic cholestasis, presence of pathognomonic anti-mitochondrial antibodies (AMA, targeting the E2 and/or E3BP subunits of the pyruvate dehydrogenase complex) and/or supportive liver histology including florid bile duct lesions. The well-established standard of care consists of the oral hydrophilic bile acid (BA) ursodeoxycholic acid (UDCA), the hitherto only Food and Drug Administration (FDA)-approved agent for PBC treatment, with proven beneficial effects on disease progression as well as transplant-free survival and liver-related mortality. A convincing long-term response to UDCA identifies a low-risk subgroup without disease progression and survival rates comparable to the general population. By contrast, an estimated one in three PBC individuals reveals UDCA suboptimal or non-response as assessed by variable biochemical surrogate endpoints with a special emphasis on serum alkaline phosphatase (ALP) activity (e.g. *Paris* or *Barcelona* criteria), thus conferring high risk of continued disease progression despite treatment ("*high risk PBC*"). Novel prognostic tools, such as the *GLOBE* score, predictive of transplant-free survival in a large cohort of 4119 UDCA-treated individuals, or the *UK-PBC risk* score have recently been reported (Lammers et al., 2015; Carbone et al., 2016). The major drawback, however, remains the *post hoc* nature of determining UDCA response, traditionally after one year, although smaller studies reported adequate reflection of long-term prognosis assessing UDCA response as early as after six months (Zhang et al., 2013). Therefore, an unmet clinical need in PBC research lies in the identification of adequate biomarkers for high-risk disease at diagnosis and prediction criteria of UDCA response applicable early on or even before treatment (Dyson et al., 2015). The reliable *a priori* identification of non-responders represents an opportunity to actively alter future disease trajectories and may be of key importance in prioritizing patients for novel and/or re-purposed second-line treatments. The changing and vital landscape of second-line options in PBC treatment is underscored by the recent conditional FDA licensing of obeticholic acid (OCA) as the first-in-class farnesoid X receptor (FXR) agonist, regulating BA synthesis and transport, after phase III randomized data (*POISE trial*) demonstrated biochemical improvement in approximately 40% of UDCA non-responders (Nevens et al., 2016).

To date, very few information is available providing reasonable projections about future UDCA response at the time of diagnosis. For example, in a recent study using pre-biopsy serum samples of 136 PBC individuals, pre-treatment serum concentrations of IL-8 and soluble CD14 were associated with poor outcome (Umemura et al., 2016). In a Chinese population, the common single nucleotide variant *rs2287618* (p.A444V) in the bile salt export pump (*ABCB11*) gene was significantly underrepresented in UDCA responsive PBC (Chen et al., 2014). In the UK-PBC cohort including 2353 patients, male gender and younger age were correlated to UDCA failure (Carbone et al., 2013).

Against this background, in the current proof-of-concept study published in *EBioMedicine*, Hardie and colleagues examined the differential transcriptomics in a small set of archived liver tissue obtained at PBC diagnosis from formalin fixed paraffin embedded (FFPE) tissue sections (all women aged 36–66 years). Extreme phenotypes were chosen for stratification, i.e. liver transplantation or sustained UDCA response >15 years (13–15 mg/kg, *Paris 1* criteria) to assign high- (n = 6) or low-risk (n = 8) status, respectively (Hardie et al., 2016). Routine histological analyses included hepatic activity index, ductopenia, Scheuer

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and Nakanuma staging, and were not able to consistently differentiate between risk groups. Reflecting a biased, though scientifically sound approach reminiscent of GWAS findings, an immune-directed RNA panel originally devised for cancer immunology was used as gene expression profiling technology previously reported to overcome the critical issue of valid RNA quantification in the presence of high-level degradation as is typical of FFPE material. Subsequently, principle component analysis (PCA) and hierarchical clustering for transcriptional signatures identified sample clustering with the identification of 34 most significantly differentially expressed genes, which were further characterized by *geneMANIA*. This analysis of the top genes in the high-risk group revealed immunobiologically relevant pathways, including induction of genes involved in T cell activation and apoptosis, interferon γ signalling and leukocyte migration as well as repression of genes in the complement system. Of interest, nine differentially expressed gene signals are shared GWAS-identified PBC loci, such as *HLA-DQ1B*, *SOCS1*, *CD80*, *TNFSF15*, *HLA-G*, *HLA-A*, *HLA-B*, *IL-18* and *STAT1*, highlighting the overarching contribution of immune-associated pathways in PBC pathogenesis. In particular, cyclin dependent kinase inhibitor 1A (CDKN1a) was 1.8-fold induced in high-risk PBC, and its downstream gene product $p21^{WAF1/Cip}$ showed higher expression levels on biliary epithelial cells (BECs) as assessed by immunohistochemistry. $p21^{WAF1/Cip}$ is a well-known marker of cellular senescence (state of irreversible cell cycle arrest), suggesting BEC senescence as an early marker of high-risk PBC. Limitations of the study include the low sample size of only 14 individuals, albeit clinically well-defined with extreme phenotypes, with inherent risks of false positives, and the pathobiologically biased selection of a set of 770 genes. Therefore, retrospective and, at best, prospective validation of the proposed prognostic classification and/or the re-fined use of $p21^{WAF1/Cip}$ immunohistochemistry in independent PBC cohorts is clearly needed.

What are the main conclusions to derive from the study? 1) High- and low-risk PBC may be biologically distinct at an early stage, as baseline mRNA expression signatures might pre-determine risk of progression. 2) BEC senescence may be an early (and clinically targetable by dedicated immunohistochemistry) hallmark of high-risk PBC. On the whole, the authors are to be commended for their work providing valuable impulses for subsequent clinical research with the prospect to move the field from response-guided to baseline risk-guided PBC treatment.

Potential Conflict of Interest

All authors state that no conflict of interest exists.

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