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AGE-DEPEDENT CHANGES IN EXTRACELLULAR MATRIX TURNOVER: AN UNDEREVALUATED ISSUE IN THE APPROACH TO CHRONIC LIVER DISEASES

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List of abbreviations: ECM, extracellular matrix; CLD, chronic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; NAFLD/NASH, non-alcoholic fatty liver disease/nonalcoholic steatohepatitis.

Progressive excess deposition of extracellular matrix (ECM) components in liver parenchyma (i.e., progressive fibrosis) is a prominent feature of any chronic liver disease (CLD) of clinical relevance due, on a worldwide perspective, to persisting injury by chronic infection by hepatitis B (HBV) or C (HCV) viruses, chronic exposure to toxins or drugs (mainly excess alcohol consumption) as well as to altered metabolic conditions or autoimmune causes [1-3]. Whatever the etiology, reiterated liver injury can lead to chronic activation of inflammatory and wound healing response that, in parallel with other mechanisms (including oxidative stress and the derangement of interactions between epithelial and mesenchymal cells) can sustain liver fibrogenesis, the major driving force for any progressive CLD [1-6]. Fibrogenic progression of CLD has a major clinical impact because can lead to cirrhosis, liver failure and/or development of hepatocellular carcinoma (HCC) [1-3,7], with no therapeutic treatment able to specifically target the mechanisms underlying fibrosis being currently approved for clinical use. Independent on the specific etiology, liver cirrhosis is the most common non-neoplastic cause of death among diseases of the hepatobiliary and gastro-intestinal tract in Europe and USA and represents the 7th most common cause of death in western countries [1-3,6-8]. Moreover, HCC is a very aggressive malignant cancer (currently the 5th most common cancer and the 3rd most common cause of cancer mortality worldwide) which very often develops on cirrhosis [9], but, as reported for NAFLD/NASH patients, may also develop in a non-cirrhotic liver [10].

An impressive amount of pre-clinical and clinical studies performed over the last three decades has been extremely successful in elucidating the most relevant cellular and molecular basis of liver fibrosis [1-7,11]. Detailed knowledge about the complex scenario of intra- and extrahepatic cells (and their interactions), mediators, signals and major mechanisms involved in fibrogenesis is now available, together with the fundamental concept that fibrosis and, possibly, even cirrhosis (at least to a certain extent) can be potentially reversible in human CLD [3,6,11]. Further relevant issues have been more

recently emerged, including the role of intestinal microbiota [4], the role of tissue hypoxia and angiogenesis [5,12] as well as the influence of epigenetic changes in modulating fibrogenic progression of CLDs [6,13]. This critical knowledge has started to be translated into novel therapeutic approaches that may serve in the future, as recently outlined [3,6], to implement the first choice approach that is to block chronic injury by curing the disease and/or removing etiology, an issue emphasized by the extraordinary results (as sustained viral response) of the most recent antiviral therapeutic protocols for HBV- and HCV-related CLD [14-17]. According to current views, novel anti-fibrotic therapeutic options able to affect CLD progression may (as single or combined therapy) target ligand receptor interactions, inhibit major profibrogenic mechanisms or promote/accelerate resolution [3,6].

Along these lines, excess and qualitatively altered deposition of ECM components can be conceptually regarded also as a consequence of dysregulated tissue remodeling (i.e., connective tissue turnover). Moreover, emerging evidence suggests that altered components and post-translational modifications of ECM proteins occurring during CLD progression may significantly contribute to initiate and drive disease progression [18]. Although any normal tissue and organ may undergo physiologically to continuous remodeling, ECM turnover in experimental animals and human beings in a CLD is of course exacerbated, leading to an increased release in the circulation of ECM components, mainly different types of collagens and collagen fragments. Detection in the serum of these markers (included in fibrogenic panels) has been proposed and tested, as many other options (see ref. [6]), as a non-invasive way to evaluate either active ECM deposition or its regression/resolution, then also to potentially monitor the efficacy of a specific therapeutic strategy [1-3,6,19-22].

In this issue of the *Journal of Hepatology* Karsdal et al. [23] provide experimental data that may significantly affect our approach to CLD fibrogenic progression or

regression, by showing unequivocally that age is relevant for the turnover of ECM components, an issue previously neglected or, more precisely, under-evaluated. Authors have systematically analyzed age-related changes in ECM turnover in the serum of rats at different ages (from 1 to 12 months). In these experiments a novel panel of serum markers has been evaluated with assays designed to detect specific domains (i.e., fragments) of selected ECM proteins like type I, II, III, IV, V and VI collagen as well as other ECM proteins that allow to differentiate collagen formation and degradation from the simple quantitative evaluation of changes in ECM turnover. Results indicate that for selected markers, like those related to collagen type I formation (P1NP) or degradation (C1M and CTX-I, from either MMP-mediated or cathepsin K-mediated degradation, respectively), with similar results found for collagen type II, the turnover rates were much higher (approx. 30 fold) in young vs old animals. Interestingly, these age-dependent changes in ECM turnover were reported to be very sharp in the first 2-3 months of age, to then reach an apparent plateau after 4-5 months of age, with turnover rate remaining stable up to 12 months. By contrast, the turnover rate of ECM proteins like collagen Type III and Type VI and elastin was age independent, whereas the turnover of collagen type IV, type V and of biglycan was upregulated (2-2.5 fold) with age. Why this message may be potentially relevant for CLD? The concept that serum levels of ECM components may be higher in young than in old individuals was already suggested by some not-recent clinical and experimental studies focused on different tissues and organs, including few studies offering data related to pediatric liver conditions [24-28]. However, the study performed by Karsdal et al. [23], by its rigorous design and straightforward results reported, is the first to unequivocally outline, at least for studies performed on rats, the existence under physiological conditions of two well defined time windows in relation to tissue and ECM turnover: an early window of “modeling” (i.e., the process by which the generation of new tissue or organ from embryogenesis to adulthood is obtained) where ECM turnover is

impressively high and rapidly down-regulated, and a later window of “remodeling” (i.e., the overall changes that maintain a tissue functional by replacing old and/or damaged proteins and cells) in which ECM turnover is stable. The higher ECM turnover rate in young rats versus older animals, particularly impressive in the first two months of age, is likely to be the consequence of several major issues affecting “modeling” of liver parenchyma, including the overall rate of body growth, a different ECM composition and a higher regenerative capability of connective tissues. Indeed, here relies the real problem: a consistent amount of experimental work published in the last three decades to investigate mechanisms involved in fibrosis progression and regression as well as on the evaluation of potential anti-fibrotic drugs, has been performed in young rodents, sometimes of just one to two months of age. As pointed out by Karsdal et al. [23] in their discussion, this raises the possibility that the under-evaluation of the influence of higher basal ECM turnover in young animals may have affected data and conclusions reached in at least some of those studies. It is of course difficult to generalize the entity and significance of the problem because of the several different protocols and strains of animals used in experimental/pre-clinical studies [29-31]. Nevertheless hepatologists must be aware of the fact that basal ECM remodeling due to normal growth has the potential to act as a confounding factor which may either mask or enhance the fibrosis related ECM readouts. Authors of this study also suggest in their conclusions that increased ECM turnover in young animals may have substantially contributed to a scenario that indeed several researchers in the field have faced in the past: exciting positive results obtained when testing anti-fibrotic agents in experimental animals (too young?) that later were found ineffective in clinical studies. The use of older/adult animals, as shown in this study using the standard CCl_4 chronic model in adult rats (then in the “remodeling” window), can help to solve the problem, offering more clean and reliable data on ECM turnover to be potentially translated to patients. As correctly stated by Authors we now need more experimental work to be

performed in order to investigate whether this issue has significant implications for tissue quality and repair processes under conditions of acute or chronic liver damage and to check whether it applies to all rodent models (including mice, either normal or genetically manipulated, largely used in preclinical studies). However, the message is clear and researchers have to take into account this “warning” in designing future studies, whatever the objective of the specific study (i.e., to monitor serum levels of ECM biomarkers, to develop therapies either affecting specific pro-fibrogenic targets/mechanisms, to accelerate resolution/regression of fibrosis or other). This study is in any case a further occasion to recall the absolute need for any researcher working in this exciting and rapidly moving field to make any effort to optimize procedures and animal models, as authoritatively suggested in a recent review by Trautwein et al. [3].

Conflict of interest

The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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