key mediator of liver damage. UPR-NNMT signaling has the potential to be developed as a therapeutic target in liver disease.

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Conflicts of interest

The authors claim no conflict of interests.

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Authors' contributions

Conceptualization, D.L., C.Y., H.H., S.H. and J.L.; Investigation, D.L., C.Y., H.H., S.H. and J.L.; Analysis, D.L., C.Y., H.H., S.H. and J.L.; Writing, D.L., C.Y., H.H., S.H. and J.L.; Data Visualization, D.L., C.Y., H.H., S.H. and J.L.; Funding Acquisition, H.H., S.H. and J.L.; Supervision, S.H., J.L..

Supplementary data

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Cirrhosis: What are all those factor VIII and protein C for?

To the Editor:

Over the last decades our understanding of cirrhotic coagulopathy has undergone considerable changes. Clinical, experimental, and pathophysiological observations helped us to view cirrhosis not as the epitome of acquired bleeding disorders, but as a disease characterized by rebalanced hemostasis and possibly even the increased risk of thrombosis.[1] Scheiner *et al.* recently published an interesting paper on this topic.[2] Based on retrospective evaluation of coagulation biomarkers and clinical observations, the authors conclude that the factor (F)VIII/protein C(PC) ratio in cirrhosis is independently associated with liver-related events/death. However, investigations of thrombomodulin-modified thrombin generation (TG) in another overlapping cohort of patients suggest that the FVIII/PC ratio is apparently unrelated with hypercoagulability.[2]

The conclusions of the above study give rise to the following considerations.

Pathophysiological considerations on FVIII and PC: One may wonder what are all those FVIII and PC for? If they are unrelated to hypercoagulability. High FVIII, being associated in non-cirrhotic patients with hypercoagulability and risk of first/recurrent thrombosis,[3] is a prototype procoagulant driver for TG. On the other hand, (thrombomodulin-activated) PC is one of the most potent naturally-occurring anticoagulants responsible for thrombin downregulation – non-cirrhotic patients with congenital PC deficiency are at increased hypercoagulability (high TG) and thrombotic risk.[4] The fact that (thrombomodulin) activated PC is the physiological inhibitor of FVIII and that FVIII and PC are respectively increased or decreased in cirrhosis, accords perfectly with the concept of the FVIII-PC axis as a crucial determinant of hypercoagulability. Consequently, the results reported by Scheiner *et al.*[2] make one wonder what underlies the contrast in the

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pathophysiology of the FVIII-PC axis in non-cirrhotic *vs.* cirrhotic patients. A possible explanation could be the complex derangement of hemostasis in cirrhotic as opposed to non-cirrhotic patients. In the former, most pro- and anticoagulants (except for FVIII and von Willebrand factor) are reduced, although on average to levels still sufficient to provide adequate hemostasis, whereas in the latter they are normal. Hence, the effect of the FVIII-PC axis on hypercoagulability must be related to the 2 situations. Since coagulation acts as an integrated system, even small differences in the coagulation proteins may result in unpredictable changes in the balance of pro *vs.* anticoagulants. Scheiner *et al.*[2] found that the FVIII/PC ratio in cirrhosis is apparently unrelated to the thrombomodulin-modified TG assay, currently used to detect the net effect on hypercoagulability supported by the FVIII-PC axis or other thrombotic mechanisms.[1,5] Unfortunately, and contrary to the general belief, TG assays do not represent a single procedure and are not standardized. They vary in terms of execution, reagent compositions (type/concentration of triggers and/or thrombomodulin)[6] and the results obtained.[5] It should be considered that these methodological variations may affect results and conclusions.

Considerations on hypercoagulability: Hypercoagulability may be defined as a multifactorial condition associated with pro *vs.* anticoagulant imbalance that can be detected by laboratory biomarkers (hereafter called biochemical hypercoagulability) and/or by the presence of circumstantial risk factors. Biochemical hypercoagulability may be due to increased procoagulants, decreased naturally occurring anticoagulants or both. Recently, other measurable determinants of hypercoagulability associated with thrombotic risk have been described. They include: (i) microvesicles derived from platelets, monocytes and other cells that carry and disseminate into the circulation the procoagulant asset possessed by parent cells;[7] (ii) neutrophil extracellular traps (NETs) that are chromatin substances released upon neutrophil activation;[8] (iii) systemic inflammation, which acts through massive release of pro-inflammatory cytokines.[9] Whatever the determinants, it should be realized that biochemical hypercoagulability *per se* does not necessarily mean occurrence of thrombosis. For example, natural models of hypercoagulability show that carriers of prothrombotic polymorphisms (heterozygous FV or prothrombin mutations) or even some carriers of congenital deficiencies of naturally occurring anticoagulants (antithrombin, PC) do not necessarily develop thrombosis during their lifetime. This is not surprising, if one considers thrombosis as a multifactorial disease, hypercoagulability as a multifactorial condition, and hemostasis as a complex/tightly regulated mechanism. None of the above can be entirely defined by consideration of one component in isolation from the others. Perhaps, a better understanding/definition of hypercoagulability and its effect (especially in cirrhosis) should be evaluated by including (in a score system) multiple biomarkers (pro- and anticoagulants) and circumstantial risk factors rather than only one in isolation. Notably, Scheiner *et al.*[2] found a trend for the association of FVIII/PC ratio *vs.* thrombomodulin-modified TG, which however disappeared after adjustment for the severity of disease. It cannot therefore be excluded that an integrated approach including the contribution of other determinants could reveal a state of biochemical hypercoagulability even in cirrhosis.

All in all, the above considerations tell us that (despite progress so far) there is still much to learn regarding the complex derangements of hemostasis associated with cirrhosis and the implications of hypercoagulability that alone or (most likely) in combination with other measurable or circumstantial risk factors may help explain disease progression and the increased thrombotic risk in cirrhosis.[10]

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