Letter to the Editor



# Persistence of fibrogenic process in direct-acting antiviral (DAA) treated patients?

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We wish to briefly comment the editorial (1) by Srikanta Dash, Ali Riza Koksal, Dong Lin on our research article entitled "*Fibrogenic signals persist in DAA-treated HCV patients after sustained virological response*" (2) that we recently published in *Journal of Hepatology*.

First of all, we shall thank the Authors for properly having framed our article in the current knowledge opened by direct-acting antiviral (DAA) therapy for HCV patients' management.

Indeed, in our opinion, the main issue is to develop strategies allowing to evaluate patient's risk of developing liver-related complications in spite of SVR (sustained virologic response). This is in the frame of both the encouraging evidence indicating the liver fibrosis process as plastic and potentially reversible (3,4) and that of cancer risk persistence even after viral clearance in relation to comorbidity factors (e.g., older age, advanced liver fibrosis and inflammation and diabetes) (5).

Our effort to combine functional and structural properties of serum-derived extracellular vesicles isolated from both healthy donors and HCV patient undergoing DAA therapy (analysed in a longitudinal study at the beginning and after SVR) allowed us to strongly correlate both miRNA and protein content to stellate cells (LX2) activation.

With respect to miRNAs, their lack of expression in HCV patients was directly related to specific stellate cell activation pathways (specific miRNAs have been functionally tested by means of miRNA mimic approach).

On the other hand, the specific role of proteins, identified as overexpressed by proteomic approach, has been only deduced by previous literature data. Moreover, only for DIAPH1 its persistent overexpression was statistically validated. As in our case, big data analysis is often functionally exploited only at the tip of the iceberg; we hope that our proteomic dataset could inspire further specific studies aiming at pinpointing new prognostic biomarkers and therapeutic targets allowing to better manage SVR patients.

Specifically, this analysis extension may be applied to CCT6A (6-8), WDR1 (9), CAND1 (10), CAP1 (11) and CRKL (12,13) that literature already suggests as pathogenetic for liver diseases.

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*Ethical Statement:* The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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