T-cell exhaustion factors related to hepatocellular carcinoma development of the hepatitis C virus etiology

ABSTRACT FOR THE GENERAL PUBLIC

HCV infections still represent an important global health problem, encompassing approximately 58 million of chronically infected individuals. Chronic course of infection (i.e., chronic hepatitis C, CHC) may lead to severe health consequences, such as fibrosis, cirrhosis, and primary hepatocellular carcinoma (HCC), one of the most common and lethal cancers.

WHO's global hepatitis elimination strategy provides a great potential for ending CHC epidemics by 2030 by employing tremendous advances in public health, including prevention, diagnostic and treatment services. However, the common latent course of infection and lack of nationwide HCV screening programs, especially in low- and middle-income countries, result in infection underdiagnosis. At the same time, despite numerous clinical trials, an effective vaccine protecting against the infection has not been developed.

Major advances in understanding HCV-related disease have been made since the virus discovery in 1989, including tremendous efforts in the implementation of highly effective treatment (i.e., direct acting antivirals, DAA). Nevertheless, the risk of HCC persists even in successfully treated patients, in particular in those with advanced fibrosis. Furthermore, the virus may persist in liver cells and/or blood immune cells, which may also represent a risk factor of HCC.

Currently, it is estimated that the number of CHC patients who are successfully treated outnumbers those infected and the proportion of post-DAA treatment HCC among newly diagnosed HCC patients is growing, increasing health burden year-by-year.

At the same time, there is still a lack of effective biomarkers and prognostic models of HCC that could be translated into individualized patients monitoring and treatment.

The determinants of HCV-related HCC are believed to be immune-related, including so called T-cell exhaustion, characteristic of chronic infections and cancer, in which these cells are exposed to prolonged and high-level stimulation. Many of the mechanisms of exhaustion induction are shared between CHC and HCC, e.g., excessive, permanent co-expression of multiple inhibitory receptors (iRs) on T-cells, which prevent these cells from performing their effector functions, mainly via inhibiting their activation. Apart from the cell membrane-bound, soluble iRs are detectable in plasma and remain bioactive (i.e., are able to bind their respective ligands). Given the involvement of iRs in shaping T-cell exhaustion in CHC and HCC, it is crucial to characterize the immune dysfunction in CHC patients with advanced liver fibrosis cured by DAAs, explore the potential of iRs as well as the fact of the virus persistence in blood immune cells as prognostic markers of HCC development as well as capability of soluble iRs to enhance T-cell function in CHC and HCC.

The aims of the present study are to assess whether:
1) successful CHC treatment is related to change in the T-cell exhaustion profile in CHC patients with advanced liver disease, and whether this profile is different in patients with HCV-related HCC;
2) T-cell exhaustion parameters as well as the virus persistence in blood immune cells of CHC patients after successful antiviral treatment may be used as prognostic markers of HCV-related HCC;
3) T-cells functions may be restored upon in vitro treatment with soluble iRs in CHC patients before and after successful antiviral treatment and in patients with HCV-related HCC.

Identifying answers to the above questions will provide a basis for a better understanding of the factors underlying HCV-related carcinogenesis, which can be translated into individualized patient monitoring and treatment, reducing socioeconomic health burden, including treatment costs, hospitalizations, and premature deaths.