Poster Abstract P8

Mitochondrial stress in patients with chronic heptatis B and advanced fibrosis

Dimitri Loureiro[1,2], Issam Tout[1,2], Cheikh Mohamed Bed[1,2], Morgane Roinard[1,2], Ahmad Sleiman[1,2], Nathalie Boyer[1,2], Stéphanie Narguet[1,2], Nathalie Pons-Kerjean[3], Corinne Castelnau[1,2], Nathalie Giuly[1,2], Vassili Soumelis[4,5], Jamel El Benna[1], Patrick Soussan[6], Richard Moreau[1,2], Valérie Paradis[1,2], Abdellah Mansouri[1,2&],Tarik Asselah[1,2&§]
[1]Université de Paris, Centre de Recherche sur l'Inflammation, Inserm U1149, CNRS ERL8252, F-75018 Paris, France.
[2]Assistance Publique-Hôpitaux de Paris (AP-HP), Department of Hepatology, Hôpital Beaujon, F-92110 Clichy, France.
[3]Assistance Publique-Hôpitaux de Paris (AP-HP), Department of Pharmacy, Hôpital Beaujon, F-92110 Clichy, France.
[4]Université de Paris, Inserm U976 HIPI Unit, F-75006, Paris, France.
[5]Assistance Publique-Hôpitaux de Paris (AP-HP), Laboratoire d'Immunologie et Histocompatibilité, Hôpital Saint-Louis, F-75010, Paris, France.
[6]Université de Paris, Inserm U1135, Paris-75012, France.
[&] Equal contribution

Background
Hepatitis B virus (HBV) infection causes oxidative stress and alters hepatic mitochondria. The aim of the study is to look for the role of mitochondrial stress in the progression of fibrosis in chronic hepatitis B (CHB).

Methods
One hundred thirty-two (n=132) treatment-naïve CHB mono-infected patients and available liver biopsies were included in the study. Liver mitochondrial DNA (mtDNA) damage was screened by long PCR and sequencing. The expression of cytochrome c oxidase subunits 1 (COX1) and 2 (COX2), Parkinson juvenile disease protein 2 (PARKIN), Phosphatase and Tensin-Induced Putative Kinase-1(PINK1), Lon Peptidase 1(LonP1), HSP60, HSP70, TNFα and IL6 was investigated by RT-qPCR and Western blotting. Patients with advanced fibrosis (F3-F4; n=41) were compared to mild-moderate fibrosis (F0-F1-F2; n=86). Patients with advanced fibrosis-cirrhosis (Metavir score, F3-F4) were compared to patients with no-mild-moderate fibrosis (F0-F1-F2).

Results
We identified various mtDNA damages including strand breaks and multiple mtDNA deletions in patients with F3-F4 as compared to patients with F0-F2. mtDNA damage was associated with alterations in mitochondrial function, mitochondrial unfolded protein response, mitophagy, and liver inflammation in patients with CHB and advanced fibrosis-cirrhosis. In vitro, significant increases of the mitochondrial formation of superoxide and peroxynitrite as well as mtDNA damage and nitration of the mitochondrial respiratory chain complexes occurred in HepG2 hepatocytes transiently expressing either HBV or Hepatitis B virus X protein (HBx).

Conclusions
Our results emphasized the importance of mitochondrial oxidative stress, mtDNA damage, and associated alterations in mitochondrial function and dynamics in the progression of fibrosis in patients with CHB.