MASTER 2 BMC
PARCOURS GENOPATH
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Titre :

Role of hepatic stellate cells in the rapid disease progression of chronic hepatitis Delta

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Sujet de stage :

Chronic hepatitis D (CHD) is the most severe form of viral hepatitis, with accelerated progression of liver fibrosis, cirrhosis, and increased risk for hepatocellular carcinoma (HCC). Mongolia has the highest load of hepatitis D virus (HDV)-related HCC in the world, with a particular expression profile and high inflammatory traits. Efficient antiviral treatment or efficient therapeutic interventions remain unavailable to this particularly vulnerable patient population.

In the liver, virally-induced fibrosis is characterized by activation of hepatic stellate cells (HSC) into mobile collagen-secreting myofibroblasts. Long term accumulation of collagen, and other extracellular fibers leads to formation of septa, the histological basis for progression towards end stage liver fibrosis and subsequent liver failure, both being major risks for HCC development. In normal liver, HSCs are quiescent, vitamin A/retinol ester storing cells and represent 5-8% of the total number of liver resident cells. When the liver is damaged, HSCs switch into an activated state, which is accompanied by loss of the characteristic vitamin A stores, metabolic changes, proliferation, contractility, and chemotaxis and extracellular matrix production.

The project, based on a series of already established preliminary data, aims to characterize the mechanisms by which HDV activates HSCs, in order to better understand the rapid disease progression that is much faster and aggressive in chronic HDV patients compared to chronic infections with other hepatitis viruses.

Modèle et techniques utilisées :

Virology : culture and activation assays of hepatic stellate cells; differentiation of hepatocyte cultures; HDV in vitro infection; part of this work will involve activities at P3 level (the candidate needs to have protective HBV vaccination status)

Patient samples: on the long run, liver samples from Mongolian HDV patients will be available for validation/extension of in vitro data

Molecular biology: RNA, DNA and protein extractions, quantification and identification ((RT)qPCR, Western, IF, IHC); genetic modulation of cell lines using CRISPR, si/shRNA approaches; cloning

Publications d'intérêt :

Transcriptome Analysis of Redox Systems and Polyamine Metabolic Pathway in Hepatoma and Non-Tumor Hepatocyte-like Cells. *Ivanova ON, Krasnov GS, Snezhkina AV, Kudryavtseva AV, Fedorov VS, Zakirova NF, Golikov MV, Kochetkov SN, Bartosch B, Valuev-Elliston VT, Ivanov AV.* **Biomolecules. 2023** Apr 21;13(4):714.

Hepatitis Delta Virus Antigens Trigger Oxidative Stress, Activate Antioxidant Nrf2/ARE Pathway, and Induce Unfolded Protein Response. *Smirnova OA, Ivanova ON, Mukhtarov F, Valuev-Elliston VT, Fedulov AP, Rubtsov PM, Zakirova NF, Kochetkov SN, Bartosch B, Ivanov AV.* **Antioxidants. 2023** Apr 21;12(4):974

Emerging anti-HDV drugs and HBV cure strategies with anti-HDV activity. *Roca Suarez AA, Batbold E, Bartosch B, Dashdorj N, Testoni B, Zoulim F.* **Liver Int. 2023** Aug;43 Suppl 1:87-95. doi: 10.1111/liv.15417.

An Update on the Metabolic Landscape of Oncogenic Viruses. Gaballah A, Bartosch B. **Cancers (Basel). 2022** Nov 23;14(23):5742.

Hypoxia sensing by hepatic stellate cells leads to VEGF-dependent angiogenesis and may contribute to accelerated liver regeneration. *Dirscherl K, Schläpfer M, Roth Z'graggen B, Wenger RH, Booy C, Flury-Frei R, Fatzer R, Aloman C, Bartosch B, Parent R, Kurtcuoglu V, de Zélicourt D, Spahn DR, Beck Schimmer B, Schadde E.* **Sci Rep. 2020** Mar 9;10(1):4392.

Metabolic Hallmarks of Hepatic Stellate Cells in Liver Fibrosis. *Khomich O, Ivanov AV, Bartosch B.* **Cells. 2019** Dec 20;9(1):24.