OTTO VON GUERICKE UNIVERSITÄT MAGDEBURG
UNIVERSITÄTSMEDIZIN MAGDEBURG
MES Molecular & Experimental Surgery

F. Weber, E. Mirzaee Kakhki, Prof. U. Kahlert, PD Dr. C. Wex, Prof. Dr. Dr. R. S. Croner

Department of General-, Visceral-, Vascular- and Transplantation Surgery

Cooperation with Prof. Tobias Cantz

REBIRTH-Center for translational regenerative medicine (MHH)

Investigating the effect of mechanotransduction in liver regeneration using hiPSC derived hepatocytes

Background

The liver has a remarkable and unique regenerative potential. After major partial liver resections, 25-30% of the residual liver volume is sufficient to avoid postoperative liver failure, whereas in patients with impaired liver function a residual volume of 40% has to be preserved. In these cases, oncological resections are accompanied by a high risk of postoperative morbidity and mortality. Recent studies have revealed promising results in the stimulation of the mechanosensitive Yap/Taz signalling pathway in liver regeneration in mice. The stimulation of this pathway is known to be promoted through the mechanosensitive Integrin/RHO/actin pathway. This mechanosensitive activation was not shown in hepatocytes yet.

Aim

We want to investigate mechanosensitive stimuli activating Yap/Taz signalling pathway in a human hepatocyte cell model to gain a further understanding of its role in liver regeneration.

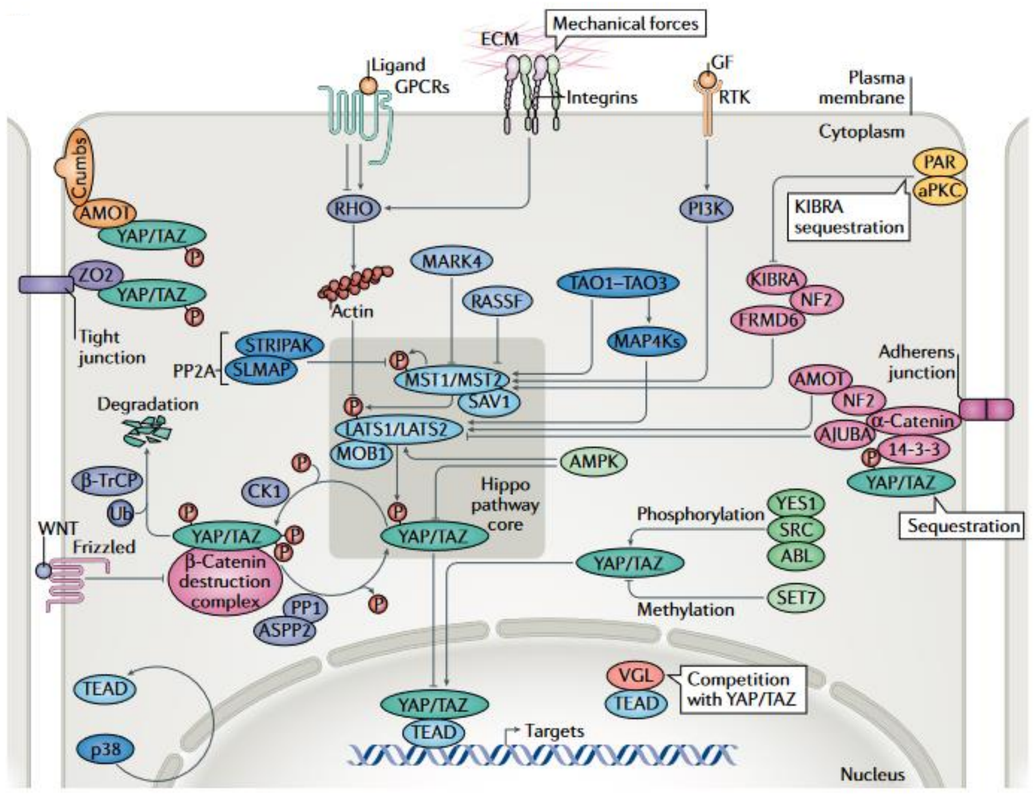


Image adapted by [2]Moya and Halder (2019)

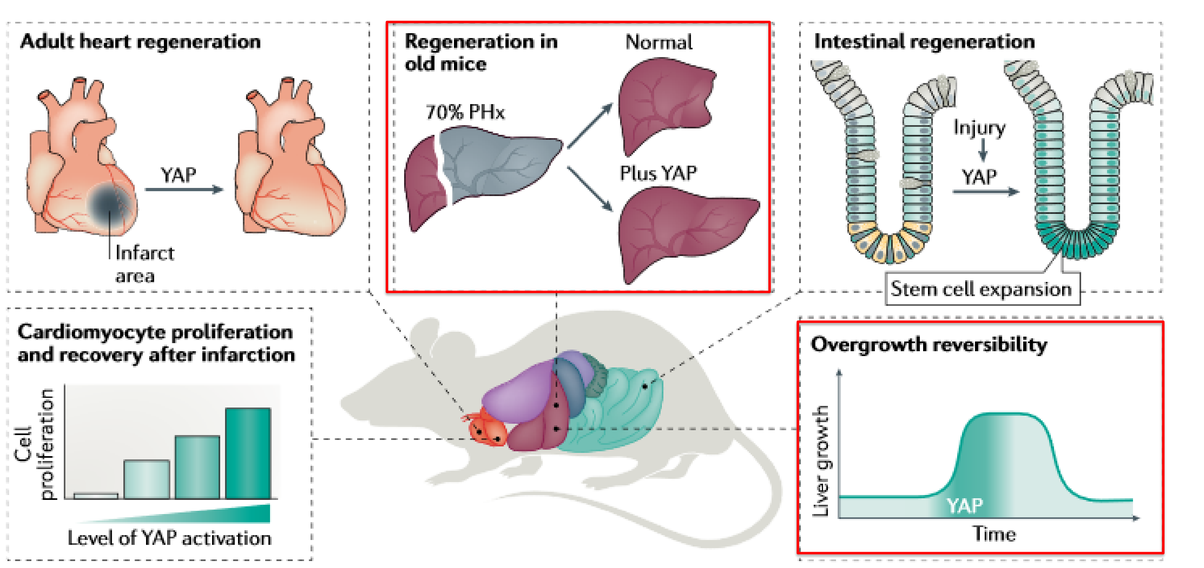


Image adapted by [2]Moya and Halder (2019)

Mechanotransduction in hepatocytes

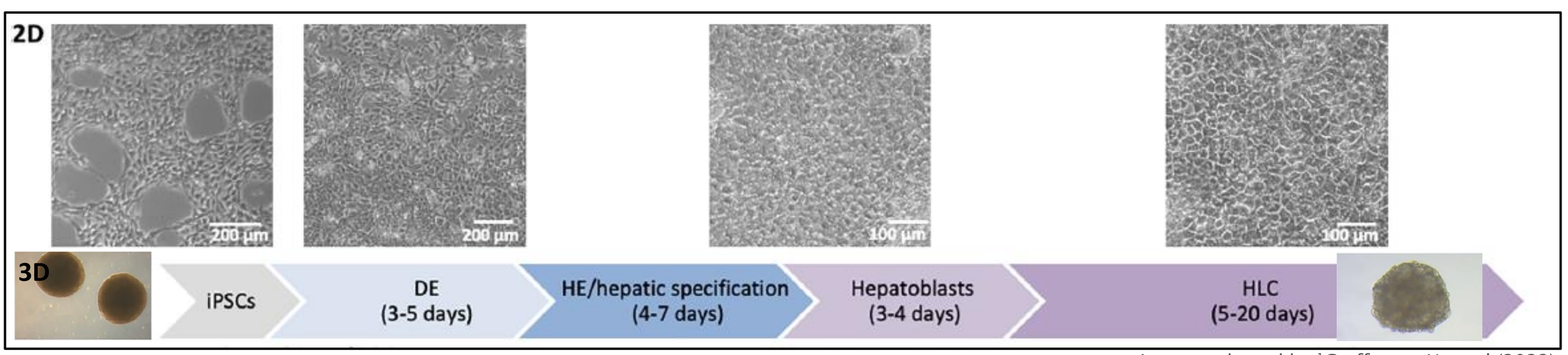
Mechanotransduction is characterized by a physical force sensed by a mechanoreceptor transmitting the signal into the cell. Mechanoreceptors are e.g. Integrins, cell-cell or cell-matrix contacts or mechanosensitive calcium channels like Piezo1. Mechanotransduction in hepatocytes can result in transcriptional regulation, cell fate changes, or bile release. To date most researchers focused on hepatic mechanotransduction in disease models like liver fibrosis or cancer, whereas less attention was broad to its role in liver regeneration.

Human iPSC derived hepatocytes

The first hepatic differentiation protocols using hiPSC were published in 2007[1]. Since then researchers focused on the enhancement of hepatic differentiation as well as the promotion of hepatic maturation (e.g. by 3D culture). While not perfectly mimicking the adult human hepatic phenotype, these hiPSC-derived hepatocytes provide a promising tool for disease modelling, drug development and toxicity screening, as well as regenerative medicine.

Outlook

1. Investigation of different physical stimuli and their impact on Yap/Taz pathway activation in human hepatocytes using 2D and 3D culture of hiPSC-derived hepatocytes
2. Further comparison of the mechanosensitive Yap/Taz response in tumor and healthy cell lines
3. Developing a new therapeutic target to promote liver regeneration potential after major partial hepatectomy



Images adapted by [1]Graffmann N. et al (2022)

[1]Graffmann N, Scherer B, Adjaye J. In vitro differentiation of pluripotent stem cells into hepatocyte like cells - Basic principles and current progress. Stem Cell Res. 2022 Mar 24;61:102763
[2]Moya IM, Halder G (2019): Hippo–YAP/TAZ signalling in organ regeneration and regenerative medicine. Nat Rev Mol Cell Biol 20, 211–226