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Caspase8-signalling in a model of liver stem cell activation and sclerosing cholangitis

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The activation of initiator caspases represents a well-known mechanism of tissue homeostasis maintenance by clearing injured cells through receptor mediated apoptosis in the pathophysiology of various liver diseases. we were interested to evaluate the relevance of caspase-8 in different liver cell types during liver stem cell activation. Mice with hepatocellular caspase8 deletion (casp8Δ_{hepa}) and mice ubiquitous deletion of caspase8 (casp8Δ_{Mx}) were applied to the DDC (3,5-diethocarbonyl-1,4-dihydrocollidine) model of hepatic stem cell activation. Hepatic stem cells were isolated and characterized by flow cytometry (FACS) and real time PCR. Higher transaminases and bilirubin levels were observed in Casp8Δ_{Mx} mice compared to controls, while casp8Δ_{hepa} animals were protected during DDC-treatment. Correlating with enhanced liver injury, casp8Δ_{Mx} mice displayed stronger proliferation in periportal areas where hepatic stem cells emerge and reside as indicated by 5-fold higher BrdU incorporation rate as well as by immunohistochemistry (CK-19) in contrast to casp8Δ_{hepa} and WT mice after 4-weeks of DDC-treatment. Further data now point to an additionally enhanced hepatic infiltration of immune-cells (CD45, F4/80, CD4) in casp8Δ_{Mx} mice. This finally resulted in a stronger fibrosis progression of the underlying sclerosing cholangitis induced by DDC in casp8Δ_{Mx} mice, as evidenced by an enhanced expression of collagen and α-SMA. Caspase8 has a distinct impact on individual liver cell types. While hepatocyte specific knockout provided protection from liver damage an ubiquitous deletion of caspase8 triggered more injury and inflammation. This was finally related to a significantly stronger activation of the liver stem cell compartment and more tissue remodelling

Biography

Kunal Chaudahry has completed his M.Sc of Molecular Medical Biotechnology from University of Ghent, Belgium and is conducting PhD at RWTH Aachen, Germany

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