Neighbor of Punc E11 in the Mdr2 -/- mouse model: Novel marker of stem/progenitor cells in regenerating adult liver

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Abstract

Background:
The isolation of hepatic stem cells is demanding due to the lack of specific surface markers. Previously, we identified Neighbor of Punc E11 (Nope) as a novel oncofetal marker of stem/progenitor cells in the murine liver. In the current study we focused on the expression pattern of Nope as a potential marker for stem/progenitor cells in normal adult liver as well as after acute (partial hepatectomy) and/or chronic liver injury (Mdr2 -/- mice).

Methods:
Liver tissues were obtained from adult Balb/c mice (10 weeks) and Mdr2 -/- mice of different age and stage of fibrosis. In subgroups with partial hepatectomy, livers were obtained 24 hours up to 7 days postoperatively. In selected mice, liver regeneration was modified by injection of DNA alkylating reagents 4 and 2 weeks before analysis. Expression levels of Nope were quantified using quantitative RT-PCR in homogenized liver tissue and after microdissection of bile ducts. Immunohistochemistry on cryosections was performed combining stainings for Nope with the biliary marker protein CK 19, an epithelial-specific Pancytokeratin (PanCK) and the canalicular membrane marker dipeptidylpeptidase (DPP) IV.

Results:
While normal adult liver shows only negligible expression of Nope, chronic liver injury in Mdr2 -/- mice leads to a considerably increased expression level of Nope. Costainings with CK19 demonstrated a bile-duct-specific expression of Nope in these mice. While acute injury in normal adult liver has no effect, an additional partial hepatectomy in the Mdr2 -/- mouse model results in sparse detection of Nope positive cell clusters if hepatocyte proliferation is blocked by DNA alkylating reagents. These Nope positive clusters are negative for CK19 but positive for PanCK and DPPIV.

Conclusion:
Here we report the expression of the oncofetal stem/progenitor cell marker Nope in the Mdr2 -/- mouse model of progressive liver fibrosis. While Nope is restricted to bile ducts in the chronic injury model, a rare population of regenerating stem/progenitor cells arises in case of an additional acute injury if physiological regeneration is blocked. We conclude that Nope is a potential marker for stem/progenitor cells in the regenerating adult liver.