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Impact of variant Notch ligands on chronic liver diseases

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Introduction
To date, the roles of individual Notch ligands in liver injury are not well defined. The current study investigated whether and how Notch ligands DLL4 and JAG1 affect liver injury.
Methods
We examined the expression of Notch ligands and receptors by immunohistochemistry (IHC) in the liver samples of 26 patients with HBV-induced liver cirrhosis. The function of recombinant Dll4 (rDll4) and rJag-1 was investigated *in vivo* in carbon tetrachloride (CCl_4) and bile duct ligation (BDL) animal models and *in vitro* in hepatocytes, Kupffer cells (KCs), and hepatic stellate cells (HSCs).
Results
DLL4 and JAG1 were the only Notch ligands expressed in liver sinusoids of examined patients. In the CCl_4 animal model, rDll4 and rJag-1 ameliorated liver fibrosis, decreased infiltration of inflammatory cells, and inhibited apoptosis. On the contrary, rDll4 and rJag-1 caused rapid death of all BDL mice within 1 week. rDll4 inhibited the expression of chemokine ligand 2 (CCL2) and infiltration of inflammatory cells in livers of BDL mice, whereas rJag-1 did not have any impact on inflammatory cells infiltration and CCL2 expression. In macrophages and HSCs, rDll4 inhibited LPS-induced CCL2 expression, whereas rJag-1 did not impact CCL2 expression. Inhibition of inflammation by rDll4 caused unrestricted bile infarct and rapid death of BDL animals. Recombinant Ccl2 (rCcl2) restored the infiltration of inflammatory cells, decreased the size of bile infarcts and rescued rDll4-treated BDL animals from death. In ACLF patients, DLL4 expression was negatively associated with expression of CCL2. In contrast to rDll4-treated BDL animals, rCcl2 did not rescue rJag-1-treated BDL animals.
Conclusion
Etiology determines the effects of DLL4 and JAG1 on liver injury. DLL4 inhibits liver inflammation through inhibiting CCL2, a key chemokine for recruitment of inflammatory cells. How Jag-1 impact liver injury requires further investigation.