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BILIARY TRACT

A new mouse model that closely resembles human cholangiocarcinoma

A recent study published in *Hepatology* has demonstrated that IL-33—in combination with the oncogenes *AKT* and *YAP*—facilitates cholangiocarcinoma development in mice. Moreover, IL-6 seems to have an important role in this process.

Cholangiocarcinomas are malignancies of the biliary tract; therapeutic advances have been modest in the past few years and overall 5-year survival is ~10%. Although rodent models of cholangiocarcinoma exist, none seem to be ideal, so Gregory Gores (Mayo Clinic, MN, USA) and colleagues aimed to generate a mouse model that more closely mimics human disease. "We pursued this project because we did not deem the current animal models of cholangiocarcinoma to be relevant to the human condition," he explains. "Many of them appeared to arise from hepatocytes and/or were time inefficient."

Thus, the researchers sought to directly transfect cells of the biliary tree with plasmids containing oncogenes; *AKT* and *YAP* were selected for transfection as they are known to contribute to the pathogenesis of human hepatobiliary malignancies. A Sleeping Beauty transposase–transposon approach was used for transfection. "We reasoned (fortunately correctly) that if we directly instilled these DNA constructs into the biliary tree it would also transfect the biliary epithelium," says Gores. Common bile duct clamping prevented the injected material from rapidly flowing into the duodenum. Lobar bile duct ligation was then performed in the mice to induce cholestasis in the local microenvironment.

Previous work by Jorge Bezerra and co-workers had demonstrated that IL-33 is a biliary mitogen, so they investigated the role of this cytokine in transfection and carcinogenesis. They found that 10 weeks after surgery for bile duct ligation and oncogene transfection (with *AKT* and *YAP*), 20% of mice developed cholangiocarcinomas; by contrast, in mice that underwent bile duct ligation, oncogene transfection and systemic administration of IL-33, 70% of animals developed cholangiocarcinomas. Importantly, these tumours were shown to be morphologically and phenotypically similar to human cholangiocarcinomas. Notably, IL-33 alone did not induce tumour development.

In a further step in the research, Gores and the team decided to investigate the role of IL-6 in this tumour development mechanism. They found that cholangiocarcinoma development after biliary transfection with *AKT* and *YAP* and administration of IL-33 was attenuated in *Il6*$^{-/-}$ mice. Interestingly, the researchers also found that IL-6 can in fact substitute for IL-33 in this model of carcinogenesis—administration of IL-6 after biliary transfection with *AKT* and *YAP* resulted in a similar rate of tumour development as with IL-33 administration. Gores reports that this finding "demonstrates that inflammatory cytokines are important in oncogenesis and biliary epithelia, especially IL-6".

"We plan to take this work forward by using other oncogenes and, more importantly, tumour mechanisms to inhibit tumour suppressor genes to more specifically study oncogenic processes in the biliary epithelia," concludes Gores. The authors also hope that this mouse model might be used as a basis to refine further models, and they suggest that it could have relevance for testing agents in a preclinical setting.

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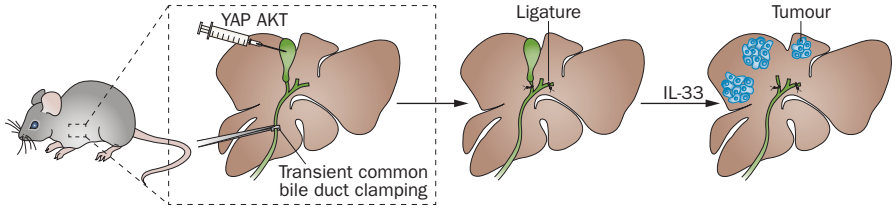
Original article Yamada, D. *et al*. IL-33 facilitates oncogene induced cholangiocarcinoma in mice by an IL-6 sensitive mechanism. *Hepatology* doi:10.1002/hep.27687



IL-33 facilitates cholangiocarcinoma development. Image produced in consultation with G. Gores.