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BILIARY TRACT

Therapeutic strategies for cholangiocarcinoma—wishing on WNT inhibitors?

Upregulated WNT signalling is a key feature of cholangiocarcinoma, and targeting WNT pathways has therapeutic potential, according to new research published in *The Journal of Clinical Investigation*. "The WNT pathway was important in driving the cancer growth and could be therapeutically targeted," reports senior author Stuart Forbes, MRC Centre for Regenerative Medicine, Edinburgh, UK.

Cholangiocarcinoma, a cancer of the biliary tract, is challenging to treat and the incidence of the disease is increasing worldwide. Generally, patients with cholangiocarcinoma have a poor prognosis as they are often diagnosed when the disease is at an advanced stage. Curative surgical resection is therefore possible in only a few patients and no curative agents are available. "Cholangiocarcinoma has such a terrible prognosis unless it presents at a resectable stage; for the majority of patients there is no effective therapy," says Forbes. "We have either been unable to offer treatment or the treatment just has not worked," he adds.

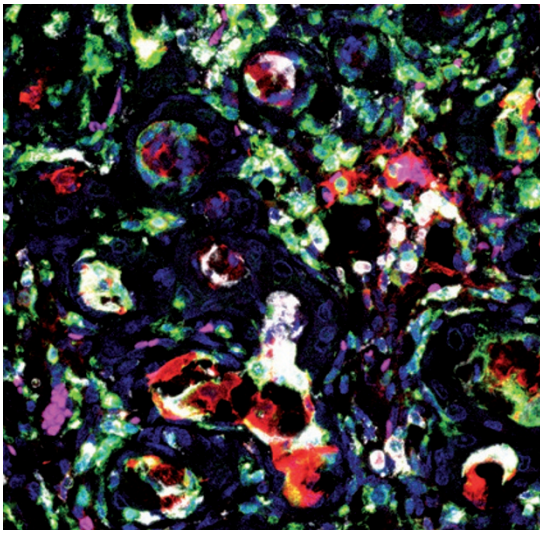
In this new study, the researchers sought to determine the mechanisms that contribute to the pathogenesis of cholangiocarcinoma, particularly as WNT signalling has been implicated in the development of a wide range of cancers. The underlying pathology of cholangiocarcinoma was investigated by using a combination of human tissue samples, cholangiocarcinoma cell xenografts and two different rodent models of cholangiocarcinoma.

First, by examining mRNA expression of WNT pathway and WNT target genes, the canonical WNT pathway was found to be highly activated in the context of human cholangiocarcinoma; compared with distal, noncancerous liver samples, WNT signalling was upregulated in human cholangiocarcinoma, including overexpression of the ligands *WNT7B* and *WNT10A*. Moreover, the researchers found that the canonical WNT pathway is progressively activated during the course of development of cholangiocarcinoma in two different rodent models that mimick the disease in humans. The models—both inducing cholangiocarcinoma chemically via thioacetamide (TAA) in rats and also in transgenic mice with intrahepatic deletion of the tumour suppressor p53 specifically in bile ducts—match the background of chronic damage, inflammation and tissue repair seen in human cholangiocarcinoma.

Importantly, inflammatory macrophages in the stroma surrounding the tumour were found to be a requirement for this highly activated WNT signalling. Immunohistochemical analysis in tissue samples from human cholangiocarcinoma and rat models confirmed that $CD68^+$ macrophages expressed WNT7B ligand, and that loss of these macrophages inhibits cholangiocarcinoma growth (tumour volume and mass) *in vivo* in xenograft and rat models and led to reduced *Wnt7b* mRNA expression.

Finally, small-molecule inhibitors (ICG001 and C59) were used to block the WNT signal, at secretion and upon β-catenin activation. Crucially, treatment with either ICG001 or C59 in animal models led to a marked decrease in tumour burden (in both size and number) throughout the liver and large-scale downregulation of WNT target genes in cholangiocarcinoma-containing tissue. No adverse effects, aside from TAA-induced disease, were observed in animals treated with either small-molecule WNT inhibitor.

"The results from the study by Boulter *et al.* provide a strong case for the role of stroma-produced WNTs, especially macrophage-derived WNT7B, in the progression and maintenance of sporadic cholangiocarcinomas," writes David Virshup, Duke-NUS Graduate Medical School, Singapore, in an accompanying commentary, adding that there are still many lessons to be learned from the WNT pathway.



Rat cholangiocarcinoma showing inflammatory cells (green), $CD68^+$ macrophages (red), CD206 expression (white) and DNA (blue). Courtesy of L. Boulter and S. J. Forbes.

In a bid to identify novel targets for treatment, the researchers plan further work using the cholangiocarcinoma experimental models to discover other factors that drive the development of this disease. They also hope to take forward their findings and commence a clinical trial of WNT inhibitors in patients with surgically unresectable cholangiocarcinoma. "There are WNT inhibitors that have been tested in patients with other forms of cancer, and as there are no real treatment options beyond palliation at this stage we are very keen on pursuing this," notes Forbes. "Given that we have set up a number of translational models of cholangiocarcinoma and have an excellent tissue resource we feel we are well placed to make inroads into this devastating cancer."

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Original article Boulter, L. *et al.* WNT signaling drives cholangiocarcinoma growth and can be pharmacologically inhibited. *J. Clin. Invest.* doi:10.1172/JCI76452