

## HEPATOCELLULAR CARCINOMA

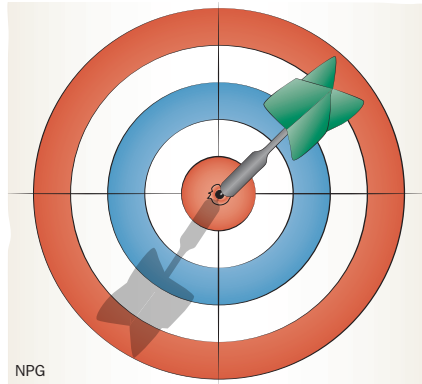
## Treatment potential of targeting Toll-like receptors in HCC

Inhibiting Toll-like receptors (TLRs) with antagonists has the potential to be a novel therapeutic technique for HCC, according to the results of a recent study.

TLRs have an important role in innate immune responses and TLR signalling has been associated with various chronic liver diseases. In addition, overexpression of TLR7 and TLR9, in particular, has been observed in several malignancies. Nonetheless, little is known about the roles of TLR7 and TLR9 in HCC. Rajiv Jalan and colleagues wanted to understand more about the pattern of TLR7 and TLR9 expression in this cancer, and whether targeting these TLRs might have beneficial effects.

Tissue microarrays showed that TLR7 and TLR9 were both overexpressed in human HCC samples compared with tissue samples from patients with cirrhosis and viral hepatitis. “These results suggested to us that a TLR7 and/or TLR9 antagonist might be useful in this disease,” explains Jalan.

The researchers then went on to examine the effects of stimulating and inhibiting



these TLRs in human HCC cell lines. “In order to try to develop a cheap and readily translatable strategy, we evaluated the effect of chloroquine (a widely available antimalarial drug), which is known to reduce TLR7 and TLR9 signalling,” says Jalan. This agent was shown to substantially reduce cell proliferation. By contrast, stimulating TLR7 led to a significantly increased rate of proliferation (stimulating TLR9 showed a nonsignificant trend towards increased cell proliferation).

In the final step, the effect of TLR7 and TLR9 inhibition with chloroquine administration was examined in two animal models. In a xenograft model, chloroquine prevented the growth of human HCC cells implanted on the surface of the liver. In a diethylnitrosamine/nitrosomorpholine-induced model of HCC, chloroquine was found to almost completely prevent the development of HCC.

The researchers plan to perform further mechanistic studies to determine whether there are any deleterious effects of this strategy. “We have also had some early discussions about organizing clinical trials to study the effect of chloroquine on the prevention of HCC in susceptible patients, and the prevention of recurrence of HCC in patients who have had potentially curative treatments,” notes Jalan.

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**Original article** Mohamed, F. E. *et al.* Effect of Toll-like receptor 7 and 9 targeted therapy to prevent the development of hepatocellular carcinoma. *Liver Int.* doi:10.1111/liv.12626