LIVER CANCER

Sorafenib resistance uncovered by novel RNAi screen

Hepatocellular carcinoma (HCC) represents a major global health problem that causes over 700,000 deaths annually worldwide. HCC is resistant to cytotoxic and targeted therapies, and although sorafenib is the standard therapy, the average survival gain is less than 3 months. This situation prompted Lars Zender and colleagues to “take advantage of our expertise in RNA interference (RNAi)-based screening technology to identify enhancers of sorafenib therapy.” The researchers developed a genetically engineered (transposon-based) mouse model of HCC that closely resembles therapy resistance of human HCC. They also used stable short hairpin RNA (shRNA) technology to identify new cancer genes and therapeutic targets.

Before this study, very little was known about the molecular mechanisms of sorafenib resistance. Now, using this unique platform the researchers were able to conduct shRNA screens in tumours *in vivo* and identify genes involved in therapy resistance. As Zender explains

“a particular strength of our approach is that we can conduct shRNA screens directly in a relevant context, that is, the screened tumour cells are never taken out of their natural microenvironment.”

His team showed that silencing Mapk14 by both shRNA and pharmacological inhibition could strongly increase the therapeutic efficacy of sorafenib in mice. Thus, induction of the Mapk14 pathway represents an important mechanism of sorafenib resistance in mouse and human liver cancers. Crucially, Mapk14 blockade was able to restore sorafenib sensitivity in tumours that had become resistant to long-term sorafenib treatment. The mechanism behind this survival advantage was the abrogation of Mapk14-dependent activation of Mek-Erk and Atf2 signalling. Furthermore, elevated levels of Mapk14–Atf2 signalling predicted a poor response to sorafenib therapy, and the expression of phosphorylated Atf2 was able to predict the therapeutic outcome of sorafenib therapy. The researchers also provide “a mechanistic dissection on how

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the Ras–Raf–Mek–Erk and the MAPK pathways crosstalk in HCC,” adds Zender.

From a clinical perspective Zender’s team are “preparing a clinical trial to explore the combination of sorafenib and the second-generation Mapk14 inhibitor, skepinone-L, for the treatment of patients with advanced-stage HCC.” They also plan to explore the role of MAPK signalling in resistance to other targeted therapies and cytotoxic agents in different types of clinically relevant tumours, and understand better how resistance develops.

Lisa Hutchinson

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