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LIVER CANCER

SALL4—A CANCER MARKER AND TARGET

Zinc finger protein SALL4 is both a marker for an aggressive subtype of hepatocellular carcinoma (HCC), and a potential target for its treatment, new findings show. "SALL4 could become an ideal cancer therapy target … since it is not expressed in most adult normal tissues, but is reactivated in a subset of cancer patients," says Li Chai, one of the lead investigators.

SALL4 is expressed in human foetal liver, but not in the healthy adult liver. However, SALL4 is re-expressed in a number of cancers, including acute myeloid leukaemia and some liver, lung, ovarian, endometrial and breast cancers. Previous work by Chai's group pointed to a role for this protein in tumorigenesis, and indicated that targeting SALL4 might have anticancer effects. "We hope in the near future we can use SALL4 expression as a targetable marker in cancer patients," says Chai. The investigators used HCC as a model to test this hypothesis.

They first examined the association between clinicopathological characteristics and levels of SALL4 expression in liver specimens from patients with or without HCC. SALL4 was expressed in >50% of the HCC samples, but remained silenced in matched (non-neoplastic) control samples. Furthermore, among the patients with HCC, those with high levels of SALL4 expression had poorer prognoses than those with low levels of SALL4 expression. Loss-of-function studies, based on both genetic (RNA interference) and pharmacological SALL4 ablation, suggested that silencing SALL4 reverses the aggressive HCC phenotype associated with SALL4 positivity. These findings led the investigators to develop SALL4-targeted therapies. *In vitro* and *in vivo* treatment of HCC cells with a competitive inhibitor of SALL4, consisting of a 12-amino-acid peptide, blocked the oncogenic role of SALL4.

The researchers are now developing small-molecule drugs that target SALL4, which (as SALL4 is not expressed in non-neoplastic cells) are expected to have little toxicity for normal tissue. "Some patients are candidates for SALL4-specific cancer treatment," Chai notes. Such treatments might include SALL4-peptide-based inhibitors, or drugs that block related pathways, such as HDAC inhibitors and HGF receptor inhibitors.

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