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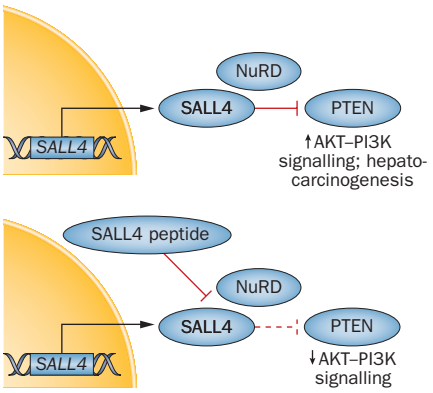
CANCER

Importance of oncofetal gene, *SALL4*, in a subset of hepatocellular carcinoma

The oncofetal gene, *SALL4*, has an important role in a subtype of aggressive hepatocellular carcinoma (HCC), and blocking the action of this gene with a short peptide could have therapeutic potential, according to the findings of a study recently published in the *New England Journal of Medicine*.

HCC is the third leading cause of cancer-related deaths worldwide. Various treatment options are available—such as surgery, liver transplantation and chemotherapy—but many patients present with advanced disease, which limits their options for curative treatment. Furthermore, sorafenib is currently the only systemic drug with proven efficacy in HCC. Improved understanding of the molecular pathogenesis of this deadly disease is urgently needed and could aid in the development of future therapies.

To this end, Li Chai, Daniel Tenen and colleagues decided to investigate the role of the oncofetal gene *SALL4* in HCC. "*SALL4* is one of the key regulators in charge of the self-renewal property of human and mouse embryonic stem cells," explain the authors. The expression of this gene decreases as development progresses, to the point that it is absent in most adult normal tissues. However, it is reactivated in some cancers, including HCC. "We are fascinated by the link between embryonic stem cells and cancer stem cells, as they share this similar self-renewal property," say Chai and Tenen. Thus, the research team embarked on a study of the 'stem-like' *SALL4* in HCC.



Role of SALL4 in a subgroup of hepatocellular carcinoma. Top: SALL4 interacts with NuRD to inhibit PTEN. Bottom: SALL4 peptide blocks the interaction between SALL4 and NuRD, releasing suppression of PTEN.

The first step in this study was to examine the expression of *SALL4* in liver specimens from patients with and without HCC. This step broadly confirmed that *SALL4* is expressed in fetal liver specimens but not in adult liver specimens, and is also upregulated in a subset of patients with HCC.

The researchers then performed a clinicopathological analysis, which showed that patients with HCC with a high expression level of *SALL4* had a worse prognosis than patients with a low expression level of the gene, independent of baseline liver function or the type of treatment the patient received. Global gene-expression data revealed that HCCs that express *SALL4* have progenitor-like gene signatures; cancers with these stem-like gene signatures are often associated with poor prognosis.

"Loss-of-function studies were then carried out to evaluate the role of *SALL4* in hepatocarcinogenesis and its potential as a molecular target for therapy," note Chai and Tenen. Genetic loss-of-function studies (using short hairpin RNA) showed that knocking out *SALL4* led to a decrease in cell viability, an increase in apoptosis and a decrease in tumorigenecity of HCC cells *in vitro*. The same research group have recently shown that a SALL4 peptide (12 amino acids in length) can also block the effects of this gene. "To assess the therapeutic effects of this peptide in HCC, we carried out *in vitro* functional assays and *in vivo* xenograft assays," say the authors.

Their previous basic research studies concluded that—as a transcription factor—SALL4 links to an epigenetic complex (nucleosome remodelling and histone deacetylase; NuRD) to modulate its target genes. The tumour suppressor *PTEN* (phosphatase and tensin homologue) has been shown to be among the target genes repressed by SALL4. In an HCC cell line, treatment with the SALL4 peptide led to decreased cell viability along with increased levels of the PTEN protein (confirming the important role of *PTEN* in this pathway).

Interestingly, in cells with undetectable endogenous *SALL4* expression, the SALL4 peptide had no effect, suggesting that this molecule could be used with minimal toxicity to normal tissues. In addition, in a mouse xenograft model, the tumour burden (that is, the overall size of tumours) at 18 days was significantly smaller in mice that received the SALL4 peptide compared with mice that did not receive the peptide.

"We hope in the near future that we can use SALL4 as a 'targetable marker' for patients with cancer," Chai and Tenen conclude. "Patients with various cancers will be screened for *SALL4* expression at time of diagnosis; the ones who are positive for SALL4 will be offered a SALL4-specific treatment regimen, which will lead to longer survival and better quality of life for these patients."

Greg Gores, an expert in the field but who was not involved in this study, agrees that SALL4 is an exciting new target that should be pursued. Nevertheless, he remains unsure as to whether these findings will translate into any new therapies. Josep Llovet, another independent commentator, adds that the value of SALL4 as a biomarker needs to be validated by independent investigators.

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