SALL4, a new target in aggressive liver cancer

Few treatment options are available for advanced-stage hepatocellular carcinoma (HCC), the third most common cause of cancer deaths worldwide. But a new therapeutic target in HCC has been identified. SALL4, a protein expressed in fetal (but not adult) liver, was re-expressed in a subgroup of adult hepatocellular carcinomas associated with the poorest prognosis.

The SALL4 transcription factor functions via interaction with the NuRD (nucleosome remodelling and histone deacetylase, HDAC) complex. This study established the potential of SALL4 as a prognostic marker and therapeutic target for HCCs. SALL4 expression was highest in an aggressive, progenitor cell-like subgroup of hepatocellular carcinoma. The tumorigenicity of HCC cells was decreased after down-regulation of SALL4, affirming its active role in hepatocarcinogenesis. Furthermore, the targeting of SALL4 with a specific 12-amino-acid inhibitor reduced the growth of this malignancy both in vitro and in vivo.

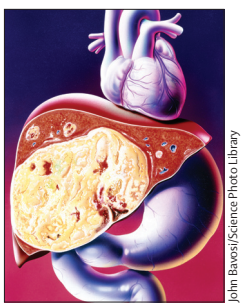
Senior author Li Chai (Brigham and Women's Hospital, Boston, MA, USA), who shares senior authorship on this report with Daniel Tenen of the National University of Singapore, said that these results might benefit patients with HCC in the future "in two ways: SALL4 might serve as a diagnostic marker that can help clinicians to classify the patients, some of whom might be suitable for ongoing clinical trials with HDAC inhibitors or MET inhibitors. And moving forward, we are actively proceeding with making a SALL4 inhibitor drug for translation into clinical application."

Chai added, "I'm really excited about this...to me, *SALL4* is on the front line for the new discovery for patients with HCC, and we look forward to advancing diagnostically and therapeutically".

Snorri Thorgeirsson (National Cancer Institute, NIH, Bethesda, MD, USA) told *The Lancet Oncology*, "this report strongly emphasises the importance of identifying homogeneous subgroups of patients with HCC—and the same applies to other solid tumours—characterised by a key oncogenic driver, for example *SALL4*, that can be a treatment target".

He added, "Clinical translation of these important findings is urgently needed in order to achieve individualised therapies and ultimately improve the poor outcome of patients with HCC". This result might be expected to occur "hopefully within the next 2 years."

Judith A Gilbert



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For the ***SALL4* study** see *N Engl J Med* 2013; **368:** 2266–76

Radiotherapy treatments for node-negative NPC

Whole-neck irradiation might be unnecessary for treatment of patients with node-negative nasopharyngeal carcinoma (NPC), according to a recent phase 2 clinical trial. The researchers demonstrated that prophylactic upper neck irradiation is sufficient treatment for patients with node-negative NPC, and suggested that whole-neck radiation can only cause harm.

Patients with node-negative NPC were randomly assigned to receive either primary plus prophylactic upper neck radiation (n=153) or primary plus whole-neck irradiation (n=148). The investigators collected data for all participants' overall survival, metastasis-free survival, and relapse-free survival over a follow-up of 39 months. No significant differences were noted in any of the three survival measures between the two groups.

But co-author Jin-Gao Li (Jiangxi Cancer Hospital, Nanchang, China) warned that the study's findings might not apply to patients with a "suspicious" metastatic node—a node that does not satisfy standard diagnostic criteria. "Because this group of patients accounted for only less than 10% of our study population, we are not sure whether it is safe to irradiate only the upper neck nodes [in these cases]", Li noted. "Further study including this specific group of patients fully assessed by MRI with PET-CT is warranted."

Ester Orlandi (Istituto Nazionale dei Tumori, Milan, Italy) also expressed concern regarding the study's limitations, noting that patients were selected according to a dated diagnostic system. "The current classification considers retropharyngeal lymph nodes as N1", she explained. "So, patients staged N0 could be N1 if retropharyngeal lymph nodes are positive. It would be useful to analyse the outcome of this subgroup of patients."

And although Daniel Spratt (Memorial Sloan-Kettering Cancer Center, New York, NY, USA) noted the significant impact of this trial, he encouraged additional research to better understand the implications of the results. "This study alone serves more as a stepping stone rather than a pivotal keystone to immediately change management", he told *The Lancet Oncology*, adding, "Further follow-up of this trial will provide insight into the late toxicity prevented by omitting the low neck fields, as preventing grade 1 acute dermatitis or mild late low neck skin atrophy is a hard sell if there is potentially up to a 5% chance of increase recurrence that has not been ruled out."

Michael Granovetter

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For the **study of radiotherapy in node-negative NPC** see *Cancer* 2013; published online June 13. doi:10.1002/cncr.28201