Oncofetal Gene SALL4 in Aggressive Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is the major form of liver cancer. HCC is highly fatal; it is the third leading cause of cancer-related deaths globally, with an overall mortality to incidence ratio of 0.93. There are more than half a million new cases diagnosed each year worldwide. Disease burden of HCC is borne in developing nations, especially in Southeast Asia and sub-Saharan Africa where hepatitis B virus infection is endemic. In Singapore, liver cancer is the fourth most frequently diagnosed cancers and third leading cause of cancer-related mortality in males, according to the Singapore Cancer Registry, Singapore Registry of Diseases Office.

Treatment of HCC remains abysmal, for early stage HCC, curative surgery and liver transplantation might be viable options, however, these treatments are often negated by tumor recurrence or metastasis. Moreover, most HCCs are diagnosed at late stage; the prognosis for advanced stage HCC remains bleak with a five-year survival rate of less than 10%. As most HCCs present at a late stage, there is an urgent need to develop better therapy. For many years, combination chemotherapy has not improved overall survival but has nonetheless been in wide usage due to its possible role in palliation. Current treatment algorithm for HCC is based solely on clinical features of HCC, the molecular characteristics of tumors are not taken into account, despite their potential clinical values. The need to understand the molecular pathogenesis of HCC and develop more effective targeted therapies remains urgent.

SALL4 is a stem cell gene – it is expressed abundantly during the embryonic developmental stage and has a role during normal mammalian development. Recently, SALL4 has emerged as an oncogene i.e. a gene that is associated with cancer. The key findings of our study are as follows:

1. We established that SALL4 is expressed in human fetal livers (as expected), shut down in non-cancerous adult livers, and re-appeared in a subgroup of HCC – oncofetal gene.

2. The expression of SALL4 is associated with the more aggressive progenitor-like subgroup of HCC. Importantly, we established that SALL4 is an independent marker for the prediction of prognosis (prognostic marker) for HCC. This is important for the management of HCC. If SALL4 is tested in the clinics, patients
who are found to express this gene should be given a more aggressive treatment regimen if possible, as they are more likely to do worse than others.

3. SALL4 has a role in liver tumor formation. By knocking down the expression of this gene in HCC cells, we found that the cells are more susceptible to cell death. From our animal model studies, we also found that knocking down of this gene renders HCC cells less tumorigenic i.e. they are less likely to form tumor in the mice. These data suggested that SALL4 is a potential therapeutic target for HCC i.e. drugs that inactivate this gene might be useful for the treatment of HCC.

4. We proposed a way to inactivate SALL4. By using a therapeutic peptide, we performed proof-of-concept studies to support our hypothesis that inactivation of SALL4 could cause HCC cell death and render the cells less tumorigenic.

We are currently developing a screening assay to find small molecules that work in a similar way as the peptide, hoping to develop a drug that has the potential to treat cancers with aberrant SALL4 expression, including liver cancer.


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