

Function of the Developmental Transcription Factor SALL4 in Cancer

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Commentary

Up-regulation of some developmental genes has been observed in cancerous tissues and cancer cells. *Sal-like 4* (*SALL4*), a member of the homologs of *Drosophila spalt* (*sal*) gene, plays a key role in early development and organogenesis. *SALL4* encodes a C2H2 multiple zinc finger protein, and is a causative gene for Okhiro/Duane radial ray syndrome, the major symptoms of which are limb malformations and ocular anomalies [1,2]. Genomes of these patients have point mutations in the *SALL4* coding sequence, which is thought to cause a loss of *SALL4* function. A knockout mouse study has shown that *SALL4* null mutant is embryonic lethal, and *SALL4* is required for embryonic stem cell proliferation [3]. *SALL4* heterozygous mouse exhibits dysplasia of anus, colon, heart, brain and kidney. The authors furthermore have revealed that *SALL4* localizes to heterochromatin regions in nuclei of embryonic stem cells. During organ regeneration observed in lower vertebrates, the developmental genes are re-activated. The *SALL4* signal has been detected in regenerating *Xenopus* limb blastema [4]. A blastema tissue is formed at a regenerating part of damaged organ. It contains cells having abilities for growth and differentiation. These studies indicate that *SALL4* is a factor for vertebrate development and organogenesis.

The *SALL4* expression has been observed in various cancers. *SALL4* has two splicing variants [5]. The mRNA of *SALL4A* has the long exon2, and *SALL4B* has the short one. Increase in the expression levels of both *SALL4* variants is observed in acute myeloid leukemia, and forced expression of *SALL4B* causes acute myeloid leukemia in mouse [5]. In leukemic cells, *SALL4* positively regulates *BMI1* gene, which encodes a polycomb protein [6]. *BMI1* suppresses the expression of cyclin dependent kinase inhibitor genes, such as *CDKN2A* (*p16*), *CDKN2C* (*p18*) and *CDKN1A* (*p21*) [7]. Thus increase in *BMI1* level enhances cell proliferation. Augmentation of *SALL4* level has also been reported in lung cancer [8]. Knockdown experiments for *SALL4* have shown that reduction in *SALL4* level increases a cell population of G1 phase, and reduces that of S phase in a lung cancer cell line, suggesting that *SALL4* supports S phase entry. Reciprocal evidence has been reported in liver cancer. In the study, *SALL4* forced expression reduced number of cells in G1 phase [9]. In addition, the study has shown that *SALL4* positively regulates the expression of *CCND1* and *CCND2*, which encode cell-cycle progression factors Cyclin D1 and D2, respectively. *SALL4* knockdown reduces the proliferative ability in breast cancer cells [10,11]. The expression of *BMI1* and *CCND1* are positively regulated by *SALL4* in breast cancer cells [12]. It could be concluded that positive regulation of cell proliferation is a common function of *SALL4* among cancers.

On the other hand, *SALL4* suppresses intercellular adhesion and maintains the motility in breast cancer cells [12], but is not involved in liver cancer cell migration [9]. Therefore, further study is required to understand the relation between *SALL4* and the migratory ability.

In order to elucidate the *SALL4* function in cancer, it is necessary to assess whether the expression of *SALL4* or activation of its function induces oncogenic transformation. In a mouse study, introduction of

human *SALL4B* triggered acute myeloid leukemia [5]. However, *SALL4* forced expression is not likely to cause transformation in normal mammary epithelial cells [12]. Therefore, experimental evidences to this end will contribute to understand the oncogenic function of *SALL4*. Another question is about the relation between *SALL4* and cancer stem cell. In normal cells, *SALL4* is considered to be a stem cell gene [3,13,14]. In addition, some studies have demonstrated that *SALL4* acts as an epigenetic factor in hematopoietic stem cells [15,16]. Although such studies have been reported in the fields of normal stem cells and leukemic cells, there are no reports in other types of cancer so far.

The *SALL4* expression seems to be a biomarker for various cancers. Up-regulation of *SALL4* level has been reported in breast cancer [10,11], lung cancer [8], colorectal cancer [17], liver cancer [9] and glioma [18], as well as in acute myeloid leukemia [5]. An increase in *SALL4* levels has also been observed in germ cell tumors, such as testicular germ cell tumor [19] and yolk sac tumor [20]. In these cancerous tissues, anti-*SALL4* immunoreactions were observed in the nuclei of cancer cells by immunohistochemistry. Furthermore, the *SALL4* expression has been detected in blood samples. In patients having early and advanced breast cancers, the *SALL4* protein level is increased in their plasma, comparing to the healthy control group [21]. These suggest that analyzing the *SALL4* expression is useful as a novel diagnostic method for cancer.

A study focusing on gastric cancer progression has reported that *SALL4* promoter region is more methylated in submucosal cancers, an intermediate stage between early and advanced cancers, than in early cancers [22]. Given that promoter methylation reduces the gene transcription level, this report implies that *SALL4* down-regulation is related to gastric cancer progression. Therefore, use *SALL4* signal as a sign of cancer progression is still controversial.

In addition to a biomarker for cancer diagnostics, *SALL4* has a possibility to be a therapeutic target. In glioma cells, miR-107 targets the *SALL4* mRNA, and the miR-107 expression is negatively correlates to the *SALL4* expression in glioma tissues [18]. Thus, the authors have suggested that enhancing the miR-107-mediated *SALL4* silencing could be a therapeutic method for glioma. A peptide inhibitor for *SALL4* has been proposed to be used as a drug for acute myeloid leukemia and liver cancer [23,24]. The peptide interrupts the interaction between *SALL4*

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and histone deacetylase complex. Treating with the peptide inhibitor reduces tumor volume in mouse transplantation experiment with liver cancer cells [24]. The SALL4 expression level is negatively correlates to overall survival in liver cancer patients [24]. Taken together, it is suggested that SALL4 might be a therapeutic target for various cancers, and studies on the SALL4 function might shed light on its role in cancer biology and could facilitate future therapeutic strategy.

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