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Commentary Open Access

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 *Dorosophila 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 Okihiro/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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