【総説】

第8回 高安賞優秀賞受賞論文

論文 「Induction and downregulation of *Sox17* and its possible roles during the course of gastrointestinal tumorigenesis」

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消化管腫瘍発生過程におけるSox17発現誘導および抑制とその役割

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Background

The constitutive activation of Wnt/β-catenin signaling causes gastrointestinal tumorigenesis in both human beings and micw. It has also been shown that β-catenin nuclear accumulation, a hallmark of Wnt activation, is particularly enhanced in the invasion front and metastasized colon cancer cells,suggesting that promotion of Wnt/β-catenin signaling is important for malignant progression. Sox17 have been shown to inhibit Wnt/β-catenin signaling ,indicating a tumor suppressor role for cancer development. On the other hand Sox17 plays a key role in definitive endoderm development. However, Sox17 expression during the course of gastrointestinal tumorigenesis has not been fully investigated yet. This study was designed to elucidate the role of Sox17 during the course of gastrointestinal tumorigenesis.

Results

K19-Wnt1/C2mE (Gan) transgenic mice develop gastric tumors caused by simultaneous activation of the Wnt/β-catenin signaling and cyclooxygenase-2/prostaglandin E2 (PGE2) pathway. The expression of Sox17 examined by microarrayanalysis was also elevated in Gan mouse tumors companying with wnt target genes but not in K19-C2mE mice (Figure 1). We next determined the Sox17-expressing cell types by immunostaining. Notably, nuclear Sox17 staining was also detected in the dysplastic epithelial cells of K19-Wnt1gastric preneoplastic lesions where Wnt/β-catenin signaling was activated.(Fig2A). Tumor epithelial cells from Gan mouse tumors formed dome-shaped spheroid structures on the primary culture dish, consisting of small epithelial cells (Fig2B). The spheroid cells showed strong accumulation of β-catenin and negative staining of Ki-67, suggesting that they were slow-cycling undifferentiated cells. Strong Sox17 expression was found only in the spheroids. These results, taken together, suggest that Sox17 is induced in the Wnt-activated undifferentiated epithelial cells. The transfection of active β-catenin expression vector caused a significant increase in the Sox17 mRNA levels in AGS gastric cancer cells and 293 cells (Fig2C). However, Sox17 expression was significantly suppressed in human gastric cancer (Fig3A) Treatment with a demethylating agent DAC induced Sox17 expression in AGS and AZ521 gastric cancer cells as well as SW480 cells (Fig3B). Transfection of Sox17 expression vector significantly suppressed the β-catenin/T-cell factor (TCF) transcriptional activity in AZ521 cells in GSK3β-independent manner (Fig3C). Importantly, the transfection of Sox17 in AGS cells significantly suppressed the colony formation efficiency (Figure 3D). Gan mouse tumors are in the early stage of tumorigenesis. We thus examined whether Sox17 is induced in the benign human gastric tumors and

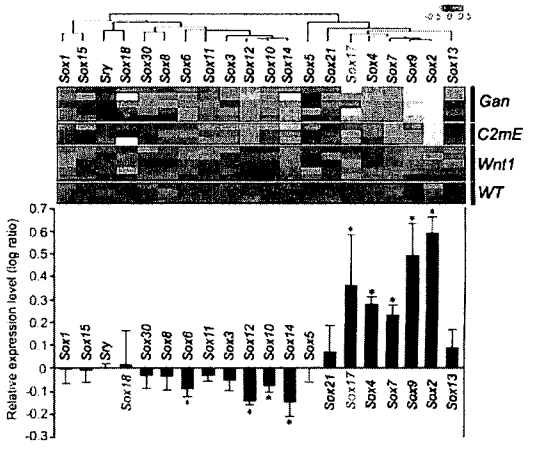

Fig. 1. Sox17 is induced in *Gan* mouse gastric tumors and *Apc Δ 716* mouse polyps.

found Sox17 is rarely detected in gastric and colon cancer tissues while induced in benign tumors by immunostaining on tissue array (Fig4). Apc$^{\triangle 716}$ mice develop intestinal polyps caused by activation of Wnt signaling whereas cis-Apc$^{\triangle 716}$ Smad4 mice develop invasive adenocarcinomas by suppression of the transforming growth factor-β pathway in addition to Wnt activation. Sox17 staining intensity in polyps was reciprocal to the β-catenin staining pattern (Fig5A). Importantly, in the invasive adenocarcinomas of cis-Apc$^{\triangle 716}$ Smad4 mice, Sox17 expression was dramatically suppressed (Fig5B). These genetic results clearly indicate that Sox17 is induced at the initiation stage of intestinal tumorigenesis and is dramatically down-regulated when tumors progress to adenocarcinoma.The histology of the K19-Sox17 transgenic mouse stomach was normal. We thus crossed K19-Sox17 mice with Gan mice to construct Gan K19-Sox17 compound transgenic mice.The mean height of the gastric tumors in Gan K19-Sox17 mice decreased significantly. Sox17 suppressed tumor development through the inhibition of cell proliferation (Fig6B). Importantly, the expression level of the Wnt target genes, Cd44 and Ephb3, in the Gan K19-Sox17 mice decreased significantly compared with that in the Gan mice (Fig6C) Sox17 target genes are upregulated in Gan mice (Fig6D).

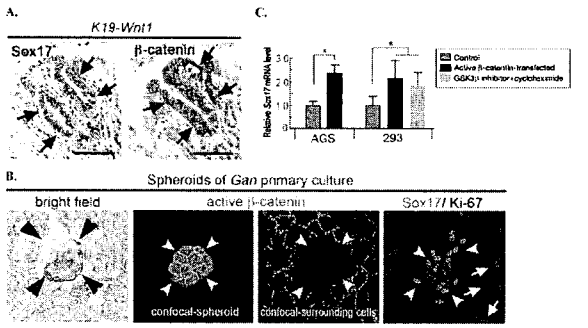

Fig. 2. Sox17 is induced within Wnt-activated epithelial cells. unphosphorylated β-catenin directly induces Sox17.

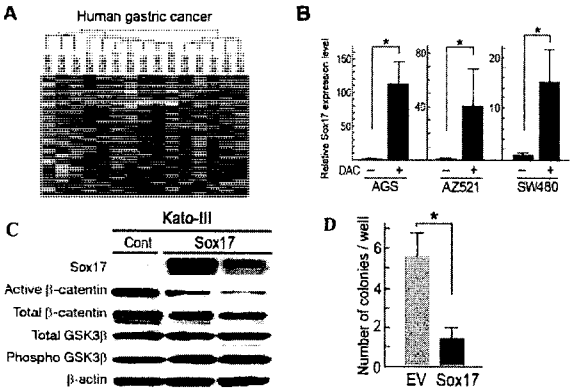

Fig. 3. Sox17 expression is downregulated in gastric cancer and could recovered by demethylation. Sox17 repress Wnt activity by decrease the active β catenin protein level.

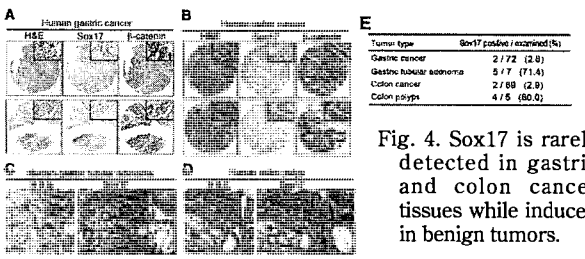

Fig. 4. Sox17 is rarely detected in gastric and colon cancer tissues while induced in benign tumors.

Conclusion

Sox17 is induced in the early stage of gastrointestinal tumorigenesis possibly caused by Wnt activation, and *Sox17* expression is downregulated during malignant progression. Accordingly, it is conceivable that *Sox17* induction protects benign tumors from malignant progression through repression of Wnt signaling. It is also possible that Sox17 plays a role in tumor development through the induction of target genes that function in endoderm development.

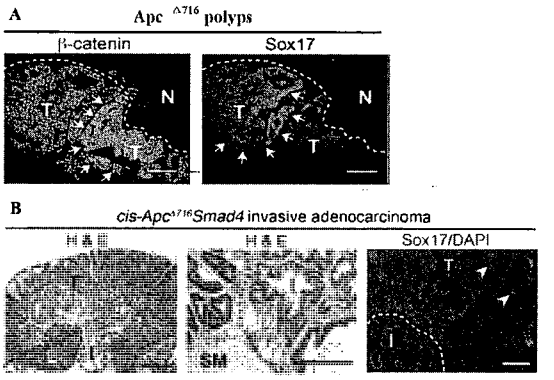

Fig. 5. Downregulation of Sox17 during malignant progression in mouse intestinal tumors.

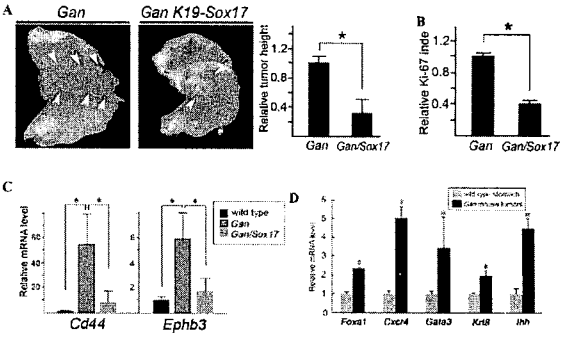

Fig. 6. Transgenic expression of Sox17 decreased *Gan* gastric tumors by inhibiting its proliferation. Sox17 target genes are upregulated in *Gan* mice.

Profile

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