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Original contribution

Expression profiles of stemness genes in gastrointestinal stromal tumor☆,☆☆

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Summary Gastrointestinal stromal tumor (GIST) is believed to originate from intestinal cells of Cajal or their stem cell precursors, and expresses stemness-related markers, such as CD117, CD34, DOG1 and nestin. To further characterize phenotypic features of GISTs, we examined expression profiles of a panel of stemness genes in GISTs, by analyzing existing gene expression profiling datasets. Our results showed that mRNA levels of B-lymphoma moloney murine leukaemia virus insertion region-1 (*BMI1*), kruppel-like factor 4 (*KLF4*), sal-like protein 4 (*SALL4*) and telomerase reverse transcriptase (*TERT*) were significantly unregulated in GISTs. Subsequently, protein expression of BMI1 and TERT was identified in GIST specimens by immunohistochemistry. Especially, we found that high expression of nuclear BMI1 was associated with large tumor size ($P = .0239$), high mitotic count ($P < .01$), high Ki-67 index ($P = .0357$), advanced National Institute of Health (NIH) criteria ($P = .0025$) and advanced World Health Organization (WHO) classification ($P < .01$) in GISTs. Functional and pathway enrichment analysis showed that most of *BMI1*'s coexpressed genes were involved in tumor growth-related process, such as regulation of cell cycle and proliferation. Furthermore, we confirmed RAS oncogene family (*RAB18*) and limb development membrane protein 1 (*LMBR1*) genes as novel targets for BMI1 in GIST cells. These results provide valuable information for the expression profiles of stemness genes in GISTs, and identified nuclear BMI1 as an important marker of GIST cell proliferation and progression.
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1. Introduction

Gastrointestinal stromal tumor (GIST), previously classified as smooth muscle tumor, is the most common mesenchymal neoplasm of the gastrointestinal tract. It was first introduced by Mazur and Clark [1] in 1983 to define a "non-epithelial tumor group consisting of spindle cells and epithelioid cells." Genotypically, the majority of GISTs harbor mutually exclusive activating mutations in c-kit and platelet-derived growth factor receptor alpha (*PDGFRA*) genes, which are early events in GIST transformation and progression. Immunophenotypically, they are positive for

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CD117 [2], CD34 [3], DOG1 (ANO1) [4] and nestin [5], and sometimes for differentiated marker actin but are almost always negative for desmin and S100 protein. Both CD117 and CD34 are stem cell markers on early hematopoietic progenitors [6,7], while intermediate filament protein nestin is a neuroectodermal stem cell marker molecule [8]. In addition, GISTs also express CD133 and CD44, both of which are widely used for isolating cancer stem cells from solid tumors [9,10].

These properties suggest that GIST may arise as partial differentiation of stem cells, and share the characteristics of both stem and differentiated cells, with poorly differentiated tumors being more likely to express stem cell markers. To test this hypothesis, we examined transcriptional profiles of a panel of stemness genes in GISTs, by analyzing existing gene expression profile databases obtained from clinical samples. We also examined the protein expression of differential genes using immunohistochemistry in

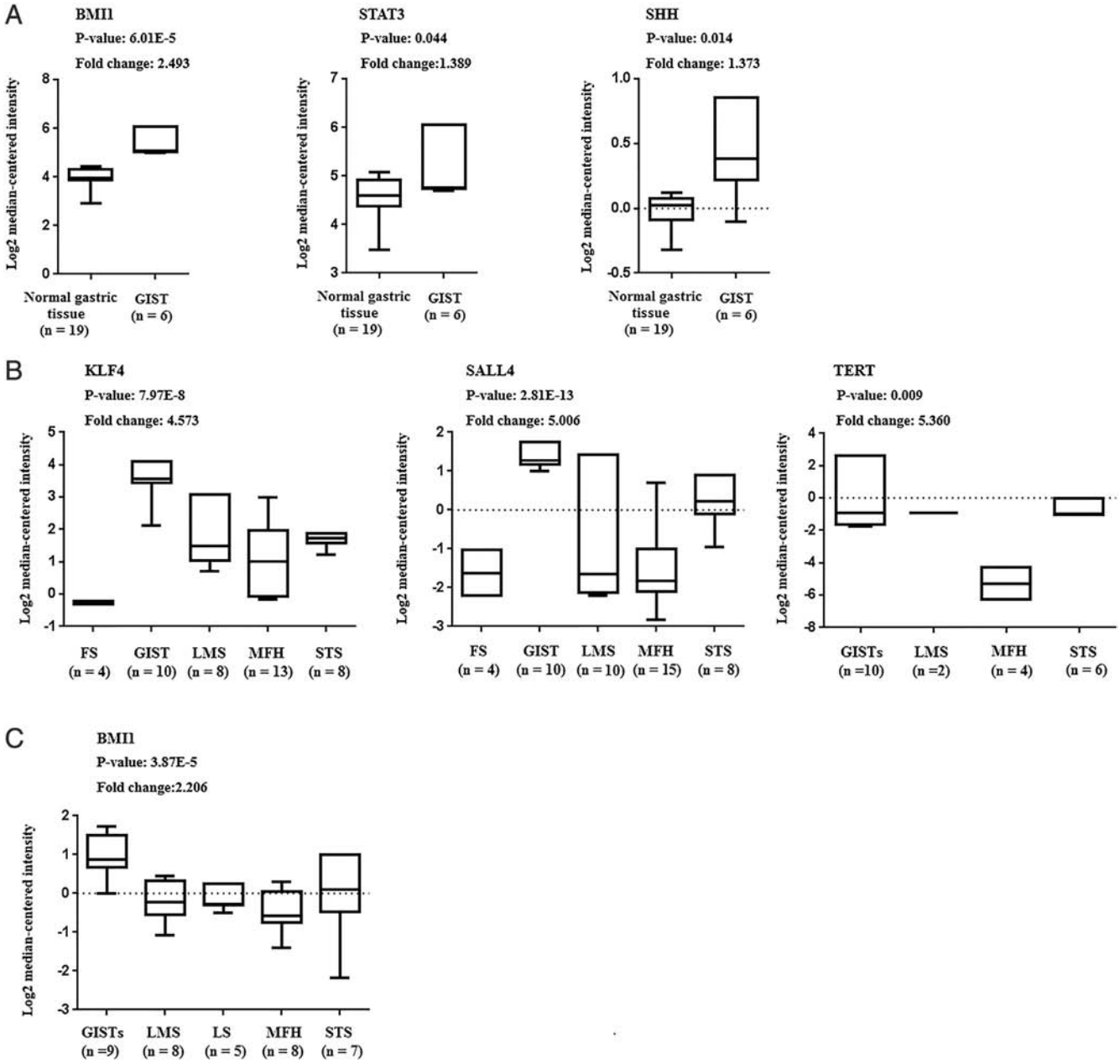

Fig. 1 Stemness genes analysis in GISTs (Oncomine database). A, Differential expression of *BMI1*, *STAT3* and *SHH* in Cho gastric. B, Differential expression of *KLF4*, *SALL4* and *TERT* in Linn sarcoma. C, Differential expression of *BMI1* expression in Nielsen multicancer. The boundaries of the boxes represent the first and third quartiles, the horizontal line within the boxes represents the median, and the ends of the whiskers represent the minimum and maximum values. FS, fibrosarcoma; GIST, gastrointestinal stromal tumor; LMS, leiomyosarcoma; MFH, malignant fibrous histiocytoma; STS, soft tissue sarcoma; LS, liposarcoma.

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