

## 5-Fluorouracil Chemotherapy of Gastric Cancer Generates Residual Cells with Properties of Cancer Stem Cells

Zhi-Yuan Xu<sup>1</sup>, Jia-Ning Tang<sup>1</sup>, Hua-Xia Xie<sup>1</sup>, Yi-An Du<sup>2</sup>, Ling Huang<sup>2</sup>, Peng-Fei Yu<sup>2</sup>, Xiang-Dong Cheng<sup>1</sup>

1. Department of Gastrointestinal Surgery, The First Affiliated Hospital of Zhejiang Chinese Medicine University, Hangzhou, Zhejiang, China 2. Department of Abdominal cancer Surgery, Zhejiang Cancer Hospital, Hangzhou, Zhejiang, China These two authors contributed equally to this work. Corresponding author: Name: Xiang-Dong Cheng, Department of Gastrointestinal Surgery, The First Affiliated Hospital of Zhejiang Chinese Medicine University, Youdian Road 54#, Hangzhou, 310006, Zhejiang, China. Tel: +86-571-87070965; Fax: +86-571-87070965; E-mail: abcsurg@gmail.com

### Abstract :

**Background:** 5-Fluorouracil (5Fu) chemotherapy is the first treatment of choice for advanced gastric cancer (GC), but its effectiveness is limited by drug resistance. Emerging evidence suggests that the existence of cancer stem cells (CSCs) contributes to chemoresistance. The aim of the present study was to determine whether 5Fu chemotherapy generates residual cells with CSC-like properties in GC. **Methods:** Human GC cell lines, SGC7901 and AGS, were exposed to increasing 5Fu concentrations. The residual cells were assessed for both chemosensitivity and CSC-like properties. B lymphoma Mo-MLV insertion region 1 (BMI1), a putative CSC protein, was analyzed by immunohistochemical staining and subjected to pairwise comparison in GC tissues treated with or without neoadjuvant 5Fu-based chemotherapy. The correlation between BMI1 expression and recurrence-free survival in GC patients who received 5Fu-based neoadjuvant chemotherapy was then examined. **Results:** The residual cells exhibited 5Fu chemoresistance. These 5Fu-resistant cells displayed some CSC features, such as a high percentage of quiescent cells, increased self-renewal ability and tumorigenicity. The 5Fu-resistant cells were also enriched with cells expressing cluster of differentiation (CD)133+ , CD326+ and CD44+ CD24- . Moreover, the BMI1 gene was overexpressed in 5Fu-resistant cells, and BMI1 knockdown effectively reversed chemoresistance. The BMI1 protein was highly expressed consistently in the remaining GC tissues after 5Fu-based neoadjuvant chemotherapy, and BMI1 levels were correlated positively with recurrence-free survival in GC patients who received 5Fu-based neoadjuvant chemotherapy. **Conclusions:** Our data provided molecular evidence illustrating that 5Fu chemotherapy in GC resulted in acquisition of CSC-like properties. Moreover, enhanced BMI1 expression contributed to 5Fu resistance and may serve as a potential therapeutic target to reverse chemoresistance in GC patients.

### Key Word :

Gastric cancer; 5-Fluorouracil (5Fu); Chemoresistance; Cancer stem cells