The meiosis-specific cohesion component stromal antigen 3 promoted cell migration and chemoresistance in colorectal cancer

Department of Gastroenterological Surgery, Graduate School of Medicine

Assistant Professor Norikatsu Miyoshi Researchmap https://researchmap.jp/nor

Professor Hidetoshi Eguchi Researchmap https://researchmap.jp/abcdabcdabcd

Abstract

We evaluated the prognostic impact and role of Stromal antigen (STAG) 3 in colorectal cancer (CRC). Analysis of 172 CRC surgical specimens revealed that high STAG3 expression was associated with poor prognosis. STAG3 knockdown inhibited cell migration and increased drug sensitivity to oxaliplatin, 5-fluorouracil, irinotecan hydrochloride hydrate, and BRAF inhibitor in CRC cell lines. Moreover, suppression of STAG3 increased γH2AX foci, Our findings suggest that STAG3 is related to poor clinical outcomes and promotes metastasis and chemotherapeutic resistance in CRC. STAG3 may be a novel prognostic marker and potential therapeutic target for CRC.

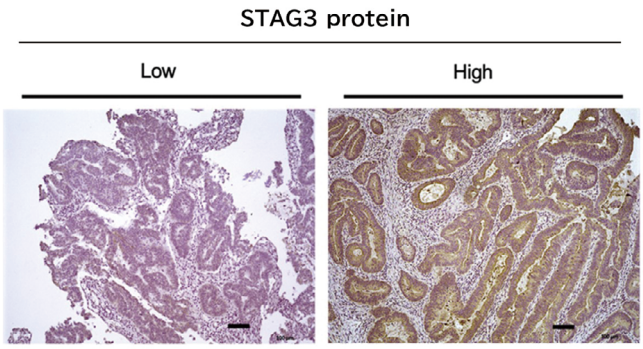
Background & Results

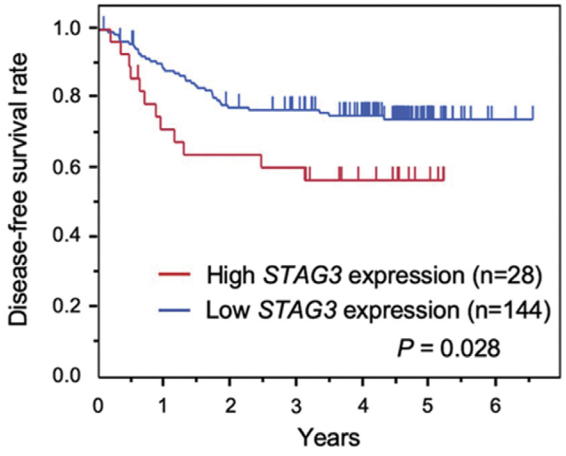
Colorectal cancer (CRC) is the second leading cause of cancer-related mortality worldwide. A variety of treatment options exist for patients with advanced CRC, depending on the identified oncogenic mutations. BRAF mutations have been detected in approximately 10% of CRC and are related to poor prognosis and chemotherapy resistance. As BRAF inhibitors have been shown to improve the survival in melanoma, their efficacy was recently also demonstrated in BRAF-mutant CRC. Thus, we hypothesized that STAG components of the cohesin complex may be associated with CRC. The cohesin subunit STAG has three paralogs in mammals: mitosis-specific STAG1 and STAG2 and meiosis-specific STAG3. While STAG1 expression correlates with carcinogenesis in CRC, the association between STAG2 or STAG3 and CRC remains unknown. Therefore, we aimed to elucidate the relationships of STAG2 and STAG3 to CRC, with a focus on changes in their expression.

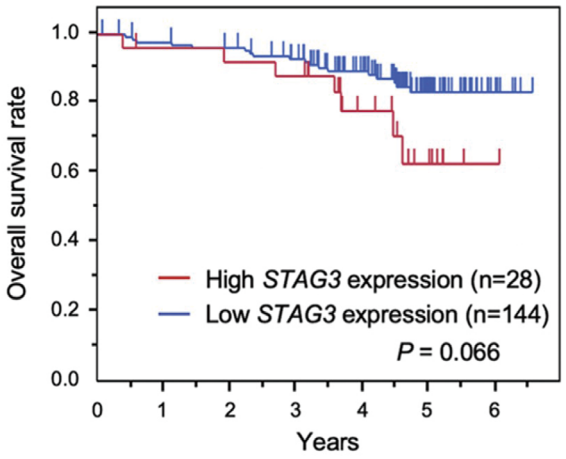
Analysis of 172 CRC surgical specimens revealed that high STAG3 expression was associated with poor prognosis. STAG3 knockdown inhibited cell migration and increased drug sensitivity to oxaliplatin, 5-fluorouracil, irinotecan hydrochloride hydrate, and BRAF inhibitor in CRC cell lines. The enhanced drug sensitivity was also confirmed in a human organoid established from a CRC specimen. Moreover, suppression of STAG3 increased γH2AX foci. Particularly, in BRAF-mutant CRC cells, STAG3 silencing suppressed the expression of snail family transcriptional repressor 1 and phosphorylation of extracellular signal-regulated kinase via upregulation of dual-specificity phosphatase 6.

Significance of the research and Future perspective

Our findings suggest that STAG3 is related to poor clinical outcomes and promotes metastasis and chemotherapeutic resistance in CRC. STAG3 may be a novel prognostic marker and potential therapeutic target for CRC.







Patent

Treatise Sasaki, Masaru; Miyoshi, Norikatsu; Fujino, Shiki et al. The meiosis-specific component stromal antigen 3 promotes cell migration and chemotherapeutic resistance in colorectal cancer. Cancer Letters. 2021, 28; 497: 112-122. doi: 10.1016/j.canlet.2020.10.006

URL

Keyword colorectal cancer, STAG3, chemotherapy, recurrence, prognossi