Water Center for Latin America & the Caribbean
FUNDACIÓN FEMSA · TECNOLÓGICO DE MONTERREY · IDB Water and sanitation initiative

JOURNAL OF ZHEJIANG UNIVERSITY SCIENCE ABC

Cite this as: Zhan-huai WANG, Qiong LI, Shu-qin RUAN, Qian XIAO, Yue LIU, Ye-ting HU, Li-feng HU, Hai-yan CHEN, Shu ZHENG, Su-zhan ZHANG, Ke-feng DING, 2014. Sunitinib mesylate inhibits proliferation of human colonic stromal fibroblasts *in vitro* and *in vivo*. *Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)*, **15**(8):701-712. [doi:10.1631/jzus.B1300306]

Sunitinib mesylate inhibits proliferation of human colonic stromal fibroblasts *in vitro* and *in vivo*

Key words: Colon cancer; Cancer-associated fibroblasts; Sunitinib mesylate; PDGF/PDGFR;

- Colorectal cancer (CRC) is a leading cause of cancer deaths worldwide. However, the prognosis of advanced and recurrent CRC remains poor; thus, CRC biology should be further explored to improve current treatment methods or develop new approaches.

- CRC cells secrete numerous growth factors and cytokines, including the platelet-derived growth factor (PDGF) family, during tumor progression. Recent reports have indicated that PDGFR-β is predominantly expressed by cancer-associated stromal cells and pericytes in human colon carcinomas.

- Putative cancer stroma consists of several cellular elements. Among these, one of the major elements is the cancer stromal fibroblast. Cancer stromal fibroblasts differ from normal fibroblasts in terms of phenotype, tumor-enhancing functions, and gene expression profiles.

- Sunitinib mesylate is an orally bioavailable small molecule that inhibits multiple molecules involved in tumor growth, proliferation, and metastasis. Sunitinib targets two important receptors, namely, vascular endothelial growth factor receptor (VEGFR) and PDGFR, which are expressed in various types of solid tumors

- In the present study, we determined the effect of sunitinib on primary human colonic fibroblasts from colon cancer in vitro and in vivo, as well as its underlying molecular mechanisms.

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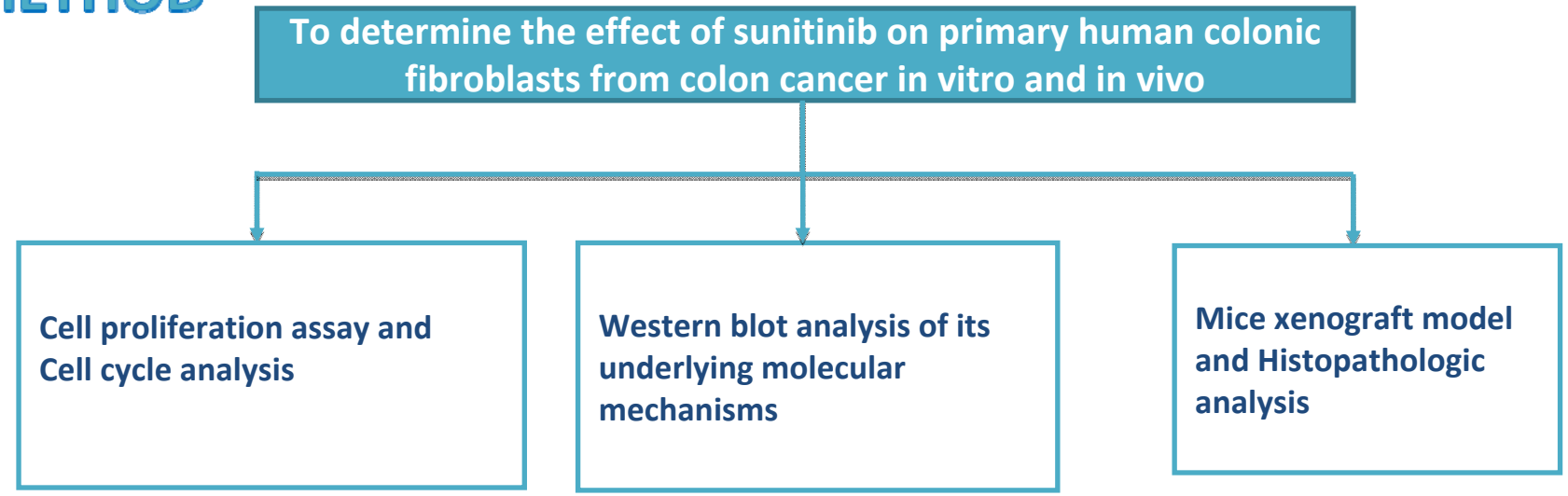
METHOD



RESULTS AND CONLUSIONS

- Significant growth inhibitory effects of sunitinib on SW620 cells and colonic fibroblasts were observed in a dose-dependent manner. 5-FU significantly inhibited SW620 cell growth in a dose-dependent manner, but had no effect on colonic fibroblasts even at 250 μM.

- Cell-cycle analysis of sunitinib treated colonic fibroblasts was performed via flow cytometry indicated a dose-dependent decrease in S and G2/M phases as well as an accumulation of cells in the G0/G1 phase

- Low-dose sunitinib blocked PDGF–BB-induced cell proliferation and PDGFR-β signaling which was indicated by western blot analysis.

- Co-injecting SW620 cells + colonic fibroblasts in nude mice generated greater tumor volumes than injecting SW620 cells alone. Sunitinib treatment inhibited SW620 cell + colonic fibroblast tumor growth more effectively than 5-fluorouracil treatment.

- In conclusion, we demonstrated that small molecular tyrosine kinase inhibitor sunitinib mesylate inhibited proliferation of primary human colonic fibroblasts from colon cancer in vitro and in vivo. Sunitinib-targeted treatment also inhibited PDGFR signaling of colonic fibroblasts by PDGF-BB stimulation. Our results indicate that sunitinib may be valuable in treating colon cancer by suppressing stromal fibroblasts. The effect of sunitinib on stromal response can augment current chemotherapy of colon cancer by establishing a synergistic approach.