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氏名	大久保　友貴
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学位論文の題名	NOTCH1 activates the Wnt/β-catenin signaling pathway in colon cancer. （大腸癌においてNOTCH1はWnt/β-catenin経路を活性化する） Oncotarget 2017; 8(36): 60378-60389
論文審査担当者	主査：　城 卓志 副査：　高橋 智，瀧口 修司

Abstract

Purpose: β-catenin/CTNNB1, a key regulator of Wnt signaling pathway in colon carsinogenesis. Translocation of CTNNB1 to the nucleus has activated Wnt signal and cellular proliferation but the precise mechanism to translocate are still unknown. There are some reports that NOTCH1 was involved in the Wnt pathway. We have therefore sought how NOTCH1 affects in Wnt/β-catenin pathway.

Experimental Design: We constructed the expression vector of Notch1 intracellular domain (NICD) and transfected into the colon cancer and normal colon epithelium cell lines in order to investigate the involvement of NOTCH1 in the β-catenin signaling pathway,. And we performed immunohistochemistry of Notch1 and CTNNB1 using cells transfected NICD and 189 colon cancer tissues. We analyzed the correlation between nuclear NICD and clinicopathological factors.

Results: Immunohistchemistry was revealed that the localization of NOTCH1 and β-catenin was similar in colon cancer tissue. After transfection of NICD expression vector into colon cancer cell lines, confirmed the expression of NICD and the localization in the nucleus by western blotting and

immunochemistry. Furthemore, NICD was induced the translocation of β-catenin to the nucleus and co-locallized with beta catenin in the nucleus. And NICD induced the proliferation of colon cancer cell line and normal colon cell line after transfection of expression vector.

Suppression of NOTCH1 by siRNA was significantly reduced the expression of CyclinD1 which is a representative downstream gene of Wnt/β-catenin signaling pathway.

The nuclear expression of NOTCH1 in 189 colon cancer cases, are involved with T factor (T12 vs T34; p=0.0013) and significant prognostic impact on the survival of surgically treated cases(Kaplan Meier; p=0.0027). Multivariate COX regression analysis showed that the prognostic impact of nuclear NOTCH1 (P = 0.0376) appears to be independent of T factor (P = 0.0086) and N factor(P=0.0267).

Conclusion : These results supported the view that NOTCH1 is an important molecule of the β-catenin/Wnt pathway and is probably related to the translocation of β-catenin into the nucleus. And these caused the cell proliferation. In future, NOTCH1 might be a good candidate of the target of colon cancer therapy.