京都大学大学院医学研究科　消化管外科学　博士課程　板谷喜朗

学位論文要約

Loss of SMAD4 From Colorectal Cancer Cells Promotes CCL15 Expression to Recruit CCR1+ Myeloid Cells and Facilitate Liver Metastasis

Yoshiro Itatani[1,2], Kenji Kawada[2]*, Teruaki Fujishita[1,4], Fumihiko Kakizaki[1], Hideyo Hirai[3], Takuya Matsumoto[2], Masayoshi Iwamoto[2], Susumu Inamoto[2], Etsuro Hatano[2], Suguru Hasegawa[2], Taira Maekawa[3],Shinji Uemoto[2], Yoshiharu Sakai[2] and Makoto Mark Taketo[1]*

Departments of Pharmacology[1], Surgery[2], and Transfusion Medicine & Cell Therapy[3], Graduate School of Medicine, Kyoto University, Kyoto, Japan. Division of Molecular Pathology[4], Aichi Cancer Center, Aichi, Japan.

ABSTRACT

BACKGROUND & AIMS: Loss of the tumor suppressor SMAD4 is correlated with progression of colorectal cancer (CRC). In mice, colon tumors that express CCL9 recruit CCR1+ myeloid cells, which facilitate tumor invasion and metastasis by secreting matrix metalloproteinase (MMP) 9 [(1)(2)].

METHODS: We used human CRC cell lines to investigate the ability of SMAD4 to regulate expression of CCL15, a human ortholog of mouse CCL9. We employed immunohistochemistry to compare levels of CCL15 and other proteins in 141 samples of human liver metastases.

RESULTS: In human CRC cell lines, knockdown of *SMAD4* increased CCL15 expression, whereas overexpression of SMAD4 decreased it. SMAD4 bound directly to the promoter region of *CCL15* gene to negatively regulate its expression; transforming growth factor-β (TGF-β) enhanced binding of SMAD4 to the *CCL15* promoter and transcriptional repression. In livers of nude mice, SMAD4-deficinet human CRC cells upregulated CCL15 to recruit CCR1+ cells

and promote the metastatic colonization. Analysis of clinical specimens showed a strong inverse correlation between levels of CCL15 and SMAD4; metastases that expressed CCL15 contained 3-fold more CCR1+ cells than those without CCL15. Patients with CCL15-expressing metastases showed significantly shorter disease-free survival (DFS) than those with CCL15-negative metastases. CCR1+ cells in the metastases expressed the myeloid cell markers CD11b and myeloperoxidase, and also MMP9.

CONCLUSIONS: In human CRC cells, loss of SMAD4 leads to upregulation of CCL15 expression. Human liver metastases with CCL15 expression contain higher numbers CCR1+ cells and these patients are associated with shorter DFS. Therapeutics that block CCL15 recruitment of CCR1+ cells may prevent metastasis of CRC to liver.

REFERENCES

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