【Grant-in-Aid for Scientific Research(S)】

Biological Sciences (Medicine, dentistry, and pharmacy I)

Title of Project：Studies on Metastasis of Digestive Cancers Using Mouse Models

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Research Area：Medicine, dentistry, and pharmacy

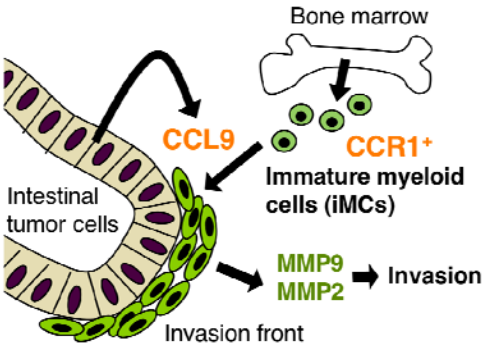
Keyword：Molecular Oncology

【Purpose and Background of the Research】

Digestive tract cancer is the leading cause of cancer death, and to control its distant metastasis is one of the most important issues. This project aims to identify novel therapeutic targets for suppressing colon cancer metastasis.

【Research Methods】

1. Mechanisms of metastasis promotion by



immature myeloid cells (iMCs, Fig.1).

Fig.1

A) To clarify the identity of the iMCs and the mechanisms of metastasis promotion induced by the iMCs.
B) To evaluate the roles of the iMCs in metastasis of human colon cancer.
C) To test the metastasis suppressing effects of the CCR1 antagonist.

2. Mechanisms of metastasis regulation by the Aes/Notch axis.
A) To study the roles of Aes in invasion and metastasis of intestinal tumors in mouse models.
B) To study the roles of AES in the metastasis of non-digestive cancers.
C) To clarify the mechanism of reduced expression of AES, and to evaluate the correlation between the reduced level of AES and prognosis of colon cancer patients.
D) To test the effects of Aes peptides on suppressing the Notch signaling and on suppressing colon cancer metastasis.

3. Roles of the signaling pathways or molecules involved in earlier stages of colon cancer progression in expansion of cancer metastasis.
A) To test the effects of RAD001, a rapamycin derivative, on expansion of the metastatic foci.
B) To clarify the mechanisms by which SMO regulates localization of the active β-catenin.

【Expected Research Achievements and Scientific Significance】

We expect to identify novel mechanisms of metastasis regulation by using mouse models that best reflect the clinical features (Fig.2). We hope our findings will help establish novel therapeutic strategies for controlling metastasis of digestive cancers.

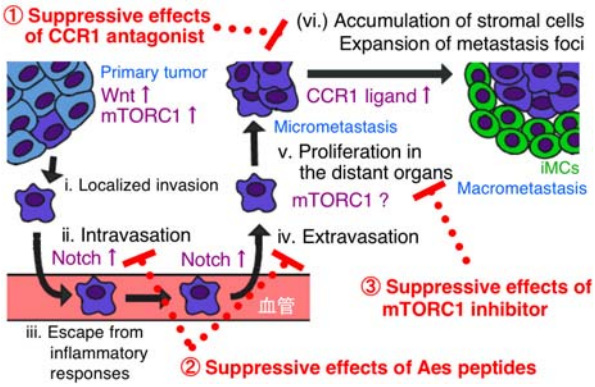


Fig.2

【Publications Relevant to the Project】

・Fujishita, T., Aoki, M., Taketo, M.M. [and 2 others] (2008) Inhibition of the mTORC1 pathway suppresses intestinal polyp formation and reduces mortality in *Apc*$^{\Delta 716}$ mice. *Proc. Natl. Acad. Sci. USA,* 2008, 105:13544-13549. (1000 Faculty Paper)

・Kitamura, T., Aoki, M., Taketo M.M. [and 9 others] (2007) SMAD4-deficient intestinal tumors recruit CCR1^{+}-myeloid cells that help invasion. *Nat. Genet.* 39:467-475.

【Term of Project】 FY2009-2012

【Budget Allocation】 159,300 Thousand Yen

【Homepage Address and Other Contact Information】

http://www4.mfour.med.kyoto-u.ac.jp/index.html