Hokkaido University
Leading Graduate School
Veterinary Science for One Health

The 10th Leading Special Lecture

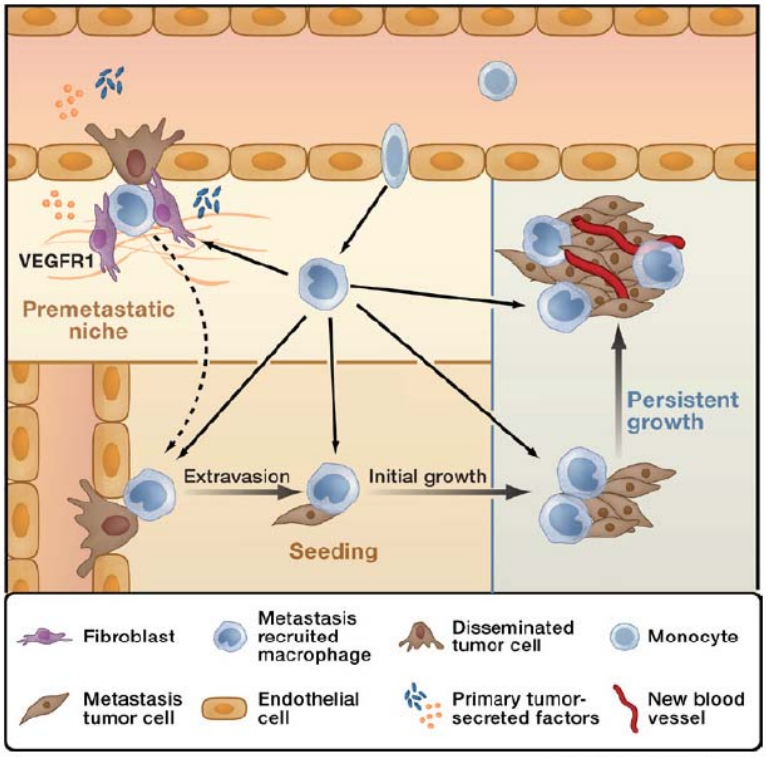
The role of chemokine in macrophage-mediated breast cancer metastasis

August 8(Thu), 2013, 17 : 00～18 : 30

Lecture Hall, Graduate School of Veterinary Medicine,
Hokkaido University, JAPAN

Dr. Takanori Kitamura

Research Associate
Albert Einstein College of Medicine



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Program

17:00～18:10

Dr. Takanori Kitamura

Research Associate (postdoc)
Department of Developmental and Molecular Biology,
Albert Einstein College of Medicine

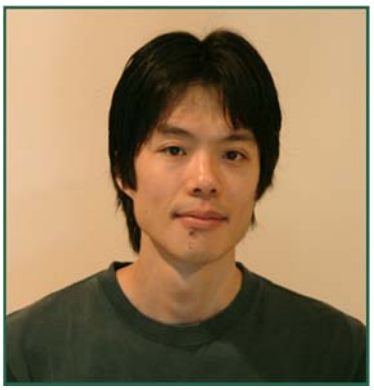
18:10～18:30

Discussion

Takanori Kitamura

Research Associate (postdoc)

Department of Developmental and Molecular Biology,
Albert Einstein College of Medicine



http://www.einstein.yu.edu/departments/developmental-molecular-biology/

Education

2000 D.V.M Veterinary Medicine ,Hokkaido University, Sapporo, Japan
2003 Ph.D. Biochemistry, Hokkaido University, Sapporo, Japan

Positions and Employment

2010- Present: Research Associate /
Department of Developmental and Molecular Biology,
Albert Einstein College of Medicine

2004-2010 : Assistant Professor /
Department of Pharmacology, Graduate School of Medicine,
Kyoto University, Japan

2003-2004 : Research Fellow /
Department of Pharmacology, Graduate School of Medicine,
Kyoto University, Japan

Award and Fellowship

2011-2014 : Breast Cancer Postdoctoral Fellowship
from U.S.A. Department of Defense

2008-2010 : Grant-in-Aid for Young Scientists (B)
from the Japan Society for the Promotion of Science

2003-2004 : Postdoctoral Fellowship
from the Japan Society for the Promotion of Science

2000 : Best Student Award: 1st Prize
from Faculty of Veterinary Medicine, Hokkaido University

The role of chemokine in macrophage-mediated breast cancer metastasis

Albert Einstein College of Medicine (Dr. Jeffrey Pollard Lab)

Takanori Kitamura

Solid tumors consist of malignant epithelial cells and normal stromal cells including fibroblasts, endothelial cells, and immune cells such as lymphocytes and macrophages. Using a mouse model of breast cancer caused by expression of Polyoma Middle T oncogene (PyMT), the Pollard lab previously reported that genetic ablation of macrophages through introduction of a null allele for colony-stimulating factor 1 (*Csf1op*) slowed the progression of cancer and dramatically suppressed lung metastases, suggesting that tumor associated macrophages (TAMs) actively contribute to the breast cancer progression.

In order for a metastasis to occur, cancer cells need to penetrate microvessels (intravasation), survive in the circulation, escape from the vessels (extravasation), and grow at the distant organs (persistent growth). Using an experimental lung metastasis model, our lab has shown that depletion of macrophages reduced the number and size of metastasis foci in the lung. These results indicate that TAMs in metastasis foci (metastasis-associated macrophages; MAMs) promote extravasation and persistent growth of cancer cells. Our recent studies have revealed that the MAMs originate from circulating inflammatory monocytes (IMs). It was also found that CC-chemokine ligand 2 (CCL2) promotes the recruitment of IMs from circulation to the metastasis sites, which increases the numbers of tumor cell-associated MAMs and metastatic foci. Because IMs express CCL2 receptor CCR2 at high levels, these results indicate that CCL2-CCR2 axis plays important role in metastatic seeding of cancer cells through the recruitment of IMs.

On the other hand, our lab has reported that MAMs also express CCR2 and that *Ccr2* deficient macrophages reduced ability to support tumor cell extravasation *in vitro*, suggesting that CCR2 activation in the MAMs also contributes to metastatic seeding through another mechanism. To identify downstream target of CCR2 signaling in MAMs, we have performed microarray analyses and found that *Ccl3* mRNA level was higher in MAMs than normal lung macrophages. Interestingly, the *Ccl3* level in MAMs was much higher than that in circulating IMs and was significantly suppressed by anti-CCL2 antibody treatment, suggesting that recruited IMs secreted chemokine (CCL3) once differentiated into MAMs via another chmokine signaling (CCL2-CCR2 axis). We also found that loss of CCL3 or its receptor CCR1 in host cells reduced the number of MAMs in the lung and the number of lung metastasis foci. These results indicate that CCL3-CCR1 axis promotes retention of MAMs and subsequent metastatic seeding of breast cancer cells.

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