造血幹細胞の発生・自己複製に関わる分子クローニングとその機能解析

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2003 Fiscal Year Final Research Report Summary

Molecular cloning of self-renewal factors for hematopoietic stem cells and analysis of those gene

Research Project

Project/Area Number

13470207

Research Category

Grant-in-Aid for Scientific Research (B)

Allocation Type

Single-year Grants

Section

一般

Research Field

Hematology

Research Institution

Kanazawa University

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hematopoietic stem cell / development / endothelial cell / TIE2 / angiopoietin-1 / self-renewal

Research Abstract

For regeneration therapy using hematopoietic stem cells(HSCs), it is necessary to expand HSCs in vitro effectively. We tried to analyze the self-renewal and maintenance of immature phenotype so called, "HSC's stemness" for in vitro expansion of HSCs. In this experiment, we focused on receptor tyrosine kinase, TIE2,which is expressed on both HSCs and endothelial cells(ECs).
We found that proliferation of HSCs are observed near ECs forming capillary in hematopoietic organ, such as fetal liver, bone marrow and so on and such HSCs produce angiopoietin-1(Ang1), a ligand for TIE2. Then, we analyzed the function of TIE2 for sternness by using constitutively active form of TIE2. Result showed that TIE2 activation promote several kinds of biological phenomena such as anti-apoptosis, delay of cell cycle, and enhancement of cell adhesion to matrix. Moreover, upon an

activation of TIE2 on ECs and hematopoietic cells(HCs), those cells selectively adhered with each other tightly. This suggests that Ang1 from HSCs stimulates TIE2 on both HSCs and ECs in the foci and becomes trigger for cell adhesion and stemness of HSCs.
Based on these experiments, we tried to isolate TIE2 activation associating gene using micro-array methods and obtained several candidate genes. E11, a novel gene of putative transcriptional factor, expresses on several stem cells in variety of organ and targeted disruption of this gene led to early embryonic lethality before HSCs develop. We will try to establish knock out mice those have HSCs specifically disrupted of E11 gene and analyze this gene in hematopoiesis precisely. Moreover, we isolated a candidate gene, galectin-3, that may associate with cell adhesion between HSCs and ECs. We have started to generate a transgenic mice expressing galectin-3 on HSCs and ECs under the transcriptional control of TIE2 promoter and will analyze the stemness of HSCs using this mice.

Research Products (22 results)

All Other

All Publications

[Publications] Koga K: "Expression of angiopoietin-2 in human glioma cells and its role for angiogenesis."Cancer Res. 61. 6248-6254 (2001)

[Publications] Zhang XQ: "Stromal cells expressing ephrin-B2 promote the growth and sprouting of ephrin-B2(+) endothelial cells."Blood. 98. 1028-1037 (2001)

[Publications] Sano H: "Functional blockade of platelet-derived growth factor receptor-beta but not of receptor-alpha prevents vascular smooth muscle cell accumulation in fibrous cap lesions in apolipoprotein E-deficient mice."Circulation. 103. 2955-2960 (2001)

[Publications] Yamada Y: "Exogenous clustered neuropilin-1 enhances vasculogenesis and angiogenesis."Blood. 97. 1671-1678 (2001)

[Publications] Suda T: "Role of hematopoietic stem cells in angiogenesis."Int.J.Hematol.. 74. 266-271 (2001)

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[Publications] Suenobu S: "A role of EphB4 receptor and its ligand, ephrin-B2,in erythropoiesis."Biochem.Biophys.Res.Commun.. 293. 1124-1131 (2002)

[Publications] Yuasa H: "Analysis of human TIE2 function on hematopoietic stem cells in umbilical cord blood."Biochem.Biophys.Res.Commun.. 298. 731-737 (2002)

[Publications] Nakajima M.: "Abnormal blood vessel development in mice lacking presenilin-1."Mech.Dev.. 120. 657-667 (2003)

[Publications] LiZ: "Defective smooth muscle development in qkI deficient mice."Development Growth.Differ.. 45. 449-461 (2003)

[Publications] Yamada Y: "Neuropilin-1 on hematopoietic cells as a source of vascular development."Blood. 101. 1801-1809 (2003)

[Publications] Koga K, Todaka T, Morioka M, Hamada J, Kai Y, Yano S, Okamura A, Takakura N, Suda T, Ushio Y.: "Expression of angiopoietin-2 in human glioma cells and its role fpr angiogenesis."Cancer Res.. 61. 6248-6254 (2001)

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[Publications] Suenobu S, Takakura N, Inada T, Yamada Y, Yuasa H, Zhang XQ, Sakano S, Oike Y, Suda T.: "A role of EphB4 receptor and its ligand, ephrin-B2, in erythropoiesis."Biochem.Biophys.Res.Commun.. 293. 1124-1131 (2002)

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[Publications] Nakajima M, Yuasa S, Ueno M, Takakura N, Koseki H, Shirasawa T.: "Abnormal blood vessel development in mice lacking presenilin-1."Mech.Dev.. 120. 657-667 (2003)

[Publications] Li Z, Takakura N, Oike Y, Imanaka T, Araki K, Suda T, Kaname, T, Abe K, Yamamura K.: "Defective smooth muscle development in qkI deficient mice."Development Growth.Differ.. 45. 449-461 (2003)

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