細胞治療・再生治療開発への挑戦

細胞育成学連続講演会2011

このシリーズでは、京都大学内外で細胞治療・再生治療の研究、臨床をされている先生方に、最先端の話題を提供していただきます。また、細胞治療を支える細胞治療センターの重要な役割にスポットをあてます。学生、教員の皆様の聴講を歓迎致します。

場所：人間健康科学科 高井ホール（171号室）
日時：毎週水曜日 16:30～18:00（計14回）

◇ 10月　5日(水): 前川　平　(京都大学医学部附属病院　輸血細胞治療部　教授)
京都大学における細胞治療・再生治療開発への挑戦ー概論ー

◇ 10月12日(水): 笠井　泰成(京都大学医学部附属病院 分子細胞治療センター 主任技師)
細胞治療における臨床検査技師の役割

◇ 10月19日(水): 伊藤　達也 (京都大学医学部附属病院　探索医療センター　助教)
治験、臨床試験に関わる規制について

◇ 10月26日(水): 岩田　博夫 (京都大学　再生医科学研究所　教授)
人工材料への細胞の接着

◇ 11月　2日(水): 川真田　伸 ((財)先端医療振興財団　再生医療支援グループ　GL)
CPCの運営コストと事業化について　-神戸での取り組み-

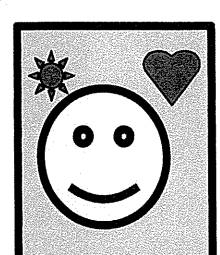
◇ 11月　9日(水): 神田　輝　(愛知県がんセンター研究所・腫瘍ウイルス学部　室長)
ウイルス抗原・がん抗原に特異的なT細胞を用いた細胞療法

◇ 11月16日(水): 仙石 慎太郎 (京都大学　細胞ー物質統合拠点（iCeMS）准教授)
幹細胞の品質評価・安定培養技術とイノベーション

◇ 11月30日(水): 森本　尚樹 (京都大学医学部附属病院　形成外科　講師)
自家培養真皮を用いた皮膚潰瘍治療

◇ 12月 7日(水): 門脇　則光 (京都大学医学部附属病院　血液・腫瘍内科 准教授)
癌免疫療法としての細胞療法

◇ 12月14日(水): 青井　貴之 (京都大学　iPS細胞研究所　教授)
細胞治療に向けたiPS細胞の現状と課題



◇ 12月21日(水): 井家　益和 ((株)J-TEC製品開発部 部長)
ヒト細胞を組み込んだ日本初の再生医療製品の開発

◇　1月 4日(水): 青山　朋樹(京都大学大学院医学研究科人間健康科学系専 准教授)
間葉系幹細胞を用いた臨床応用

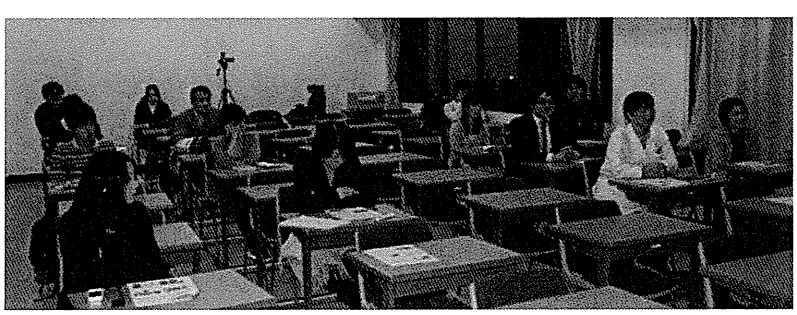
◇　1月11日(水): 細田 公則 (京都大学大学院医学研究科人間健康科学系専攻 教授)
iPS細胞由来脂肪細胞を用いた脂肪萎縮症の成因解明、および細胞治療法の開発

◇　1月18日(水): 一山　智 (京都大学医学部附属病院　検査部　教授)
免疫不全患者における感染症の診断と治療

*当講演は修士選択科目「細胞育成学」を広く一般公開するものです

臨床検査展開学, 細胞育成士養成プロジェクト　高桑徹也　TEL/FAX: 075-751-3931

**** 講 義 風 景 ***



臨床検査展開学演習

Seminar for Innovational Laboratory Medicine

区　分	専門実践科目	
所　属	職　名	氏　名
医療検査展開学講座	教　授	高桑徹也
医療検査展開学講座	准教授	伊吹謙太郎
理学療法学講座	准教授	青山朋樹
臨床看護学講座	教　授	細田公則
輸血細胞治療部	教　授	前川　平
血液・腫瘍内科	講師	門脇則光
移植外科	助教	興津　輝
形成外科	講師	森本尚樹
探索医療センター	助教	伊藤達也
輸血細胞治療部	主任技師	笠井泰成
再生医科学研究所	教務補佐	上田路子

単位数	2単位	授業形態	演習
時間数	30時間	対象回生	1回生
開講期	後期	必修・選択	必修

授業概要と学習目標

細胞治療とは、ヒトの細胞を輸注、移植することによって行う治療法の総称であり、従来から行われている輸血治療を原型とし、造血幹細胞移植、細胞移入免疫療法、遺伝子治療、再生医療などがこれに含まれます。細胞治療の今後の発展性を考えると、「細胞育成」という役割を持つ人材が必要不可欠で、これは臨床検査技術学を主体とした領域となると考えられます。求められる能力は、単に細胞が培養できるというだけでなく、1. 細胞治療の基礎知識、理解、2. 細胞治療センター(CPC)の運営管理の考え方の理解と実践、3. 安全な細胞の育成、調製法の理解と実践、さらには, 4. 細胞治療研究に必要な基礎技術の修得, 5. 細胞治療研究の実際と多岐にわたります。当コースでは、細胞治療の最先端について学ぶとともに、細胞治療を背後で支える細胞治療センターの紹介、見学、実際の運営法等について学びます。

授業計画と内容

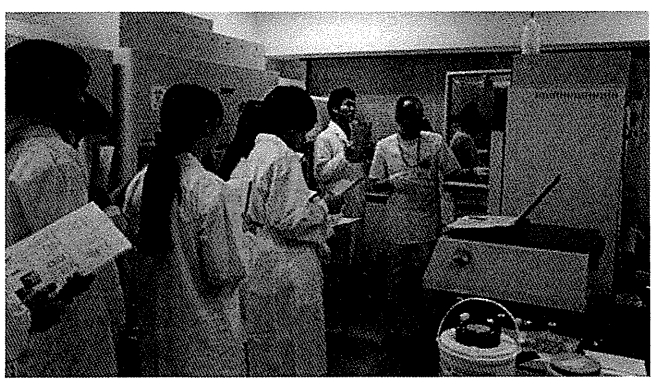
1	ガイダンス:細胞育成士とは	高桑徹也、青山朋樹
2	細胞治療・再生治療とは -研究成果を患者さんに届けるために今何が必要か-	前川　平
3	GMPに準拠したCPCについての概念、運営法、実際1	笠井泰成
4	GMPに準拠したCPCについての概念、運営法、実際2	笠井泰成
5	GMPに準拠したCPCについての概念、運営法、実際3	笠井泰成
6	新しい治療における法制度について(GCP)	伊藤達也
7	病院における感染症の問題点	伊吹謙太郎
8	移植外科:糖尿病に対する膵島移植	興津　輝
9	整形外科:大腿骨頭壊死に対する間葉系幹細胞移植	青山朋樹
10	血液内科:培養樹状細胞を用いた白血病治療	門脇則光
11	形成外科:自家培養真皮を用いた皮膚潰瘍治療	森本尚樹
12	内分泌内科:iPS細胞を用いた脂質代謝異常の解明	細田公則
13	細胞育成士の実際	上田路子

成績評価	レポート、出席
教科書	無し

細胞育成学実践論実習風景

無菌培養の基礎

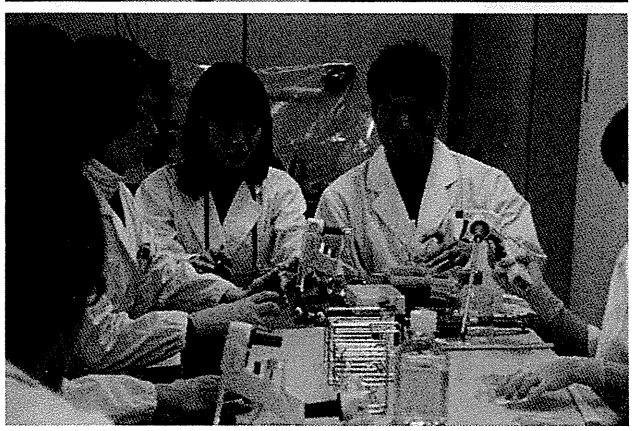
機器説明



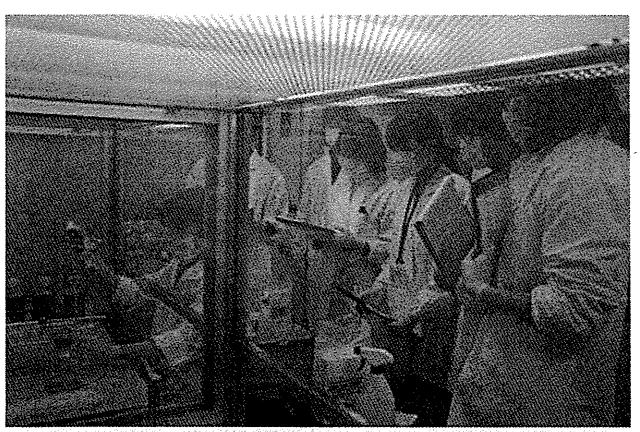
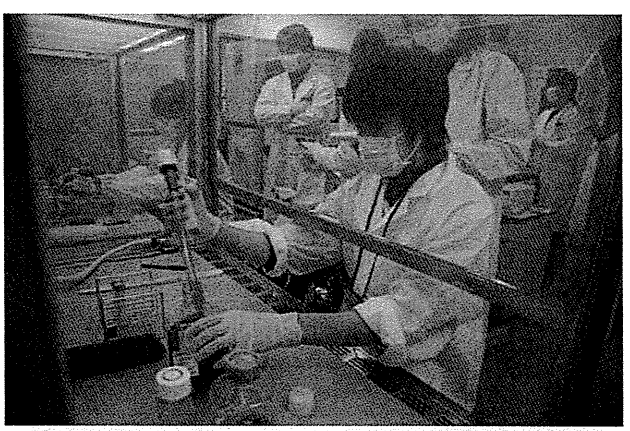
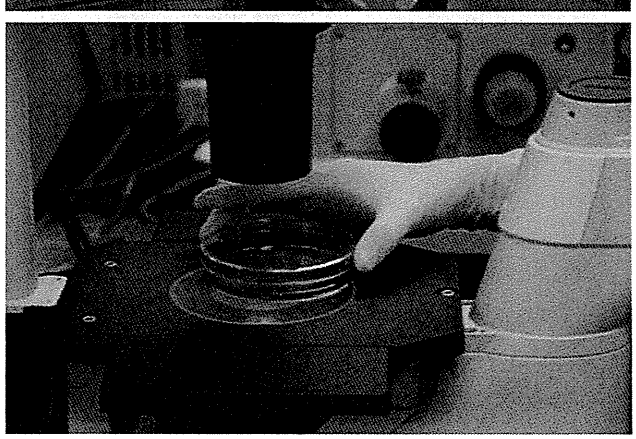
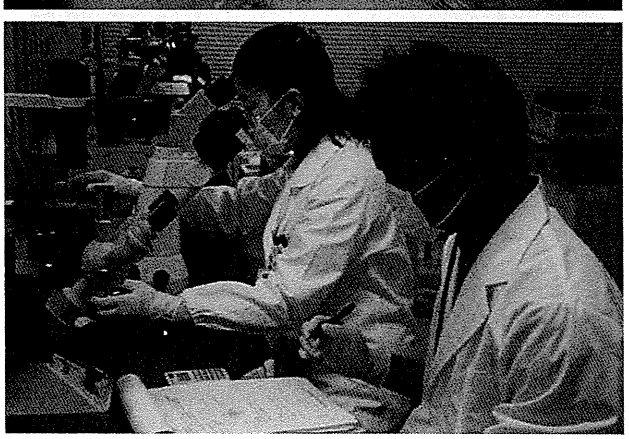
試薬説明、ロット管理

無菌培養の実践講義

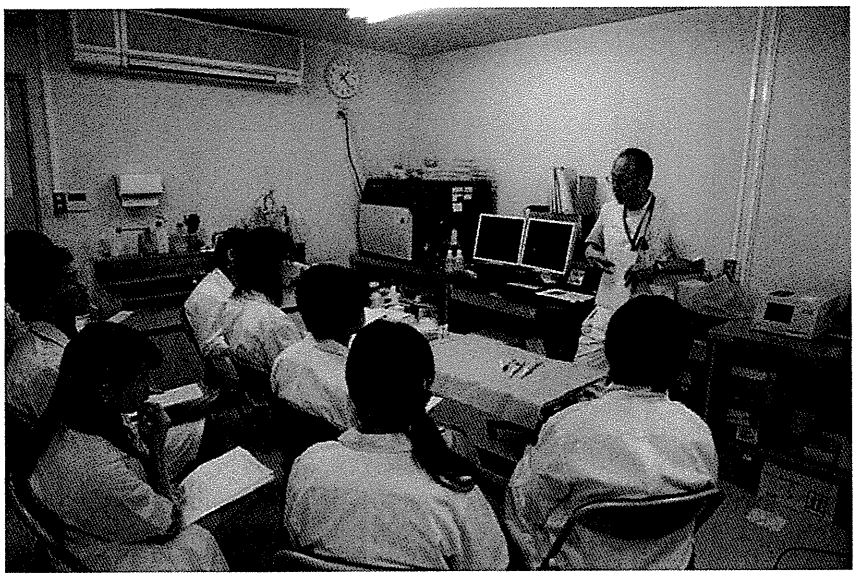


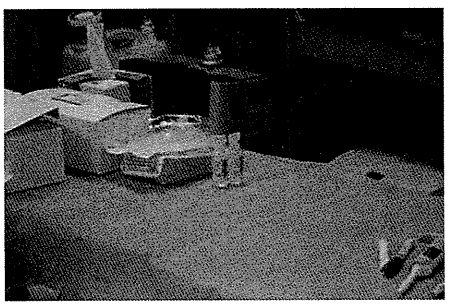


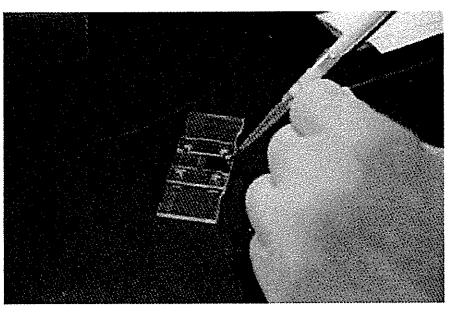

細胞培養実習

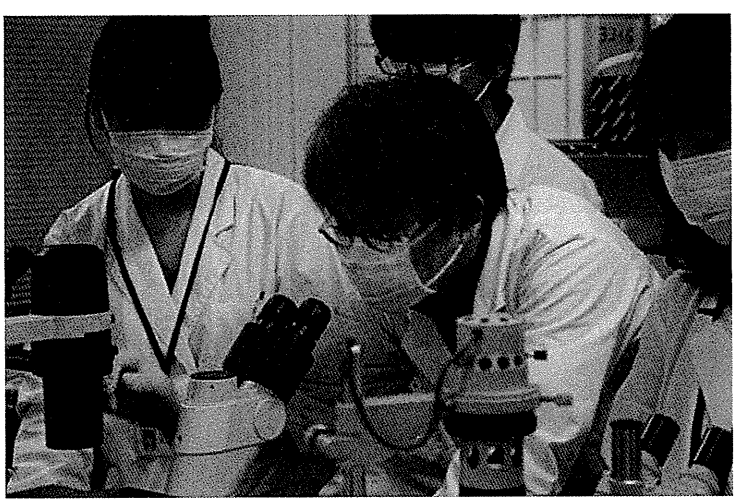





品質管理

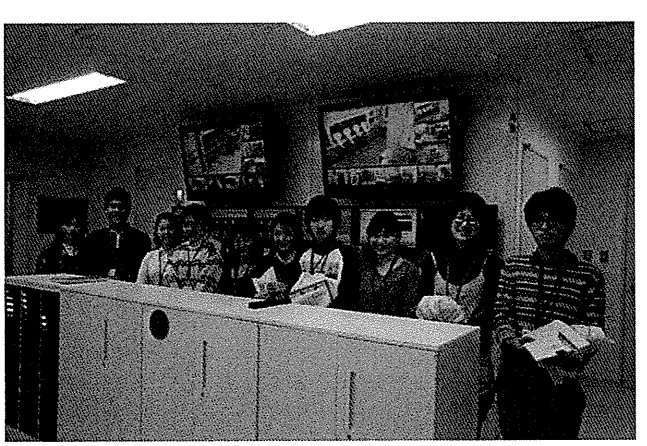








CPC(FiT)見学



研究成果の刊行に関する一覧表 （英文）

	発表者氏名	論文タイトル名	発表誌名	巻名	ページ	出版年
1	Tsubakimoto Y, Yamada H, Yokoi H, Kishida S, Takata H, Kawahito H, Matsui A, Urano N, Nozawa Y, Hirai H, Imanishi J, Ashihara E, Maekawa T, Takahashi T, Okigaki M, Matsubara H	Bone marrow angiotensin AT1 receptor on bone marrow stem cells that regulates monocyte/macrophage lineage differentiation from hematopoietic stem	Arterioscler Thromb Vasc Biol	29	1529-1536	2009
2	Yuasa T, Sato K, Ashihara E, Takeuchi M, Malta S, Tsuchiya N, Habuchi T, Maekawa T, Kimura S	Intravesical administration of γδ T cells successfully prevents the growth of bladder cancer in the murine model	Cancer Immunol Immunother	58	493-502	2009
3	Koto K, Horie N, Kimura S, Murata H, Sakabe T, Matsui T, Koto K, Watanabe M, Adachi S, Maekawa T, Fushiki S, Kubo T	Clinically relevant dose of zoledronic acid inhibits spontaneous lung metastasis in a murine osteosarcoma model	Cancer Lett	274	271-278	2009
4	Ashihara E, Kawata E, Nakagawa Y, Shimazaski C, Kuroda J, Tanaka R, Yokota A, Murotani Y, Takeuchi M, Kamitsuji Y, Inaba T, Taniwaki M, Kimura S, Maekawa T	beta-catenin small interfering RNA successfully suppressed progression of multiple myeloma in a mouse model	Clin Cancer Res	15	2731-2738	2009
5	Takeuchi M, Kimura S, Ashihara E, Maekawa T	Dual BCR-ABL/LYN tyrosine kinase inhibitor INNO-406	Drug of the Future	34(4)	261-269	2009
6	Kaido T, Egawa H, Tsuji H, Ashihara E, Maekawa T, Uemoto S	In-hospital mortality in adult recipients of living donor liver transplantation: experience of 576 consecutive cases at a single center	Liver Transpl	15	1420-1425	2009
7	Matsumoto S, Tanaka F, Sato K, Kimura S, Maekawa T, Hasegawa S, Wada H	Monitoring with a non-invasive bioluminescent in vivo imaging system of pleural metastasis of lung carcinoma	Lung Cancer	66	75-79	2009
8	Kitaori T, Ito H, Yoshitomi H, Aoyama T, Fujii T, Mimori T, Nakamura T	Severe erosive arthropathy requiring surgical treatments in systemic lupus erythematosus.	Mod Rheumatol	19	431-436	2009
9	Takakuwa T, Miyauchi A, Aozasa K	Aberrant somatic hypermutations in thyroid lymphomas	Leukemia Research	33	649-654	2009

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	発表者氏名	論文タイトル名	発表誌名	巻名	ページ	出版年
10	Oji Y, Kitamura Y, Kamino E, Kitano A, Sawabata N, Inoue M, Mori M, Nakatsuka S, Sakaguchi N, Miyazaki K, Nakamura M, Fukuda I, Nakamura J, Tatsumi N, Takakuwa T, Nishida S, Shirakata T, Hosen N, Tsuboi A, Nezu R, Maeda H, Oka Y, Kawase I, Aozasa K, Okumura M, Miyoshi S, Sugiyama H	WT1 IgG antibody for early detection of nonsmall cell lung cancer and as its prognostic factor	Int J Cancer	125	381-387	2009
11	Yokoi H, Yamada H, Tsubakimoto Y, Takata H, Kawahito H, Kishida S, Kato T, Matsui A, Hirai H, Ashihara E, Maekawa T, Iwai M, Horiuchi M, Ikeda K, Takahashi T, Okigaki M, Matsubara H	Bone marrow AT1 augments neointima formation by promoting mobilization of smooth muscle progenitors via platelet-derived SDF-1a.	Arterioscler Thromb Vasc Biol	30	60-67	2010
12	Ryu K, Murata H, Koto K, Horie N, Matsui T, Nishigaki Y, Sakabe T, Takeshita H, Itoi M, Kimura S, Ashihara E, MaekawaT, Fushiki S, Kubo T.	Combined effects of bisphosphonate and radiation on osteosarcoma cells	Anticancer Research	30(7)	2713-2720	2010
13	Kamio N, Hirai H, Ashihara E, Tenen DG, Maekawa T, Imanishi J	Use of bicistronic vectors in combination with flow cytometry to screen for effective small interfering RNA target sequences	Biochem Biophys Res Commun	393(3)	498-503	2010
14	Tanaka R, Squires MS, Kimura S, Yokota A, Nagao R, Yamauchi T,Takeuchi M, Yao H,Reule M, Smyth T, Lyons JF, Thompson NT, Ashihara E, Ottmann OG, Maekawa T.	Activity of the multitargeted kinase inhibitor, AT9283, in imatinib-resistant BCR-ABL-positive leukemic cells	Blood	116(12)	2089-2095	2010
15	Kawata E, Ashihara E, Nakagawa Y, Kiuchi T, Ogura M, Yao H, Sakai K, Tanaka R, Nagao R, Yokota A, Takeuchi M, Kimura S, Hirai H, Maekawa T.	A combination of a DNA-chimera siRNA against PLK-1 and zoledronic acid suppresses the growth of malignant mesothelioma cells in vitro.	Cancer Lett	294	245-253	2010

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16	Takeuchi M, Ashihara E, Yamazaki Y, Kimura S, Nakagawa Y, Tanaka R, Yao H, Nagao R, Hayashi Y, Hirai H, Maekawa T.	Rakicidin A effectively induces apoptosis in hypoxia adapted Bcr-Abl positive leukemic cells.	Cancer Sci	102	591-596	2010
17	Takeuchi M, Kimura S, Kuroda J, Ashihara E, Kawatani M, Osada H, Umezawa K, Yasui E, Imoto M, Tsuruo T, Yokota A, Tanaka T, Nagao R, Nakahata T, Fujiyama Y, Maekawa T.	Glyoxalase-I is novel target Bcr-Abl(+) leukemic cells acquiring stem like characteristics in a hypoxic environment.	Cell Death Differ	17	1211-1220	2010
18	Ashihara E, Kawata E, Maekawa T	Future prospect of RNA interference for cancer therapies	Curr Drug Targets	11	345-360	2010
19	Ohsaka A, Kikuta A, Ohto H, Ohara A, Ishida A, Osada K, Kimitamari A, Iwai A, Kai T, Maekawa T, Hoshi Y	Guidelines for safety management of granulocyte transfusion in Japan	Int J Hematol	91	201-208	2010
20	Taniguchi K, Shimazaki C, Ochiai N, Maruya E, Akatsuka Y, Ashihara E, Maekawa T, Taniwaki M, Saji H	Modified ELISPOT assay may predict T-cell hyporesponsiveness to non-inherited maternal antigens	Int J Lab Hematol	32	163-168	2010
21	Hamaguchi M, SenoT, Yamamoto A, Kohno M, Kadoya M, Ishino H, Ashihara E, Kimura S, Tsubakimoto Y, Takata H, Yoshikawa T, Maekawa T, Kawahito Y.	Loxoprofen Sodium, a Non-Selective NSAID, Reduces Atherosclerosis in Mice by Reducing Inflammation.	Journal of Clinical Biochemistry and Nutrition	47	138-147	2010
22	Yokota A, Kimura S, Tanaka R, Takeuchi M, Yao H, Sakai K, Nagao R, Kuroda J, Kamitsuji Y, Kawata E, Ashihara E, Maekawa T	Osteoclasts are involved in the maintenance of dormant leukemic cells	Leuk Res	34	793-799	2010
23	Ushiki T, Kizaka-Kondoh S, Ashihara E, Tanaka S, Masuko M, Hirai H, Kimura S, Aizawa Y, Maekawa T, Hiraoka M.	Noninvasive tracking of donor cell homing by near-infrared fluorescence imaging shortly after bone marrow transplantation.	PLOS One	5:e11114	1-12	2010

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	発表者氏名	論文タイトル名	発表誌名	巻名	ページ	出版年
24	Ito K, Aoyama T, Fukiage K, Otsuka S, Furu M, Jin Y, Nasu A, Ueda M, Kasai Y, Ashihara E, Kimura S, Maekawa T, Kobayashi A, Yoshida S, Niwa H, Otsuka T, Nakamura T, Toguchida J	A novel method to isolate mesenchymal stem cells from bone marrow in a closed system using a device made by nonwoven fabric	Tissue Eng Part C Methods	16	81-91	2010
25	Sekimoto M, Imanaka Y, Shirai T, Sasaki H, Komeno T, Lee J, Yoshihara K, Ashihara E, Maekawa T	Risk-adjusted assessment of incidence and quantity of blood use in acute-care hospitals in Japan: an analysis using administrative data	Vox Sanguinis	98(4)	538-546	2010
26	Jin Y, Shima Y, Furu M, Aoyama T, Nakamata T, Nakayama T, Nakamura T, Toguchida J	Absence of Oncogenic Mutations of RAS Family Genes in Soft Tissue Sarcomas of 100 Japanese Patients	Anticancer Res	30(1)	245-252	2010
27	Jin Y, Kato T, Furu M, Nasu A, Kajita Y, Mitsui H, Ueda M, Aoyama T, Nakayama T, Nakamura T, Toguchida J.	Mesenchymal stem cells cultured under hypoxia escape from senescence via down-regulation of p16 and extracellular signal regulated kinase.	Biochem Biophys Res Commun	391	1471-1476	2010
28	Yamada M, Tanaka B, Nagai K, Aoyama T, Ichihashi N.	Trail-Walking Exercise and Fall Risk Factors in Community-Dwelling Older Adults: Preliminary Results of a Randomized Controlled Trial.	J Am Geriatr Soc	58	1946-1951	2010
29	Aoyama T, Okamoto T, Fukiage K, Otsuka S, Furu M, Ito K, Jin Y, Ueda M, Nagayama S, Nakayama T, Nakamura T, Toguchida J.	Histone modifiers, YY1 and p300, regulate the expression of cartilage-specific gene, chondromodulin-I, in mesenchymal stem cells.	J Biol Chem	285	29842-29850	2010
30	Kaszynski RH, Akatsuka S, Hiratsuka T, Jin G, Ozeki M, Okuno T, Nakamura T, Manabe T, Takakuwa T, Hiai H, Toyokuni S, Tamaki K, Tsuruyama T	A Quantitative trait locus responsible for inducing B-cell lymphoblastic lymphoma is a hotspot for microsatellite instability	Cancer Sci	101	800-805	2010
31	Tsuruyama T, Imai Y, Takeuchi H, Hiratsuka T, Maruyama Y, Kanaya K, Kaszynski R, Jin G, Okuno T, Ozeki M, Nakamura T, Takakuwa T, Manabe T, Tamaki K, Hiai H	Dual retrovirus integration tagging: identification of new signaling molecules Fiz1 and Hipk2 that are involved in the IL-7 signaling pathway in B lylymphomas	J Leukoc Biol	88(1)	107-115	2010

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	発表者氏名	論文タイトル名	発表誌名	巻名	ページ	出版年
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Bone Marrow Angiotensin AT_1 Receptor Regulates Differentiation of Monocyte Lineage Progenitors From Hematopoietic Stem Cells

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Background—The angiotensin II (Ang II) type 1 (AT_1) receptor is expressed in bone marrow (BM) cells, whereas it remains poorly defined how Ang II regulates differentiation/proliferation of monocyte-lineage cells to exert proatherogenic actions.

Methods and Results—We generated BM chimeric apoE$^{-/-}$ mice repopulated with AT_1-deficient (Agtr1$^{-/-}$) or wild-type (Agtr1$^{+/+}$) BM cells. The atherosclerotic development was significantly reduced in apoE$^{-/-}$/BM-Agtr1$^{-/-}$ mice compared with apoE$^{-/-}$/BM-Agtr1$^{+/+}$ mice, accompanied by decreased numbers of BM granulocyte/macrophage progenitors (GMP:c-Kit$^+$Sca-1$^-$Lin$^-$CD34$^+$CD16/32$^+$) and peripheral blood monocytes. Macrophage-colony-stimulating factor (M-CSF)–induced differentiation from hematopoietic stem cells (HSCs:c-Kit$^+$Sca-1$^+$Lin$^-$) to promonocytes (CD11b^{high}Ly-6G^{low}) was markedly reduced in HSCs from Agtr1$^{-/-}$ mice. The expression of M-CSF receptor c-Fms was decreased in HSCs/promonocytes from Agtr1$^{-/-}$ mice, accompanied by a marked inhibition in M-CSF–induced phosphorylation of PKC-δ and JAK2. c-Fms expression in HSCs/promonocytes was mainly regulated by TNF-α derived from BM CD45$^-$CD34$^-$ stromal cells, and Ang II specifically regulated the TNF-α synthesis and release from BM stromal cells.

Conclusions—Ang II regulates the expression of c-Fms in HSCs and monocyte-lineage cells through BM stromal cell–derived TNF-α to promote M-CSF–induced differentiation/proliferation of monocyte-lineage cells and contributes to the proatherogenic action. (***Arterioscler Thromb Vasc Biol.* 2009;29:1529-1536.)

Key Words: bone marrow progenitors ■ angiotensin ■ monocyte ■ atherosclerosis ■ M-CSF

The angiotensin II (Ang II) type 1 (AT_1) receptor exerts proatherogenic actions.[1] AT_1 receptor–deficient (Agtr1$^{-/-}$) mice showed a significant reduction of atherosclerotic development,[2,3] and treatment with AT_1 receptor blocker (ARB) reduced the size of atherosclerotic lesions both in experimental animals and humans.[4] AT_1 receptors are present in a variety of cells, including endothelial cells, vascular smooth muscle cells, and bone marrow (BM) stem cells and progenitors.[5,6] Recently, Cassis et al demonstrated that Ang II–induced atherosclerosis was significantly attenuated in LDL receptor–deficient (LDLr$^{-/-}$) mice whose BM cells were repopulated with Agtr1$^{-/-}$ cells.[7] Fukuda et al also reported that atherosclerotic lesion development was significantly reduced in apoE-deficient (apoE$^{-/-}$) mice with Agtr1$^{-/-}$ marrow.[8] However, no information regarding the role of the BM-AT_1 receptor on the differentiation/proliferation and properties of BM stem cells and progenitors has been reported in these previous studies.

Monocytes and macrophages play a crucial role in the pathogenesis of atherosclerosis, which is characterized by plaque progression, destabilization, and subsequent plaque rupture, through foam cell formation, migration/proliferation of resident vascular smooth muscle cells, and degradation of extracellular matrix.[9] Along with the previous studies showing the effect of diet-induced hypercholesterolemia on BM and leukocyte,[10] Swirski et al reported that hypercholesterolemia induced a surprisingly profound expansion of blood monocytes as well as BM monocyte-lineage cells.[11] However, the relative contribution of the BM renin–angiotensin system to hypercholesterolemia-associated monocytosis has not been fully investigated.[12]

In the present study, we focused on the action of the AT_1 receptor expressed in BM cells and studied whether (1) Ang II affects the differentiation/proliferation from BM stem cells into monocyte-lineage cells, and (2) hypercholesterolemia-associated monocytosis contributes to the development of AT_1-mediated atherosclerosis. Our results demonstrated for the first time that (1) Ang II promotes M-CSF–induced differentiation from hematopoietic stem cells (HSCs; c-Kit$^+$Sca-1$^+$Lin$^-$) into monocyte-lineage cells through up-regulation of the M-CSF receptor c-Fms, and that (2) TNF-α

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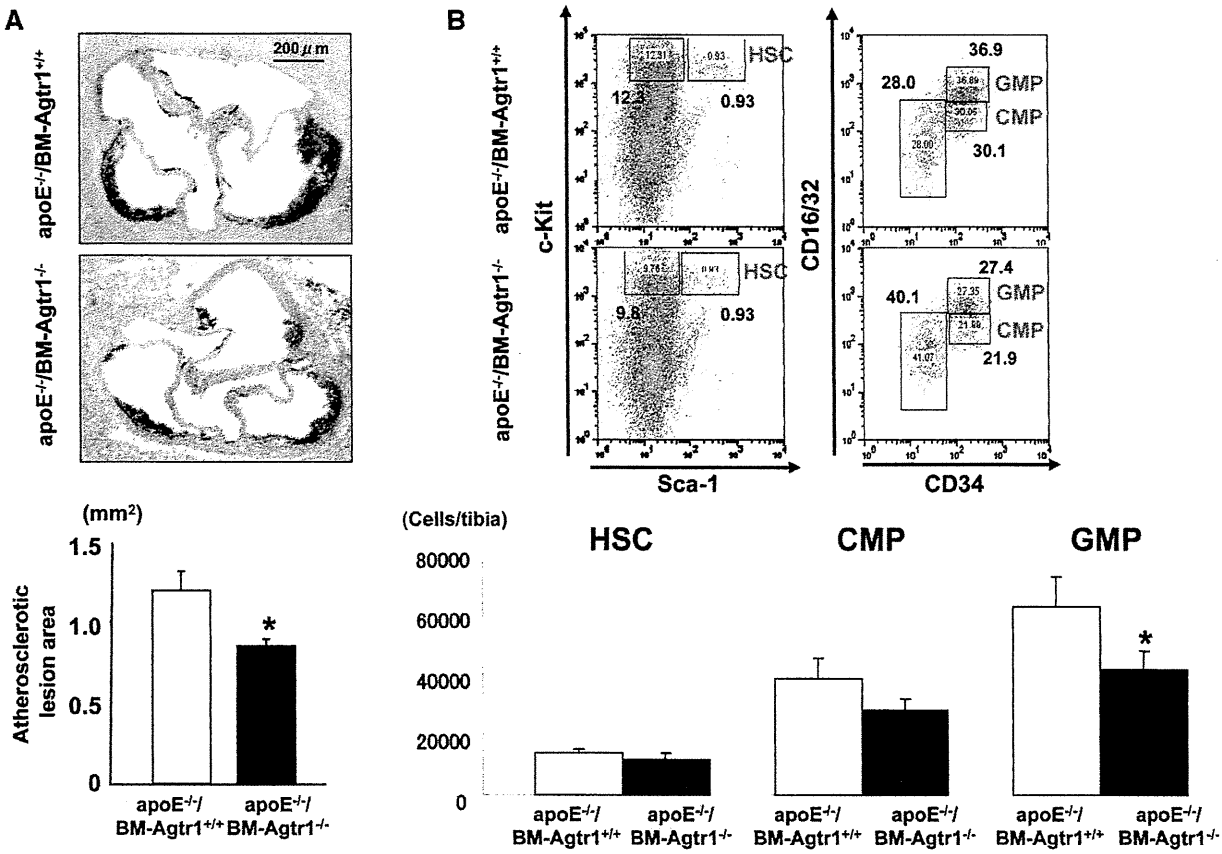

Figure 1. Attenuated atherosclerosis accompanied by the reduction of monocyte-lineage cells on ablation of marrow AT_1. A, Two-month-old apoE$^{-/-}$ mice whose BM was repopulated with Agtr1$^{-/-}$ or Agtr1$^{+/+}$ cells. Quantitative analysis showing the lower area of atherosclerotic lesions in apoE$^{-/-}$/BM-Agtr1$^{-/-}$ mice than apoE$^{-/-}$/BM-Agtr1$^{+/+}$ mice. Values are the mean±SE for at least 8 mice in each group. *P<0.05 vs apoE$^{-/-}$/BM-Agtr1$^{+/+}$ mice. B, Flow cytometry of c-Kit and Sca-1 expression in lineage-negative BM populations and CD16/32 and CD34 expression in c-Kit^{+}Sca-1^{-}lineage-negative BM populations of apoE$^{-/-}$/BM-Agtr1$^{+/+}$ and apoE$^{-/-}$/BM-Agtr1$^{-/-}$ mice fed a Western diet for 2 months. Quantitative analysis showing a decrease in GMP number in apoE$^{-/-}$/BM-Agtr1$^{-/-}$ mice. HSCs indicates hematopoietic stem cells; CMP, common myeloid progenitors; GMP, granulocyte and macrophage progenitors. Values are the mean±SE for at least 5 mice in each group. *P<0.05 vs apoE$^{-/-}$/BM-Agtr1$^{+/+}$ mice.

derived from BM CD45^{-}CD34^{-} stromal cells growth-controlled by Ang II specifically regulates the c-Fms expression in promonocytes (CD11b^{high}Ly-6G^{low}), thus leading to the increased numbers of circulating monocytes that modulate AT_1-mediated proatherogenic activities.

Methods

A full description of all methods can be found in the Data Supplement (available online at http://atvb.ahajournals.org).

Animal Preparation

ApoE$^{-/-}$ mice (C57BL/6) and AT1a receptor-deficient (Agtr1$^{-/-}$) mice (C57BL/6) were obtained from Taconic Co Ltd (Germantown, NY) and Tanabe Seiyaku Co Ltd (Osaka, Japan), respectively. BM cells of 2-month-old female apoE$^{-/-}$ recipient mice were repopulated with male Agtr1$^{-/-}$ or Agtr1$^{+/+}$ cells. The percentage chimerism determined by transplanting GFP-overexpressing BM cells was 96±2% of peripheral blood mononuclear cells.[13] Furthermore, BM CD45^{-}CD34^{-} stromal cells, HSCs, and myeloid progenitors (MP:c-Kit^{+}Sca-1^{-}Lin^{-}) were almost completely (more than 99%) replaced by GFP-positive cells (supplemental Figure I). All animal experiments were conducted according to the Guidelines for Animal Experiments at Kyoto Prefectural University School of Medicine.

Statistical Analysis

All data are expressed as the mean±SE. Mean values were compared using ANOVA. If a statistical significant effect was found, Fisher test was performed to detect the difference between the groups. P<0.05 was considered statistically significant.

Results

BM-AT_1 Deficiency Attenuates Atherosclerosis Concomitant With the Reduction of BM Monocyte-Lineage Cells

Consistent with the previous reports,[8] apoE$^{-/-}$/BM-Agtr1$^{-/-}$ mice showed a significant reduction of atherosclerotic lesions compared with apoE$^{-/-}$/BM-Agtr1$^{+/+}$ mice (31%, P<0.05; Figure 1A). At 3 months after BMT, the numbers of white blood cells and monocytes were similar between the 2 groups (supplemental Table I). However, after 2 months of a Western diet feeding, white blood cells and monocytes were significantly less abundant in apoE$^{-/-}$/BM-Agtr1$^{-/-}$ mice than apoE$^{-/-}$/BM-Agtr1$^{+/+}$ mice by 40% and 39%, respectively (P<0.05; supplemental Table II).

HSCs (c-Kit^{+}Sca-1^{+}Lin^{-}) have been shown to differentiate into common myeloid progenitors (CMP:c-Kit^{+}Sca-1^{-}Lin^{-}CD34^{+}CD16/32^{-}) and then granulocyte/macrophage progenitors (GMP:c-Kit^{+}Sca-1^{-}Lin^{-}CD34^{+}CD16/32^{+}), followed by the terminal differentiation into BM promonocytes (CD11b^{high}Ly-6G^{low}).[14,15] We examined BM-AT_1–me-