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－国際的に卓越した教育研究拠点形成のための重点的支援－

International Research day

東京医科歯科大学
グローバルCOEプログラム

歯と骨の分子疾患科学の国際教育研究拠点

デント・メドミクスのインテリジェンスハブ

October 30th~31st, 2012
Tokyo Medical and Dental University

http://www.tmd.ac.jp/cmn/gcoe/index.html

Tokyo Medical and Dental University

International Research day

October 30th~31st, 2012

Tuesday Oct 30th, 2012

10：00 − 11：00	**Bjorn Reino Olsen**	(Moderator : Olga Safronova)
	Vascular endothelial growth factor (VEGF) is a regulator of bone formation and osteoblastic differentiation	
11：00 − 11：30	**Mikihito Hayashi**	(Moderator : Samir Kumar Pal)
	Semaphorin 3A regulates bone homeostasis by inhibiting osteoclast and promoting osteoblast synchronously	
11：30 − 12：00	**Paksinee Kamolratanakul**	(Moderator : Warunee Pluemsakunthai)
	Achievement of bone regeneration and bone remodeling, the animal experimental studies to clinical trial in bone tissue engineering paradigms	
12：00 − 13：30	Lunch	
13：30 − 14：00	**Koji Fujita**	(Moderator : Dawud Abduweli)
	Vitamin E decreases bone mass by stimulating osteoclast fusion	
14：00 − 14：30	**Noriaki Ono**	(Moderator : Chiho Watanabe)
	Nestin-positive cells in endochondral bone development	
14：30 − 15：00	**Shingo Sato**	(Moderator : Takehito Ono)
	The pericyte as a cell of origin for sarcomas	
15：00 − 15：30	Break	
15：30 − 16：00	**Hiroyuki Inose**	(Moderator : Yukihiko Hashida)
	A microRNA regulatory mechanism of osteoblast differentiation	
16：00 − 16：30	**Ganburged Ganjargal**	(Moderator : Nurmaa Dashzeveg)
	The role of fibrillin-1 in periodontal ligaments	
16：30 − 17：00	**Yoshio Ohyama**	(Moderator : Makiri Kawasaki)
	Modulation of matrix mineralization by Vwc2-like proteins	
17：00 − 17：30	Break	
17：30 − 18：30	**Noriaki Ono**	(Moderator：Rumana Khanom)
	Grant Writing and Career Path	
19：00 − 20：30	Reception (Tokyo Garden Palace Hotel)	

Wednesday Oct 31st, 2012

10：00 − 10：30	**Yukiko Maeda**	(Moderator : Marwa Madi)
	Global Small RNA Profiling During Osteoblast Differentiation	
10：30 − 11：00	**Verica Pavlic**	(Moderator : Mayumi Ogita)
	Laser dentistry challenges in Bosnia and Herzegovina	
11：00 − 11：30	**Ayako Kimura**	(Moderator : Calorina Duarte)
	Molecular elucidation of pathophysiology of bone and cartilage disorders	
11：30 − 12：00	**Mara Gomez Flores**	(Moderator : Hisanori Hasegawa)
	Proteomics for Alzheimer Disease for Biomarkers Discovery	

C O N T E N T S

Vascular endothelial growth factor (VEGF) is a regulator of bone formation and osteoblastic differentiation

Bjorn Reino Olsen, M.D., Ph.D.

Dean for Research, Harvard School of Dental Medicine, Boston, MA

Vascular endothelial growth factor-A (VEGF) and its cell surface tyrosine kinase receptors (VEGFR1 and VEGFR2) are critical for cardiovascular development and postnatal homeostasis, but they also have important non-vascular functions. During cartilage development, VEGF serves as a survival factor for chondrocytes, and secretion of VEGF by hypertrophic chondrocytes during endochondral bone formation is essential for the invasion of mesenchymal stem cells, osteoclasts, sprouting endothelial cells and hematopoietic precursor cells into the hypertrophic cartilage and, thus, for establishment of primary ossification centers.

The mesenchymal stem cells, located in the perichondrium of cartilage templates of endochondral bones, respond to VEGF produced by hypertrophic chondrocytes, migrate into the cartilage via tunnels produced by osteoclasts and differentiate into the osteoblasts, osteocytes and stromal cells that form the primary spongiosa of endochondral bones. Paradoxically, not only do these stem cells respond to VEGF produced by hypertrophic chondrocytes, but they also express high levels of VEGF. This raises the question of how VEGF produced by hypertrophic chondrocytes can have a chemotactic effect on the stem cells when the VEGF receptors on their surface may be occupied by their own VEGF. To address this question as well as the broader question of what the function of VEGF, produced by mesenchymal stem cells, may be we generated mice in which expression of VEGF was knocked down in the stem cells. We took advantage of the fact that the transcription factor Osterix is expressed by mesenchymal stem cells before they differentiate into osteoblasts and used an Osterix-Cre based strategy to conditionally knock down VEGF expression in the cells.

These mice exhibited no major defects in their development but showed postnatal progressive osteoporosis with reduced bone density and increased bone marrow fat. In cultures of bone marrow-derived mesenchymal stem cells from the conditional mutant mice osteoblast differentiation was reduced while adipocyte differentiation was increased. In a series of in vitro experiments we found that VEGF stimulates expression and activity of Runx2, critical for osteoblast differentiation, while it represses the levels of PPAR γ 2, essential for adipocyte differentiation, in mesenchymal stem cells. VEGF was also found to interact with the nuclear envelope protein lamin A/C in that lamin A protein levels increased in the stem cells when levels of VEGF were reduced and levels of VEGF were reduced when levels of lamin A/C were reduced. Finally, we found that the effects of VEGF on osteoblast and adipocyte differentiation could not be explained by the canonical pathway for VEGF action, namely, secretion of VEGF and binding of VEGF to the cell surface receptors VEGFR1 and VEGFR2. Instead, the data support the conclusion that these effects of VEGF are due to a novel intracellular activity.

Previous studies of lamin A/C in mesenchymal stem cells have shown that decreased levels of this nuclear envelope protein results in reduced osteoblast and increased adipocyte differentiation. Our data suggest that VEGF mediates these effects of lamin A/C. Interestingly, mutations in lamin A/C are associated with premature aging and levels of VEGF expression are notably reduced in multiple cells types, including mesenchymal stem cells, with age. Coupled with the finding that bone marrow mesenchymal stem cells from patients with osteoporosis are more likely to differentiate into adipocytes than osteoblasts compared with cells from patients with normal bone mass, our data support the speculation that strategies aimed at preventing a reduction of intracellular VEGF levels in mesenchymal stem cells will be useful in preventing age-dependent osteoporosis.

For details and references, see Liu A, Berendsen AD, Jia S, Lotinun S, Baron R, Ferrara N, and Olsen BR. (2012) Intracellular VEGF regulates the balance between osteoblast and adipocyte differentiation. J. Clin. Invest. doi:10.1172/JCI61209.
(The paper was published online August 13, 2012 and will be published in print in the September 1, 2012 issue of the journal)

CURRICULUM VITAE

Education

1967 Ph.D. University of Oslo, Norway
1967 M.D. University of Oslo Medical School, Norway

Position

1996-2002 Professor of Oral Biology, Harvard School of Dental Medicine, Boston, MA
1996-2002 Chairman, Harvard-Forsyth Department of Oral Biology, Harvard School of Dental Medicine, Boston, MA
2002- Professor of Oral and Developmental Biology, Harvard School of Dental Medicine, Boston, MA
2002-2005 Chairman, Department of Oral and Developmental Biology, Harvard School of Dental Medicine, Boston, MA
2005- Dean for Research, Harvard School of Dental Medicine, Boston, MA

Award and Honors

2000 Honorary Doctor of Science Degree, University of Medicine and Dentistry of New Jersey
2000 Honorary Doctor of Science Degree, University of Oslo, Norway
2001 Distinguished Faculty Award, Harvard School of Dental Medicine
2006 H.C. Jacobæus Prize and lecturer, H.C. Jacobæus' Forelæsninger Foundation, Sweden
2006 Member, ScanBalt Academy
2006 Senior Research Prize, American Society of Matrix Biology
2007 Co-chairman, Gordon Research Conference "Cartilage Biology & Pathology"
2009 Chairman, Gordon Research Conference "Cartilage Biology & Pathology"
2009 Co-chairman, Gordon Research Conference "Bones and Teeth"
2010 IADR Distinguished Scientist Award for Craniofacial Biology Research
2010 ISMB Distinguished Investigator Award
2010 American Association for the Advancement of Science Fellow
2011 Henry Gray Award, American Association of Anatomists
2011 Chairman, Gordon Research Conference "Bones and Teeth"
2011 Fellow, American Association of Anatomists
2011 Honorary Doctor Degree, Okayama University, Japan

Publications

1. Boye, E, Olsen, BR. Signaling mechanisms in infantile hemangioma. Curr Opin Hematol. 2009, 16:202–208. PMCID: PMC2895461
2. Mukherjee, PM, Wang, CJ, Chen, I-P, Jafarov, T, Olsen, BR, Yueki, Y, Reichenberger, EJ. Cherubism gene Sh3bp2 is important for optimal bone formation, osteoblast differentiation and function. Am J Orthod Dentofacial Orthop. 2010, 138:140.e1-140.e11.
3. Faye, C, Chautard, E, Olsen, BR, Ricard-Blum, S. The first draft of the endostatin interaction network. J. Biol. Chem. 2009, 284:22041-22047. PMCID: PMC2755928
4. Besschetnova, TY, Kolpakova-Hart, E, Guan, Y, Zhou, J, Olsen, BR, Shah, JV. Identification of signaling pathways regulating primary cilium length and flow-mediated adaptation. Curr. Biol., 2010, 20:182-187. PMC2990526.
5. Harnagea, C, Vallie`res, M, Pfeffer, CP, Wu, D, Olsen, BR, Pignolet, A, Legare, F, Gruverman, A.Two-dimensional nanoscale structural and functional imaging in individual collagen type-I fibrils. Biophys J, 2010, 98: 3070-3077. PMC2884257
6. Nicolae, C, Olsen, BR. Unexpected matrix diseases and novel therapeutic strategies. Cell Tissue Res. 2010, 339:155–165. Review
7. Xu, L, Polur I, Lim C, Servais JM, Dobeck J, Li Y, Olsen BR. Early-onset osteoarthritis of mouse temporomandibular joint induced by partial discectomy. Osteoarthr Cartilage 2009, 17:917-922. PMC2941347
8. Gebauer, JM, Keene, DR, Olsen, BR, Sorokin, LM, Paulsson, M, Wagener, R. Mouse AMACO, a kidney and skin basement membrane associated molecule that mediates RGD-dependent cell attachment. Matrix Biol 2009, 28:456-462. (No BRO grant)
9. Jinnin, M, Ishihara, T, Boye, E, Olsen, BR. Recent progress in studies of infantile hemangioma. J Derm. 2010, 37:283-298. Review.
10. Faye, C, Inforzato, A, Bignon, M, Hartmann, DJ, Muller, L, Ballut, L Olsen, BR, Day, AJ, Ricard-Blum, S. Transglutaminase-2: a new endostatin partner in the extracellular matrix of endothelial cells. Biochem. J. 2010, 427:467-475. PMCID: PMC2876729.
11. Jeng, L, Olsen, BR, Spector, M. Engineering endostatin-producing cartilaginous constructs for cartilage repair using non-viral transfection of chondrocyte- and mesenchymal stem cell (msc)-seeded collagen scaffolds. Tiss Eng Part A, 2010, 16:3011- 3021. PMC3189205
12. Clarkin, C, Olsen, BR. On bone-forming cells and blood vessels in bone development. Preview. Cell Metabol, 2010, 12:314-316. Preview. PMC3031181
13. Medici, D, Shore, EM, Lounev, VY, Kaplan, FS, Kalluri, R, Olsen, BR. Conversion of vascular endothelial cells into multipotent stem-like cells. Nat Med 2010, 16: 1400-1406. PMC3209716
14. Liu, Y, Jia, S, Lotinun, S, Baron, R, Ferrara, N, Olsen,

BR. VEGF stimulates trabecular bone formation and suppresses marrow adipogenesis in mice by intracrine mechanisms. JCI, in press.
15. Papadaki, ME, Lietman, SA, Levine, MA, Olsen, BR, Kaban LB, Reichenberger, EJ. Cherubism: Best clinical Practice. . Orphanet J Rare Dis. 2012, 7 Suppl 1:S6. PMC3359956
16. Reichenberger, EJ, Levine, MA, Olsen, BR, Papadaki, ME, Lietman, SA. The role of SH3BP2 in the pathophysiology of cherubism. Orphanet J Rare Dis. 2012, 7 Suppl 1:S5. PMC3359958
17. Medici, D, Olsen, BR. Transforming blood vessels into bone. Cell Cycle 2011, 10:362-363.
18. Mauney, J, Olsen, BR, Volloch V. Matrix remodeling as stem cell recruitment event: a novel in vitro model for homing of human bone marrow stromal cells to the site of injury shows crucial role of extracellular collagen matrix. Matrix Biol. 2010, 29:657-663.
19. Medici, D, Olsen, BR. Rapamycin inhibits proliferation of hemangioma endothelial cells by reducing HIF-1-dependent expression of VEGF. PLoS ONE, in press.
20. Jeng, L, Olsen, BR, Spector, M. Engineering endostatin-expressing cartilaginous constructs using injectable biopolymer hydrogels. Acta Biomat, 2012, 8:2203-2212.
21. Berendsen, A, Olsen, BR. Tankyrase loses its grip on SH3BP2 in cherubism. Cell, 2011, 147:1222-1223.
22. Adams, A, McBratney-Owen, B, Newby, B, Bowen, M, Olsen, BR, Warman, ML. Presphenoidal synchondrosis fusion in the DBA/2J mouse strain is influenced by a locus on chromosome 11. Mammal Genome, in revision.
23. Medici, D. and Olsen, B.R. (2012). Transformation of Vascular Endothelial Cells into Multipotent Stem-Like Cells: Role of the Activin-Like Kinase-2 Receptor. Stem Cells and Cancer Stem Cells: Therapeutic Applications in Disease and Injury. Springer
24. Foldager, CB, Toh, WS, Olsen, BR, Spector, M. Basement membrane molecules in normal and degenerated cartilage tissues. Submitted for publication.
25. Katebi N, Kolpakova-Hart E, Lin CY, Olsen BR. The mouse palate and its cellular responses to midpalatal suture expansion forces. Ortho Craniofac Res, 2012, in press.
26. Jumlongras, D, Lachke, SA, O' Connell, DJ, Aboukhalil, A, Li, X, Choe, SE, Robertson, EA, Olsen, BR, Bulyk, ML, Amendt, BA, and Maas, RL. An Evolutionarily Conserved Enhancer Regulates Bmp4 Expression in Developing Incisor and Limb Bud. PLoS ONE, in press.
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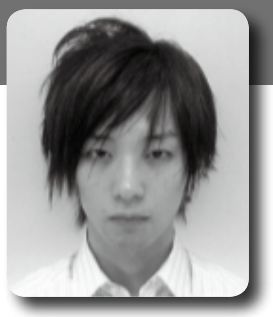
MEMO

Semaphorin 3A regulates bone homeostasis by inhibiting osteoclast and promoting osteoblast synchronously



Mikihito Hayashi, Ph.D.

Japan Science and Technology Agency, ERATO,
Takayanagi Osteonetwork project

Bone homeostasis is maintained by the crosstalk between bone-forming osteoblasts and bone-resorbing osteoclasts. Osteoclast differentiation is strictly controlled by osteoblast lineage cells to maintain adequate bone volume since excessive osteoclastic bone resorption has been implicated in the pathogenesis of various osteopenic conditions. However, an inhibitory factor of osteoclast differentiation derived from osteoblasts was not identified except for osteoprotegerin (Opg), a decoy receptor for RANKL. Here we show that a conditioned medium of Opg-deficient calvarial cells contains factors that inhibit osteoclast formation. By means of functional screening and mass spectrometric analysis, we identified that one of these factors is the axon guidance molecule Semaphorin 3A (Sema3A).

Sema3a$^{-/-}$ mice exhibited a severe low bone mass phenotype accompanied by enhanced osteoclast differentiation. Sema3A-induced inhibition was mediated by the modulation of DAP12-induced ITAM signaling. Neuropilin-1 (Nrp1), a receptor for Sema3A, competed with TREM2 for Plexin-A1, thereby functioning as a suppressor of the Plexin-A1-TREM2-DAP12-induced costimulatory signal. The inhibition of RhoA activation is also involved in the inhibitory effect of Sema3A on the migration of osteoclast precursor cells.

In addition to an osteoclastic phenotype, Sema3a$^{-/-}$ mice also showed a severe defect in osteoblast differentiation and an increase in adipocyte differentiation in bone marrow. These findings suggest that Sema3A promotes mesenchymal cell differentiation toward osteoblasts, but not adipocytes. Sema3A stimulated the canonical Wnt/ β -catenin signaling pathway, at least in part, through FARP2-mediated activation of Rac1 during osteoblast differentiation. The osteopenic phenotype in Sema3a$^{-/-}$ mice was recapitulated by mice in which the Sema3A-binding site of Nrp1 had been genetically disrupted.

We further investigated the therapeutic potential of Sema3A in a bone regeneration model of cortical bone defects induced by drill hole injury. The local administration of Sema3A into the injured site accelerated bone regeneration. Sema3A treatment reduced bone loss after ovariectomy by both inhibiting osteoclastic bone resorption and promoting osteoblastic bone formation synchronously. Thus, Sema3A is a promising new therapeutic target in bone and joint diseases. This study demonstrates that Sema3A expressed by osteoblast lineage cells functions as an osteoprotective factor with the capacity to bring both osteoblasts and osteoclasts into a condition which favors bone mineral increase.

CURRICULUM VITAE

Education

B. Sc. 03/2004 Tokyo University of Science, Tokyo, Japan
M. Sc. 03/2006 Kyoto University, Kyoto, Japan
Ph. D. 03/2010 Tokyo Medical and Dental University, Tokyo, Japan

Position

Japan Science and Technology Agency, ERATO, Takayanagi Osteonetwork project
Post-doctoral Fellow, 04/2010-present

Award and Honors

2010 3rd International Conference on Osteoimmunology Travel Award
2012 4th International Conference on Osteoimmunology Travel Award
2012 JSBMR Young Investigator Award
2012 ASBMR Young Investigator Travel Grant

Publications

1. Yu Kato, Yoshimasa Tanaka, Mikihito Hayashi, Katsuya Okawa, Nagahiro Minato. Involvement of CD166 in the activation of human $\gamma\delta$ T cells by tumor cells sensitized with nonpeptide antigens. J Immunol. 177(2):877-84 (2006).
2. Keizo Nishikawa, Tomoki Nakashima, Mikihito Hayashi, Takanobu Fukunaga, Shigeaki Kato, Tatsuhiko Kodama, Satoru Takahashi, Kathryn Calame, Hiroshi Takayanagi. Blimp1-mediated repression of negative regulators is required for osteoclast differentiation. Proc Natl Acad Sci USA. 16; 107 (7) 3117-22 (2010).
3. Mikihito Hayashi, Tomoki Nakashima, Tatsuhiko Kodama, Andrew P. Makrigiannis, Noriko Toyama-Sorimachi, Hiroshi Takayanagi. Ly49Q, an ITIM-bearing NK receptor, positively regulates osteoclast differentiation domains. Biochem Biophys Res Commun. 393, 432-438 (2010).
4. Erik Idrus, Tomoki Nakashima, Ling Wang, Mikihito Hayashi, Kazuo Okamoto, Tatsuhiko Kodama, Nobuyuki Tanaka, Tadatsugu Taniguchi, Hiroshi Takayanagi. The role of the BH3-only protein Noxa in bone homeostasis. Biochem Biophys Res Commun. 410, 620-625 (2011).
5. Tomoki Nakashima, Mikihito Hayashi, Takanobu Fukunaga, Kosaku Kurata, Masatsugu Oh-hora, Jian Q Feng, Lynda F Bonewald, Tatsuhiko Kodama, Anton Wutz, Erwin F Wagner, Josef M Penninger, Hiroshi Takayanagi. Evidence for osteocyte regulation of bone homeostasis through RANKL expression. Nat Med. 17, 1231-1234 (2011).
6. Mikihito Hayashi, Tomoki Nakashima, Masahiko Taniguchi, Tatsuhiko Kodama, Atsushi Kumanogoh, Hiroshi Takayanagi. Osteoprotection by Semaphorin 3A. Nature. 485, 69-74 (2012)
7. Tomoki Nakashima, Mikihito Hayashi, Hiroshi Takayanagi. New insights into osteoclastogenic signaling mechanisms. Trends Endocrinol Metab. in press

MEMO

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Achievement of bone regeneration and bone remodeling, the animal experimental studies to clinical trial in bone tissue engineering paradigms.

Paksinee Kamolratanakul, D.D.S., Ph.D.

Department of oral and maxillofacial surgery,
Chulalongkorn University, Bangkok, Thailand

In many cases of patients who suffer from bone disease or bone defect after surgical resection or trauma, bone reconstruction and bone repair are required.Various of the experimental researches are developed in order to achieve bone regeneration aspect. The appropriate animal models are selected to test the hypothesis based on concept of bone regeneration by tissue engineering. According to biological components involved in tissue engineering of bone; cells, scaffolds and signaling molecules are considered and utilized to create bone regeneration and balance of bone remodeling. Here, we emphasized on signaling molecules; PGE2 specific receptor agonist (EP4), PTH and TRPV4 which regulate bone repair and remodeling in different bone tissue engineering paradigms.

Owing to a role of EP4 on bone formation, critical-sized defect model demonstrated the combination of EP4 and low-dose BMP-2 in nanogel scaffold heals bone defect and regenerate proper newly-formed bone.

Consistently, PTH promotes bone formation when apply intermittently in normal condition but not in TRPV4 deficiency mice. Deletion of TRPV4 results in imbalance of bone remodeling, possibly via impairment of osteoclastogenesis. Consequently, PPRTg-induced bone formation is enhanced by TRPV4 deficiency, at least in TRPV4 heterozygous mice

Signaling molecules in various experimental conditions those mimics to clinical conditions may be the keys to achieve bone repair and regeneration, leading to development of clinical treatment in patient hereafter.

CURRICULUM VITAE

Education

2005 Doctor of Dental Surgery, Chulalongkorn University, Bangkok, Thailand

2006 Graduate diploma in clinical sciences degree in oral surgery, Chulalongkorn University, Bangkok, Thailand

2011 Doctor of philosophy in dental science, Tokyo Medical and Dental University, Tokyo, Japan

2012 Visiting scholar in oral and maxillofacial surgery training, University of California, Los Angeles, Los Angeles, CA, USA

Present Residency training in oral and maxillofacial surgery, Chulalongkorn University, Bangkok, Thailand

Award and Honors

2010 Most excellent award from Global Center of Excellence program entitled, "International research center for molecular science in tooth and bone disease", Tokyo Medical and Dental University, Tokyo, Japan

2010 Young investigator travel grant for plenary poster presentation award, American Society for Bone and Mineral research (ASBMR), ASBMR Annual meeting, Canada

Publications

1. Nanogel-based scaffold delivery of Prostaglandin E2 receptor-specific agonist in combination with a low dose of growth factor heals critical size bone defect in mice, Kamolratanakul P,et al.Arthritis Rheum. 2011 Apr;63(4):1021-33
2. Osteopontin deficiency enhances parathyroid hirmone/ parathyroid hormone related peptide receptor (PPR) signaling-induced alteration in tooth formation and odontoblastic morphology, Morishita M, et al.Tissue Cell. 2011 Jun;43(3):196-200

MEMO

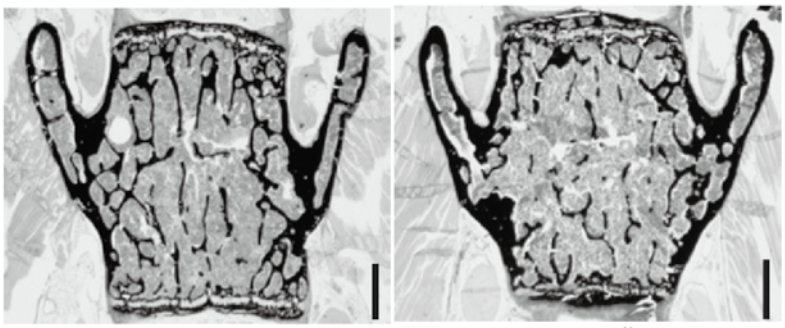
MEMO

Vitamin E decreases bone mass by stimulating osteoclast fusion.

Koji Fujita M.D., Ph.D.

Mayo clinic, Division of Endocrinology, Diabetes, Metabolism, & Nutrition

Bone homeostasis is maintained by the balance between osteoblastic bone formation and osteoclastic bone resorption. Osteoclasts are multinucleated cells that are formed by mononuclear preosteoclast fusion. Fat-soluble vitamins such as vitamin D are pivotal in maintaining skeletal integrity. However, the role of vitamin E in bone remodeling is unknown. We show that mice deficient in α -tocopherol transfer protein (Ttpa−/− mice), a mouse model of genetic vitamin E deficiency, have high bone mass as a result of a decrease in bone resorption. Cell-based assays indicated that α -tocopherol stimulated osteoclast fusion, independent of its antioxidant capacity, by inducing the expression of dendritic-cell–specific transmembrane protein, an essential molecule for osteoclast fusion, through activation of mitogen-activated protein kinase 14 (p38) and microphthalmia-associated transcription factor, as well as its direct recruitment to the Tm7sf4 (a gene encoding DC-STAMP) promoter. Indeed, the bone abnormality seen in Ttpa−/− mice was rescued by a Tm7sf4 transgene. Moreover, wild-type mice or rats fed an α -tocopherol–supplemented diet, which contains a comparable amount of α -tocopherol to supplements consumed by many people, lost bone mass. These results show that serum vitamin E is a determinant of bone mass through its regulation of osteoclast fusion.



Normal diet α-toc diet

CURRICULUM VITAE

Education

Medical School	Tokyo Medical and Dental University, graduated in March 2002.
Post-Graduate School	Tokyo Medical and Dental University, Graduate school of Orthopedic Surgery, graduated in March 2011.
Ph. D.	March 2011.

Position

2002-2003	Resident in Tokyo Medical and Dental University Hospital Faculty of Medicine
2003-2004	Medical Staff in Orthopedic Surgery, Saitama Red Cross Hospital, Japan
2004-2005	Medical Staff in Orthopedic Surgery, Saku Central Hospital, Japan
2005-2007	Medical Fellow in Orthopedic Surgery, Minato Red Cross Hospital, Japan
2008	Board Certified Orthopedic Surgeon by the Japanese Orthopedic Association

Award and Honors

2009 Excellent Poster award in the 26th Naito Conference
2010 Plenary Poster award in the ASBMR annual meeting

Publications

1. Clinical results: AO-C3 distal radius fracture treated with volar locking plate system.
   Fujita K, Wakabayashi Y, Shinomiya K. JSSH 2009
2. Bone metabolism and Neuropeptide.
   Fujita K, Takeda S. HORM FRONT GYNECOL 2010
3. A microRNA regulatory mechanism of osteoblast differentiation.
   Inose H, Ochi H, Kimura A, Fujita K, Xu R, Sato S, Iwasaki M, , Siomi H, Ito H, Arai Y, Shinomiya K, Takeda S. Proc Natl Acad Sci U S A. 2009
4. Runx1 and Runx2 cooperate during sternal morphogenesis.
   Kimura A, Inose H, Yano F, Fujita K, Ikeda T, Sato S, Iwasaki M, Martin JF, Iseki S, Shinomiya K, Takeda S. Development. 2010
5. Vitamin E decreases bone mass by stimulating osteoclast fusion.
   Fujita.K, Iwasaki.M, Ochi.H, Fukuda.T, Ma.C, Miyamoto. T, Takitani.K, Negishi-Koga.T, Sunamura.S, Kodama.T, Takayanagi.H, Tamai.H, Kato.S, Arai.H, Shinomiya.K, Itoh.H, Okawa.A, Takeda S. Nature Medicine 2012

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Nestin-positive cells in endochondral bone development

Noriaki Ono, D.D.S., Ph.D.

Endocrine Unit, Massachusetts General Hospital and
Harvard Medical School, Boston, MA

Nestin-positive cells that support hematopoietic stem cells are putative mesenchymal stem cells in adult bone marrow. The relationship of these cells to osteoblast precursors is poorly understood. Previous studies have shown that, during early endochondral bone development, osterix-expressing osteoblast precursors in the perichondrium translocate to the marrow space, many of them in a pericyte-like manner. To determine the possible involvement of nestin-positive cells in this process, we studied triple-mutant mice carrying a green fluorescent protein under the nestin promoter (Nes+ or Nes-GFP) and a constitutive or an inducible cre recombinase under various promoters (Prx1-Cre, and Col2a1-CreER, Osx-CreER that activate a Rosa26 tomato reporter upon tamoxifen injection). At embryonic day 10.5 (E10.5), Nes+ cells were distributed throughout the limb bud, largely in a reticular pattern. All of these cells were in the Prx1-lineage, with some of them co-expressing the endothelial marker, CD31. When the distinct growth cartilage started to elongate at E12.5, Nes+ cells were found in the innermost portions of the perichondrium (PC), but not within the cartilage itself. At E13.5, Osx-lineage cells began to appear in the PC adjacent to the incipient hypertrophic cartilage. In this part of the PC, most of the Nes+ cells were either in the Osx lineage or positive for CD31 immunoreactivity, but not in the Col2 lineage. We thereafter chased the descendents of these Osx lineage cells (Osx-E13.5 cells) and Col2 lineage cells (Col2-E13.5 cells) using a pulse-chase protocol in which tamoxifen was given at E13.5 and mice were harvested at subsequent times. Both Osx-E13.5 cells and Col2-E13.5 cells translocated into the future marrow space, proliferated and differentiated into osteoblasts of the spongiosa. After 3 days of chase at E16.5, many of Osx-E13.5 cells, but none of Col2-E13.5 cells in the spongiosa expressed Nes-GFP. When chased further for 7 days until the time of birth (P0), Osx-E13.5 cells rarely expressed Nes-GFP in the spongiosa, while many Col2-E13.5 cells expressed Nes-GFP both in the perichondrium and spongiosa. Upon further chase by postnatal day 21, Osx-E13.5 cells disappeared almost completely with only a few cells remaining in the diaphysis, whereas Col2-E13.5 cells extensively contributed to chondrocyte, osteoblast/cyte and bone lining cell populations, with many co-expressing Nes-GFP. These findings indicate that Nes+ cells are heterogeneous in the embryonic perichondrium, and that a subset of Nes+ cells becomes Osx+ cells and a subset of Col2+ cells becomes Nes+ cells during endochondral bone development. In addition, while Osx-E13.5 cells do not indefinitely renew themselves, Col2-E13.5 cells contribute to multiple bone cell lineages at least until postnatal day 21

CURRICULUM VITAE

Education

DDS, 2003（summa cum laude）#3609
Faculty of Dentistry, Tokyo Medical and Dental University
Ph.D. in Dental Science, 2007, #1654
Orthodontic Science and Bone Biology, Tokyo Medical and Dental University Graduate School
Clinical supervisor: Dr. Kunimichi Soma
（Orthodontic Science, TMDU）
Research supervisor: Dr. Masaki Noda（Molecular Pharmacology, Medical Research Institute, TMDU）

Position

Adjunct Lecturer, 2009-present
Orthodontic Science, Tokyo Medical and Dental University Graduate School
Clinical Instructor（part-time）, 2010-present
AGE Orthodontics Program, Department of Development Biology, Harvard School of Dental Medicine
Instructor in Medicine, 2012-present
Massachusetts General Hospital, Harvard Medical School

Award and Honors

1. Nagao Academic Award (for summa cum laude), 2003, Tokyo Medical and Dental University, Japan
2. Kobayashi Ikueikai Award (for excellence in clinic), 2003, Tokyo Medical and Dental University, Japan
3. Plenary Poster Presentation Award, ASBMR, 2005, American Society for Bone and Mineral Research
4. Best Research Proposal Award, 2006, 21st Century Center of Excellence Program "Frontier Research on Molecular Destruction and Reconstruction of Tooth and Bone"
5. Award for Excellent Presentation, 2007, The Japanese Orthodontic Society
6. Award for Excellent Paper, 2008, Ochanomizu Society for Tokyo Medical and Dental University Alumni of Dentists
7. Young Investigator Award, 2012, American Society for Bone and Mineral Research

Publications

1. Ono N, Nakashima K, Schipani E, Hayata T, Ezura Y, Soma K, Kronenberg HM, Noda M: Constitutively active parathyroid hormone receptor signaling in cells in osteoblastic lineage suppresses mechanical unloading-induced bone resorption. J Biol Chem. 2007 Aug 31;282(35):25509-16.
2. Ono N, Nakashima K, Rittling SR, Schipani E, Hayata T, Soma K, Denhardt DT, Kronenberg HM, Ezura Y, Noda M: Osteopontin negatively regulates parathyroid hormone receptor signaling in osteoblasts. J Biol Chem. 2008 Jul 11;283(28):19400-9.
3. Morishita M, Ono N, Miyai K, Nakagawa T, Hanyu R, Nagao M, Kamolratanakul P, Notomi T, Rittling SR, Denhardt DT, Kronenberg HM, Ezura Y, Hayata T, Nakamoto T, Noda M: Osteopontin deficiency enhances parathyroid hormone/ parathyroid hormone related peptide receptor (PPR) signaling-induced alteration in tooth formation and odontoblastic morphology. Tissue Cell. 2011 Jun;43(3):196-200.
4. Ono N, Nakashima K, Schipani E, Hayata T, Ezura Y, Soma K, Kronenberg HM, Noda M: Constitutively active PTH/ PTHRP receptor specifically expressed in osteoblasts enhances bone formation induced by bone marrow ablation. J Cell Physiol. 2012 Feb;227(2):408-15.
5. Ohishi M, Ono W, Ono N, Khatri R, Marzia M, Baker EK, Root SH, Wilson TL, Iwamoto Y, Kronenberg HM, Aguila HL, Purton LE, Schipani E: A Novel Population of Cells Expressing Both Hematopoietic and Mesenchymal Markers Is Present in the Normal Adult Bone Marrow and Is Augmented in a Murine Model of Marrow Fibrosis. Am J Pathol. 2012 Feb;180(2):811-8.
6. Usumi-Fujita R, Hosomichi J, Ono N, Shibutani N, Kaneko S, Shimizu Y, Ono T: Occlusal hypofunction causes periodontal atrophy and VEGF/VEGFR inhibition in tooth movement. Angle Orthod. 2012 Jun 18.
7. Song L, Liu M, Ono N, Bringhurst FR, Kronenberg HM, Guo J: Loss of wnt/ β -catenin signaling causes cell fate shift of preosteoblasts from osteoblasts to adipocytes. J Bone Miner Res. 2012 Jun 22. doi: 10.1002/jbmr.1694.

MEMO

MEMO

The pericyte as a cell of origin for sarcomas

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Developmental and Stem Cell Biology, the Hospital for Sick Children

Sarcomas are malignancies derived from mesenchymal tissues such as bone, muscle, fat, and cartilage. With modern surgical techniques, chemotherapy, and radiation therapy, the survival rate of sarcomas has much improved over the past three decades. However, the molecular mechanisms in the occurrence and growth of sarcomas have yet to be elucidated. Even the cell of origin for most sarcomas still remains unclear. Although there are several cases of in vitro evidence that sarcomas are derived from mesenchymal progenitor or stem cells, this hypothesis has not been proven in vivo.

We previously performed a high-throughput screening to identify cell surface makers in the tumor initiating cell population in sarcomas. This screen found that the expression of NG2 and CD146, both markers of pericytes, were enriched in the sarcoma initiating subpopulation. Pericytes are mesenchymal cells surrounding endothelial cells in capillaries, venules, and small arterioles, and these cells have mesenchymal progenitor properties. These findings raise the possibility that sarcomas are derived from pericytes in which an oncogenic mutation occurs.

To test this hypothesis, we first generated Ng2-Cre; Rosa26R-LacZ mice to label NG2-expressing cells and their progenies, and confirmed by beta-galactosidase staining that LacZ was expressed in the expected cells, such as pericytes, in normal murine tissues.

We then crossed Ng2-Cre; Rosa26R-LacZ mice with p53+/- mice, which are known to develop several types of sarcomas, and used beta-galactosidase staining to investigate the expression of LacZ in murine sarcomas. We found that murine sarcomas expressed LacZ, showing that the sarcomas are derived from NG2- expressing cells, most likely from pericytes.

Furthermore, we generated Ng2-Cre mediated p53 conditional knockout mice (Ng2-Cre; $p53^{loxP/loxP}$ mice) to determine whether p53 inactivation in pericytes could induce sarcoma formation. Interestingly, almost all of Ng2-Cre; $p53^{loxP/loxP}$ mice developed some types of sarcomas, especially osteosarcoma, after 7 months of age. These findings show that sarcomas can arise from oncogenic mutations in pericytes. To determine important neoplastic changes in pericytes, we are currently comparing the gene expression profile, the genomic DNA sequence, or the copy number variation between sarcoma cells and pericytes harvested from the same Ng2-Cre; $p53^{loxP/loxP}$ mouse.

Identifying the cell of origin for sarcomas is important not only in understanding their underlying etiology, but also in developing novel therapeutic approaches to sarcomas based on suppressing the changes causing the cell of origin to undergo malignant change.

CURRICULUM VITAE

Degrees

03/2000 Medical Doctor（M.D.）, Tokyo Medical and Dental University, Tokyo, Japan

03/2007 Medical doctoral degree（PhD）, Department of Orthopedic Surgery, Tokyo Medical and Dental University, Graduate School, Tokyo, Japan
Supervisors: Dr. Kenichi Shinomiya and Dr. Shu Takeda

Current Position

09/2010-present Postdoctoral Fellow, Program in Developmental and Stem Cell Biology, the Hospital for Sick Children, Toronto, Ontario Canada
Supervisor: Dr. Benjamin Alman

Previous Positions

04/2000-03/2002 Resident, Kawashima Orthopedic Hospital, Oita, Japan

04/2002-05/2003 Clinical Fellow, Nissan Tamagawa Hospital, Tokyo, Japan

06/2003-12/2003 Clinical Fellow, Kawaguchi General Hospital, Saitama, Japan

01/2004-03/2004 Clinical Fellow, Tokyo Medical and Dental University Hospital, Tokyo, Japan

04/2004-03/2007 Center of Excellence (COE) Program Research Fellow, Tokyo Medical and Dental University, Tokyo, Japan

04/2007-04/2009 Clinical Fellow, Cancer Institute Hospital, Tokyo, Japan

05/2009-08/2010 Research Fellow, Institute for Frontier Medical Sciences and Center for iPS Cell Research and Application, Kyoto University, Kyoto, Japan

09/2010-present Postdoctoral Fellow, Program in Developmental and Stem Cell Biology, The Hospital for Sick Children, Toronto, Ontario Canada

Award and Honors

2004 Research Competition, the 21st Century Center of Excellence (COE) Program, Tokyo Medical and Dental University, Tokyo, Japan

03/2007 Graduated from Tokyo Medical and Dental University, graduate school with a first-class honors degree

09/2007 Young Investigator Travel Grants, the American Society for Bone and Mineral Research, 29th Annual Meeting, Hawaii, USA

09/2007 Most Outstanding Abstract Award, the American Society for Bone and Mineral Research, 29th Annual Meeting, Hawaii, USA

12/2007 Orthopedic Alumni Association Research Award, Tokyo Medical and Dental University, Tokyo, Japan

12/2008 22th Medical Alumni Association Research Award, Tokyo Medical and Dental University, Tokyo, Japan

02/2009 25th Inoue Research Award for Young Scientists, Tokyo, Japan

05/2009 Medical Association Award, Tokyo Medical and Dental University, Tokyo, Japan

05/2009 Japanese Orthopedic Association Research Award, Fukuoka, Japan

2010 Grant-in-Aid for Exploratory Research, Japan Society for the Promotion of Science (JSPS), Japan

2010 Institutional Program for Young Researcher Overseas
Visits, Tokyo Medical and Dental University, Tokyo, Japan

2011 Restracomp fellowship, The Hospital for Sick Children
Research Training Centre, Canada

2011 Grants for foreign study, KANAE Foundation for the Promotion of Medical Science, Tokyo, Japan

Publications

Peer Reviewed Papers:

1. Sato S, Sasaki M, Ihara H, and Kawashima M "A case of familial osteochondrosis dissecans" Orthopedics & Traumatology, 51(4), 883-890, 2002
2. Sato S, Yoshida H, Kitahara K, Ebata S, Wakabayashi Y, and Sato H "Occurrence frequency of intraoperative and postoperative complications of spine surgery" Orthopedic Surgery, 57(9), 1189-1194, 2006
3. Kamekura S, Kawasaki Y, Hoshi K, Shimoaka T, Chikuda H, Maruyama Z, Komori T, Sato S, Takeda S, Karsenty G, Nakamura K, Chung UI, and Kawaguchi H. "Contribution of runt-related transcription factor 2 to the pathogenesis of osteoarthritis in mice after induction of knee joint instability" Arthritis & Rheumatism, 54(8), 2462-2470, 2006
4. Sato S, Kojima M, Hanada R, Kimura A, Abe T, Matsumoto T, Iwasaki M, Inose H, Ida T, Mieda M, Takeuchi Y, Fukumoto S, Fujita T, Kato S, Kangawa K, Shinomiya K, and Takeda S "Central control of bone remodeling by Neuromedin U" Nature Medicine, 13(10), 1234-1240, 2007
5. Nakamura T, Imai Y, Matsumoto T, Sato S, Takeuchi K, Igarashi K, Harada Y, Azuma Y, Krust A, Yamamoto Y, Nishina H, Takeda S, Takayanagi H, Metzger D, Kanno J, Takaoka K, Martin TJ, Chambon P, and Kato S. "Estrogen Prevents Bone Loss via Estrogen Receptor α and Induction of Fas Ligand in Osteoclasts" Cell, 130, 811-823, 2007
6. Sato S, Kimura A, Ozdemir J, Asou Y, Miyazaki M, Jinno T, Ae K, Liu X, Osaki M, Takeuchi Y, Fukumoto S, Kawaguchi H, Haro H, Shinomiya K, Karsenty G, and Takeda S "The Distinct Role of the Runx Proteins in Chondrocyte Differentiation and Intervertebral Disc

Degeneration" Arthritis & Rheumatism, 58(9), 2764-2775, 2008 *The figure of this article made the cover of this journal.
7. Inose H, Ochi H, Kimura A, Fujita K, Xu R, Sato S, Iwasaki M, Sunamura S, Takeuchi Y, Fukumoto S, Saito K, Nakamura T, Siomi H, Ito H, Arai Y, Shinomiya K, and Takeda S "A microRNA regulatory mechanism of osteoblast differentiation" Proc Natl Acad Sci USA, 106(49), 20794–20799, 2009
8. Kimura A, Inose H, Yano F, Fujita K, Ikeda T, Sato S, Iwasaki M, Jinno T, Ae K, Fukumoto S, Takeuchi Y, Itoh H, Imamura T, Kawaguchi H, Chung UI, Martin JF, Iseki S, Shinomiya K, and Takeda S "Runx1 and Runx2 cooperate during sternal morphogenesis" Development, 137(7), 1159-1167, 2010
9. Wang CY, Wei Q, Han I, Sato S, Azarnier RG, Whetstone H, Poon R, Hu J, Zheng F, Zhang P, Wang W, Wunder J, Alman BA "Hedgehog and Notch Signaling Regulate Self-Renewal of Undifferentiated Pleomorphic Sarcomas" Cancer Research, 72(4), 1013-1022, 2012

Non-Peer Reviewed Papers:

1. Sato S "Sports injuries in sprinter: Muscle strain of thigh & avulsion fracture of pelvis" Orthopedic Surgery, 58(8), 1092-1098, 2007
2. Sato S and Manabe J "Surgical treatment of bone metastasis" Nursing Art, 54(11), 1141-1146, 2008
3. Sato S, Ueno T, Matsueda K, Takano K, Shimoji T, Tanizawa T, and Matsumoto S "Serial arterial embolization for sacral giant cell tumor" Journal of Joint Surgery, 28(6), 713-718, 2009
4. Sato S and Takeda S "Investigating the role of central nervous system in bone metabolism" Molecular Rheumatology and Therapy, 2(4), 179-182, 2009
5. Sato S and Takeda S "The role of Runx family in chondrocyte differentiation and intervertebral disc degeneration" Orthopedic Surgery, 61(10), 1149-1153, 2010

MEMO

A microRNA regulatory mechanism of osteoblast differentiation

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Growing evidence shows that microRNAs (miRNAs) regulate various developmental and homeostatic events in vertebrates and invertebrates. Osteoblast differentiation is a key step in proper skeletal development and acquisition of bone mass; however, the physiological role of non-coding small RNAs, especially miRNAs, in osteoblast differentiation remains elusive. Here, through comprehensive analysis of miRNAs expression during osteoblast differentiation, we show that miR-206, previously viewed as a muscle-specific miRNA, is a key regulator of this process. miR-206 was expressed in osteoblasts, and its expression decreased over the course of osteoblast differentiation. Overexpression of miR-206 in osteoblasts inhibited their differentiation, and conversely, knockdown of miR-206 expression promoted osteoblast differentiation. In silico analysis and molecular experiments revealed Connexin 43 (Cx43), a major gap junction protein in osteoblasts, as a target of miR-206, and restoration of Cx43 expression in miR-206-expressing osteoblasts rescued them from the inhibitory effect of miR-206 on osteoblast differentiation. Finally, transgenic mice expressing miR-206 in osteoblasts developed a low bone mass phenotype due to impaired osteoblast differentiation. Our data show that miRNA is a novel regulator of osteoblast differentiation.

CURRICULUM VITAE

Education and position

1994-2000	M.D. Tokyo Medical and Dental University, Faculty of medicine, Japan
2000-2002	Resident, Department of Orthopedic surgery, Tokyo Medical and Dental University Hospital
2002-2003	Clinical Fellow, Orthopedic surgery, Ome Municipal General Hospital
2003-2004	Clinical Fellow, Orthopedic surgery, Tutiura Kyodo Hospital
2004-2005	Clinical Fellow, Orthopedic surgery, Suwa Central Hospital
2005-2006	Clinical Fellow, Orthopedic surgery, Kudanzaka Hospital
2006-2010	Ph.D., Tokyo Medical and Dental University Graduate School, Faculty of medicine
2010-2011	Post-Doctral Fellow, Department of Genetics and Development, Columbia University
2011-2012	Clinical fellow, Orthopedic surgery, Tokyo Medical and Dental University Hospital
2012-Present	Assistant Professor, Department of Orthopedics, Tokyo Medical and Dental University

Publications

1. Sato S, HANADA R, KIMURA A, ABE T, MATSUMOTO T, IWASAKI M, INOSE H, IDA T, MIEDA M, TAKEUCHI Y, FUKUMOTO S, FUJITA T, KATO S, KANGAWA K, KOJIMA M, SHINOMIYA K, TAKEDA S: Central control of bone remodeling by neuromedin U. Nat Med 13(10): 1234-40, 2007
2. INOSE H, OCHI H, KIMURA A, FUJITA K, XU R, SATO S, IWASAKI M, SUNAMURA S, TAKEUCHI Y, FUKUMOTO S, SAITO K, NAKAMURA T, SIOMI H, ITO H, ARAI Y, SHINOMIYA K, TAKEDA S : A microRNA regulatory mechanism of osteoblast differentiation. Proc Natl Acad Sci U S A 106: 20794-20799, 2009.
3. KIMURA A, INOSE H, YANO F, FUJITA K, IKEDA T, SATO S, IWASAKI M, JINNO T, AE K, FUKUMOTO S, TAKEUCHI Y, ITOH H, IMAMURA T, KAWAGUCHI H, CHUNG U, MARTIN J, ISEKI S, SHINOMIYA K, TAKEDA S : Runx1 and Runx2 cooperate during sterna morphogenesis. Development 137(7): 1159-67, 2010.
4. INOSE H, ZHOU B, YADAV V, GUO E, KARSENTY G, DUCY P : Efficacy of serotonin inhibition in mouse models of bone loss. J. Bone Miner Res. 26(9): 2002-2011, 2011.
5. WEI J, SHI Y, ZHENG L, ZHOU B, INOSE H, WANG J, GUO E, GROSSCHEDL R, KARSENTY G : Mir-34s inhibit osteoblast proliferation and differentiation in the mouse by targeting SATB2. J Cell Biol 197(4):509-521, 2012.
6. KUROIWA T, YOSHII T, SAKAKI K, INOSE H, TOMIZAWA S, KATO T, KAWABATA S, SHINOMIYA K, OKAWA A: Vertebral locking lesion following cervical spine fracture in ankylosing spondylitis. Orthopedics. 35(6):1005-1008, 2012
7. IWASAKI M, PIAO J, KIMURA A, SATO S, INOSE H, OCHI H, ASOU Y, SHINOMIYA K, OKAWA A, TAKEDA S: Runx2 haploinsufficiency ameliorates the development of Ossification of the Posterior Longitudinal Ligament. PLoS ONE. (in press)

MEMO

MEMO

The role of fibrillin-1 in periodontal ligaments

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Marfan syndrome is an autosomal dominant disease characterized by aneurysm and dilatation of the aortic root, tall stature, and ectopia lentis. These manifestations reflect excessive signaling of transforming growth factor (TGF)- β . Moreover, patients are frequently associated with severe periodontitis which is a chronic inflammation of the gingiva, periodontal ligament and alveolar bone. Elastic system fibers are generally formed by elastin and microfibrils, but PDLs are mainly composed of the latter. Compared with the wellknown function of collagen fibers to support teeth, little is known about the role of elastic system fibers in PDLs.

To clarify their role, we examined PDLs of mice underexpressing fibrillin-1 (mgR mice), which is one of the major microfibrillar proteins. The PDLs of homozygous mgR mice showed one-quarter of the elastic system fibers of wild-type (WT) mice. A close association between the elastic system fibers and the capillaries was noted in WT, homozygous and heterozygous mgR mice. Interestingly, capillaries in PDLs of homozygous mice were dilated or enlarged compared with those of WT mice. A comparable level of type I collagen, which is the major collagen in PDLs, was expressed in PDL-cells of mice with three genotypes. However, multi-oriented collagen fiber bundles with a thinner appearance were noted in homozygous mice, whereas well-organized collagen fiber bundles were seen in WT mice. There was a marked decrease in periostin expression, which is known to regulate the fibrillogenesis and crosslinking of collagen.

Recently, angiotensin II receptor blockers (ARBs) were discovered as an effective drug that can prevent aortic aneurysm and dilation in Marfan syndrome by inhibiting TGF- β signaling. To investigate the effect of ARB on the progression of periodontitis, the application of a potent ARB, telmisartan, was examined in a mouse model of Marfan syndrome (Mg Δ). Mg Δ and wild-type mice were challenged with Porphyromonas gingivalis that causes chronic periodontitis, with and without telmisartan application. The amount of resorption was significantly larger in the former than the latter. Immunoarray and ELISA demonstrated that interleukin (IL)-17 and tumor necrosis factor (TNF)- α levels were significantly higher in infected Mg Δ mice than infected wild-type mice. Telmisartan treatment significantly suppressed the alveolar bone resorption of infected Mg Δ mice and levels of TGF- β , IL-17, TNF- α in infected Mg Δ mice to levels seen in infected wild-type mice. This study suggests that ARB can prevent the severe periodontitis frequently seen in Marfan syndrome.

These observations suggest that the microfibrillar protein, fibrillin-1, is indispensable for normal tissue architecture and gene expression of PDLs.

CURRICULUM VITAE

Education

DDS 1996-2002 The Higher Institute of Medical Science, University of Havana
Havana, Cuba

Ph.D 2005-2010 Molecular biology and Orthodontics
Tokyo Medical and Dental University
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Publications

1. Suda N, Shiga M, Ganburged G, Moriyama K Journal of Experimental Zoology part B Molecular Development Evolution, 2009 Jul 15: 312 B(5): 503-9
   Marfan syndrome and its disorder in periodontal tissues
2. Suda N, Bazar A, Bold O, Jigjid B, Garidkhuu A, Ganburged G, Moriyama K Orthodontics Craniofacial Research, 2010 May; 13(2): 114-7
   A Mongolian patient with hypohidrotic ectodermal dysplasia with a novel P121S variant in EDARADD
3. Ganjargal Ganburged, Naoto Suda, Masahiro Saito, Yosuke Yamazake, Keitaro Isokawa, Keiji Moriyama Cell Tissue Research, 2010 Sep; 341(3): 381-95
   Dilated capillaries, disorganized collagen fibers and differential gene expression in periodontal ligaments of hypomorphic fibrillin-1 mice
4. Saito M, Kurokawa M, Oda M, Oshima M, Tsutsui K, Kosaka K, Nakao K, Ogawa M, Manabe RI, Suda N, Ganjargal G, Hada Y, Noguchi T, Teranaka T, Sekiguchi K, Yoneda T, Tsuji T
   Journal of Biological Chemistry, 2011 August 31
   ADAMTSL6 rescues fibrillin-1 microfibril disorder in Marfan syndrome mouse model through the promotion of fibrillin-1 assembly

MEMO

MEMO

Modulation of matrix mineralization by Vwc2-like proteins

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Periodontology and Oral Biology, Boston University,
Boston, MA,

Objectives: Bone morphogenetic proteins (BMPs) have been applied to various clinical settings including craniofacial reconstruction, and bone/cartilage repair and regeneration for bone bioengineering. However, there are still several problems for the clinical use of BMPs; poor expression control of BMP genes, poor control of retention and release of BMPs, etc. There are a number of extracellular modulators identified as BMP antagonists, such as chordin and noggin, which exert inhibitory effects on BMP functions. However, at present, little is known about the extracellular modulators that promote BMP functions. We identified Willebrand factor C domain-containing protein 2-like (Vwc2l, also known as Brorin-like) as a new cysteine knot protein (CKP) family member. The objectives of this present study are to analyze the effect of Vwc2l on osteoblast mineralization and to investigate its molecular mechanism.

Methods: The expression of novel Vwc2l transcript variants was examined by PCR. The effect of Vwc2l protein on osteoblast mineralization in vitro was analyzed by mineralized nodule formation assay and the expression of Osterix, one of the key osteogenic markers, induced by these isoform proteins was demonstrated by real time PCR.

Results: Vwc2l transcript variants were detected in more ubiquitous tissues by RT-PCR. In osteoblasts, the induction of Vwc2l expression was observed at matrix mineralization stage. When Vwc2l was stably transfected into osteoblasts, the matrix mineralization was markedly accelerated in Vwc2l-expressing clones compared to that in the control. The expression of Osterix was significantly increased by addition of all Vwc2l isoform proteins.

Conclusion: Vwc2l is a novel secreted protein that promotes matrix mineralization by modulating Osterix expression.

CURRICULUM VITAE

Degree

2000 Doctor of Dental Surgery in Tokyo Medical and Dental University, Tokyo, Japan

2004 Ph.D. in Molecular and pharmacology supervised by Prof. Masaki Noda
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Position

2003-2004 Super Student of 21st Century Center of Excellence (COE) Program of Japan Society for the Promotion of Science in Laboratory of Molecular Pharmacology, Tokyo Medical and Dental University, Tokyo, Japan

2004-2007 Major in Department of Maxillofacial Surgery in Tokyo Medical and Dental University

2007-2010 Medical Staff in Department of Maxillofacial Surgery in Tokyo Medical and Dental University

2010-present Post Doctorate Fellow Boston University Henry M. Goldman School of Dental Medicine

Award and Honors

2002 Award of plenary poster 24th Annual Meeting of the American Society for Bone and Mineral Research San Antonio Texas U.S.A. September 20-24, 2002

2004 Award of Kobayashi Scholarship Society Osteopontin - deficiency suppresses growth of B16 melanoma cells implanted in bone and osteoclastgenesis in cocultures.

2004 Award of annual competition of Medical research institute of Tokyo Medical and Dental University. Osteopontin - deficiency suppresses growth of B16 melanoma cells implanted in bone and osteoclastgenesis in cocultures.

2008-2010 Grant-in-Aid for Young Scientists. Japan Society for the Promotion of Science Research Fellowships for Young Scientists

Publications

ORIGINAL, PEER REVIEWED ARTICLES:

1. Ohyama, Y., Nemoto, H., Rittling, S., Tsuji K., Amagasa T., Denhardt, D.,Nifuji, A., Noda, M. Osteopontin-deficiency suppresses growth of B16 melanoma cells implanted in bone and osteoclastogenesis in cocultures J Bone Miner Res (shorten as in Pubmed) 2004 19(10):1706-11.
2. Ohyama, Y., Nifuji, A., Maeda, Y., Amagasa, T., Noda, M. Spaciotemporal association and BMP regulation of SOST and Osterix expression during embryonic osteogenesis. Endocrinology. 2004 Oct; 145(10):4685-92.
3. Maeda, K., Suzuki, T., Ohyama, Y., Nakakuki, K., Yamashiro, M., Okada, N., Amagasa, T. Colorimetric analysis of unstained lesions surrounding oral squamous cell carcinomas and oral potentially malignant disorders using iodine. Int J Oral Maxillofac Surg. 2009 Dec 5.
4. Maeda, K., Yamashiro, M., Michi, Y., Suzuki, T., Ohyama, Y., Okada, N., Amagasa, T. Effective staining method with iodine for leukoplakia and lesions surrounding squamous cell carcinomas of the tongue assessed by colorimetric analysis. J Med Dent Sci 2009; 56: 123-130
5. Nifuji, A., Ideno, H., Ohyama, Y., Takanabe, R., Araki, R., Abe, M., Noda, M., Shibuya, H. Nemo-like kinase (NLK) expression in osteoblastic cells and suppression of osteoblastic differentiation. Experimental cell research 2010 Epub on Jan 29
6. Sato, H., Uzawa, N., Takahashi, K., Myo, K., Ohyama, Y., Amagasa, T. Prognostic utility of chromosomal instability detected by Fluorescence in situ hybridization in Fine-needle aspirates from oral squamous cell carcinoma. BMC cancer 2010 April accepted
7. Michikawa C, Uzawa N, Sato H, Ohyama Y, Okada N, Amagasa T. Epidermal growth factor receptor gene copy number aberration at the primary tumour is significantly associated with extracapsular spread in oral cancer. Br J Cancer. 2011 Mar 1;104(5):850-5. Epub 2011 Feb 8
8. Nakata Y, Uzawa N, Takahashi K, Sumino J, Michikawa C, Sato H, Sonoda I, Ohyama Y, Okada N, Amagasa T. EGFR gene copy number alteration is a better prognostic indicator than protein overexpression in oral tongue squamous cell carcinomas. Eur J Cancer. 2011 Oct;47(15):2364-72. Epub 2011 Aug 16.
9. Ohyama Y, Katafuchi M, Almehmadi A, Venkitapathi S, Jaha H, Ehrenman J, Morcos J, Aljamaan R, Mochida Y. Modulation of matrix mineralization by Vwc2-like protein and its novel splicing isoforms. Biochem Biophys Res Commun. 2012 Feb 3;418(1):12-6. Epub 2011 Dec 22.
10. Michikawa C, Uzawa N, Kayamori K, Sonoda I, Ohyama Y, Okada N, Yamaguchi A, Amagasa T. Clinical significance of lymphatic and blood vessel invasion in oral tongue squamous cell carcinomas. Oral Oncol. 2012 Apr;48(4):320-4. Epub 2011 Dec 16.

CASE REPORTS

1. Ohyama, Y., Hasegawa, K., Miyamoto, H., Nakakuki, K. Clinical study of the 16 cases of foreign bodies' insertion in the maxillary sinus. Japanese Journal of Oral and Maxillofacial Surgery 54（4）253～255　2008

MEMO

Global Small RNA Profiling During Osteoblast Differentiation

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MicroRNAs (miRNAs) negatively and post-transcriptionally regulate expression of multiple target genes to support anabolic pathways for bone formation. By global miRNA array analysis, we found miR-218 was induced during osteoblast differentiation. Furthermore, we demonstrated miR-218 promoted commitment and differentiation of bone marrow stromal cells by activating a positive Wnt signaling loop. In a feed forward mechanism, miR-218 stimulates the Wnt pathway by down regulating three Wnt signaling inhibitors: Sclerostin (SOST), Dickkopf2 (DKK2) and secreted frizzled-related protein2 (SFRP2). In turn, miR-218 expression is up regulated in response to stimulated Wnt signaling and functionally drives Wnt related transcription and osteoblast differentiation, thereby creating a positive feedback loop.

To further explore undiscovered miRNAs which take potential role during osteoblasts differentiation, we performed a systemic profiling of small RNAs in skeletal tissue. Deep sequencing technology has the ability to identify all known and unknown small RNAs including novel miRNA and other non-coding RNAs. Therefore we used a Deep sequencing approach to analyze expression of small RNAs during osteoblast differentiation. Primary calvarial osteoblasts were collected from neonatal mice and small RNA libraries were generated at three differentiation points of osteoblasts (i.preosteoblast, ii. osteoblast, iii. mature osteoblast). Deep sequence data of these libraries consisted of 64.9~65.2% of miRNA, 32.3~33% of other ncRNAs such as piwi RNA and 1.3~1.8% of unknown and previously unidentified small RNAs. Of the 1112 known miRNAs, 42 miRNAs were up regulated and 45 miRNAs were down regulated more than two fold during differentiation. To understand the function of miRNA expression dynamics in osteoblast differentiation, the top 100 Target genes of the 18 significantly up regulated miRNAs and 24 significantly down regulated miRNAs were identified. Gene ontology analysis revealed that these targeted genes were enriched in Bone development and Wnt signaling category. To find miRNAs which regulate osteoblast differentiation, we transfected some of most up regulated miRNAs and most down regulated miRNA, miR-1983 into MC3T3E1 osteoblasts. We found miR-142 up regulated and miR-1983 down regulated the expression of osteoblast marker genes. In addition, miR-142 down regulated the target gene, TGF β receptor Ⅰ. miR-1983 down regulated Wnt signaling targets, Tcf-1and Lef-1 mRNA level.

In summary, we performed global miRNA studies during osteoblast differentiation and revealed miRNAs that regulate osteoblast differentiation through modulation of Wnt and TGF β signaling.

CURRICULUM VITAE

Education

1994-1998 B.S., Mathematical Physics, Ritsumeikan University, Shiga, Japan

1998-2000 M.S., Department of Bioscience, Nara Institute of Science and Technology, Nara, Japan

2000-2004 Ph.D., Department of Molecular Pharmacology Tokyo Medical and Dental University, Tokyo, Japan
Advisor: Dr. Masaki Noda

Position

2004 to 2010 Research Associate, Department of Developmental Biology
Harvard School of Dental Medicine, Boston, MA
Supervisor: Dr. Beate Lanske Ph.D.

2010 to Present Postdoctoral Fellow, Department of Cell Biology
University of Massachusetts Medical School, Worcester, MA
Supervisor: Drs.Gary Stein, Janet Stein, Andre Van Wijnen, Jane Lian

2012 to Present Instructor, Department of Medicine
University of Massachusetts Medical School, Worcester, MA
Supervisor: Drs. Ellen Gravallese, Jane Lian

Award and Honors

2003 Super student award and research grant (21st Century COE Program, Tokyo Medical and Dental University)

2003 Travel Award (International Bone and Mineral Society (IBMS))

2006 Young Investigator Award (American Society for Bone and Mineral Research (ASBMR))

2006 Harold M. Frost Young Investigator Award (American Society for Bone and Mineral Research (ASBMR))

2006 Dean's Scholars Award (Harvard School of Dental Medicine)

2007 Dean's Scholars Award (Harvard School of Dental Medicine)

Publications

1. Noda M, Kashimada K, Takamoto M, Yumoto K, Maeda Y, Usui M, Ishijima M. The meaning of phosphate in bone formation Clin Calcium. (Japanese). 2001 Oct;11(10):1315- 20.
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Laser dentistry challenges in Bosnia and Herzegovina

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Institute of Dentistry（Zavodzastomatologiju）, Banja Luka, Bosnia and Herzegovina

During my PhD studies in Tokyo Medical and Dental University（TMDU）, I successfully completed research related to the effects of low-level Er:YAG laser irradiation on bone regeneration. Study showed promising results in enhanced MC3T3-E1 osteoblast proliferation following low-level Er:YAG laser irradiation with various combinations of laser settings（fluence 0.7– 17.2 J/cm^2）, mainly by activation of MAPK/ERK. Results suggested use of low-level Er:YAG laser as a successful treatment modality for enhancing bone regeneration in various fields of medicine and dentistry.

After completing PhD project, for which I was multiply awarded, I returned back to my home country-Bosnia and Herzegovina（B&H）, where I started to work at University of Banja Luka, as an assistant professor in the Department of Dentistry, Section of Periodontology and Oral Medicine.

The current situation in B&H, regarding the use of lasers in dentistry, is typical for a low-income country, where lasers are still not fully incorporated in everyday dentistry, mainly due to the high costs of laser devices. Therefore, legal requirements on safe use of lasers are nonexistent or insufficient. In B&H a single law is regulating all non-ionic radiation, including lasers, but without any attention given to the distinct characteristics of lasers. Further, neither national standards nor internationally available standards on safe use of lasers are in use. Ministry of Health and Social Welfare recognized a need to address the issue of current or future laser usage in B&H, prescribing standards on potential laser hazards, laser safety measures and ways to ensure and improve patient safety in laser dentistry. As an expert on laser dentistry in B&H, I was privileged to be invited by B&H certification and accreditation body to develop and adapt national standards on safe use of lasers in B&H, based on internationally accepted standards and containing requirements related to use of dental lasers and laser safety. It is expected that future to these standards will provide a basic of safety practices in laser dentistry, and consequently, improve patient safety in laser dentistry in B&H and contribute in improving dental health care quality.

Apart from participating in creating a legal base for safe use of lasers in B&H dentistry, I am working on several projects, mainly related to the effects of low-level laser therapy on mouth diseases and conditions, such as recurrent aphthous stomatitis（RAS）, Herpes simplex infections, xerostomia…

CURRICULUM VITAE

Education

1997-2004 DDS University of Banja Luka, Medical Faculty, Department of Dentistry

2005-2010 PhD Tokyo Medical and Dental University, Department of Hard Tissue Engineering, Section of Periodontology, Tokyo, Japan

Position

2008 – 2010 AISS research fellow, The Global Century Center of Excellence (GCOE) Program; "International Research Center for Molecular Science in Tooth and Bone Diseases", Tokyo Medical and Dental University, Tokyo, Japan

2010 – present Assistant Profesor at Section of Periodontology and Oral Medicine, Department of Dentistry, Medical Faculty, University of Banja Luka, Bosnia and Herzegovina.

2012 – present Specialist Trainee in Periodontology, Institute of Dentistry (Zavod za stomatologiju), Banja Luka, Bosnia and Herzegovina

Award and Honors

2004 University of Banja Luka, Medical Faculty, Department of Dentistry, Banja Luka, Bosnia and Herzegovina – Class of 2004 Best Student Award

2010 World Federation for Laser Dentistry (WFLD), Dubai, United Arab Emirates (UAE) – First Prize for Poster Presentation

2010 The Dr. Eugene M. Seidner Student Scholarship Recipient by American Academy of Laser Dentistry (ALD), Miami, USA – Second Prize Winner

2012 Developed Accreditation Standards for Dental Ambulances and Standards for Safe Use of Lasers in Dentistry for The Republic of Srpska Agency for Certification, Accreditation and Quality Improvement in Health Care, Bosnia and Herzegovina

2012 World Federation for Laser Dentistry's (WFLD) Country Representative for Bosnia and Herzegovina

Publications

1. Removal of melanin hyperpigmentation by Er:YAG laser using Chisel tip. Aoki, K. Mizutani, AA. Takasaki, S. Ishii, V. Aleksic, CY. Wang, Y. Izumi. Journal of Japanese Society for Laser Dentistry 2009;20(1):23. (in Japanese)
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7. Mehanizam dejstva nisko-energetske Er:YAG laserske iradijacije na proliferaciju osteoblasta. V. Pavlic. Scripta Medica 2010;41(2):97-99. (in Serbian)
8. Biologic effects of low-level Er:YAG laser. A. Aoki, V. Aleksic, I. Ishikawa, Y.Izumi. J Japan Soc Laser Surg Med. 2011;32: 64-70.
9. The effects of low-level laser therapy on xerostomia (mouth dryness). V. Pavlic. Med Pregl. 2012;65:247-50.
10. Patient Safety in Laser Dentistry in Republic of Srpska. V. Pavlic, V. Vujic-Aleksic. Vojnosanit Pregl. 2012 (in press)
11. Dental laser safety: A proposal for improving patient safety in Bosnia and Herzegovina. V. Pavlic, V. Vujic-Aleksic. J Clin Periodontol. 2012, 39 (Suppl); 13:306.
12. Low-level laser therapy in bone repair: a literature review. V. Pavlic, A. Aoki, V.Vujic-Aleksic, Y.Izumi. Med Oral Patol Oral Cir Bucal. 2012 (WFLD 2012)

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Molecular elucidation of pathophysiology of bone and cartilage disorders

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Chondrocyte differentiation is strictly regulated by various transcription factors including Runx2 and Runx3. However, the physiological role of Runx1 in chondrocyte differentiation remains to be elucidated. To address that, we generated chondrocyte-specific Runx1-deficient mice（α 1（II）Cre/Runx1flox mice）and mesenchymal cell-specific Runx1-deficient mice（Prx1Cre/Runx1flox mice），because Runx1-/- mice die early in utero. Furthermore, we crossed them with Runx2 mutant mice to obtain chondrocyte-specific or mesenchymal cell-specific Runx1/Runx2 double mutant mice（α 1（II）Cre/DKO mice and Prx1Cre/DKO mice, respectively）. α 1（II）Cre/Runx1flox and α 1（II）Cre/DKO mice were grossly normal. In contrast, Prx1Cre/Runx1flox mice displayed a delay in the calcification of the sternum, and Prx1Cre/DKO mice completely lacked the sternum. Histologically, in the prospective sternum of Prx1Cre/DKO mice, mesenchymal cell condensation developed normally; however, commitment to the chondrocytic lineage was seriously impaired. In line with that observation the expression of α 1（II）collagen, Sox5 and Sox6 in the prospective sternum of Prx1Cre/DKO mice was severely attenuated by in situ hybridization, while Sox9 expression was unchanged. Molecularly, transient transfection of Runx1 or Runx2 in mesenchymal cell increased endogenous Sox6 and Sox5 expression, which led to α 1（II）collagen induction. Thus, we demonstrated that Runx1 and Runx2 cooperatively regulate chondrocyte lineage commitment through the induction of Sox5 and Sox6.

Malignant fibrous histiocytoma（MFH），which has an aggressive biological behavior and a poor prognosis, is the most common type of soft tissue sarcoma in older adults. However, the molecular pathogenesis of MFH is largely unknown. It has been suggested that genetic abnormalities are implicated in the cause of MFH, namely, genetic alterations, including aberration of DNA copy number such as gene amplifications and deletions, may lead to activation of oncogenes and inactivation of tumor suppressor genes. To identify genomic alterations involved in MFH oncogenesis, we performed DNA copy number analysis of MFH cases by using CGH array. We observed high-level amplification at chromosome region 2q11, 2q24, 2q31, 2q36, 4q16, 8p11, 16q22, 17p13, 22q11, Xq25（ratio > 2）. In addition, we found homozygous deletion at chromosome 10q23, 13q13, 13q14, 17q13, which spanned known tumor suppressor genes including p53. These chromosome regions may harbor genes important for MFH oncogenesis and progression, and may be potentially useful for diagnostic purposes.

CURRICULUM VITAE

Education

2004 B.S. Tokyo Gakugei University
2006 M.S.（Medical Science）, Tokyo Medical and Dental University
2010 Ph.D.（Medical Science）, Tokyo Medical and Dental University

Position

April 2009 to July 2010
Research Fellow of the Japan Society for the Promotion of Science
Tokyo Medical and Dental University
July 2010 to present
Research Assistant Professor
Department of Molecular Bone and Cartilage Pathology,
Hard Tissue Genome Research Center,
Tokyo Medical and Dental University

Publications

1. Sato S, Hanada R, Kimura A, Abe T, Matsumoto T, Iwasaki M, et al. Central control of bone remodeling by neuromedin U. Nat Med. 2007;13(10):1234-40.
2. Sato S, Kimura A, Ozdemir J, Asou Y, Miyazaki M, Jinno T, et al. The distinct role of the Runx proteins in chondrocyte differentiation and intervertebral disc degeneration: findings in murine models and in human disease. Arthritis Rheum. 2008;58(9):2764-75.
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4. Suzuki D, Yamada A, Amano T, Yasuhara R, Kimura A, Sakahara M, et al. Essential mesenchymal role of small GTPase Rac1 in interdigital programmed cell death during limb development. Dev Biol. 2009;335(2):396-406.
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Proteomics for Alzheimer Disease for Biomarkers Discovery

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Alzheimer's disease (AD) is the most common type of dementia that affects around 24.3 million people worldwide, with rapid demographic growth in elderly population an is expected to increase in developing countries. AD has become one of the most severe progressive social, economical and medical burden in many countries all over the world. AD brains are characterized by the presence of extracellular deposits of amyloid- β (A β) containing plaques and intracellular neurofibrillary tangles (NFTs) composed by paired helical filaments of hyperphosphorylated Tau protein. AD, seems to be the result of a series of complex events involving both genetic and environmental factors; among the main factors are, the oxidative stress and the mitochondrial damage. Initial changes in brain might occur decades prior to the onset of clinical symptoms. One approach for early diagnosis might be the discovery of biomarkers present in initial stages of the disease and follow up by the disorder's progression as well as the identification of targets for developing new drugs. The main goal is, to identify related proteins in the evolution of AD, using target proteins with iTRAQ and analyze them through mass spectrometry. Our results showed the identification of over 604 proteins and we have found that some protein expression were up-regulated and down-regulated, compared to those found in normal brain. Previous reports have shown the participation of that GAPDH protein could be used as a biomarker for early diagnose, and is specific for AD. Moreover, we have identified other proteins related in mitochondrial damage and stress, proteins like transferring and Heat Shock Proteins. In conclusion, we intent to offer a broad approach about the expression of many different proteins in AD's brains and in normal (brain) ones, this would allow to have some specific biomarkers for early diagnose of AD.

CURRICULUM VITAE

Education

D.D.S. (September 1995-September 2000) Faculty of Dentistry, Centro Cultural "Justo Sierra", Mexico City, Mexico.

Ph.D. (April 2004-March 2008) in Periodontology & Hard Tissue Engineering, Graduate School of Medical & Dental Sciences, Tokyo Medical & Dental University, Tokyo, Japan.

Position

1. Research Student (April 2003-March 2004) Department of Periodontology & Hard Tissue Engineering, Graduate School of Medical & Dental Sciences, Tokyo Medical & Dental University, Tokyo, Japan.
2. Advanced Super Student (April 2004-March 2008) Global Center of Excellence (GCOE) Program, International Research Center for Molecular Science in Tooth and Bone Disease at Tokyo Medical and Dental University, Tokyo, Japan.
3. Research fellow (April 2004- March 2008) The Institute of Advanced Biomedical Engineering and Science (IABMES) at Tokyo Women´s Medical University, Tokyo, Japan.
4. Research Fellow (November 2008-) Center for Research and Advanced Studies (CINVESTAV), Department of Cell Biology, Mexico City, Mexico.

Award and Honors

1. "ad hoc" reviewer for the Journal Tissue and Cell, Elsevier.
2. Advanced Super Student (April 2004-March 2008) Global Center of Excellence (GCOE) Program, International Research Center for Molecular Science in Tooth and Bone Disease at Tokyo Medical and Dental University, Tokyo, Japan
3. Member of the "Sistema Nacional de Investigadores en México (SNI)" México 2011- (National System of Researchers in Mexico).

Publications

1. Mara Gomez Flores, Masateru Hasegawa, Masayuki Yamato, Ryo Takagi, Teruo Okano and Isao Ishikawa. Cementum-Periodontal Ligament Complex Regeneration using the Cell Sheet Technique, Journal of Periodontal Research, 2008 Jun;43 (3) :364-71
2. Mara Gomez Flores, Reiko Yashiro, Kaoru Washio, Masayuki Yamato, Teruo Okano and Isao Ishikawa. Periodontal ligament cell sheet promotes periodontal regeneration in athymic rats, Journal of clinical Periodontology, 2008 Dec; 35 (12) : 1066-72
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4. Benito Minjarez, Mara Gomez-Flores, Sanchez del Pino MM, Jose Luna-Muñoz, Jorge Sosa-Melgarejo, Raul Mena and Juan Pedro Luna-Arias. Quantitative proteomics for identification of novel targets Alzhimer's disease by iTRAQ. In revision.
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