

SYMPOSIUM ON EDUCATION AND SCIENCE

Plenary Lecture

Strategic Internationalization of Hiroshima University

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I am happy to congratulate Faculty of Dentistry in Hiroshima University on the occasion of its 40th anniversary. I am very honored to be here to give a talk on the strategy in the internationalization of Hiroshima University.

It is well recognized that university reforms are now going on almost everywhere in the world. This phenomenon is an outcome of the globalization of higher education and the world-wide competitive society which emerged after the end of the cold world war period. Now that competitiveness in higher education is growing rapidly at an international level, it is important for us, Hiroshima University, to present clearly our internationalization strategy. With regard to the internationalization strategy, it is necessary to show what is our fundamental policy, what are priority items to be carried out and how we organize our system for the internationalization of Hiroshima University.

SYMPOSIUM ON EDUCATION

Special Lecture 2

To Consider e-Learning in Dental and Medical Education in Japan

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All of Japanese medical and dental schools have constructed information-technology network systems. But only about 10% of medical, dental, pharmaceutical, and health professional schools are using e-learning, and 60 % are negative for planning to introduce e-learning systems. The IT or e-learning systems in medical and dental education in Japan are seen in the on line self-learning media for dissection for gross anatomy and media for simulated training systems for clinical diagnosis, treatments, and skills and the on line problem-based learning systems constructed through the electronic health records in the university hospital to approach data of the clinical examinations and clinical images such as X-ray and MRI images. And this paper introduce the author's experience to build up an atlas of histology, explanation movies for histology practice using images collected for broad casting TV programs for lifelong-learning of citizen of public, and e-learning constructed by students in a subject to study medical research techniques.

New Era of Education in Dentistry

Towards the Education of "Universal Dentist" in the Age of Globalization

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The Japanese Model Core Curriculum (JMCC) and the Profile and Competences for the European Dentist (PCED) had apparently different goals and objectives; however, they share a characteristic of defining core educational objectives all dental graduates have to fulfill. The purpose of this study was to compare mainly the contents and the expected level of achievement

without getting hung up too much on details. JMCC tended to focus on the cognition level of students, which could be explained by the fact that questions in the Computer-Based Testing (CBT) in Common Achievement Test (CAT) were prepared based on the specific behavioural objectives (SBOs) in JMCC. PCED was characterized by competences covering a wide range of knowledge base and those concerning students' attainment on the behavioral level. There were also some competences of importance which were not enunciated in JMCC. The results of this study were expected to offer useful information for the future revision of JMCC.

Development of Dental Curriculum Guidance in the United Kingdom

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This paper describes the process by which the United Kingdom General Dental Council developed the second edition of curriculum guidance for undergraduate Dental degree programmes entitled "The First Five Years, a frame work for Dental Education". It explores the national and international drivers for change and how these influenced the the content of the document. The key change is the organization into three domains: (i) What the Dentist is able to do (ii) How the Dentist approaches Practice (iii) The Dentist as a Professional. There was increased emphasis on IT skills, law, ethics and professionalism, integration with the education of other members of the dental team, health and safety issues, outreach teaching, the need for continuing professional development, pain and anxiety control. It looks ahead to the challenges posed by further international developments, in particular the Bologna declaration.

Dental Education and Research Priorities in Kazakhstan

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Dental school programs in Kazakhstan are five years long, but from next year 1year internship will be included and the programs will be 6 years long. All medical academies will have own medical centers by governmental financial support. The Ministry of Health of Kazakhstan and Dental School of the Semipalatinsk State Medical Academy established some research priorities for the period 2002 to 2007: 1. Congenital Oral and Craniofacial Diseases in the area adjacent to the Semipalatinsk Nuclear Test Site (SNTS). 2. Some clinical features of Dental, Oral and Craniofacial Disorders in the Semipalatinsk Region of Kazakhstan. 3. Clinical Approaches to the Diagnosis, Treatment and Prevention of Dental, Oral and Craniofacial Disorders. Our experts together with specialists from Hiroshima University have done some joint research projects in the area adjacent to SNTS. Screening study suggested that the inhabitants in exposed villages might be considered as a population at risk for high frequency of cleft palate and tooth loss and also suggests more detailed research of dental disorders. Exposed inhabitants are really needed a specially designed rehabilitation program. We trust that our research and clinical collaboration with the Dental School of Hiroshima University will be deeper and more fruitful at the nearest future.

Internationalization Strategies of Taipei Medical University

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This report is composed of three parts: (1) Introduction to Taipei Medical University, (2) Internationalization strategies of Taipei Medical University, (3) Plans and strategies of internationalization in the following three years. The first part introduces every division (including academic and administration division) of Taipei Medical University. In which, five

colleges (college of medicine, college of oral medicine, college of pharmacy, college of nursing and college of public health and nutrition) are particularly described. The second part contains not only internationalization strategies and goals of our university but also outcomes of these strategies. About internationalization strategies, we focus on learning English and promoting the communication of international academic. We hope to contact and communicate with whole world hereby. Our effort is worth, now, we have contracted sixteen sister schools in America, Europe and Asia. Besides from 1999, the students of TMU began to have short-term internships abroad, the same year, TMU started to have foreign students' short-term internships in our hospitals. The last part is extension of the second part. How to stride forward to internationalization? The complete plan is necessary. In the next three years, we hope that all the students, teachers and staff have opportunities to take part in international affairs, cultivate world view and be a person with foresight.

Curriculum Integration for Dental Education; A Lesson Learned from Real Experiences of Development and Implementation

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This paper presents a dental school's experience of curriculum development and the process of implementation. It includes the things that can be expected to happen or that may go beyond expectations in the development of new curriculum for the College of Dentistry (School of Dentistry), Seoul National University

In 2002, the Ministry of Education and Human Resources Development of Korea announced introduction of new school system in which provides medical and dental education after bachelor's degree. This "Professional Graduate School" system is one of the greatest challenges for Korean dental education. Now Korean dental schools chose two different dental education systems from 2005, the six year dental college system and the four year professional dental graduate school system. College of Dentistry, Seoul National University chose the new system. The school also changed curriculum. The change of dental education system is one, but not all of the reason for the curricular reform. Through the sophisticated process of problem identification and needs assessments, we chose the integrated curriculum. A careful planning and organization process were applied. The whole process of curriculum development took ten month. The evaluation is still going on. Even the curriculum intended to apply the solid principles and aims towards sound objectives; the curriculum evaluation in the present is not very encouraging. It casts lots of pending questions. Promising part of the new curriculum has the flexibility and readiness to change of environment.

Airlangga University Dental Education System: Present and Future Plan

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Airlangga University Dental Education started in 51 years ago on November 10th 1954. Since then many changes have been made until now for a better educational system. The future vision of Airlangga University Faculty of Dentistry is to be the best institution and independent in national, regional and international areas in dentistry science and technology fulfilling the community needs. Its missions are to educate and teach dentistry with basic medical and dentistry sciences in order to increase the level of community health services in general and the stomatognathic function in particular. The future missions are to do the diagnostic preventative research with predictive medicine approach, and to provide better community health services. The faculty of dentistry has four dental education degrees, which are Doctor Dental Surgeon (DDS), dental laboratory technician, Master of Science (MS), and dental specialist (e.g. pediatric

dentist, oral surgeon etc). Dental education for the DDS degree takes 5 years (10 semesters) with a total of 177 semester credit points. Now the curriculum of dental education is changing step by step to a competence based curriculum. The education and research collaboration with other faculties of dentistry is being conducted including with Hiroshima University.

Dental Hygienist Education in the New Era

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The task of dental hygienists, whose main role in the past was to assist a dentist in treating a patient in a dental clinic, have shifted from therapeutic to preventive ones; furthermore, dental hygienists have come to play a central role in the management of dental care of patients. Under such circumstances, it has become urgently necessary to set up educational and research institution in the field of welfare and nursing care. Thus, four-year faculties which educate future generations of dental hygienists have been set up at Niigata University in fiscal 2004. The new undertaking at the Niigata University Faculty of Dentistry have just begun. The teaching staff and the students are working together to formulate an ideal image of the medical care professional befitting the new age, an image which can withstand future evaluation.

Innovation of Dental Education System for Researcher, Dentist, Dental Hygienist and Dental Technician in Hiroshima University

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Hiroshima University Faculty of Dentistry's goal is to become the worldwide research and education center in Dentistry. It seems to constitute the dental education by two missions: core and characteristic. Hiroshima University Faculty of Dentistry has clarified their characteristic mission and improved dental education system to reinforce the innovative part of the education. We started two programs to cultivate researchers/educators who will be a world-wide leader of dental research and education in addition to excellent dental practitioners, the frontier dental science course and the advanced dental clinician course in 2000. The students who completed new education system gave good score to the frontier dental science. The basic clinical knowledge level of students is the same between two courses before starting clinical training. Hiroshima University Faculty of Dentistry had School for Dental Hygienists and Dental Technicians School. These two schools are integrated and reorganized to the School of Oral Health Science in 2005. Hiroshima University firstly established the School of Oral Health Science with four-year programs for dental hygienists and dental technicians in Japan. The liberal arts education is reinforced in both four-year programs. The purpose of our four-year program in oral health science is to cultivate educators in dental hygienists school, researchers in Universities, and nursing teachers who work sickbay of elementary or junior high school. The purpose of our four-year program in oral health engineering is to cultivate educators in dental technicians school and researchers in Universities or dental materials/products companies in addition to excellent dental technicians.

SYMPOSIUM ON SCIENCE

Special Lecture 1

Phosphate Regulates Expression of SIBLINGs and MMPs in Cementoblasts

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Introduction: Cementoblasts, the cells responsible for tooth root cementum formation, are especially sensitive to local phosphate and pyrophosphate during development, as evidenced by cementum phenotypes resulting from altered phosphate/pyrophosphate distribution. SIBLING family members BSP, OPN, and DMP-1 are regulated by phosphate in cementoblasts and have been shown to activate three specific matrix metalloproteinase (MMP) partners: MMP2, MMP3, and MMP9, respectively, *in vitro*. The aim of this study was to examine regulatory effects of phosphate on SIBLING and MMP expression in cementoblasts, *in vitro*.

Materials & Methods: Immortalized murine cementoblasts were treated with inorganic phosphate, *in vitro*, and effects on gene expression (by real time RT-PCR and mouse total genome microarray) were observed. Dose-response (0.1-10 mM phosphate) and time-course (1-48 hr) assays were performed. A sodium-phosphate uptake inhibitor, foscarnet, was used to better define phosphate-mediated effects on cells.

Results: Three SIBLING family members were regulated by phosphate: OPN (increased over 300% of control), DMP-1 (increased over 3,000% of control), and BSP (decreased). MMP3 was dramatically increased (4,000% of control), paralleling regulation of its partner OPN. Both MMP2 and MMP9 were slightly down-regulated. Time-course experiments indicated a response for SIBLING and MMP genes within 24 hr. Use of foscarnet demonstrated that phosphate uptake was required for observed changes in gene expression.

Discussion: These results indicate an effect of phosphate on cementoblast SIBLING and MMP expression *in vitro*. During cementum formation, phosphate may be an important regulator of cementoblast activity, including modulation of biomineralization, attachment, and matrix modification.

Special Lecture 3

Regulation of Hematopoietic Stem Cell and Its Interaction with Stem Cell Niche

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Hematopoietic stem cells (HSCs) are responsible for Blood cell production throughout the lifetime of individuals. Interaction of HSCs with their particular microenvironments, known as stem cell niches, is critical for maintaining the stem cell properties, including self-renewal capacity and the ability of differentiation into single or multiple lineages. In the niche, the niche cells produce signaling molecules, extracellular matrix, and cell adhesion molecules, and regulate stem cell fates. Recently, long-term bone marrow (BM) repopulating (LTR) HSCs exist frequently in BM trabecular bone surface, and it was clarified that an osteoblast (OB) is a critical component for sustainment of HSCs. HSCs balance quiescence and cell division in the osteoblastic niche and also maintain the potential for long-term hematopoiesis. Especially, the quiescent state in the cell cycle is thought to be indispensable for the maintenance of hematopoietic stem cells (HSCs). We demonstrate that c-Kit⁺Sca-1⁺Lineage⁻ (KSL) HSCs expressing the receptor tyrosine kinase Tie2 are quiescent and anti-apoptotic, transplantable and comprise a side-population (SP) of HSCs, which contact closely to Angiopoietin-1 (Ang-1), a ligand for Tie2, expressing osteoblasts in the BM niche. Tie2 and Ang-1 are part of a key signaling interaction between HSC and osteoblasts. Tie2 and Ang-1 are expressed in a complementary pattern, and interaction of Tie2 and Ang-1 induced integrin dependent cell adhesion of HSCs to osteoblasts and extracellular matrix. This signaling pathway regulates functional criteria of HSC in the BM niche, including quiescence, anti-cell death and tight adhesion. These observations led us to a novel model in which Ang-1 produced by osteoblasts

activates Tie2 on the HSCs and promote tight adhesion of HSCs to the niche, resulting in quiescence and enhanced survival of HSCs.

Session 1 Immunology and Microbiology in Mucosal Diseases

Secretory IgA Immune Responses as the Mucosal Frontline

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The recognition that host defenses are mediated via mucosal barriers dates back several thousand years. Ingestion of *Rhus* leaves to modify the severity of reactions to poison ivy is a centuries old practice among native North Americans. A similar practice has been carried out among Asian countries as well, where lacquer craftsmen desensitized themselves via the ingestion of sumac extracts. The modern concept of local immunity, however, developed by Besredka in the early 1900s, followed by the discovery of IgA in 1953, and its isolation and characterization in 1959. Studies in the early 1960s demonstrated the presence of IgA in a unique form in milk and, shortly thereafter, in other external secretions. These studies were followed by the discovery of the secretory component and the identification of the J chain. The remarkable immunological observations were soon complemented by the identification and characterization of the gut-associated lymphoid tissue (GALT), the findings of mucosal circulation of antigen-sensitized or reactive IgA committed B cells from GALT to other mucosal surfaces such as aero-digestive tract, genital tract and glandular tissues (e.g., salivary, lacrimal and mammary glands, and the definition of immunologically unique mucosal T cells. It should be emphasized that studies of the induction of salivary IgA responses to cariogenic bacterium, *Streptococcus mutans*, have made tremendous contribution to the characterization and understanding of the immunity at mucosal surfaces. A series of immunologically important investigations in the field of caries immunity definitively played a leadership role for the establishment of principal for the mucosal immune system. In the past decades, our concept of the mucosal immune system has been expanded to include M cells, mucosal dendritic cells and macrophages, Th1/Th2 cells, regulatory T cells and other effector cell networks, and the mucosal cytokines. Finally, the biological significance of the mucosal immune system increasingly is being realized and appreciated in the context of human infections acquired via mucosal portals of entry, including classical infectious diseases as well as newly emerging infectious diseases which lead to the desire for the development of mucosal vaccine.

Antimicrobial Peptides in Human Gingival Keratinocytes

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The innate immune system is the primary defense against bacterial infection. Epithelial cells are first defense system as not only physical barrier, but also production of several factors including antimicrobial peptides. Antimicrobial peptides produced by human are recently drawn attention due to the relevance to some diseases and also new chemotherapeutic agents. Tooth decay and periodontal disease are infectious disease caused by oral bacteria. We focused on two major antimicrobial peptides, human β -defensins (hBD) and LL37 in human gingival keratinocytes (HGK) to see the interaction of these peptides with periodontopathogenic bacteria. HGK constitutively expressed hBD1, while they inducibly expressed hBD2, hBD3 and CAP18 upon contact with periodontopathogenic bacteria. The level of their expression varied

according to clinical isolates. Synthetic antimicrobial peptides of hBD1-3 and LL37 were evaluated for their antimicrobial activity to periodontopathogenic bacteria including *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia* and *Fusobacterium nucleatum*. We found these four peptides had bactericidal activity against all bacteria tested, although the degree of antibacterial activity was variable among strains and species. The antibacterial activity of hBD1 was less effective than those of other peptides. These results suggest that HGK produce several antimicrobial peptides in response to oral bacteria, although the induction ability and susceptibility to these peptides are different among species and strains.

War and Peace at Mucosal Immune System

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That a highly integrated and finely regulated mucosal immune system exists alongside and separate from the peripheral system might at first seem redundant and puzzling. Why should such a separated and sophisticated system be necessary when the peripheral immune system already seems to ensure immunity for the host? There can be no doubt about the sophistication and elegance of the mucosal immune system. It presents a well-tuned, two part defense, one more structured and localized, one more diffuse (McGhee and Kiyono, 1999). In the first, foreign antigens are encountered and selectively taken up into highly structured sites for the initiation of immune responses. In the second, diffuse collections of effector cells, such as B- and T lymphocytes, differentiated plasma cells, macrophages, dendritic cells, as well as eosinophils, basophils, and especially mast cells. Together, the two either produce mucosal and serum antibody responses and T cell-mediated immunity (CMI) or systemic energy, commonly termed mucosally induced tolerance. Such a separate and sophisticated system may well have evolved as a major defense mechanism against mucosally encountered infectious agents. In the human adult, the mucosal surface is enormous (e.g., the gastrointestinal tract alone is larger than 300 m²) and so requires a significant expenditure of lymphoid cells and effector molecules for immunity. This review paper will highlight the multiple roles for lymphoreticular cells and effector molecules, including IgA, mucosal vaccine, tolerance, and inflammation.

Session 2 Mechanisms and Assessment of Oral Functions and Sensation

Biomechanical and Clinical Assessment for Jaw Movement and the Related TMJ Loading in Patients with Temporomandibular Joint Disorders

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Temporomandibular joint disorders (TMD) have been demonstrated to be a multifactorial in nature. Possible explanations for the causes have been documented in the literature indicating excessive loading during jaw movement and the subsequent biomechanical imbalance in the TMJ may be assumed as an initial factor for a series of degenerative changes, resulting in condylar resorption and deformity. Therefore, an evaluation of the biomechanical environment in the TMJ would lead to a better understanding of the inducing mechanism of TMJ pain and disability, which result in proper diagnosis and available treatment planning for TMD. Recently, we developed an individual three-dimensional modeling system for the TMJ components based on the magnetic resonance (MR) image and the subsequent analysis of the TMJ loading during jaw movement. The present study was thus designed to introduce biomechanical and clinical assessment of jaw movement and the subsequent joint loading in patients with TMD.

Furthermore, we would like to show a case of TMD patient treated with orthodontic approach to introduce an example of the assessment with this system.

Taste Representations in the Mouse Brain Revealed by Genetic Tracing

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Taste perception in mammals is mediated by the specialized epithelial cells (taste receptor cells), which are arranged in taste buds in the oral space. To address the question as to how taste information is processed in the central nervous system, we applied a genetic approach to transsynaptically delineate the neuronal circuitries of bitter and sweet taste by selectively expressing the transsynaptic tracer, tWGA-DsRed, in either bitter- or sweet/umami-responsive taste receptor cells in mice, and by visualizing the spatial distribution of tWGA-DsRed in the brain. By mapping connections formed by small subsets of neurons, which process and integrate the information of bitter taste, separated from sweet taste, this genetic approach may be valuable for investigating the molecular aspects underlying the construction and refinement of taste neuronal circuitries to mediate taste discrimination, contrastive behavioral responses, emotional states and taste-associated learning.

Mechanisms of Pain Sensitization and the Treatment

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Hyperalgesia and allodynia, major symptoms of neuropathic pain can results after nerve injury or chronic inflammation. Trigeminal neuropathic pain resulting from alterations in peripheral and central noxious transmission systems often produced after nerve injury by pulpectomy or tooth-extraction or from temporomandibular joint inflammation. Neuropathic also occurs in some disease state, diabetic peripheral neuropathy, post-herpetic neuropathy and trigeminal neuralgia. Allodynia is characterized by long lasting pain evoked by essentially non-painful stimuli such as just light touch and tolerance to medication with conventional analgesics.

Neuropathic pain is probably not a result of a single pathological mechanism, but the final product of an altered peripheral and central processing. Recent advances in pain research revealed that many factors derived from neurons and also non-neuronal neighboring residents participate in the initiation, development and maintenance. Among them, lipid mediators such as prostaglandins, lysophosphatidic acid and platelet-activating factor are recently found to play conspicuous roles for development of allodynia and hyperalgesia in spinal cord. Further advance by using cellular biological and molecular techniques would dig into the mechanisms underlying neuropathic pain and illustrate the new strategy and target candidate for drug development.

There are also needs for tools and methods to assess neuropathic pain, common guidelines on classification, diagnosis and management, and evidence-based approach to the treatment of neuropathic pain.

Session 3 Signaling Molecules in Development and Cancer

In Vitro Organogenesis using Amphibian Pluripotent Cells

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In the embryonic development of vertebrate, sequential cleavage is followed by the gastrulation as the first dynamic event of morphogenesis. Mesodermal induction is the most important event for normal body patterning such as the gastrulation, neural induction and formation of various organs. In the study to search for the mesodermal inducing factor, we reported “activin” as a strong mesoderm-inducible factor by the “animal cap assay”, the in vitro assay system using amphibian pluripotential cell mass. We found that activin has mesodermal and endodermal inducing activity in dose-dependent manner, and then established the in vitro induction system for various types of tissues and organs including craniofacial cartilage from animal cap cells by the treatments with activin and other inducing factors. Embryonic transplantation method showed that the treatments of animal cap cells for the induction of pronephros, beating heart were able to induce normally functional organs in vivo. These in vitro induction methods are useful for investigation of the molecular mechanisms of organ formation and body patterning in vertebrate development.

Genetic Alterations of Wnt Signal Components in Cancer Cells

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The genetics of development and cancer have converged in the identification of intra- and extra-cellular signaling pathways that are aberrantly regulated in cancer and are also central to embryonic patterning. The Wnt signaling pathway has provided an outstanding example of this. The genes for β -catenin, APC, and Axin in the Wnt signaling pathway are often mutated in human cancers. In all such cases, the common denominator is the accumulation of cytosolic and nuclear β -catenin and the activation of transcriptional factor Tcf/Lef. The resulting gene expression profile should provide a significant clue as to cancers carrying defects in the Wnt signaling pathway. In this review, the regulation of the β -catenin stability by Axin and APC, and their genetic alterations in human cancers are described.

Developmental Signaling Disorders in Craniofacial Anomalies and Cancer

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It has been suggested that various gene disorders elicit anomalies and cancers. In this paper, involvement of mutation of Sonic Hedgehog (SHH), Patched (PTCH), Tie-2 and FGFR3b in craniofacial anomalies and oral cancers is described. The main points are as follows.

- (1) A patient with median cleft lip/madibular has a novel SHH missense mutation.
- (2) PTCH mutation is observed in nevoid basal cell carcinoma/Gorlin Syndrome. Furthermore, The PTCH mutation is also observed in squamous cell carcinoma (SCC) cells, and the loss of PTCH function plays a major role in the acquisition of oncogenic potential in these SCCs.
- (3) The mutation of Tie2 (G833DTie2) is found in human intramuscular haemangiomas of the capillary type. There are significant characteristics of the G883D mutation with respect to transforming activity and VEGF expression.
- (4) Keratinocyte growth factor receptor/FGFR2b induces differentiation and apoptosis in human salivary adenocarcinoma cells, which inhibits the growth of them. The mutation of FGFR3b may be involved in the progression of oral squamous cell carcinomas.

Session 4 Growth Factors and Scaffolds for Tissue Regeneration

Development of Periodontal Tissue Regeneration Therapy with New Bioactive Agents

-Studies on Brain-derived Neurotrophic Factor and Ameloblastin Peptide-

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To develop the periodontal regeneration therapy using bioactive agents, effects of two potential agents, brain-derived neurotrophic factor (BDNF) and a synthetic peptide of ameloblastin on growth and differentiation of periodontal ligament cells in vitro and tissue healing in vivo. Both agents enhanced proliferation and mineralization of the periodontal ligament cells and induced periodontal tissue regeneration. We showed that BDNF and the ameloblastin peptide could be used as the promising medication to promote periodontal tissue regeneration.

Gene Therapy for Periodontal Bioengineering

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Although significant advancements have been achieved in periodontal therapy over the last decade, predictable regeneration of the tooth-supporting tissues is a challenge in periodontology and oral implantology. Recently, gene therapy, a new therapeutic approach for genetic and acquired diseases, has been applied for tissue bioengineering in multiple clinical situations, including the craniofacial complex, among them defects resulting from periodontal disease. The use of gene therapy vectors has enhanced the bioavailability and targeting of multiple growth and host immune factors to repair alveolar bone defects. Early pre-clinical studies utilizing both *ex vivo* and *in vivo* gene transfer strategies demonstrate the feasibility of using gene therapy for periodontal tissue engineering. This review highlights the current progress made in the field of periodontal regenerative medicine via gene targeting approaches.

Present Status of Biomaterial-based Regenerative Medical Therapy

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Recent research development of biomedical engineering including biomaterials and drug delivery system (DDS) as well as basic biology and medicine of cells relevant to regenerative phenomena has enabled cells to induce regeneration repairing of defective or injured tissues as well as substitute the biological functions of damaged organs. For successful tissue regeneration, it is undoubtedly indispensable to give cells a local environment where cells can efficiently proliferate and differentiate to result in induction of tissue regeneration. Tissue engineering is one of the biomedical technologies and methodologies to create this regeneration environment and consequently cure diseases based on the cell-induced regeneration potential of patients themselves. The regeneration repairing of tissues and organs has been realized by making use of biomaterials and DDS technology or methodology in a surgical or internally medical manner.

Cell scaffolding and the controlled release system of growth factor and genes are prepared from biomaterials and given to accelerate the proliferation and differentiation of key cells for induction of tissue regeneration. This paper overviews the present status of biomaterial-based regenerative medical therapy by introducing concrete examples of tissue regeneration with cell scaffolding and DDS.

Session 5 Bone Biology and Cell Therapy

Skeletal Development Through the Regulation of Chondrocyte and Osteoblast Differentiation by Runx2

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Runx2 is a transcription factor that belongs to Runx family (Runx1, Runx2, and Runx3). Runx2 interacts with many other transcription factors and co-regulators in the transcriptional regulation of its target genes. Cbfb is one of the co-regulators, forms heterodimers with Runx2, and is required for Runx2-dependent transcriptional regulation. Runx2 is essential for the commitment of multipotent mesenchymal cells into the osteoblastic lineage, because Runx2-deficient mice show complete lack of bone formation due to the absence of osteoblasts. Further, Runx2 inhibits adipocyte differentiation, because Runx2-deficient calvarial cells spontaneously differentiate into adipocytes. Overexpression of Runx2 in osteoblasts inhibits osteoblast maturation but decreased the expression of major bone matrix protein genes. Therefore, Runx2 triggers the gene expression of bone matrix proteins, while keeping the osteoblastic cells in an immature stage. Moreover, Runx2 strongly inhibits the transition of osteoblasts into osteocytes. Runx2 and Runx3 double knockout mice showed that Runx2 and Runx3 have redundant functions in chondrocytes, and that they are essential for chondrocyte maturation. Runx2 directly induces Ihh expression and coordinates the proliferation and differentiation of chondrocytes. Therefore, Runx2 regulates bone formation by regulating osteoblast differentiation as well as chondrocyte maturation.

Transcriptional Regulation of Osteoblast Differentiation and Function

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Osterix (Osx) is a zinc finger containing transcription factor that is highly specific to osteoblasts *in vivo*. To uncover physiological roles of Osx during mouse development, the Osx gene is disrupted by homologous recombination in ES cells. Osx-null mutants show a complete lack of bone formation, indicating that Osx is necessary for osteoblast differentiation and bone formation. Runx2/Cbfa1, the other crucial factor for bone formation is expressed in Osx-null mutants, whereas Osx is not expressed in Runx2/Cbfa1-null mutants, indicating that Osx acts downstream to Runx2/Cbfa1. In Osx-null mutants, Runx2/Cbfa1 expressing cells express typical chondrocyte molecular markers, suggesting that chondrocytes and osteoblasts derive from common progenitor cells. In this paper, recent progress on identification of common progenitors of chondrocytes and osteoblasts during mouse embryogenesis, and on further analysis of a role of Osx in postnatal bone metabolism will be discussed.

Application of Mesenchymal Stem Cells (MSC) to Regenerative Dentistry and Identification of Molecular Markers for MSC

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We characterized human bone marrow-derived mesenchymal stem cells (MSC) by identification of molecular markers and used these markers in clinical studies for treatment of periodontal disease: Auto-transplantation of MSC into periodontal defects enhanced regeneration of cementum, periodontal ligament and alveolar bone. Stem cell therapy could be a new frontier in dentistry.

Basic and Clinical Studies of Periodontal Tissue Regeneration by Transplantation of Own Bone Marrow Mesenchymal Stem Cells

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Use of suitable cells seeded into periodontal defects would be a powerful strategy to promote regeneration of periodontal tissue. Recent interest has focused on mesenchymal stem cells (MSCs) isolated from bone marrow, which have the potential for multilineage differentiation. Transplantation of bone marrow-derived MSCs into periodontal osseous defects would be a useful option for periodontal tissue regeneration. We have been investigating a possibility of MSCs therapy for periodontal diseases.

Our animal studies indicated that transplanted MSCs into experimentally periodontal defects survive and differentiate into appropriate periodontal cells, resulting in enhancement of periodontal tissue regeneration. Based on these scientific evidences, clinical experience entitled “periodontal tissue regeneration by transplantation of own bone marrow MSCs” has been started. Human bone marrow cells are obtained from the iliac crest and expanded in vitro at Cell and Tissue Engineering Center in Hiroshima University Hospital. MSCs are, then, isolated and mixed with Atelocollagen at final concentration of 2×10^7 cells/ml. These MSCs in Atelocollagen are transplanted into periodontal osseous defects at the periodontal surgery. This review article summarizes our animal studies and initial clinical experience of periodontal tissue regeneration by transplantation of own bone marrow MSCs.

Tissue-engineering of Orthopaedic Surgery

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Articular cartilage has a poor healing capacity due to its lack of vessels, nerve supply, and isolation from systemic regulation. Numerous methods have been attempted to enhance the repair of full-thickness articular cartilage defects, including abrasion arthroplasty; microfracture;

transplantation of chondrocytes, perichondrium, and periosteum; and osteochondral graft. However, no known treatment has regenerated long-lasting hyaline cartilage.

Recently, a regenerative medicine using a tissue-engineering technique for cartilage repair has been given much attention in the orthopaedic field. In 1994, Brittberg et al introduced a new cell technology in which chondrocytes expanded in monolayer culture were transplanted into the cartilage defect of the knee. As a second generation of chondrocyte transplantation, since 1996 we have been performing transplantation of tissue-engineered cartilage made ex vivo for the treatment of osteochondral defects of the joints. This signifies a concept shift from cell transplantation to tissue transplantation made ex vivo using tissue-engineering technique.

Recent Advances in Tissue Engineering of Cartilage, Bone and Tendon

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Tissue engineering employs seed cells and biodegradable materials to generate various tissues in vivo or in vitro. Since the initiation of tissue engineering in 1980's, the development of tissue engineering research might be artificially divided into three stages. In the first stage, many studies focused on proving the concept that various tissues could be engineered in vivo using immunodeficient animals; in the second stages, studies are investigating the possibility of engineering tissue in large immunocompetent animals; the third stage will be to explore the possibility of engineering tissue in human and its clinical application. In current stage, most investigations are still limited to the second stage, although there are few reports of clinical applications. During the past 1-2 years, tremendous progress was made in regards to the development of new seed cell source and new biomaterials for tissue engineering. However, this article focuses on reviewing the advancement in the animal studies of cartilage, bone and tendon engineering.