東京医科歯科大学

TOKYO MEDICAL AND DENTAL UNIVERSITY

International Summer Program 2010

5-8 September 2010

Infection and Immunity

PROGRAM & ABSTRACT BOOK

Contents

ISP 2010 PROGRAM

Date/Time	*Event*	*Venue*

Sunday, 5 September: Registration and Welcome Reception

17:00-17:30 **Registration** — M&D Tower 2F Auditorium 1

17:30-18:00 **Orientation**
MC: Kevin Cleary (TMDU)
Welcome Address: Sei Sasaki (Trustee / Planning and International Exchange, TMDU)
Introduction to the ISP2010: Miyuki Azuma (ISP2010 Chairperson, TMDU)
Program Schedule: Ikuko Morio (Director / International Exchange Center, TMDU)

18:00–20:00 **Welcome Reception** — "Grill Saints"
MC: Kevin Cleary (TMDU)

Monday, 6 September: Lecture Course, Day 1

9:20–9:30 **Opening Remarks** — M&D Tower 2F Auditorium 1
Junji Tagami (Dean / Faculty of Dentistry, TMDU)

9:30-12:00 **Lecture Course 1**
Chair: Nobuo Ohta (TMDU) / Miyuki Azuma (TMDU)

9:30–10:15 Hajime Karasuyama (TMDU)
Title: Immunology: Past, present and future

10:15–11:00 James W. Kazura (Case Western Reserve University, USA)
Title: Emerging and Re-emerging infectious diseases in developing countries: Current and the future prospect

Coffee Break, 15 min

11:15–12:00 Nobuo Ohta (TMDU)
Title: Neglected Tropical Diseases: New challenges for the research promotion

12:00–13:00 Lunch Break

13:00–14:30 **Group Discussions** — M&D Tower Seminar Rooms

Group	Room No.	Facilitators
A	# 4 (22F)	Hajime Karasuyama, Yuichi Izumi (TMDU)
B	# 7 (14F)	Nobuo Ohta, Tetsuya Taga (TMDU)
C	#11 (6F)	Miyuki Azuma, Akinori Kimura (TMDU)
D	# 9 (8F)	Takeshi Tsubata, Mari Kannagi (TMDU)

Date/Time	*Event*	*Venue*

15:00-15:20 **Introduction to the University** — M&D Tower 2F
Ikuko Morio (Director of International Exchange Center, TMDU) — Auditorium 1

15:20–16:55 **Campus Tour**

17:00–19:00 **Poster Session** — M&D Tower 2F
Supervisor: Tetsuya Taga (TMDU) — Foyer

Tuesday, 7 September: Lecture Course, Day 2

9:00-12:15 **Lecture Course 2** — M&D Tower 2F
Chair: Yuichi Izumi (TMDU) / Mari Kannagi (TMDU) — Auditorium 1

9:00–9:45 Yoshihiro Ogawa (TMDU)
Title: Macrophages: Role in metabolic diseases

9:45–10:30 Nawarat Wara-aswapati Charoen (Khon Kaen University, Thailand)
Title: Pathogenesis of periodontal diseases as bacterial infection: Oral - systemic implications

Coffee Break, 15 min

10:45–11:30 Shoji Yamaoka (TMDU)
Title: How to see and control virus replication

11:30–12:15 Miyuki Azuma (TMDU)
Title: Dendritic cells: Control of immunity and tolerance

12:15–13:30 Lunch Break

13:30-17:00 **Optional Program**
- Laboratory visit
- Exposure to Japanese culture
- Guided walk in the neighborhood

18:00–20:00 **Social Hour** — M&D Tower 26F
MC: Kevin Cleary (TMDU) — Faculty Lounge
ISP2010 Address: Sei Sasaki (Trustee / Planning and International Exchange, TMDU)
Presentation of ISP2010 Certificates: Takashi Ohyama (President, TMDU)

Date/Time	*Event*	*Venue*

Wednesday, 8 September: ISP Symposium 2010 & 9th Surugadai International Symposium

9:00–9:10 **Opening Remarks** — M&D Tower 2F Auditorium 1
Kikuo Ohno (Dean / Faculty of Medicine, TMDU)

9:10-11:25 **Morning Session**
Chair: Toshiaki Ohteki (TMDU)

9:10– 9:55 Masanori Hatakeyama (University of Tokyo, Japan)
Title: Helicobacter pylori CagA as a bacterial oncoprotein

9:55–10:40 Nawarat Wara-aswapati Charoen (Khon Kaen University, Thailand)
Title: Modulation of Wnt5a in periodontal diseases

10:40–11:25 Ruslan Medzhitov (Yale University School of Medicine / HHMI, USA)
Title: Host defense: Immunity and immunopathology

11:25–13:00 **Lunch Break**

13:00-14:30 **Afternoon Session** — M&D Tower 2F Auditorium 1
Chair: Takeshi Tsubata (TMDU) / Tetsuya Taga (TMDU)

13:00–13:45 Toshiaki Ohteki (TMDU)
Title: Interferons wake up sleeping hematopoietic stem cells

13:45–14:30 Paola Ricciardi-Castagnoli (Singapore Immunology Network, Singapore)
Title: Immune regulatory role of dendritic cells during sterile and non-sterile inflammation

Coffee Break, 15 min

14:45–15:30 Takeshi Tsubata (TMDU)
Title: Membrane-bound lectins and humoral immunity

15:30–16:15 James W. Kazura (Case Western Reserve University, USA)
Title: Progress and challenges toward malaria vaccine development

16:15–17:00 Hirokazu Tamamura (TMDU)
Title: Anti-HIV inhibitors and AIDS vaccines

17:00–17:15 **Closing Remarks** — M&D Tower 2F Auditorium 1
Shigetaka Kitajima (Director / Medical Research Institute, TMDU)

Takashi Ohyama

President
Tokyo Medical and Dental University

Message from the President

Tokyo Medical and Dental University (TMDU) is unique in the respect that all of our divisions are related to education of health care professionals and/or bioscience research. As shown by our university mission, "Cultivating Professionals with Knowledge and Humanity", all of the faculty and staff at TMDU have been doing their best to help our students become world-class health care professionals and/or bioscience researchers.

An important part of our history, which has now reached 80 years as a dental school and 50 years as a medical school, has been the precious experience of teaching many international students, who I believe have helped advance the level of medicine and dentistry in their home countries after returning to practice and teach. On our side, we have been able to appreciate different cultures and cultivate intellectual sympathy through the invaluable experience of educating international students. Furthermore, it is a great honor and pleasure for us to know that our international student alumni have continually encouraged their friends, colleagues and students to join us in our academic endeavors.

In terms of international outreach, we are especially proud of three overseas education/research collaboration centers — in Ghana, Chile, and Thailand — which we founded just last year. At these centers we aim to promote collaborative research and to advance the professional development of medical and dental professionals in each local area. We look forward to the various scholarly exchanges of knowledge and personnel which these centers will provide.

In terms of international activities here in Japan, we are very pleased to be able to organize our second International Summer Program, ISP2010. Our inaugural program of last year, ISP2009, was an all-around success, and we trust that ISP2010 will be an even better achievement for all concerned. Specifically, I hope that your experience at ISP2010, in addition to helping you develop professionally, will pique your academic curiosity and encourage you to explore the unique features of our university.

Sei Sasaki

Trustee / Vice-President
Planning / International Exchange
Strategy Meeting
Tokyo Medical and Dental University

Message of Welcome

It is our great pleasure to welcome you to the Tokyo Medical and Dental University (TMDU) International Summer Program 2010.

Reflecting the rapid globalization of every aspect of life today, it is necessary for universities to become truly international institutions. The International Summer Program (ISP), launched last year, is one of the most important ways that we at TMDU are accelerating our international outreach. The aim of the ISP is to bring together students and young scientists from Asia, to study and discuss fundamental and emerging topics with leading scientists. To that end, we have provided nearly 30 scholarships for attendance at the ISP. We hope that the future leaders we have invited to ISP will have a good chance to familiarize themselves with TMDU through this program and realize how their educational career may be enriched by overseas study.

The theme for ISP2010 is “Infection and Immunity” and the program consists of two parts. The Lecture Course will feature lectures by leading researchers from abroad and from Japan that give the outline and fundamental knowledge of the theme. The second part, the ISP Symposium 2010, which will be held as a joint program with the 9th Surugadai International Symposium of the Medical Research Institute of TMDU, will feature presentations by specially invited researchers from overseas, and this part will give cutting edge knowledge of the theme. In addition, we will have time for group discussion, poster sessions, a campus tour, and laboratory visits. Through these activities we hope all participants communicate each other, exchange ideas and find new things for their future plans.

TMDU is located in the center of Tokyo, the capital of Japan, and the place where over 12 million people live. TMDU is a convenient base from which to explore the city, with its mix of exciting new places and historical, traditional areas where you can enjoy the taste of the culture of the Edo period of Tokyo. We are arranging social programs to help introduce the city to you.

We hope that the ISP2010 will be both academically and professionally beneficial to you, and that you make lasting friendships with other ISP2010 participants. Thank you very much for your participation, and best wishes for your future career.

Profiles and Abstracts of Lecture Course Speakers

Hajime Karasuyama

(Tokyo Medical and Dental University)

Biodata

Hajime Karasuyama, MD., PhD. has been a professor in the Department of Immune Regulation at Tokyo Medical and Dental University Graduate School since 2000. He was a scientific member of the Basel Institute for Immunology in Switzerland, twice, in 1984-1987 and 1990-1995, followed by being head of the Department of Immunology at The Tokyo Metropolitan Institute of Medical Science from 1995-2000. The aims of the Karasuyama's laboratory are to elucidate the genetic, molecular and cellular mechanisms underlying immunological disorders such as allergy and immunodeficiencies, and to develop new strategies that control them. His group has recently illuminated previously-unappreciated roles of basophils in acute and chronic allergic reactions as well as protective immunity against parasites (Immunity 2005; Immunity 2008; Nat. Rev. Immunol. 2009; J. Clin. Invest. 2010). They have also clarified the genetic origins and molecular mechanisms that cause the primary immunodeficiency 'hyper-IgE syndrome', which is characterized by severe atopic-dermatitis with high serum IgE levels and recurrent bacterial and fungal infections (Immunity 2006; Nature, 2007; J. Exp. Med. 2009). This finding has enabled earlier and definite diagnosis of this primary immunodeficiency that greatly enhances QOL of patients. Thus, the studies in Karasuyama's laboratory have made the bridges 'From Bench to Clinic' and 'From Clinic to Bench'.

Lecture Course: Immunology: Past, present and future

Abstract

In this introductory lecture, I would like to overview the past, present and future of immunology, particularly in association with infectious disorders, instead of presenting our own studies.

Our environment contains a variety of infectious agents, including viruses, bacteria, fungi, and parasites, which can cause serious and sometimes fatal diseases. The primary function of the immune system is defense against these infectious agents. The term immunity is derived from the Latin word immunitas, which in ancient Rome originally described the exemption of an individual from service or duty to the state. The phenomenon of acquired immunity or immunological memory—those who had once survived a disease might often be spared further involvement on its return—was already described by the historian Thucydides in his report of the plague of Athens in 430 B.C., even though no one knew at that time what elicited the disease and how they were protected from the second attack. Taking advantage of this phenomenon, Edward Jenner, an English physician, documented at the end of the 18th century the first clear example of manipulation of the immune response to protect humans from infections, namely successful vaccination against smallpox, leading to the eradication of smallpox from the earth in 1980. However, it was not until late in the 19th century that Robert Koch and Louis Pasteur proved that infectious diseases are caused by microorganisms, each one responsible for a particular disease. A mechanism of protection against infectious microorganisms was first identified in 1890 by Emil von Behring and Shibasaburo Kitasato who discovered that the serum of animals immunized (vaccinated) with bacteria-derived toxins (diphtheria and tetanus toxins) contained substances, called antitoxins (we now know as antibodies), that neutralized the activity of the toxins. Antitoxic sera from experimental animals were quickly tested in infected children, leading to remarkable and rapid cures. This is a great milestone of medicine, microbiology and immunology, and a prototype of translational research.

Thus, the advance in immunology has been closely associated with studies on infectious diseases. However, we now appreciate that in addition to protection against pathogens, our immune system is also involved in immune surveillance of malignant transformation of normal cells that constitute our body. Furthermore, dysregulation of immune responses results in unwanted outcomes such as allergy, autoimmunity and other inflammatory disorders. Nowadays, immunology also needs to deal with artificial settings such as organ transplantation. Modern immunology using newly developed technology, including establishment of monoclonal antibodies, long-term cell culture system, recombinant DNA techniques, creation of genetically engineered (transgenic and knock-out) mice, has greatly advanced our understanding of players and their functions in the immune system. Some of findings in animal models are now clinically applied, and the monoclonal antibodies specific to proinflammatory cytokines and their receptors are successfully used to treat autoimmune disorders such as rheumatoid arthritis. Further basic studies and clinical trials are definitely needed to control immunological disorders, including emerging and re-emerging infectious diseases.

James W. Kazura

(Case Western Reserve University, USA)

Biodata

Advancing fundamental knowledge of the mechanisms underlying susceptibility to infection and the pathogenesis of disease due to malaria and chronic worm infections endemic in tropical areas of the world is the focus of Dr. Kazura's work. The ultimate goal is to use this knowledge to develop preventative and interventional strategies that are culturally appropriate and cost effective.

A major emphasis of research is to integrate the tools of human molecular immunology and genetics into field-based studies conducted in collaboration with research and public health colleagues based in disease-endemic countries. Active studies concerned with human falciparum malaria are aimed at determining whether and how naturally-occurring immunity to liver-stage and blood-stage Plasmodium falciparum evolves during the course of infancy and the mechanisms underlying the stability of this immunity. The emphasis is on two vaccine candidate molecules, P. falciparum Liver Stage Antigen-1 and Merozoite Surface Protein-1. This work is done in collaboration with colleagues from Papua New Guinea, Kenya and Australia. Active studies focused on human worm infections are concerned with lymphatic filariasis and are aimed at testing integrated strategies for control and elimination of this disease. The major emphasis is to evaluate whether attainment of control and eradication endpoints defined by vector and human infection rates effected by annual single dose mass drug administration can be accelerated by integration with vector control using insecticide-impregnated bed nets. These population-based studies are being conducted with colleagues from the Papua New Guinea Institute of Medical Research and Imperial College, London.

In addition to research, Dr. Kazura has been active in promoting tropical medicine as a scholarly and scientific discipline through participation on numerous NIH and WHO committees and other venues such as editorial service on major tropical disease journals. He is highly committed to the training and education of junior colleagues from the United States and developing countries through NIAID training grants and Fogarty International Center sponsored training grants awarded in collaboration with colleagues from Kenya and Papua New Guinea.

Lecture Course: Emerging and re-emerging infectious diseases in developing countries: Current situation and the future prospect

Abstract

Recent concerns related to the global spread of life-threatening microbial pathogens such as avian influenza reflect the emergence of life-threatening infectious diseases in human populations for which there is little individual and herd immunity or treatment. This lecture will describe the salient ecological, epidemiological, and immunological variables that underlie outbreaks of zoonoses in Asia and sub-Saharan Africa, e.g. SARS, Rift Valley Fever, and selected parasitic helminthiases. The objective is to illustrate the importance of multidisciplinary approaches to predict, prevent and manage zoonotic diseases, which account for 75% or more of infectious diseases that have emerged over the past 10 years.

Nobuo Ohta

(Tokyo Medical and Dental University)

Biodata

Dr. Nobuo Ohta graduated from Shinshu University School of Medicine in 1977, and then from the Graduate School of TMDU in 1981. His PhD thesis was "Genetic control of susceptibility to schistosomiasis japonica in humans", and ever since then, his main research subject has focused on basic and applied fields of human schistosomiasis. After he became Professor of Nagoya City University in 1993, he joined TMDU as a Professor in 2006. He is Chair of Section of Environmental Parasitology, Graduate School of TMDU, and has also been the principal investigator of the Ghana-TMDU research collaboration project since 2008.

His recent works are on immunomodulation of host responses during schistosomal infection, development of anti-Schistosoma japonicum vaccine, development of new drugs for schistosomiasis, and investigating the molecular basis of the host-susceptibility of S. japonicum. Not only laboratory works, but also field research in China, West Africa and SE Asia are promoted, and international joint projects in China, Thailand, Philippines, Ghana and elsewhere are ongoing. He has been a member of the Advisory Committee for International Parasite Controls of the Japanese Government, and collaborations with JICA, WHO and other organizations are underway to build a global network for NTD control.

Lecture Course: Neglected tropical diseases: New challenges for the research promotion

Abstract

There are two categories of infectious diseases in the world: three major diseases (HIV/AIDS, tuberculosis and malaria) vs Neglected Tropical Diseases (NTDs). Such the classification is not necessarily on biological background, but rather based on political situations. NTDs are distributed in rural areas in many developing countries, and victims of NTDs are poor and politically silent people. NTDs are heterogenous disease complex containing parasitic (schistosomiasis, soil-transmitted helmintheases, filariasis, trypanosomiasis, leishmaniasis and others), bacterial (leprosy, trachoma, buluri uncers and others) and viral (Dengue fever) infections. Although disease mortalities of NTDs are not so high, serious damages due to NTDs are apparent in reference to the DALY scores.

The necessity of NTD control has been approved by various international meetings and WHO is the main organization for implementing control activities. There are 9 strategic areas in WHO activities on NTDs control, and promotion of basic and operational research is one of the key factors for the success. Disease assessment, high-quality medicines and diagnostic tools, vector management and/or access to innovation are outcomes, in part, of research activities. To achieve success in these subjects, strengthening partnership and networks among researchers in various research fields. Application of molecular techniques for diagnosis of patients or detection of infected vectors is supportive to disease assessment which is one of the key strategies in NTDs control. Basic biological research on pathogens provide information for development of new drugs. One of the success cases is ascofulanone, which was once screened as an anti-cancer drug, but was not, after all, effective against cancer cells. However, research on the energy metabolism of African trypanosomes strongy suggested the efficacy of ascofulanone against African trypanosomes, and it's strong trypanosomicidl effects were shown both in vitro and in vivo.

In this lecture, I will talk on the recent ontributions from basic research for controlling NTDs. NTDs had been neglected by policy makers, and furthermore, researchers on NTDs were also neglected because of the limited interest from other researchers. After a recent WHO campaign to announce the importance of NTDs on human health and welfare, basic researchers, if not so many, became aware of the impact of NTDs research, and a big progress in this research field has been appearing. Japan is one of the countries which is making a big contribution for the control of NTDs, and progress of NTD research in Japan will be introduced.

Yoshihiro Ogawa

(Tokyo Medical and Dental University)

Biodata

Dr. Ogawa is a Professor in the Department in the Molecular Medicine and Metabolism, Medical Research Institute, Tokyo Medical and Dental University. He received his M.D. and Ph.D. degrees from Kyoto University, Kyoto, Japan. While earning his Ph.D. degree, he worked with Hiroo Imura and Kazuwa Nakao at the Kyoto University Graduate School of Medicine. He carried out his postdoctoral training as Research Fellow of the Japan Society for the Promotion of Science at Kyoto University. Before joining Tokyo Medical and Dental University in 2003, he was an Assistant Professor of Department of Endocrinology and Metabolism, Kyoto University Graduate School of Medicine. His current research interest is the pathophysiologic and therapeutic implication of 1) chronic inflammation and 2) epigenetic modification in lifestyle-related metabolic diseases such as obesity, diabetes, and atherosclerosis.

Lecture Course: Macrophages: Role in metabolic diseases

Abstract

In contrast to “acute inflammation” which is resolved by an active termination program, “chronic inflammation” is characterized by persistent interaction between parenchymal and stromal cells in response to tissue stress or malfunction, thereby leading to functional maladaptation and tissue remodeling. Being a major cell type of the innate immune defense against infecting pathogens, macrophages are a key player that participates in the initiation and resolution of chronic inflammation, and in the maintenance of tissue homeostasis.

Adipose tissue is capable of communicating with multiple organs or tissues by virtue of its large number of adipocytokines, and thus influences a variety of physiologic and pathophysiologic processes. Recent evidence has suggested that obesity is a state of a chronic low-grade inflammation; obesity-induced adipose tissue inflammation results in the dysregulation of adipocytokine production, thereby contributing to the development of the metabolic syndrome. On the other hand, obese adipose tissue is characterized by adipocyte hypertrophy, followed by increases in angiogenesis, macrophage infiltration, and pro-inflammatory adipocytokine production, which may be referred to as “adipose tissue remodeling”. Using an in vitro co-culture system composed of 3T3-L1 adipocytes and macrophages, we have provided evidence that a paracrine loop involving saturated fatty acids and tumor necrosis factor α (TNFα), which are derived from adipocytes and macrophages, respectively, establishes a vicious cycle that aggravates inflammatory changes in obese adipose tissue. During the paracrine interaction between adipocytes and macrophages within obese adipose tissue, saturated fatty acids, which are released in large quantities from hypertrophied adipocytes via the macrophage-induced lipolysis, may serve as an endogenous ligand for Toll-like receptor 4 (TLR4)/myeloid differentiation factor 2 (MD-2) complex, a major pathogen sensor in innate immunity, to activate macrophages for the regulation of metabolic homeostasis.

Sustained interaction between endogenous ligands derived from parenchymal cells and pathogen sensors expressed in stromal immune cells should lead to chronic/homeostatic inflammatory responses ranging from the basal homeostatic state to diseased tissue remodeling, which has been referred to as “homeostatic inflammation”. Understanding the role of macrophages in adipose tissue remodeling as homeostatic inflammation would lead to the identification of novel therapeutic strategies to prevent or treat obesity-induced adipose tissue inflammation.

Reference: T. Suganami & Y. Ogawa. Adipose tissue macrophages: their role in adipose tissue remodeling. J. Leukoc. Biol. 88: 33-39, 2010.

Nawarat Wara-aswapati Charoen

(Khon Kaen University, Thailand)

Biodata

Dr. Nawarat Wara-aswapati received her DMSC in Oral Biology and certificate in Periodontology from Harvard School of Dental Medicine, USA. Her research combines the basic and clinical sciences and has focused on molecular mechanisms of gene regulation, bone biology, immunology, infection, and periodontology. An American Board-certified periodontist, she practices periodontology at the School's Dental Hospital. Dr. Wara-aswapati has received numerous honors during her academic career, including The Joseph L. Henry Award from Harvard School of Dental Medicine, The 2000 George W. Teuscher Golden Pen Award from the American Society of Dentistry for Children, "Paper of the week" from Journal of Biological Chemistry, and the JSPS Invitation Fellowship Award for Research in Japan. In 2009, she was named Dean of the Faculty of Dentistry, Khon Kaen University, Thailand.

Lecture Course: Pathogenesis of periodontal diseases as bacterial infection: Oral - systemic implications

Abstract

Periodontitis is an inflammatory disease caused by gram-negative periodontopathic bacteria which can induce the production of host inflammatory mediators, eventually leading to the breakdown of tooth-supporting tissues. In the past decade, emerging evidence has suggested the association of periodontal diseases with several systemic diseases and conditions such as adverse pregnancy outcomes, diabetes mellitus (DM), cardiovascular diseases (CVDs), respiratory diseases, Alzheimer's disease and cancer. Therefore, it has been well acknowledged that periodontal diseases can impact overall health. Although much epidemiologic data support these associations of periodontal diseases with systemic diseases, a cause-and-effect relationship has not been clearly established.

In this lecture, we will review the growing evidence of the link between periodontal diseases and three important systemic conditions including adverse pregnancy outcomes, DM and CVDs. Possible mechanisms of the associations between periodontal diseases and these systemic diseases will be discussed along with the roles of periodontopathic bacteria and inflammatory cytokines, interleukin 1β (IL-1β), IL-6, tumor necrosis factor α (TNF-α), prostaglandin E2 (PGE2), C-reactive protein (CRP) in the pathogenesis of these systemic conditions. Studies carried out by our group will be presented.

It has been assumed that periodontal treatment would reduce the insult imposed by the periodontal pathogens and consequently host inflammatory responses. Although several trials have suggested the potential roles of periodontal therapy in the prevention or reduction of the systemic diseases, further randomized controlled trials are warranted to confirm the benefits of periodontal treatment in systemic conditions. In this lecture, the published literature on the effects of periodontal intervention on pregnancy outcomes, DM and CVDs will also be reviewed.

Shoji Yamaoka

(Tokyo Medical and Dental University)

Biodata

Professor and Chair, Department of Molecular Virology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University

M.D., Kyoto University

Ph.D., Molecular Medicine, Kyoto University

Dr. Yamaoka joined the School of Medicine of Tokyo Medical and Dental University (TMDU) in 1999 as an Associate Professor in the Department of Microbiology. Since 2007, he has been a Professor in the Department of Molecular Virology at TMDU's Graduate School of Medical and Dental Sciences. Before coming to TMDU, he worked as a surgeon for 5 years, became an Assistant Professor at the Institute for Virus Research, Kyoto University (1994-1999), and studied at the Unité de Biologie Moléculaire de l'Expression Génique, Institut Pasteur Paris, France (1996–1999).

Dr. Yamaoka is the discoverer of NF-κB essential modulator (NEMO), whose mutations cause severe immune-deficiency in humans. His research currently deals with two major subjects, constitutive activation of the transcription factor NF-κB in cancer cells and host cell factors regulating HIV-1 replication. In particular, he established genetic screens to identify cellular proteins required for viral oncogenesis or interfering with virus replication.

Lecture Course: How to see and control virus replication

Abstract

The importance of viral diseases is increasingly obvious. In 2009, a new triple reassortment strain of influenza A virus called "novel H1N1" emerged and spread worldwide within months. Human Immunodeficiency Virus type 1 (HIV-1) is the causative agent of AIDS and is prevalent mainly in developing countries. More than 30 million people are living with this virus, while AIDS cannot be completely cured by current antiviral drugs. These RNA viruses are characterized by their frequent mutations and eventual acquirement of drug-resistance. Thus, for a better control of viral diseases, it is necessary to target host cell factors that regulate virus replication. In fact, a virus can be defined as an infectious entity whose genomes are composed of nucleic acids and which OBLIGATELY replicate inside host cells, where it uses cellular proteins or machinery and meets antiviral immunity. In this context, identifying such cellular factors represents the first step in developing rational therapeutic strategies for viral diseases. This lecture will firstly deal with how viruses generally replicate inside cells from a virus standpoint, and then provide examples of host cell factors that support or interfere with virus replication. We will then focus on one lethal virus, HIV-1, which infects and kills human hematopoietic cells such as a subset of T-lymphocytes, macrophages and dendritic cells, leading to progressive immunodeficiency. After entering a cell, HIV-1 converts its single-strand RNA genome to double-strand DNA (reverse transcription) and goes into the nucleus where it is integrated to the host cell genome (integration). Integrated viral DNA (provirus) is then transcribed to RNAs, which go out to the cytoplasm where viral proteins and genome assemble to bud from the cell membrane. This is just a simple description of the life cycle of HIV-1, and each process of virus replication is thought to involve multiple host cell factors that may positively or negatively regulate virus replication. For example, a cytidine deaminase APOBEC3G induces A to G mutation in the viral genome; LEDGF functions as a target site-selection factor, directing integration of viral DNA to sites of high transcriptional activity in the host chromosome; Cyclin T plays a key role in viral RNA synthesis; TSG101 supports trafficking and assembly of viral proteins; Tetherin prevents viral particles from leaving cells. Such factors have been discovered through binding to viral proteins, screens of shRNAs or investigation of restrictive or permissive cell lines, but perhaps, there remain unknown a number of cellular proteins that are essentially involved in the progression of virus replication. We have employed an expression cloning strategy to get cellular proteins, forced expression of which can efficiently suppress HIV-1 replication. We can study how some of those proteins interferes with HIV-1 replication through quantifying viral reverse transcription products, integrated provirus and expression of viral gene products.

Miyuki Azuma

(Tokyo Medical and Dental University)

Biodata

Miyuki Azuma received her D.D.S. (1984) and Ph.D. (1988) degrees from TMDU. After receivng her Ph.D., she worked as a clinical fellow at the Department of Oral & Maxillo-facial Surgery in TMDU (-1990), a postodoctral fellow at DNAX Research Institute in CA, USA (-1992), an assistant professor in the Department of Immunology in Juntendo University School of Medicine. (-1996), and a staff scientist at National Children's Medical Research Center (-2000). She then rejoined TMDU in 2000 as a professor in the Department of Molecular Immunology. She has been investigating the function of lymphocyte cell surface molecules, especially T cell costimulatory molecules, controlling immunity and tolerance. Her research goal is to develop new immunotherapies targetting costimulatory molecules for immune-mediated disorder including infection and cancer.

Lecture Course: Dendritic cells: Control of immunity and tolerance

Abstract

The immune system is an organization of cells and molecules with specialized roles in defending against infection. There are two fundamentally different types of responses to invading microbes; innate immunity and acquired immunity. It has been generally accepted that DCs function as professional antigen-presenting cells to induce antigen-specific T cell responses and control the magnitude and quality of the T cell responses. In addition, recent discoveries revealed that DCs play crucial roles for maintenance or induction of immunological tolerance. Thus, DCs can control acquired/adaptive immunity positively and negatively. Even in the steady state, DCs are broadly distributed in lymphoid and non-lymphoid organs. Unique subsets of DCs exist at the front line of defence such as skin and mucosa and act as sentinel cells for microorganisms. DCs recognize pathogen-derived antigens using pathogen-associated recognition receptors like toll-like receptors and the receptor-mediated signals induce a panel of proinflammtory cytokine secretion by which innate inflammatory responses are triggered. These signals change the status of DCs from immature to mature and the antigen-captured DCs migrate from peripheral sites to regional lymph nodes to present antigens to T cells. How strong or which types (i.g. Th1, Th2, or Th17 effector T cells or regualtory T cells) of T cell immune responses are provoked is dependent upon the properties of DCs that are determined by the factors from antigens and local microenvironment. DCs express various co-signal receptors and cytokines which affect differentiation and activation of T cells. Thus, DC is a crucial cell type that triggers both innate and adaptive immune systems. The innate immune responses triggered by DCs greatly affect subsequent adaptive immune responses.

In this lecture, I will review update of DC biology in the immune system.

Profiles and Abstracts of Symposium Speakers

Masanori Hatakeyama

(The University of Tokyo)

Biodata

Masanori Hatakeyama received his M.D. (1981) and Ph.D. (1986) degrees from the Graduate School of Medicine, Hokkaido University, Japan, and became a research associate at Osaka University (1986-1991). He then finished his postdoctoral studies in molecular oncology with Robert A. Weinberg at the Whitehead Institute, Boston (1991-1994). He is now a professor at the Graduate School of Medicine, Univeristy of Tokyo. Before his current appointment, he was a member and Chief at the Cancer Institute, Japanese Foundation for Cancer Research, Tokyo (1995-1999) and was a professor at the Institute for Genetic Medicine, Hokkaido University (1999-2009). His current investigations focus on the molecular mechanisms that underlie gastric carcinogenesis. He is also actively investigating regulation of the cell cycle by mitogenic signals.

Symposium Talk: Helicobacter pylori CagA as a bacterial oncoprotein

Abstract

Chronic infection with *Helicobacter pylori* cagA-positive strains is the strongest risk factor for the development of gastric carcinoma. The cagA gene-encoded CagA is delivered into gastric epithelial cells by the bacterial type IV secretion system, although the underlying mechanisms remain uncertain. Recently, we found that direct contact of H. pylori with epithelial cells induces rapid externalization of phosphatidylserine (PS) to the outer leaflet of the plasma membrane. CagA, which is also exposed on the bacterial surface via type IV secretion, interacts with the membrane-externalized PS. The CagA-PS interaction triggers the entry of CagA into host epithelial cells, which also requires energy-dependent host cell processes distinct from known endocytic pathways. In polarized epithelial cells, delivered CagA is tethered to the inner leaflet of the plasma membrane again through interaction with PS. Thus, host membrane PS plays a key role in delivery and intracellular localization of H. *pylori CagA*.

Following delivery and membrane localization, CagA undergoes tyrosine phosphorylation by Src kinases. Tyrosine-phosphorylated CagA acquires the ability to specifically bind to and aberrantly activate SHP-2 tyrosine phosphatase, gain-of-function mutations of which are associated with a variety of human malignancies. CagA-activated SHP-2 deregulates Erk MAP kinase signaling. CagA also binds partitioning-defective 1 (PAR1)/microtubule affinity-regulating kinases (MARK) independently of tyrosine phosphorylation. The CagA-PAR1 interaction inhibits the PAR1 kinase activity and thereby causes junctional and polarity defects. Because PAR1 regulates the cell polarity by controlling microtubule stability and microtubules are also essential components of mitotic spindles, CagA-mediated PAR1 inhibition influences mitotic spindle function as well. Hence, cells expressing CagA display a delay in the transition from prophase to metaphase during mitosis. Consequently, chronic exposure of cells to CagA induces chromosomal instability. The observations indicate that CagA, on one hand, stimulates uncontrolled cell proliferation through deregulation of SHP-2 and, on the other hand, induces chromosomal instability via perturbing the microtubule-based mitotic spindle. These CagA activities may collectively contribute to the progression of multistep gastric carcinogenesis.

H pylori CagA is known for its geographical variation in structure and, based on the molecular polymorphism, can be subdivided into two major isoforms, Western CagA and East Asian CagA. Notably, East Asian CagA binds more strongly to SHP-2 than Western CagA does. To consolidate oncogenic potential of CagA, we generated transgenic mice that systemically express East Asian CagA. The established CagA transgenic mice developed adenocarcinomas of the stomach and small intestine. The mice also developed myeloid leukemias and B-cell lymphomas. In striking contrast, transgenic mice expressing phosphorylation-resistant CagA did not show any pathological abnormalities. These results provide direct evidence for the oncogenic potential of CagA in vivo and indicate the importance of tyrosine-phosphorylated CagA for in vivo tumorigenesis. More recently, we generated Western CagA-transgenic mice. Comparison of Western CagA-transgenic mice with those expressing East Asian CagA revealed that East Asian CagA is more oncogenic than Western CagA in vivo. Differential oncogenic potential of geographically distinct CagA isoforms may underlie the higher incidence of gastric carcinoma in East Asian countries compared to the incidence of that in Western countries.

Nawarat Wara-aswapati Charoen

(Khon Kaen University, Thailand)

Symposium Talk: Modulation of Wnt5a in periodontal diseases

Abstract

N. Wara-aswapati[1], H. Nanbara[2], Y. Yoshida[3], T. Nagasawa[4], R. Yashiro[1], Y. Bando[2], H. Kobayashi[2], J.A. Boch[5] and Y. Izumi[2, 6]

[1] Department of Periodontology, Faculty of Dentistry, Khon Kaen University, Khon Kaen, Thailand;
[2] Section of Periodontology, Department of Hard Tissue Engineering, Graduate School, Tokyo Medical and Dental University, Tokyo, Japan;
[3] Department of Immunology, School of Medicine, University of Occupational and Environmental Health, Fukuoka, Japan;
[4] Department of Periodontology and Endodontology, Health Science University of Hokkaido, Hokkaido, Japan;
[5] Department of Oral Medicine, Infection and Immunity, Harvard School of Dental Medical, Boston, MA, USA;
[6] Global Center of Excellence Program, International Research Center for Molecular Science in Tooth and Bone Diseases, Tokyo Medical and Dental University, Tokyo, Japan.

Periodontitis is an inflammatory disease caused by gram-negative periodontopathic bacteria which can lead to loss of tooth-supporting structures and alveolar bone resorption. Wnt signaling molecules play important roles in bone biology, apoptosis and chronic inflammation. Recent studies have suggested an association of these molecules with various disorders including cardiovascular diseases, rheumatoid arthritis, and osteoarthritis. We previously demonstrated that Wnt5a mRNA expression was upregulated in chronic periodontitis tissue when compared to non-periodontitis tissue. In this research symposium, our current study on the modulation of Wnt5a mRNA expression by periodontopathic bacteria will be presented.
Human monocytic cell line THP-1 cells were stimulated with Porphyromonas gingivalis, its lipopolysaccharide (LPS), Aggregatibacter actinomycetemcomitans, TNF-α and IFN-γ. To investigate the involvement of NF-κB and JAK/STAT pathways in the modulation of Wnt5a expression, we used inhibition assay, transfection, luciferase assay, and EMSA. The levels of Wnt5a mRNA were determined by real-time RT-PCR. Our results showed that P. gingivalis LPS upregulated Wnt5a and NF-κB mRNA expression in THP-1 cells. P. gingivalis LPS-induced Wnt5a mRNA levels were suppressed by a JAK/STAT inhibitor (AG490) and a STAT1 inhibitor (fludarabine). Two different NF-κB pathway inhibitors were also capable of suppressing P. gingivalis LPS-induced Wnt5a mRNA expression. Furthermore, the induction of Wnt5a mRNA expression was augmented by co-stimulation with IFN-γ and overexpression of STAT1, but was suppressed by STAT1 siRNA.
Our study suggests that Wnt5a upregulation by P. gingivalis LPS in THP-1 cells is dependent upon NF-κB and STAT1. The modulation of Wnt5a expression by periodontopathic bacteria may play an important role in the periodontal inflammatory process.

(This study was supported by grants from the Japanese Ministry of Education (GCOE) Program, International Research Center for Molecular Science in Tooth and Bone Diseases, and the JSPS Invitation Fellowship for Research in Japan)

Ruslan Medzhitov

(Yale University School of Medicine / HHMI, USA)

Biodata

Ruslan Medzhitov was an undergraduate at Tashkent State University and obtained his PhD from Moscow State University in 1993. He worked as a postdoctoral fellow with Dr. Charles A. Janeway Jr. at Yale University School of Medicine from 1994 to 1999. In 1997 he identified a human homologue of Drosophila Toll (now known as TLR4). He since contributed to the characterization of the mammalian TLR family. Ruslan became an Assistant Professor at Yale University School of Medicine in 1999 and full Professor in 2003. He was selected as a Searle Scholar in 2000. He is currently the David W. Wallace Professor of Immunobiology at Yale University School of Medicine and an Investigator of the Howard Hughes Medical Institute. He recently was elected a member of the National Academy of Sciences. His awards include: The William B. Coley Award for Distinguished Research in Basic and Tumor Immunology from the Cancer Research Institute, A Master of Arts Privatum at Yale University, The Emil von Behring Award, AAI –BD Biosciences Investigator Award, A Doctor Honoris Causae at the University of Munich, Blavatnik Award for Young Scientists from the New York Academy of Arts and Sciences, Howard Taylor Ricketts Award from the University of Chicago, and the Lewis S. Rosenstiel Award from Brandeis University.

Symposium Talk: Host defense: Immunity and immunopathology

Abstract

Infectious diseases are caused by both direct pathogen damage to the host, as well as by the collateral damage inflicted by the immune response. Therefore, immune protection is a trade-off between pathogen elimination and immunopathology. How this trade-off is optimally resolved is incompletely understood, but it likely involves immune regulatory strategies that are still poorly characterized. In addition, host defense from infections can be achieved by two distinct strategies: resistance and tolerance. Whereas the resistance mechanisms aim to eliminate pathogen burden, the tolerance mechanisms allow the host to tolerate the presence of pathogens by minimizing their harmful effects on the host. The differential roles of these distinct defense strategies in animal immunity is unknown. These problems may be particularly well illustrated by the high morbidity and mortality of bacterial pneumonia following influenza virus infection, which will be the focus of this presentation.

Toshiaki Ohteki

(Tokyo Medical and Dental University)

Biodata

Dr. Toshiaki Ohteki is a professor in the Department of Biodefense, Medical Research Institute, Tokyo Medical and Dental University, and a representative of a research program supported by JST CREST. He received his Ph.D. from Tohoku University (1991), and was a postdoctoral fellow at the Ludwig Institute for Cancer Research, Switzerland and the Ontario Cancer Instutute, Canada (1992-1998). His current research projects focus on biodefense and maintenance of immunological homeostasis, which include mechanism of tolerance induction and its failure in mucosa-associated lymphoid tissue, differentiation and the homeostasis of dendritic cells, and regulation of hematopoiesis by immune system.

Symposium Talk: Interferons wake up sleeping hematopoietic stem cells

Abstract

Hematopoietic stem cells (HSCs) are pluripotent cells with the capacity for the life-long production of the entire lineage of mature hematopoietic cells. Under steady-state conditions, most HSCs are quiescent residents of the BM niche, a state that preserves their capacity to self-renew. Type I interferons (IFNs) are essential for establishing the host antiviral state, their role in hematopoietic homeostasis remains unstudied. We found that type I IFNs induce proliferation and exhaustion in HSCs, and that IRF2, a transcriptional suppressor of type I IFN signaling, preserves the self-renewal and multi-lineage differentiation capacity of HSCs. Our findings may lead to improvements for BM-transplantation and type-I IFN-based therapies for viral infections and cancer.

As virus infection stimulates host immune cells to induce type I IFNs, we consider the importance of viral infection-induced type I IFNs in the activation of HSCs. Interestingly, we found that acute infection with both RNA and DNA viruses stimulates HSC proliferation in WT mice, mice lacking type I IFN signaling or type II IFN signalings, whereas such HSC proliferation is completely impaired in mice lacking both type I and type II IFN signaling, suggesting stringent requirements of either type-I or -II IFN signaling, but not others, for HSC activation in viral infection. Immunological significance of IFN-induced HSC activation will be discussed.

References:

Sato T., et al. Nat Med 15, 696-700 (2009) Essers M.A., et al. Nature 458, 904-908 (2009).

Paola Ricciardi-Castagnoli

(Singapore Immunology Network, Singapore)

Biodata

Professor Paola Castagnoli is presently the Scientific Director of the A*STAR Centre of Immunology SIgN and she is on leave of absence as Chair of Immunology and General Pathology at the University of Milano-Bicocca, Milan, Italy. From 1975-1998 she was a member of the National Research Council and has been a Visiting Scientist at MIT and a postdoctoral fellow at Stanford University. She is an EMBO member. She has been awarded by the European Union a prestigious Marie Curie Chair at the Institute Pasteur of Paris where she was also a member of the Scientific Council. Since 2002 she has been the President of the European Network of Immunology Institutes (ENII). She has been part of European Networks of Excellence supported by the EU and she serves as a member of the SAB of several academic and nonacademic research institutes. She is part of the Editorial Board and Executive Committee of several international scientific journals. With her research group she has published 165 papers in extenso in international peer reviewed journals.

Symposium Talk: Immune regulatory role of dendritic cells during sterile and non-sterile inflammation

Abstract

In recent decades, most of the knowledge regarding dendritic cell (DC) biology resulted mainly from recognition of microbial patter molecules through a variety of germline-encoded pattern receptors, such as the Toll-like receptor family members. It is now believed that immune cells could react also to host molecules released in their microenvironment upon cellular stress or tissue damage triggering inflammation even in the absence of pathogens. These molecules are part of a diffuse surveillance network devised to alert our body defence of a danger, and are therefore also referred to as endogenous danger signals or DAMPs. One host-derived molecule mostly characterized is the crystallized form of uric acid known as monosodium urate (MSU). MSU represents the etiological agent of gout, a metabolic-related arthritis characterized by abnormal deposition of MSU crystals in joints and periarticular tissues. It has been shown that MSU has the ability to activate the NALP3 inflammasome, an intracellular multimeric protein complex that links the sensing of microbial products and metabolic stress to the proteolytic processing of the proinflammatory cytokines interleukin (IL)-1β and IL-18 to active forms. Mutations in NALP3 components of inflammasome lead to dysregulated activation and release of IL-1b resulting in several auto-inflammatory diseases known as cryopyrinopathies. Little is known about the role of NALP3 in DCs, and how this could affect both innate and adaptive immune responses. The characterization of mechanisms underlying MSU-induced inflammation in DCs will be discussed.

Takeshi Tsubata

(Tokyo Medical and Dental University)

Biodata

Dr. Takeshi Tsubata joined TMDU in 1996 as a Professor in the Department of Immunology, MRI. In 2003, he became a Professor in the Laboratory of Immunology, Graduate School of Biomedical Sciences, TMDU. His research interest is how B lymphocyte fate after antigen stimulation is determined, whether normally activated as in naïve B cells, or rapidly activated as in memory B cells, or during apoptosis. Also, his group is interested in developing new strategies to improve infection immunity and to control autoimmune diseases and allergies by modulating B cell responses. His group has been focusing on molecules and molecular mechanisms that regulate B cell activation and apoptosis including membrane-bound lectins CD22 and CD72.

Symposium Talk: Membrane-bound lectins and humoral immunity

Abstract

B lymphocytes express membrane-bound lectins that regulate B cell signaling such as CD22 (also known as Siglec-2) and CD72. CD22 is a member of the Siglec family, and specifically recognizes α 2,6 sialic acid. CD72 contains a C-type lectin-like domain in the extreacellular part, although it is not yet formally proven whether CD72 recognizes glycans. Both CD22 and CD72 contain immunoreceptor tyrosine-based inhibition motifs (ITIMs) in the cytoplamic regions, and are inhibitory co-receptors that negatively regulate B cell antigen receptor (BCR) signaling by recruiting and activating the SH2 domain-containing protein tyrosine phosphatase 1 (SHP-1).

In spite of the inhibitory function of CD22, most of the previous studies demonstrated that antibody responses to antigens are not augmented in CD22-deficient mice. However, we demonstrated that activation of CD22-deficient B cells is augmented at the early phase of the immune responses. CD22-deficeint B cells initiate antibody responses earlier and terminate it earlier than wild-type B cells. Thus, CD22 regulates time course of antibody production during immune responses. Time course of antibody production is crucial for infection immunity. After vaccination, memory B cells rapidly respond to antigens and produce antibodies, thereby removing pathogens before serious symptoms are generated. Thus, CD22 is an ideal target to augment infection immunity by inducing rapid antibody production.

CD72 polymorphism is associated with autoimmune diseases in both humans and mice. We established CD72 congenic mice carrying the background of MRL/lpr, C57BL/6/lpr and NOD mice, and also CD72-deficient mice. Analysis of these mice clearly demonstrated that CD72 polymorphism regulates development of both SLE-like autoimmune diseases in lpr mice, and type 1 diabetes in NOD mice. Thus, CD72 plays a crucial role in the regulation of self-tolerance and autoimmunity, and may be a good target for the development of new therapies for these autoimmune diseases.

James W. Kazura

(Case Western Reserve University, USA)

Symposium Talk: Progress and challenges toward malaria vaccine development

Abstract

Despite remarkable advances in malaria genetics, genomics, and cell biology over the past several decades, there is only one product that progressed to large scale field trials in the primary target population: RTS,S which is based on the Circumsporozoite Protein, and which is now undergoing phase 3 clinical trials in African infants, who represent the group at highest risk of severe malaria and death from Plasmodium falciparum malaria. The political and scientific landscape on which continuing malaria vaccine development will occur has recently changed – there is now a global call for not simply malaria control, i.e. reducing the burden of malaria-related illness in endemic populations, but for local elimination and ultimately, global eradication of this pathogen. Concomitantly, substantial progress has been made in reducing transmission in many endemic areas through the use of vector control such as universal deployment of long lasting insecticide treated bednets. This symposium will address how these expectations and public health interventions affect the scientific and clinical challenge to future malaria vaccine development and testing.

Hirokazu Tamamura

(Tokyo Medical and Dental University)

Biodata

In 1988, Dr. Hirokazu Tamamura graduated from the Faculty of Pharmaceutical Sciences, Kyoto University, and then entered the Master Course of Graduate School of Pharmaceutical Sciences, Kyoto University. In May, 1989, he left the master course halfway and became an Assistant Professor at the Faculty of Pharmaceutical Sciences, Kyoto University. He received his Ph. D. from the Pharmaceutical Sciences from Kyoto University in 1995, where he became a Lecturer in 1997, and an Associate Professor in 2005. In April, 2005, he moved to Tokyo as a full professor at Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University. Dr. Tamamura studied abroad at the National Cancer Institute/NIH in 1999-2000. He is the head of the Department of Medicinal Chemistry and his research fields are chemical biology, medicinal chemistry, peptide-protein chemistry and organic chemistry. Concerning medicinal chemistry, anti-cancer agents, anti-HIV inhibitors and AIDS vaccines have been developed.

Symposium Talk: Anti-HIV inhibitors and AIDS vaccines

Abstract

AIDS is a scary disease which threatens public health, and the number of HIV-infected and AIDS patients is still increasing. Recently, highly active anti-retroviral therapy (HAART), which involves a combinational use of reverse transcriptase inhibitors and HIV protease inhibitors, has brought great success in the clinical treatment of AIDS patients. However, HAART has serious clinical problems including the emergence of multi-drug resistant HIV-1 strains, severe side effects and high costs. These drawbacks encouraged us to find novel drugs and increase repertoires of anti-HIV agents with various action mechanisms. The recent discovery of the dynamic supramolecular mechanism in HIV-entry has provided potentials to find a new type of drugs. To date, we have synthesized HIV-entry inhibitors, especially coreceptor CXCR4 antagonists. In addition, protease inhibitors based on a combinatorial design, and CD4 mimics in consideration of synergic effects with other entry inhibitors or neutralizing antibodies have been developed. The development of the above anti-HIV agents is based on the concept of reverse chemical genomics, in which target molecules are fixed. On the other hand, based on the concept of forward chemical genomics, in which active compounds are searched according to the screening of random libraries, effective peptide leads such as integrase inhibitors have been discovered. As such, from a point of view on chemical biology, anti-HIV leads have been found utilizing reverse and forward chemical genomics. Furthermore, vaccine-based therapy is still thought to be a promising treatment for AIDS, because the number of HIV-infected and AIDS patients is remarkably increasing in developing countries, in which the treatment of drug-based therapy requiring high costs might be difficult. Thus, peptidic antigen molecules based on artificial remodeling of the dynamic structures of surface proteins in HIV-entry have been synthesized and evaluated for induction of neutralizing antibodies. These anti-HIV agents might be important and useful compounds in consideration of cocktail therapy of AIDS. In addition, the present concept of chemical biology for the development of anti-HIV agents is essential for drug discovery in medicinal chemistry.

ISP2010 Invited Participants

ISP2010 Invited Participants

A

SAMREEN AHMED

Pakistan

National University of Singapore

W.NURFAHIZUL IZZATI W.ALIAS

Malaysia

Poster #6

National University of Singapore

EI EI AUNG

Myanmar

Nilar Specialist Clinic

Poster #17

B

RAMESH BASNET

Nepal

Tribhuwan University

DHANUSHKA LEUKE BANDARA

Sri Lanka

University of Peradeniya

ARUNDHATI CHANDRASHEKHAR BHINGARE

India

University of Pune

C

XUYONG CHEN

China

Peking University Health Science Center

Poster #20

TANITA CHUCHARTPONG

Thailand

Prince of Songkla University

F

KWADWO KYEREME FREMPONG

Ghana

Noguchi Memorial Institute for Medical Research

Poster #3

K

KAING KONG

Cambodia

University of Health Science

L

CHUN WEI LEE

Malaysia

Universiti Sains Malaysia

Poster #5

JUAN LI

Malaysia

Peking University
School and hospital of Stomatology

Poster #12

M

PAOLO MARK BONDAD MANZANO

Philippines

University of the East

N

NYEIN ZARNI NAING

Myanmar

Kyaw Dental Centre

Poster #16

TRUONG MANH NGUYEN

Vietnam

Vietnam Odonto Stomatology Association (VOSA) & Faculty of Odonto Stomatology

Poster #10

P

RUNGTIWA PUNPA

Thailand

Srinakharinwirot University

Poster #9

R

MD. TAIBUR RAHMAN

Bangladesh

International Center for Diarrhoeal Disease Research, Bangladesh

Poster #2

T

BIMALA TIWARI

Nepal

Kathmandu University

W

JUNHUI WANG

China

Shanxi Medical University

Poster #19

WENG KIN WONG

Malaysia

Poster #13

Y

HALEESA YANFUL

Ghana

Noguchi Memorial Institute for Medical Research

HUANKAI YAO

China

Tianjin University

NAUNG YE

Myanmar

Prince of Songkla University

Z

YOGHATAMA CINDYA ZANZER

Indonesia

Bogor Agricultural University

Poster #21

JING ZHANG

China

China Medical University

XIAOHONG ZHANG

China

Sichuan University

Poster #14

ISP2010 TMDU Participants

ISP2010 TMDU Participants

A

NURSARAT AHMED

Bangladesh

Poster #11

JIANBO AN

China

Poster #1

C

YUJIA CAO

China

Poster #8

URAIWAN CHOKECHANACHAISAKUL

Thailand

D

WENG DONG

China

G

T.D.C.P. GUNASEKARA

Sri Lanka

H

BIJAYA HAOBAM

India

NAY CHI HTUN

Myanmar

M

KATARINA MACUHOVA

Slovakia

SAAD HABIB-E-RASUL MULLAH

Bangladesh

P

SURESH PANTHEE

Poster #4

Q

PHAM NGUYEN QUY

Vietnam

Poster #7

X

CHEN XI

China

Poster #15

Abstracts of ISP2010 Poster Presenters

Poster No. 1

Jianbo An

(Tokyo Medical and Dental University)

Title: Losartan inhibits LPS-induced inflammatory signaling through a PPARγ-dependent mechanism in human THP-1 macrophages

Abstract

Jianbo An[1,2], Toshiaki Nakajima[1,2], Keiji Kuba[2,3,4], Akinori Kimura[1,2]

[1]Laboratory of Genome Diversity, Graduate School of Biomedical Science, [2]Department of Molecular Pathogenesis and [3]MTT Program, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan

[4]Department of Biological Informatics and Experimental Therapeutics, Akita University Graduate School of Medicine, Akita, Japan

Macrophages play critical roles in the pathogenesis of atherosclerosis by activating the innate immune system and producing inflammatory cytokines. Accumulating evidence indicates that angiotensin type 1 receptor (AT1R) blockers exert anti-inflammatory effects in inflammatory diseases including atherosclerosis. In this study, we investigated the effect of losartan, an AT1R blocker, on the pro-inflammatory gene expression induced by bacterial lipopolysaccharide (LPS) in a well-defined in vitro human THP-1 macrophage system. We found that losartan significantly attenuated the LPS-induced expression of pro-inflammatory genes *TNF-α, IL-8*, and COX-2. However, exogenous angiotensin II (AngII) had no effect on LPS-induced inflammatory signaling despite the expression of AT1R. In addition, losartan did not block LPS-induced IκB phosphorylation, which is downstream of Toll-like receptor activation. Peroxisome proliferator–activated receptor-gamma (PPARγ) antagonists GW9662 and T0070907 reversed the inhibitory effects of losartan on LPS-induced *TNF*-α and *IL-8* expression in THP-1 macrophages. These observations suggest that losartan inhibits LPS-induced pro-inflammatory gene expression in macrophages by activating the PPARγ pathway rather than by the competitive inhibition of AT1R binding to AngII.

Poster No. 2

MD. Taibur Rahman

(International Center for Diarrhoeal Disease Reasearch, Bangladesh)

Title: Cytokine responses in Viblio cholerae O1 infected patients and oral cholera vaccine recipients

Abstract

Alison Kuchta*[1], Taibur Rahman*[1], Taufiqur R Bhuiyan[1], Arifuzzaman M[1], Rasheduzzaman Rashu[1], Ashraful I Khan[1], Fahima Chowdhury[1], Amit Saha[1], Edward T Ryan[2,4,5], Stephen B Calderwood[#2.,4], Firdausi Qadri#1, Jason B Harris[#1,3]

*indicates co-first authors, [#]indicates co-senior authors.

[1]International Centre for Diarrhoeal Disease Research (ICDDR,B) Dhaka, Bangladesh; [2]Division of Infectious Diseases, Massachusetts General Hospital, Boston Massachusetts; Departments of [3]Pediatrics, [4]Medicine and [5]Microbiology and Molecular Genetics Harvard Medical School, Boston, Massachusetts.

Background

Vibrio cholerae O1 causes diarrheal disease that is life-threatening without appropriate treatment. Natural infection confers over 90% protective immunity for 5-7 years, while oral cholera vaccines confer up to 3 years of protection at varying degrees. The CD4+ T-cell responses to *V. cholerae* O1 infection has not been well characterized but may contribute to the development of longer lasting B-cell responses seen after infection.

Methods

To examine the profile of cytokine secreting $CD4^+$ T cells following either cholera infection or vaccination, we enrolled *V. cholerae* O1 infected Bangladeshi adult cholera patients and Dukoral vaccine recipients. The $CD4^+$ T-cell responses were assessed by intracellular cytokine staining assay following stimulation of peripheral blood mononuclear cells with *V. cholerae* specific antigens or by Luminex assay in antigen stimulated whole blood culture supernatants. $CD4^+$ T cells producing IFN-γ, IL-13, IL-10 and IL-17 were analyzed at multiple time points after infection or vaccination and compared with responses in healthy adult controls.

Results

Using both methods, stimulation with *V.* cholerae antigen resulted in increased proliferation of Th1 cytokine producing $CD4^+$ T cells at the acute and early convalescent stages following disease. In patients, the IFN-γ and IL-17 production was significantly elevated seven days after infection. IL-13 was also significantly elevated in the patient population; however the overall response was more skewed towards a Th1 response. Comparatively, the cytokine response in vaccinees was not as robust and shifted towards a Th2 response.

Conclusion

These results show that, in a cholera endemic population, $CD4^+$ T-cell responses are demonstrable at acute and early convalescence stages after infection and following vaccination in adults, and that there are significant differences in the characteristics of patient and vaccinee responses. Further studies are needed to address whether differences in the initial $CD4^+$ T-cell response in patients and vaccinees contribute to differences in the subsequent duration of protective immunity.

Key Words: *V. Cholerae,* natural infection, patients, vaccine recipients

Poster No. 3

Kwadwo Kyereme Frempong

(Noguchi Memorial Institute for Medical Research, Ghana)

Title: Biochemical and knockdown resistance of Anopheles gambiae to permethrin and deltamethrin (pyrethroids) at Kpone-On-Sea in the Greater Accra region of Ghana

Abstract

Anopheles gambiae is the most predominant malaria vector in Ghana and has been reported to confer resistance to pyrethroids. This resistance is linked to kdr gene mutation which affects the sodium channel gate in the nervous system. Oxidases, esterases and glutathione S-transferase have also been reported to confer resistance to pyrethroids through insecticide detoxification. It is not well known whether resistant mosquitoes exhibit both or one mechanism at a time and why some resistant mosquitoes do not possess the kdr gene mutation. Adult *Anopheles gambiae* were collected from four sectors at Kpone-On-Sea using human landing catches and larvae were also collected from different breeding sites. W.H.O susceptibility test for permethrin (0.75%), deltamethrin (0.05%) and DDT (4%) were conducted for five replicates each using twenty F1 adult female mosquitoes. PCR was used to test for presence of kdr gene mutation, species identification and molecular forms using one leg of each mosquito. Enzyme activities were measured on the same set of mosquitoes for oxidases, esterases and glutathione S-transferase using biochemical assays. Questionnaires on insecticide use were administered to 320 adults residing in the study area. In all, permethrin recorded 49.5% mortality, deltamethrin 81.1% and DDT 40%. Out of 160 *An. gambiae* tested using PCR, 94.4% were *An. gambiae s. s.* and 5.6% An. arabiensis. An. gambiae s. s. which were further digested recorded 86.1% M forms and 13.9% S forms. Kdr frequency in tested An. gambiae s. s. was 72.8% RR, 23.8% SS and 3.3% RS. Oxidases and α esterases were the two enzymes which significantly recorded a mean difference in activity between the *An. gambiae* field population and the Kisumu susceptible strains. *An. gambiae* population at Kpone-On-Sea was found to be more susceptible to 0.05% deltamethrin relative to 0.75% permethrin and 4% DDT. The *kdr* gene frequency was higher in the S forms (95.2%) compared to the M forms (69.2%). Mosquitoes that survived the bioassay tests and did not possess the *kdr* gene mutation were found to exhibit high activity for either oxidases and/or α esterase. Some *An. gambiae* individuals were found to exhibit both resistant mechanisms.

Poster No. 4

Suresh Panthee

(Tokyo Medical and Dental University)

Title: Development of screening system and identification of biomediators of reveromycin A biosynthesis

Abstract

Suresh Panthee, Yushi Futamura, Shunji Takahashi, and Hiroyuki Osada Chemical Biology Department, RIKEN, ASI

Reveromycin A (RM-A) is the major secondary metabolite produced by *Streptomyces reveromyceticus*. It is a potential drug seed for the treatment of bone disorders like osteoporosis as it induces apoptosis specifically in osteoclasts and then inhibits bone resorption. RM-A showed the inhibitory activity on eukaryotic protein synthesis through the inhibition of isoleucyl-tRNA synthetase. Sequencing of RM-A biosynthetic gene cluster in *S. reveromyceticus* revealed that 21 genes work in a coordinated manner to produce this polyketide compound. Various reports have shown that some small molecules are capable of regulating secondary metabolite production in different actinomycetes. We also found that production of RM-A was enhanced by the addition of tomato juice to the culture medium of *S. reveromyceticus*. Thus, we are focusing our work on finding a small molecule (biomediator) that enhances RM-A biosynthesis in *S. reveromyceticus*.

Purification of tomato juice did not succeed as it could not lead to convincing results. Next, we screened the chemical library of natural products and natural product derivatives from RIKEN NPDepo. Biomediator activity of compounds was judged by culturing *S. reveromyceticus* in the presence of compounds (1 μg/ml) and quantifying the amount of RM-A in the broth. RM-A has antifungal activity against plant pathogenic fungi. First screening was done by applying the broth to *Magnaporthe oryzae* to monitor growth inhibition. From this screening, 136 putative hits were identified from a total of 3155 compounds.

RM-A blocks the progression of cell cycle of a temperature sensitive mutant of Rous sarcoma virus transformed NRK (tsNRK) cells from G1 phase to S phase as well as reverses the transformed morphology of the cells. Second screening of putative hits was performed by judging the reversal of transformed phenotype of tsNRK cells by RM-A in the broth. The broth of 11 compounds selected from the second screening was subjected to HPLC analysis using authentic RM-A as reference. One compound with carboline core, NPD 2639 was identified as a biomediator of RM-A biosynthesis. NPD 2639 also enhanced the production of actinorhodin by *S. lividans* 1326 at the same concentration suggesting that the biomediator might be generalized to other Streptomyces spp.

Poster No. 5

Chun Wei Lee

(Universiti Sains Malaysia)

Title: Identification of potential biomarkers in excretory secretary (ES) antigen to detect Helicobacter pylori infection in different gastric pathologies

Abstract

Helicobacter pylori infections are associated with various gastric diseases and it was also classified as class I carcinogen by the World Health Organization. There is a wide spectrum of clinical outcomes by *H. pylori*, ranging from ulceration to gastric cancer. The pathogenicity of the infection depends on the strain virulence, host susceptibility and environmental co-factors. Hence, there comes an urgent need to identify useful biomarkers to facilitate development of highly specific and sensitive diagnostic kit for *H. pylori*. The present study was conducted to detect the antigenic proteins of excretory antigen of H. pylori with immuno blotting of serum samples from different gastric pathologies (19 = Chronic gastritis, 2 = Duodenal ulcer, 5 = Peptic ulcer, 4 = normal scope). *H. pylori* used in this study was isolated from biopsy sample of peptic ulcer patient in Malaysia. Excretory secretory antigen (ES) is chosen due to its higher specificity and sensitivity in comparison to other antigenic preparations. By using SDS-PAGE, different proteins were found in the excretory antigen, but the most promising were the three potential bands with the molecular weight of 60 KDa (sensitivity 86.6%), 25 KDa (sensitivity 86.6%) and 13 KDa (sensitivity 76.6%) by immune blotting.

Key words: excretory antigen, *Helicobacter pylori,* immunoblotting

Poster No. 6

W.Nurfahizul Izzati W.Alias

(Universiti Sains Malaysia)

Title: Characterization of a monoclonal antibody against Shigella flexneri for the development of a rapid detection test for shigellosis

Abstract

Introduction: Shigellosis is an acute bloody diarrhoea which is a major public health burden in the world especially in developing countries. Current method for diagnosis of shigellosis using culture technique is time-consuming, laborious and lack of sensitivity. As such, rapid diagnostic test which is highly sensitive, specific, simple and rapid is highly desired. Monoclonal antibody (MAb) is one of the important reagents necessary for development of rapid diagnostic test. In a previous study, a specific protein of 35 kDa protein was identified for *Shigella* spp.

Aim: The purpose of this study is to produce and characterize the monoclonal antibody against 35 kDa protein of *S. flexneri*.

Methods: The 35 kDa protein was isolated and purified from *Shigella's* surface associated protein. The production of MAb against this protein was carried out by the research team from Finlay Institute, Havana, Cuba. The titre of the antibody was determined by ELISA using whole cells of *Shigella*. The specificity and sensitivity of MAb was analysed using dot-EIA and Western blotting techniques by reacting with *Shigella* spp. and various enteric bacteria.

Results: High titre of MAb was produced against the 35 kDa protein. It was demonstrated to bound to the specific 35 kDa protein as well as with whole cells of *S. flexneri*. No cross-reaction was observed when tested with other related enteric bacteria.

Conclusion: This study showed that this MAb is specific to *Shigella* spp. and has potential to be used for development of rapid detection test for *Shigella* directly from stool specimen.

Poster No.
7

Pham Nguyen Quy

(Tokyo Medical and Dental University)

Title: Generation of transgenic mice expressing a fluorescent lysosomal marker

Abstract

Author(s): Pham Nguyen Quy; Eisuke Itakura, Noboru Mizushima, Department of Physiology and Cell Biology, TMDU

Lysosomes are single membrane-bound cytoplasmic organelles serving as major catabolic compartments in almost all eukaryotic cells. Characterized by low pH and a broad spectrum of more than 60 different hydrolases, lysosomes are the terminal station of the endocytic and autophagic pathways.

To analyze the behavior of mammalian lysosomes in vivo, we have generated transgenic mice systemically expressing RFP fused to LAMP1, a transmembrane glycoprotein predominantly found in lysosomal membranes. The transgenic mice are healthy, fertile and do not show any abnormal phenotype. LAMP1-RFP was expressed as bright small cytoplasmic dots in almost all examined tissues. Immunostaining study confirmed the colocalization of these signals with endogenous LAMP2, another lysosomal marker protein.

Although Lamp1-RFP dots showed perinuclear accumulation in most tissues, there were several exceptions. Lamp1-RFP dots localized in the pericanalicular areas of hepatocytes while they distributed mainly in the apical and basal side of intestine and lens epithelium respectively. While Lamp1-RFP signals were observed as dots near the plasma membrane of parietal cells (gastric glands) and the zona glomerulosa (adrenal gland), they decorated the esophageal stratified squamous epithelium and skin stratum corneum as extremely bright band-like structure. These results suggest that there might be cell-type and tissue-specific differences in the morphology and distribution of lysosomes.

This transgenic mouse model would be a useful tool to study the behavior of mammalian lysosomes in vivo under different pathophysiological conditions.

Poster No.
8

Yujia Cao

(Tokyo Medical and Dental University)

Title: Overexpression of B7-H1 in keratinocytes regulates epithelial - mesenchymal transition and accelerates squamous cell carcinoma formation

Abstract

Yujia Cao, Lu Zhang, Yosuke Kamimura, Patcharee Ritprajak, Masaaki Hashiguchi, Sachiko Hirose, and Miyuki Azuma

B7-H1 (CD274) is often induced on human tumor cells and its expression has been shown to be involved in immune escape mechanisms by tumor cells. B7-H1 is also inducible in normal tissue cells under various inflammatory conditions, but little is known about the involvement of B7-H1 in the conversion of normal to tumor cells. Here, we found that a keratinocyte (KC)-specific transgene of B7-H1 exhibited accelerated skin tumor formation in a 3-methylcholantrene (MCA)-induced squamous cell carcinoma (SCC) model. Inflammatory responses induced by MCA-injection or TPA-painting in the supra-dermis were clearly inhibited in B7-H1 transgenic mice (B7-H1tg). Blockade of either B7-H1 or PD-1 by neutralizing mAbs revealed that the reduced inflammation was dependent on B7-H1 and PD-1 interactions. KCs from B7-H1tg mice showed constitutive reduction of E-cadherin, and the SCC derived from B7-H1tg mice showed more obvious loss of E-cadherin and higher expression of the transcription factors Slug and Twist. These results indicate that up-regulation of B7-H1 in KCs promotes the epithelial-mesenchymal transition and accelerates carcinogenesis. Our results provide a new insight into B7-H1 function: persistent overexpression of B7-H1 may cause intrinsic changes within the cell and promote carcinogenesis.

Poster No. 9

Rungtiwa Punpa

(Srinakharinwirot University, Thailand)

Title: HMGB1 expression in human gingival and PDL fibroblast activated by *Porphyromonas gingivalis*

Abstract

Rungtiwa Punpa. Narongsak Laosrisin, Nirada Dhanesuan.

High mobility group box1 (HMGB1) protein is a nuclear protein which is recognized as a late inflammatory cytokine but plays important roles in many inflammatory diseases. Periodontitis is a chronic inflammatory disease that leads to loss of tooth supporting structures. Previously, we investigated HMGB1 expression in oral fibroblasts including human gingival and periodontal ligament fibroblasts. It was found that both cells expressed HMGB1 RNA and protein in cell lysates. Furthermore, it showed upregulation of HMGB1 RNA after lipopolysacharide (LPS) of Escherichia coli treatment. This study aimed to investigate the expression of HMGB1 in human gingival and periodontal ligament fibroblasts after activated by LPS of *Porphyromonas gingivalis (Pg.)*

Materials and methods: Both types of cell were cultured and activated by LPS of *Pg*,. Twenty-five μg/ml and 50 μg/ml of LPS of *Pg*, were used in LPS treatment group. Sterile distilled water was used as a control. Duration of treatment were 24 hours for RNA extraction and 48 hours for cell lysate extraction. The expression of HMGB1 mRNA was determined by RT-PCR and HMGB1 protein in cell lysate was determined by Western blot.

Results: Both HMGB1 mRNA and protein expression were upregulated in human gingival fibroblast when activated by LPS of *Pg*, while only HMGB1 protein level was upregulated in human periodontal ligament fibroblast.

Conclusion: The results showed that the purified LPS of *Pg*. can activate the expression of HMGB1 in human gingival and human periodontal ligament fibroblasts. It is possible that HMGB1 may play role in the pathogenesis of periodontal disease. Further investigation is required for detailed role of HMGB1 in periodontal disease.

Poster No. 10

Truong Manh Nguyen

(Vietnam Odonto Stomatology Association (VOSA) & Faculty of Odonto-Stomatology)

Title: Infection in mandibular after fixation fractures surgery with plate and screws: Case Report

Abstract

In recent years, as Viet nam develops economially, the quantity and kinds of vehicles in traffic has been increasing quickly, hence the rate of maxillofacial trauma is very high. Mandibular fractures are especially troubling because of damage to shape and function (as per a report of patients who had maxillofacial trauma and were treated in Department of Trauma and Reconstruction maxillofacial at National Odonto-Stomatology Hospital, Ha Noi, Viet Nam). Now we have many methods of treating mandibular fractures. One treatment, which is used commonly in the world, is the rigid fixation with plate and screws system. Complications following the fixation of mandibular fractures are rare, from a literature review and authors's experience, and it appears that the most common complication is infection and osteomyelitis. Some other complications are delayed healing, nonunion, nerve disorders, and malunion.
The reason for infection developing may be due to three factors:

- Surgeons: skill, experience in operation
- Patient lesions: preoperative oral sepsis, severity of fractures, teeth in the line of fracture, fracture in mixed dentition, displacement of fractures fragment
- Others: prolonged time prior to treatment, poor compliance by the patient, alcoholic or metabolic disturbances

Next we examined one patient with mandibular infection was treated for mandibular fractures by using the plate and screws system
Clinical symptoms of infection, such as in soft tissue infection and osteomyelitis (acute or chronic), include:swelling, pain, purulent exudate in the soft tissue outside the bone may be through the skin or mucosa. Radiography feature usually present blotchy islands of dead bone referred to as sequestrum (in acute osteomyelitis); bone more radiopaque than normal is referred to as osteosclerosis (in chronic osteomyelitis), in reality, acute osetomyelitis almost always appears.

Treatment for normal maxillofacial infections:

Drainage purulent
Determine and remove causative factor and dead bone fragments, maybe by plates and screws
Use reconstruction plate if bone tissue was destroyed severely,
Use antibiotics
Following-up short and long term carefully

Poster No. 11

Nursarat Ahmed

(Tokyo Medical and Dental University)

Title: Potential control of HIV-1 replication in macrophages by commensal organisms stimulating TLR4

Abstract

Nursarat Ahmed[1], Takaya Hayashi[1], Atsuhiko Hasegawa[1], Hiroyuki Furukawa[1], Noboru Okamura[2], Toshio Chida[2], Takao Masuda1, Mari Kannagi[1]

Institutes:

[1]Department of Immunotherapeutics, Graduate School, Tokyo Medical and Dental University, [2]Laboratory of microbiology and Immunology, Graduate School of Health Care Sciences, Tokyo Medical and Dental University

Enormous efforts have been made on vaccine development and some vaccines have successfully induced HIV-1-specific T-cell responses. However, protection from HIV-1 infection has not yet been accomplished. In spite of the difficulty to develop protective HIV-1 vaccines, it has been reported that a small subgroup of female sex-workers in Nairobi, Kenya remained resistant for HIV-1 infection without apparent hereditary reasons. The presence of local HIV-1-specific immune responses and sporadic late seroconversion in this group suggested that HIV-1 infection was minimized mostly at the site of infection by a transient mechanism. We hypothesized that innate immunity might be involved in the resistance for HIV-1 infection, and investigated what conditions could limit HIV-1 replication in macrophages, as macrophages are initial targets of HIV-1 infection and also the main mediators of innate immunity. We established a HIV-1 reporter monocytic cell line, THP-1/NL4-3luc, which could be differentiated into macrophage-like cells in vitro. Stimulation of TLR3 and TLR4 by their ligands suppressed HIV-1 replication in THP-1/NL4-3luc cells partly through IFN-β-mediated mechanisms. We also examined the effects of commensal bacteria as a candidate to mediate such signals, and found that some commensals suppressed HIV-1 replication, whereas some enhanced it. Similar results were obtained when using monocyte-derived macrophages. Reporter assays using TLR2 or TLR4 ligand-expressing cells revealed that the bacteria with suppressive effects preferentially stimulated TLR4, whereas the ones with enhancing effects stimulated TLR2. These findings imply that certain commensal bacteria preferentially stimulating TLR4 might contribute to produce local environments resistant for HIV-1 infection.

Poster No.
12

Juan Li

(Peking University School and Hospital of Stomatology, China)

Title: The Noninvasive Test in the Diagnosis of Oral Hairy Leukoplakia

Abstract

Objective: The purpose of this study was to explore the possibility of diagnosing oral hairy leukoplakia (OHL) by means of noninvasive tests.

Method: Exfoliative cytology and virus DNA specimens were obtained from lesions of 40 HIV sero-positive participants, who demonstrated clinical features of oral hairy leukoplakia. Cytologic smears were processed according to routine Papanicolaou (PAP) stain procedure for detection of morphologic changes and periodic acid-Schiff (PAS) stain procedure for detection of C. albicans hypha invading the parakeratin layer of the epithium under standard microscopy. DNA was extracted from exfoliative cells of OHL lesions, with which realtime fluorescent quantitative polymerase chain reaction (PCR) was used to detect the Epstein-Barr virus (EBV) DNA.

Result: Of the 31 DNA samples, 26 (83.9%) were positive for EBV DNA. 23 (79.3%) of 29 cases demonstrated condensation and margination of nuclear chromatin (nuclear beading), while 19 (65.5%) of 29 cases displayed enlarged binucleation or multinucleation. And 18 (62.1%) cases both, and 24 (82.8%) cases either demonstrated nuclear beading and binucleation or multinucleation. Compared with quantitative PCR positive reaction for EBV DNA, the sensitivity of PAP stain used for detection of evidence of virus infection in OHL is 80% (Criteria: either nuclear beading or binucleation or multinucleation was seen). All of the 5 quantitative PCR negative for EBV DNA cases were suggested having virus infection by PAP stain. C.albicans hyphes were noted in 83.3% (15/18) cytologic smears.

Conclusion: Noninvasive tests, PAP stain for virus infection morphologic change, and exfoliative cell PCR positive reaction for EBV DNA are efficient methods to screen the OHL in HIV sero-positive individuals.

Poster No. 13

Weng Kin Wong

(Universiti Sains Malaysia)

Title: Demonstration of potential antigenic components of excretory-secretory antigen for serodiagnosis of amoebic liver abscess

Abstract

Wong Weng Kin[1], Tan Zi Ning[2], Nurulhasanah Othman[1], Lim Boon Huat[2], Zeehaida Mohamed[3] and Rahmah Noordin[1]

[1]Institute for Research in Molecular Medicine, Universiti Sains Malaysia, Malaysia

[2]School of Health Sciences, Universiti Sains Malaysia, Malaysia

[3]Department of Medical Microbiology and Parasitology, School of Medical Sciences, Universiti Sains Malaysia, Malaysia

Amoebiasis is a cosmopolitan parasitic disease caused by *Entamoeba histolytica*. The disease has become a globalized problem due to the ease of world travel. According to WHO report, this disease affects about 10% of the world population. Humans get infected through the ingestion of the infective stage cysts. The symptomatic patient may present with amoebic dysentery, amoebic colitis, and amoebic liver abscess (ALA). ALA is potentially fatal if early diagnosis and treatment is not sought. Currently, the diagnosis for ALA often depends on clinical symptoms, radiological imaging and serological test. Indirect Haemagglutinin (IHA) and TechLab E. histolytica II are commonly used for the diagnosis in Amoebiasis. However, previous reports revealed that these two tests showed low sensitivity for the serodiagnosis of ALA.

The present research aims at identifying novel potential antigen(s) of *E. histolytica* that can improve the serodiagnosis of ALA. We are investigating the excretory-secretory antigens (ESA) of this parasite as reports had shown that ESA showed good sensitivity for detection of amoebic cysts passers, amoebic dysentery cases and ALA. Seven serum samples from human cases of ALA were used, these were positive by IHA as well by real-time PCR of the abscess fluid. Thus far, our Western blot study had shown that ESA (7/7) showed better sensitivity for detection of ALA as compared to crude soluble antigen (5/7).

Acknowledgement

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Poster No.
14

Xiaohong Zhang

(College of Pre-clinical and Forensic Medicine, Sichuan University, China)

Title: Preparation, identification and application of a monoclonal antibody against delta-like-1

Abstract

The Notch family of proteins plays a key role in determining cell fates, such as proliferation, differentiation, and apoptosis. Through the interaction of Notch ligands and receptors, the Notch signal pathway precisely controls the differentiation of the lineage cells. Delta-like-1 is the ligand of Notch-1 in the Notch signal pathway. Human delta-like-1 genes, with a length of 3040bp, OFR encoding 723 amino acids locate on chromosome 6q27. Delta-like-1 proteins have been reported to express on glioma. Thus the antibody against human delta-like-1 might be an effective tool to investigate the role of notch signal pathway. The goal of this project is to prepare and identify the monoclonal antibody (mAb) against human delta-like-1, further to investigate if delta-like-1 is related to autoimmue disease using made antibody.

First, we prepare of anti-delta-like-1 monoclonal antibody, including two stable monoclonal hybridoma cell lines of 3H11C11A9E3 and 2D5D11F8F1. The affinity constants(Kaff) of MAbs against delta-like-1 were measured by non-competitive ELISA, and Kaff of MAbs 3H11C11A9E3 and 2D5D11F8F1 were 3.98×107 L/mol and 3.28×107 L/mol. second, we characterize of anti-delta-like-1 monoclonal antibody and use methods of Western blot analysis against cell lysate of cultured glioma cells (U251 cells) and immunocytochemistry using U251 cells grown on coverslips; third, in our preliminary experiment, we found that delta-like-1 molecule expressed in SLE and RA using immunofluorescence technique. Thereby, we have been interesting in further study of delta-like-1 in the relationship with autoimmue disease using the antibodies we made. Currently, we are collecting the samples of autoimmune disease and investigating the relationship between delta-like-1 molecule and autoimmune disease.

Poster No.
15

Chen Xi

(Tokyo Medical and Dental University)

Title: Polymorphism of vacuolar protein sorting 13 homolog C (VPS13C) gene associates with blood pressure

Abstract

Chen Xi, Koichi Miyaki, Sinobu Ikeda, Masaaki Muramatsu

Dept. Molecular Epidemiology, Medical Research Institute, TMDU

* Division of Clinical Epidemiology, Department of Clinical Research and Informatics, National Center for Global Health and Medicine

Background: Vacuolar protein sorting 13 homolog C (VPS13C), belongs to the VPS13 family, which is originally found in yeast and involved in intracellular trafficking of a number of transmembrane proteins. A recent genome wide association study (GWAS) identified that a single nucleotide polymorphism (SNP) in the VPS13C gene, rs17271305, is associated with 2-h glucose level after oral glucose tolerance test in European population. We aimed to determine the effect of this SNP in Japanese population.

Methods: Two cohorts of Japanese men (n = 735) were included. Clinical information was obtained and genotyping was performed by TaqMan assay. Statistical analysis was done by SPSS 13.0 software.

Results: We analyzed the association of rs17271305 with glycemic traits, such as Hba1c and FPG in our cohort, but we could not obtain positive results. Instead, we identified that this SNP was significantly associated with blood pressure (βSBP = 3.720, PSBP = 0.011, βDBP = 2.764, P DBP = 0.004). Both systolic and diastolic blood pressures were higher in the GG+AG genotype group than in the AA group ($p<0.03$). When total energy intake was taken into account, the prevalence of dyslipidemia was significantly higher for the GG+GA genotype group, only in the highest energy intake tertile ($p= 0.033$).

Conclusion: VPC13C (rs17271305) was not associated with glycemic traits in Japanese men. Rather, we found that it may affect blood pressure levels, and under the interaction of energy intake, it may affect lipidemia. The function of VPC13C on metabolic phenotypes warrants further study.

Poster No. 16

Nyein Zarni Naing

(Kyaw Dental Centre, Myanmar)

Title: Health care financing in Myanmar: Review and outlook

Abstract

Health is the most fundamental amenity of living. Adequate and sustainable financial support is a vital requirement for providing health services with the objective of raising the health status of the people. Health care financing comes to appear as a critical instrument in figuring efficient and equitable health care delivery system. Financing health care is a major problem in almost all of low and middle income countries as a result of both explicit and implicit hindrances.

The poster aims to shed light on the health care financing system in Myanmar to excavate the roots of inhibitions to fulfill the better health outcomes and to figure out alternative solutions to finance health care in line with existing needs. By analyzing the national health accounts of Myanmar from the year 1995 to 2005, it illustrates the performance of health care financing in Myanmar alongside 10 years period.

It is found that, in Myanmar, sources of mobilizing health care mainly come from government tax revenue, social security funds, out-of-pocket payment and international assistance. The financing agents are Ministry of Health, other ministries, Social Security Board, Co-operatives, private clinics, voluntary organizations (NGOs, religious societies). Nonetheless, health care financing mainly relies on catastrophic out-of-pocket payment by people (88% of total health expenditure) while the government contribute very little only 0.9% of total government expenditures and around 10% of total health expenditure. Social health insurance is functioning but the coverage is too low (0.89%). Noticeably, there is no private insurance system in Myanmar.

The poster appraises the current practices of health care financing in Myanmar and discusses about the possible approaches of financing health care coping with country's need and existing circumstances such as encouraging community financing and decentralization in health sector. Myanmar definitely needs a comprehensive reform to attain efficiency and equity in health care provision in which there is an array of implications are to concern including political commitment, quality of health care, provider payment, administrative structure, fund management, community awareness and community demand.

Poster No. 17

Ei Ei Aung

(Nilar Specialist Clinic, Myanmar)

Title: The relationship between oral health status and reported oral hygiene behavior among adolescents

Abstract

Co-Author : Thant Sin, Yin Wai Hlaing, Su Yee Myo Zaw University of Dental Medicine, Yangon. Union of Myanmar

Oral diseases are rarely life-threatening although a healthy mouth undoubtedly improves the quality of life. Dental caries and periodontal diseases can be considered as behavioral diseases because they can be prevented simply by good oral hygiene and by restricting the intake of suger. Tooth brushing is the most effective oral hygiene method and the universally recommended frequency has been twice a day. Although the reported twice a day brushing frequency is high in some studies, geographical and gender differences existed. This study aims to assess the relationship between oral health status and reported tooth brushing frequency among 15-year old adolescent population.

Epidemiological study using clinical examination assessing dental caries and periodontal disease according to the WHO survey method and interview method determining tooth brushing behavior was carried out among 160 15-year old subjects from one township during June, 2008.

The study found that all subjects reported they brush regularly and almost two-thirds of the sample (71.9%) reported that they brush twice a day. Female reported significantly higher frequency of twice a day brushing than male (83.8% vs 60.0%). There are no differences in caries and periodontal condition between genders but males had a significantly lower mean number of calculus sextant than females (0.81 vs 1.55). There was no relationship between oral health status and tooth brushing frequency in total sample: however males who reported twice a day brushing had significantly lower calculus score than those who brush once a day.

Poster No.
18

Nay Chi Htun

(Tokyo Medical and Dental University)

Title: Cumulative effect of 13 polymorphisms on blood pressure and prevalence of hypertension

Abstract

Nay Chi Htun[1], Koichi Miyaki[2], Shinobu Ikeda[1], Masaaki Muramatsu[1]

[1] *Department of Molecular Epidemiology, Medical Research Institute, Tokyo Medical and Dental University.*
[2] *Division of Clinical Epidemiology, Department of Clinical Research and Informatics, National Center for Global Health and Medicine*

BACKGROUND

Hypertension (HT) is a multi-factorial disease, resulting from various environmental and polygenic factors. Recent genetic studies have identified multiple common variants that affect blood pressure (BP) levels. The aim of this study is to determine the gene-environment interaction, as well as the cumulative effect of these genetic factors.

METHODS

A total of 745 Japanese men from two separate cohorts participated in this study. 13 genetic loci including COMT, ATP2B1, GREB1, CYP11B2, CSK, CNNM2, AGTR2, ACADSB, PTK2B, ABCA1, HPCAL1, CDH13 and PTGIS were genotyped by TaqMan assay. Statistical analysis was performed with SPSS software (Ver 11).

RESULTS

Among these 13 SNPs, COMT val158met (rs4680) showed the strongest association with the prevalence of HT (OR=2.396, p=0.001) and BP traits. The AA genotype of COMT had higher adjusted SBP (+4.16 mmHg, P<0.001) and DBP (+2.38 mmHg, P=0.001) than the AG+GG group. This SNP also showed significant interaction with energy intake level on the prevalence of HT (p for interaction = 0.031). Associations between genotypes and HT or BP were also detected for six other SNPs in ATP2B1, GREB1, CYP11B2, CSK, CNNM2, and PTGIS, albeit at much weaker levels. Despite the marginal or non-significant effect of other individual loci, the cumulative effect of these 13 SNPs were significant. SBP and DBP increased in a stepwise fashion as the number of risk allele increased (1.143x, p=0.001, and 0.914x, p<0.001, respectively). Combined impact of genetic loci together with consideration of environmental factors warrants further study for the understanding of BP regulation.

Poster No.
19

Junhui Wang

(Shanxi Medical University, China)

Title: MPO function to the protein nitration after mechanical trauma

Abstract

Main Research Contents: Mechanical trauma can lead to myocardial damage, but the mechanism is still unclear. We have found that mechanical trauma can cause myocardial cells to apoptosis and increase the level of nitration in cardiac muscular tissues. However, its' mechanism is also undiscovered. Our research is to approach the main signal transduction pathways of myocardial cells apoptosis through examining the expression and activity of caspase-8, caspase-9 and caspase-12 in muscular tissues after mechanical trauma. Through investigating coronary artery endodermis function, the expression of ICAM-1 and MPO in muscular tissues, and relationship of MPO, nitration and apoptosis to reveal the possible mechanisms of MPO function to the protien nitration after mechanical trauma.

Main research aims:

1. To view and find out the the main signal transduction pathways of myocardial cells apoptosis after mechanical trauma.
2. To identify whether MPO will increase and its mechanism through examining the function of coronary artery endodermis, the expression and activity of ICAM-1 and MPO in cardiac muscular tissues.
3. To identify the rule of PMN-MPO in protein nitration and its mechanism in myocardial cells apoptosis.

Poster No.
20

Xuyong Chen

(Peking University Health Science Center, China)

Title: A mathematical model illustrating low-level sustained signals of tonic signaling pathway

Abstract

Tonic signal is a kind of background signal within the B cell with no extracellular relation based on present data. These signals can generate signals operating at multiple stages of B-cell development, and provide surviving signals for resting B cells.

Lyn is a key component in tonic signaling pathway. In resting B cells, lyn can transform among three distinct states sequentially — lyn-Cp (inactivated), lyn (primed) and lyn* (activated) with negative feedback and positive feedback loops. The level of Lyn* is critical as it can generate different downstream signals that lead to various biological functions. Here we construct a mathematical model to illustrate this low-level signal of Lyn*.

This model encompasses 21 chemical species and 27 reactions. The input is the total concentration of lyn and the output is the concentration of lyn*. We describe these reactions by a series of ordinary differential equations (ODE). The ODEs can be solved numerically using MATLAB, with results properly fit into two experimental observations: (1) it can well recapitulate the sustained low-level signal of tonic signaling pathway, which is significant for the survival of resting B cell; (2) at each developmental stage of B cell the intensity of tonic signal varies due to different level of Lyn*.

Poster No. 21

Yoghatama Cindya Zanzer

(Bogor Agricultural University, Indonesia)

Title: Potential role of vitamin A rich-weaning foods based on orange-fleshed sweet potatoes and fermented soy (tempe) in immune function and infection facing undernutrition problems and vitamin A deficiency in South-East Asia

Abstract

Yoghatama Cindya Zanzer[1)], Lilik Kustiyah, Firdaus

[1)]Author to whom correspondence should be addressed *yoghatama_cindyazanzer@yahoo.com)*

The first two years of life, called 'a golden age', has an important role for a good nutritional status and productivity on adult ages due to neural, brain, and body composition development. The World Health Organization (WHO) suggests that an infant should be introduced with weaning foods after receiving 6 months of exclusive breastfeeding (1,2,3). However, recent problems faced by South-East Asian countries is poor infants' nutritional intake lead to undernutrition and vitamin A deficiency. Vitamin A becomes an important nutrient due to its role in the differentiation of immune system cells, maintenance of mucosal surfaces, in the generation of antibody responses, in haematopoiesis and in the function of T and B lymphocytes, natural killer (NK) cells and neutrophils (4,5,6,7). Lack of vitamin A leads to reduced synthesis of RBP (retinol-binding protein) in response to infection and hence further impairment of immune responses (4). Therefore, dietary vitamin A intake is associated with a significant reduction in mortality (8,9,10,11,12,13), diarrheal and respiratory infections (14), and risks of stunting or wasting (15). Recently, several small controlled feeding trials showed increased serum retinol or improvements in vitamin A status after relatively short periods (3 weeks / 4 months) of feeding β-carotene-rich plant foods (16,17,18,19,20,21,22). Therefore, a suitable proportion of orange-fleshed sweet potatoes (Ipomoea batatas.) rich in β-carotene combined with Indonesian indigenous fermented soy (tempe) rich in protein with others valuable functional benefits will be an affordable nutritious weaning foods rich in vitamin A, protein, antioxidant and antibacterial content facing undernutrition and vitamin A deficiency in South-East Asia.

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International Summer Program 2010 Working Group

Chairperson

Miyuki Azuma

Members

Kazunari Akiyoshi
Kevin Cleary
Yuichi Izumi
Matazo Izutani
Mari Kannagi
Hajime Karasuyama
Akinori Kimura
Koji Masuda
Ikuko Morio
Yoko Okita
Nobuo Ohta
Tetsuya Taga
Yoshihiro Takemoto
Takeshi Tsubata