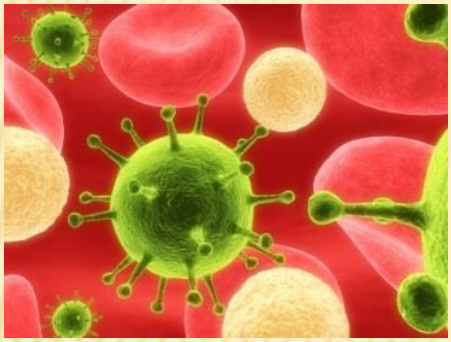
SENRI LF

2014 Senri Life Science International Symposium on

"Innate Immunity, Cytokines, and Immune Regulation"



Date : January 31st (Friday), 2014 10:00-17:00

Venue : Senri Life Science Center Building

5th floor "Life Hall"

Coordinated by

Shizuo Akira & Shimon Sakaguchi

Immunology Frontier Research Center, Osaka University

SPONSORED BY SENRI LIFE SCIENCE FOUNDATION

2014 Senri Life Science International Symposium
"Innate Immunity, Cytokines, and Immune Regulation"

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10:00- 10:10 Opening address

Tadamitsu Kishimoto (President of Senri Life Science Foundation) p.2

Chair : Shimon Sakaguchi (Osaka University)

10:10-10:50 "The non-canonical Inflammasome Pathway"

〈Talk 1〉 **Vishva M. Dixit (Genentech Inc., USA)** p.4

10:50-11:30 "Regnase-1, a ribonuclease essential for the regulation of immune responses"

〈Talk 2〉 **Shizuo Akira (Osaka University, Japan)** p.8

11:30-12:10 "Dendritic cell diversification in immune regulation"

〈Talk 3〉 **Kenneth Murphy (Washington University School of Medicine, USA)** p.12

12:10-13:10 **Lunch**

13:10-13:50 "Compartmentalized and systemic control of tissue immunity by commensals"

〈Talk 4〉 **Yasmine Belkaid (NIAID, NIH, USA)** p.16

Chair : Shizuo Akira (Osaka University)

13:50-14:30 "Memory T cells"

〈Talk 5〉 **Marc K. Jenkins (University of Minnesota Medical School, USA)** p.20

14:30-15:10 "Control of immune responses by regulatory T cells"

〈Talk 6〉 **Shimon Sakaguchi (Osaka University, Japan)** p.24

15:10-15:30 **Coffee break**

15:30-16:10 "The immune response in tuberculosis: from mouse models to human disease"

〈Talk 7〉 **Anne O' Garra (MRC National Institute for Medical Research, UK)** p.28

16:10-16:50 "A new era for the therapy of autoimmune inflammatory diseases"

〈Talk 8〉 **Tadamitsu Kishimoto (Osaka University, Japan)** p.32

16:50-17:00 Closing remarks

Shizuo Akira (Osaka University, Japan) p.36

Described time includes questions and answers.

Opening Address

Tadamitsu Kishimoto, MD.,PhD.

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<MEMO>

〈Talk 1〉
"The non-canonical Inflammasome Pathway"

Vishva M. Dixit, MD.

Title:

Vice President, Research
Genentech, Inc.
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Educational History:

1982 – 1986	Postdoctoral Fellow: Department of Biological Chemistry, Washington University School of Medicine
1981 – 1986	Resident: Department of Laboratory Medicine, Barnes Hospital, Washington University School of Medicine
1980 – 1981	Intern: Department of Medicine, Kenyatta National Hospital
1980	University of Nairobi, M.D.
1975 – 1980	University of Nairobi, Nairobi, Kenya

Research and professional experience

Current Appointments:

2005 – Present	Vice President, Early Discovery Research, Genentech
2006 – Present	Director, Genentech Postdoctoral Program
2006 – Present	Board of Directors, Genentech Foundation
2003 – Present	Genentech Research Review Committee Member
1999 – Present	Professor, Department of Pharmaceutical Chemistry, University of California, San Francisco
2011	Scientific Editor for *Cancer Discovery*

Past Genentech Appointments:

2003 – 2005	Vice President, Molecular Oncology
2000 – 2003	Senior Director, Molecular Oncology
1997 – 2000	Director, Molecular Oncology

Past Academic Appointments:

University of Michigan Medical School

1995 – 1997 Professor, Department of Pathology
1991 – 1995 Associate Professor, Department of Pathology
1986 – 1991 Assistant Professor, Department of Pathology

Washington University School of Medicine

1982 – 1986 Research Associate, Department of Biological Chemistry

Awards and Honors

2013 Member, National Academy of Sciences
2012 Member, Institute of Medicine, National Academy of Sciences
2012 Foreign Member, European Molecular Biology Organization
2012 Member, Association of American Physicians
2011 Member, American Academy of Arts and Sciences
2011 Zubrod Memorial Distinguished Guest Lecturer, University of Miami, Miami, FL
2011 HICC Distinguished Lecture, Columbia University, New York, NY
2010 The 2010 Dan H. Campbell Memorial Lecturer
2009 Karl Landsteiner Lecture, Vienna, Austria
2008 Doherty Lecture, St. Jude Hospital, Memphis, TN
2007 Daljit S. and Elaine Sarkaria Lecture, UCLA, Los Angeles, CA
2003 Kenneth Sell Memorial lecture, Emory University, Atlanta, GA
2000 UCSF Dean's Research Seminar, San Francisco, CA
1999 Menten Lectureship, University of Pittsburgh, Pittsburg, PA
1998 Blaffer Seminar, MD Anderson Cancer Center, Houston, TX
1998 General Motors Cancer Research Foundation, Mott Prize Selection Committee
1997 Directors Lecture, National Institute of Health, Bethesda, MD
1996 Hans Bloemendel Lecture, Netherlands
1996 Member, American Society for Clinical Investigation
1996 Warner-Lambert/Parke Davis Award in Experimental Pathology
1983 Josiah Macy Postdoctoral Fellowship Award
1980 Kamala Memorial Award for Best Overall Medical Student

Abstract

Caspase-1 activation by inflammasome scaffolds comprised of intracellular nucleotide-binding oligomerization domain (NOD)-like receptors (NLR) and the adaptor ASC is believed essential for production of the pro-inflammatory cytokines interleukin (IL)-ß and IL-18 during the innate immune response. We found that C57BL/6 gene-targeted mice that caspase-11 (also known as caspase-4) is critical for caspase-1 activation and IL-1ß production in macrophages infected with *Escherichia coli*, *Citrobacter rodentium*, or *Vibrio cholerae*. Mouse strain 129 exhibited similar defects in IL-1ß production and harboured a mutation in the *Casp11* locus that attenuated caspase-11 expression. This finding is important because published targeting of the *Casp1* gene was done using 129 ES cells. *Casp1* and *Casp11* are too close in the genome to be segregated by recombination so the published $Casp1^{-/-}$ mice lack both caspase-11 and caspase-1. Interestingly, $Casp11^{-/-}$ macrophages secreted IL-1ß normally in response to ATP and monosodium urate, suggesting that caspase-11 is engaged by a non-canonical inflammasome. $Casp1^{-/-}Casp11^{129mt/129mt}$ macrophages expressing caspase-11 from a C57BL/6 BAC transgene failed to secrete IL-1β regardless of stimulus, confirming an essential role for caspase-1 in IL-1ß production. Caspase-11 rather than caspase-1, however, was required for non-canonical inflammasome-triggered macrophage cell death, indicating that caspase-11 orchestrates both caspase-1-dependent and -independent outputs. Finally, loss of caspase-11 rather than caspase-1 protected mice from a lethal dose of lipopolysaccharide (LPS). These data highlight a unique proinflammatory role for caspase-11 in the innate immune response to clinically significant disease states.

References

1. Chinnaiyan, A.M., O'Rourke, K., Tewari, M., and V.M. Dixit: FADD, a Novel Death Domain-Containing Protein, Interacts with the Death Domain of FAS and Initiates Apoptosis. **Cell** Vol. 81:505-512 (1995).
2. Tewari, M., Quan, L.T., O'Rourke, K., Desnoyers, S., Zheng, Z., Beidler, D.R., Poirier, G.G., Salvesen, G., and V.M. Dixit: Yama/Cpp32ß, a Mammalian Homolog of CED-3, is a CrmA-Inhibitable Protease that Cleaves the Death Substrate Poly (ADP-Ribose) Polymerase. **Cell** Vol. 81:801-809 (1995).
3. Muzio, M., Chinnaiyan, A.M., Kischkel, F.C., O'Rourke, K., Shevchenko, A., Scaffidi, C., Bretz, J.D., Zhang, M., Ni, J., Gentz, R., Mann, M., Krammer, P.H., Peter, M.E., and V.M. Dixit: FLICE, a Novel FADD-homologous ICE/CED-3-like Protease, is Recruited to the CD95 (Fas/APO-1)

Death-Inducing Signaling Complex (DISC). **Cell** Vol. 85:817-827 (1996).

4. Muzio, M., Ni, J., Feng, P., and V. M. Dixit: IRAK (Pelle) Family Member IRAK-2 and MyD88 as Proximal Mediators of IL-1 Signaling. **Science** Vol. 278:1612-1615 (1997).
5. Humke, E.W., Shriver, S.K., Starovasnik, M.A., Fairbrother, W.J., and V.M. Dixit: ICEBERG: A Novel Inhibitor of Interleukin-1ß Generation. **Cell** Vol. 103:99-111 (2000).
6. Mariathasan, S., Newton, K., Monack, D.M., Vucic, D., French, D.M., Lee, W.P., Roose-Girma, M., Erickson, S., and V.M. Dixit: Differential activation of the inflammasome by caspase-1 adapters ASC and Ipaf. **Nature** Vol. 430:213-218 (2004).
7. Mariathasan, S., Weiss, D.S., Newton, K., McBride, J., O'Rourke, K., Roose-Girma, M., Lee, W.P., Weinrauch,Y., Monack, D.M., and V.M. Dixit: Cryopyrin activates the inflammasome in response to toxins and ATP. **Nature** Vol. 440:228-232 (2006).
8. Kayagaki, N., Warming, S., Lamkanfi, M., Walle, L.V., Louie, S., Dong, J., Newton, K., Qu, Y., Liu, J., Heldens, S., Zhang, J., Lee, W.P., Roose-Girma, M., and Dixit V.M. Non-canonical inflammasome activation targets caspase-11. **Nature** Vol. 479: 117–121 (2011).
9. Qu, Y., Misaghi S., Izrael-Tomasevic, A., Newton, K., Gilmour, L. L., Lamkanfi, M., Louie, S., Kayagaki, N., Liu, J., Komuves, L., Cupp, J. E., Arnott, D., Monack, D., and Dixit V. M. Phosphorylation of NLRC4 is critical for inflammasome activation. **Nature** Vol. 490; 539-542 (2012).
10. Kayagaki, N., Wong, M.T., Stowe, I.B., Ramani, S.R., Gonzalez, L.C., Akashi-Takamura, S., Miyake, K., Zhang, J., Lee, W.P., Muszynski, A, Forsberg, L.S., Carlson, R.W., Dixit, V.M. Non-canonical inflammasome activation by intracellular LPS independent of TLR4. **Science** Vol. 341:1246-1249 (2013).

〈Talk 2〉
“Regnase-1, a ribonuclease essential for the regulation of immune responses”

Shizuo Akira, MD., PhD.

Title:

Director & Professor, WPI Immunology Frontier Research Center, Osaka University
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Educational History:

1977	M.D. Osaka University, School of Medicine
1977-1978	Clinical Training at Osaka University Hospital
1980-1984	Ph.D. Osaka University, School of Medicine

Professional History:

1978-1980	Physician in the Department of Internal Medicine, Sakai Municipal Hospital, Sakai, Osaka
1984-1985	Fellowship of the Japan Society for the Promotion of Science in the Institute for Molecular and Cellular Biology, Osaka University
1985-1987	Research Fellow in the Department of Microbiology and Immunology, California University, Berkeley
1987-1995	Research Associate in the Institute for Molecular and Cellular Biology, Osaka University
1995-	Associate Professor in the Institute for Molecular and Cellular Biology, Osaka University
1996-1999	Professor of Biochemistry, Hyogo College of Medicine
1996-2002	Research Head in CREST (Core Research for Evolutional Science and Technology) and SORST (Solution Oriented Research for Science and Technology) of Japan Science and Technology Corporation (JST)
1999-present	Professor of Department of Host Defense, Research Institute for Microbial Diseases, Osaka University
2002-2007	Project Director of AKIRA Innate Immunity, ERATO (Exploratory Research for Advanced Technology) of Japan Science and Technology Corporation (JST)
2007-present	Director, WPI Immunology Frontier Research Center (WPI-IFReC), Osaka University
2011.10-2012.3	Senior Visiting Scientist, Quantitative Biology Center, RIKEN
2011.10-present	Professor Emeritus, Hyogo College of Medicine
2012.1-2013.3	Senior Advisor, Research Center for Allergy and Immunology, RIKEN
2013.4-present	Senior Advisor, RIKEN Center for Integrative Medical Sciences (-2014.3)
2013.7-present	Distinguished Professor, Osaka University (-2016.6)

Honors & Awards:

2001 Inoue Prize for Science (Inoue Foundation of Science)
2001 The Hideyo Noguchi Memorial Award for Medical Sciences
2002 Osaka Science Prize (Osaka Science & Technology)
2003 Takeda Prize for Medical Science (Takeda Science Foundation)
2004 The Prize of Princess Takamatsu Cancer Research Fund
2004 Plenary Lecture TOLL2004 (First International Toll Meeting), Taormia, Italy
2004 Robert Koch Prize (Robert Koch Foundation, Germany)
2005 Medal with Purple Ribbon (Japanese Cabinet Office)
2006 Asahi Prize (Asahi Shinbun)
2006 2004-2005 "Hottest Researcher" (Thomson Scientific)
2006 William B. Coley Award for Distinguished Research in Basic Immunology (Cancer Research Institute, USA)
2007 Uehara Prize (Uehara Memorial Foundation)
2007 2005-2006 "Hottest Researcher" (Thomson Scientific)
2007 Doctor honoris causa (Technical University of Munich, Department of Medicine)
2007 Dunham Lectures (Harvard Medical School)
2007 Imperial Prize and Japan Academy Prize (Japan Academy)
2007 Milstein Award (International Society for Interferon and Cytokine Research)
2007 Thomson Research Front Award (Thomson Scientific)
2008 Dyer Lecture (NIH)
2009 Marsh Lecture (The Feinstein Institute for Medical Research)
2009 Keystone Symposia: Pattern Recognition Molecules and Immune Sensors of Pathogens. Keynote Lecture
2009 Lacey Lecture (Washington University at St. Louis)
2009 National Academy of Sciences of USA, Foreign Associate
2009 Person of Cultural Merit (Japanese Government)
2009 Hans Bloemendal Medal (University of Nijmegen, Netherland)
2010 Fellow of the American Academy of Microbiology
2010 17th Dundee Cell Signaling Lecture (University of Dundee, Scotland)
2010 Keio International Medical Science Prize (Keio University)
2010 Avery-Landsteiner Prize (German Society for Immunology)
2010 Honorary lifetime member (International Endotoxin and Innate Immunity Society)
2010 EMBO Associate Member
2010 The 2011 Canada Gairdner International Award
2012 The Frederik B. Bang Award (Twelfth International Conference of the International Endotoxin and Innate Immunity Society

Abstract

Immune responses are accompanied by dynamic changes in gene expression. Gene expression is controlled at multiple points, including signal transduction, transcription and mRNA stability. So far, transcriptional regulation has been extensively studied. Many transcription factors including NF-κB and AP-1 are involved in induction of genes involved in inflammatory and immune responses. However, recent studies have revealed that control of gene expression at the mRNA level is as important as transcriptional control in the immune response. Gene expression profiles obtained from human Jurkat T cells stimulated with PMA plus ionomycin revealed that regulation of mRNA stability may account for as much as 50% of all measurements of changes in total cellular polyA mRNA. We have recently identified a novel gene named Zc3h12a which has a CCCH-type zinc finger domain. The knockout mice developed spontaneous autoimmune diseases accompanied by splenomegaly and lymphadenopathy. Subsequent studies showed that Zc3h12a is a nuclease involved in destabilization of IL-6 and IL-12 mRNA via the stem loop structure present in the 3'UTR of these genes. We renamed it Regulatory RNase-1 (Regnase-1) based on the function. I would like to discuss the role of Regnase-1 in the immune response.

<MEMO>

〈Talk 3〉
“Dendritic cell diversification in immune regulation”

Kenneth Murphy, MD., PhD.

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Educational History:

1974-1978	BA, Summa Cum Laude, Chemistry, Rice University, Houston, TX
1978-1984	MD, PhD, Johns Hopkins University School of Medicine, Baltimore, MD
1984-1988	Resident-in-Training, Department of Pathology, Washington University School of Medicine, Barnes Hospital, St. Louis, MO
1988-1989	Chief Resident, Anatomic Pathology, Washington University School of Medicine, St. Louis, MO
1986-1990	Postdoctoral training with Dr. Dennis Y. Loh, Department of Medicine, Washington University School of Medicine, St. Louis, MO

Professional History:

1989-1994	Assistant Professor, Department of Pathology, Washington University School of Medicine, St. Louis, MO
1994-1999	Associate Professor, Department of Pathology, Washington University School of Medicine, St. Louis, MO
1997-2003	Associate Investigator, Howard Hughes Medical Institute, Washington University School of Medicine, St. Louis, MO
1999-Present	Professor, Department of Pathology, Washington University School of Medicine, St. Louis, MO
2003-Present	Investigator, Howard Hughes Medical Institute, Washington University School of Medicine, St. Louis, MO

Honors and Awards:

1975-1977	Board of Governors Scholar, Rice University, Houston, TX
1977	Phi Beta Kappa
1978	B.A. Summa Cum Laude, Rice University, Houston, TX
1978	Z.W. Salsburg Memorial Award, Department of Chemistry, Rice University, Houston, TX
1978-1984	Medical Scientist Training Program Award, Johns Hopkins University School of Medicine, Baltimore, MD
1984	D.I. Macht Memorial Prize, Johns Hopkins University School of Medicine, Baltimore, Maryland
1988-1990	Juvenile Diabetes Foundation Career Development Award
2009	Distinguished Investigator Award, Washington University School of Medicine
2012	William B. Coley Award for Distinguished Research in Basic Immunology, Cancer Research Institute

Abstract

We previously focused on the transcriptional basis of T-cell subset development, since these subsets coordinate the selective activation of various modules of immunity that defend against different types of pathogens. We recognized that the cytokine mediators we found to control T cell differentiation were produced by cells of the innate immune system, we next sought to understand the physiologic basis that links infection by various pathogens to the induction of an appropriate immune module. Dendritic cells (DCs) are immune lineage sensor cells responsible for detecting infection and initiating effector responses. Discovered through their capacity to activate naïve T cells, DCs also can drive effector activity in innate lymphoid cells (ILCs) by the production of mediators, activating cytokines that can also determine the type of immunity induced. Over time, DCs have been recognized as comprising several subsets defined by differing patterns of overlapping markers that may manifest distinct functions. Our work over the past 5 years has been aimed at defining the transcriptional basis of DC diversification into subsets with unique functional properties. To demonstrate the dedicated roles of these subsets in vivo, we developed models in which DC subsets defined by their unique transcriptional programs could be selectively deleted in vivo, and then analyzed the consequences of these changes for immunity to various types of pathogens. A surprising outcome of these studies has been the finding that DC subsets can exert critical and non-redundant roles in innate immune defense, in addition to their expected role in driving adaptive immune responses. The results of these types of studies suggest that DCs might have already diverged during evolution before the emergence of RAG-dependent adaptive immunity, and before they played a role in adaptive immunity. Instead, DCs may have originally served to detect pathogens of differing character and to then coordinate the selective activation of the distinct subsets of ILCs that amplify pathogen-appropriate effector modules. This could imply that the transcriptional machinery underlying DC diversification might be found in organisms lacking RAG-dependent adaptive immunity.

<MEMO>

〈Talk 4〉
“Compartmentalized and systemic control of tissue immunity by commensals”
Yasmine Belkaid, PhD.

Title:

Mucosal Immunology Section, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Disease, NIH, Bethesda 20892, USA,
Immunology Graduate group, University of Pennsylvania, Philadelphia, PA 19104, USA

Educational History:

1989	B.S., Biochemistry, University of Science & Technology Houari Boumediene of Algiers, Algeria
1990	M.S., with Honors, Biochemistry**,** University of Science & Technology Houari Boumediene of Algiers, Algeria.
1991	Diplome d' Etude Approfrondie (DEA), Orsay University, Pasteur Institute, Paris, France
1996	Ph.D.**,** with Distinction**,** Immunology**,** Orsay University, Pasteur Institute, Paris, France

Professional history:

2008-Date	Senior Investigator, Chief Mucosal immunology section, Laboratory of Parasitic Diseases National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland
2007-Date	Adjunct Assistant Professor of Pathology and Laboratory Medicine, University of Pennsylvania
2005–2008	Head Mucosal Immunology Unit, Laboratory of Parasitic Diseases National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland
2002–2005	Assistant Professor, Division of Molecular Immunology Cincinnati Children's Hospital Medical Center, Department of Pediatrics University of Cincinnati, College of Medicine, Cincinnati, Ohio
2001–2002	Staff Scientist, Medical Entomology Section, LPD, NIAID, NIH, Bethesda, Maryland
1996–2001	Fogarty Fellow, Intracellular Parasite Biology Section, LPD, NIAID, NIH, Bethesda, Maryland
1995	Lecturer, Practical General Immunology Course Pasteur Institute
1989	World Health Organization Immunology Research and Training Center Department of Pathology, University Medical Center of Geneva, Switzerland
1988	World Health Organization Immunology Research and Training Center Department of Pathology, University Medical Center of Geneva, Switzerland

Honors & Awards:

2013	NIH Director's Award 2013 for groundbreaking contribution on the influence of the microbiota in host defense.
2012	NIAID Merit Award
2011	NIAID Merit Award
2010	NIAID Merit Award
2007	NIAID Merit Award
2003–2007	Ellison Foundation New Scholar Award in Infectious Diseases,
1997–1998	Phillips Foundation Award,
1996–1997	Phillips Foundation Award,
1994–1996	Foundation Marcel Merieux Award,
1991–1993	World Health Organization, Tropical Disease Research Fellowship,

Abstract

The body is composed of various tissue microenvironments with finely tuned local immunosurveillance systems, many of which are in close apposition with distinct commensal niches. Mammals have formed an evolutionary partnership with the microbiota that is critical for metabolism, tissue development, and host defense. Despite our growing understanding of the ramifications imposed by this host-microbe alliance on immunity in the gastrointestinal (GI) tract, the degree to which individual microenvironments are controlled by resident microbiota remains unclear. We uncovered an autonomous function for the skin microbiota in controlling the local inflammatory milieu and tuning resident T lymphocyte function. Highlighting the importance of local commensal stimulation, we find that protective immunity to a cutaneous pathogen is critically dependent on skin flora and independent of gut commensals. Further, our data demonstrate that the IL-1/MyD88 pathway is essential for skin T cell function and reveal that commensals co-opt this pathway to locally tune the function of T cells. These findings underscore the importance of the flora as a distinctive feature of tissue compartmentalization and unveil unique mechanisms of immune regulation by resident commensal niches in health and disease. We will discuss the potential implications of this dialogue for the establishment of immune homeostasis, protective responses, and tissue pathology.

<MEMO>

〈Talk 5〉
“Memory T cells”

Marc K. Jenkins, Ph.D.

Title:

University of Minnesota Medical School, Center for Immunology, Distinguished McKnight Professor
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E-mail address: jenki002@umn.edu
URL: http://www.micab.umn.edu/faculty/Jenkins.html

Educational History:

1980	B.S., Microbiology, University of Minnesota
1985	Ph.D., Immunology, Northwestern University, Mentor: Dr. Stephen D. Miller
1985-88	Postdoctoral Fellowship, NIH, Laboratory of Immunology, Mentor: Dr. Ronald H. Schwartz

Professional History:

1980-81	Research Technician, Departments of Surgery and Microbiology, University of Minnesota, Minneapolis, Minnesota
1985-87	Guest Researcher, Laboratory of Immunology, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
1987-88	Staff Fellow, Laboratory of Cellular and Molecular Immunology, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
1988-93	Assistant Professor, Department of Microbiology, University of Minnesota, Minneapolis, Minnesota
1993-98	Associate Professor, Department of Microbiology, University of Minnesota, Minneapolis, Minnesota
1997-2013	Associate Director, University of Minnesota Center for Immunology
1998-Date	Professor, Department of Microbiology, Center for Immunology, University of Minnesota, Minneapolis, Minnesota
2013-Date	Director, University of Minnesota Center for Immunology
2013-Date	President, American Association of Immunologists

Honors and Awards:

1984 Chicago Chapter Sigma Xi Research Competition
1989 Pew Scholars in the Biomedical Sciences Award
2002 American Association of Immunologists-Huang Foundation Meritorious Career Award
2002 Distinguished McKnight University Professor Award
2003 Award for Outstanding Contributions to Postbaccalaureate, Graduate, and Professional Education, University of Minnesota
2003 Institute for Scientific Information Highly Cited Researcher
2004 Academy for Excellence in Health Research, University of Minnesota Academic Health Center.
2008 NIH NIAID Merit Award
2009 1987 *Journal of Experimental Medicine* paper featured as a "Pillars of Immunology" article by the *Journal of Immunology*
2011 Senior Investigator Award, University of Minnesota Medical School.

Abstract

The capacity of vertebrate hosts to clear primary infection and develop immune memory to secondary infection depends on lymphocytes that express clonally unique receptors specific for antigens from the infecting microbe. CD4+ T cells express αβ T cell antigen receptors (TCRs) that recognize short microbial peptides bound to major histocompatibility complex II (MHCII) molecules on host cells, and provide protection from certain intracellular microbes. My presentation will focus on the mechanisms whereby rare naïve CD4+ T cells that express TCRs specific for a given microbial peptide-MHCII ligand become activated during infection to proliferate and differentiate into effector cells, a fraction of which become memory cells.

<MEMO>

〈Talk 6〉
“Control of immune responses by regulatory T cells”

Shimon Sakaguchi, MD., PhD.

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Educational History:

1970-1972	Kyoto University Premedical Course
1972-1976	Kyoto University Medical School

Professional History:

1976-1978	Resident, Department of Pathology, Kyoto University Medical School and Hospital
1978-1981	Visiting Investigator, Laboratory of Pathology, Aichi Cancer Center Research Institute
1981-1983	Senior Research Fellow, Institute for Immunology, Kyoto University Medical School
1981-1983	Joint Appointment at the Blood Transfusion Service, Kyoto University Hospital
1983-1985	Postdoctoral Fellow, Department of Immunology and Infectious Diseases, The Johns Hopkins Medical Institutions
1986-1987	Postdoctoral Fellow, Department of Biophysics, The Johns Hopkins Medical Institutions
1987-1989	Visiting Scientist, Division of Immunology and Rheumatology, Stanford University Medical Center
1989-1991	Assistant Professor, Department of Immunology, Scripps Research Institute
1992-1994	Investigator, Science and Technology Agency of Japan
1994-1997	Head, Department of Immunopathology, Tokyo Metropolitan Institute of Gerontology
1998-2011	Chair and Professor, Department of Experimental Pathology, Institute for Frontier Medical Sciences, Kyoto University
2007-2011	Director, Institute for Frontier Medical Sciences, Kyoto University
2011-present	Professor, Department of Experimental Immunology, Immunology Frontier Research Center, Osaka University
2012-present	Vice-director, Immunology Frontier Research Center, Osaka University
2013-present	Osaka University Distinguished Professor

Honors & Awards:

1986 Lucille P. Markey Scholar Award in Biomedical Science

2003 Mochida Science Award

2004 Cancer Research Institute's William B. Coley Award for Basic Immunology and Tumor Immunology

2005 Takeda Medical Award

2005 Takamine Memorial Sankyo Award

2007 The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology, The Government of Japan

2008 The Keio Medical Science Prize

2009 Medal with Purple Ribbon

2012 Asahi Prize

2012 Japan Academy Award

2012 Election to Foreign Associate of the National Academy of Sciences USA

Abstract

Naturally arising $CD25^+CD4^+$ regulatory T cells (Tregs), which specifically express the transcription factor Foxp3, are engaged in the maintenance of immunological self-tolerance and immune homeostasis by suppressing aberrant or excessive immune responses, such as autoimmune disease and allergy. Key issues for understanding immunological functions of natural $CD25^+Foxp3^+CD4^+$ Tregs include: how they develop in the thymus and the periphery, how they suppress immune responses , and how their functional and lineage stability is established and maintained.

Assuming that Foxp3 controls the gene(s) responsible for Treg-mediated suppression, we have shown that Treg-specific deficiency of CTLA-4 results in spontaneous development of systemic lymphoproliferation, fatal T cell-mediated autoimmune disease, and hyper-production of IgE as observed in Foxp3 mutant or deficient mice. Treg-specific CTLA-4 deficiency impairs *in vivo* and *in vitro* suppressive function of Tregs, in particular Treg-mediated down-regulation of CD80 and CD86 expression on dendritic cells. In addition, the expression of CTLA-4 by developing Treg cells contributes to their acquisition of a self-skewed TCR repertoire. Thus, CTLA-4 plays critical roles in Treg-mediated suppression and their development.

Foxp3 is essential for the development of Tregs, yet its expression is insufficient for establishing the Treg cell lineage. We have recently shown that Treg development is achieved by the combination of two independent processes, *i.e.*, the expression of Foxp3 and the establishment of Treg-specific CpG hypomethylation pattern. Both are induced by TCR stimulation. The Treg-type CpG hypomethylation begins in the thymus and continues to proceed in the periphery, and can be fully established without Foxp3. The hypomethylation is required for $Foxp3^+$ T cells to acquire Treg-type gene expression, lineage stability, and full suppressive activity. Thus, those T cells in which the two events have concurrently occurred are developmentally set into the Treg cell lineage. This model explains how Treg cell fate and plasticity is controlled, and can be exploited to generate functionally stable Tregs.

How these findings can be exploited in clinical settings will be discussed.

<MEMO>

〈Talk 7〉
"The immune response in tuberculosis: from mouse models to human disease"
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Educational History:

1983	Graduated from MRC, National Institute for Medical Research, London, Division of Microbiology (PhD Microbial Biochemistry)
1983-1987	Postdoctoral Fellow, Immunology, MRC, National Institute for Medical Research, London.
1987-1989	Postdoctoral Fellow, DNAX Research Institute, Palo Alto, CA.

Research Positions:

1989-1993	Senior Research Associate, DNAX Research Institute, Palo Alto, CA.
1993-1996	Staff Scientist, DNAX Research Institute, Palo Alto, CA.
1996-2000	Senior Staff Scientist, DNAX Research Institute, Palo Alto, CA.
2000-2001	Principal Staff Scientist (Director Level on the Research Track), DNAX Research Institute, CA.
2001-	Head, Division of Immunoregulation, MRC National Institute for Medical Research, London, UK.

Honors & Awards:

2nd of Highly Cited Authors in Immunology, 1992–2002 (ISI Science Indicators).
Election as Fellow of the Academy of Medical Sciences, UK–2005.
Election as an AAAS Fellow, in the Section on Medical Sciences
(American Association for the Advancement of Science)–2006.
Election as Fellow of The Royal Society, UK, 2008.
Election to EMBO membership, 2009.

Memberships and Professional Activities:

Editorial Board:
Editor: Journal of Experimental Medicine
Associate Editor: Immunity
Editorial Board: Immunology

Abstract

Tuberculosis (TB), caused by infection with *Mycobacterium tuberculosis* (*M. tuberculosis*), is a major cause of morbidity and mortality worldwide and efforts to control TB are hampered by difficulties with diagnosis, prevention and treatment. Most people infected with *M. tuberculosis* remain asymptomatic, termed latent TB, with a 10% lifetime risk of developing active TB disease, but current tests cannot identify which individuals will develop disease. We identified a whole blood transcript signature for active TB correlating with radiological extent of disease and reverting to that of healthy controls following treatment. A subset of latent TB patients had signatures similar to those in active TB patients. We also identified a distinct transcript signature that discriminated active TB from other inflammatory and infectious diseases. The immune response to *M. tuberculosis* is complex and incompletely characterized. Modular and pathway analysis of the blood transcriptome revealed that the TB signature was dominated by a neutrophil ‐driven interferon (IFN) ‐inducible gene profile, consisting of both IFNγ and Type I IFNαβ signalling. Comparison with transcriptional signatures in purified cells and flow cytometric analysis indicated that this TB signature reflects both changes in cellular composition and altered gene expression. Our studies demonstrate a hitherto under ‐appreciated role of Type I IFNαβ signalling in human TB pathogenesis, which has implications for vaccine and therapeutic development. Our subsequent studies now provide further knowledge regarding potential mechanisms underlying the contribution of type I IFN to TB and will be discussed in depth.

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Most relevant publications to the abstract

1. Berry, M.P.R., Graham, C.M., McNab, F.W., Xu, Z., Bloch, S.J. Oni, T., Wilkinson, K.A., Banchereau, R., Skinner, J., Wilkinson, R.J.W., Quinn, C., Blankenship, D., Dhawan, R., Cush, J.J., Mejias, A., Ramilo, O., Kon, O.M., Pascual, V., Banchereau, J., Chaussabel, D., and O’ Garra, A. 2010. Transcriptional Profiling Reveals an Interferon-Inducible Neutrophil-Driven Signature in Human Tuberculosis. Nature. 466, 973-77.
2. Redford, P., Boonstra, A., Read, S., Pitt, J., Graham, C., Stavropoulos, E., Bancroft, G., and O'Garra, A. 2010. Enhanced protection to Mycobacterium tuberculosis infection in IL-10-deficient mice is accompanied by an earlier and enhanced Th1 response in the lung. Eur J

Immunol. 40(8): 2200-10.

3. Redford PS, Murray PJ, O'Garra A. 2011. The role of IL-10 in immune regulation during M. tuberculosis infection. Mucosal Immunol. Mar 30.
4. McNab, F. W., Berry, M.P.R, Graham, C.M., Bloch, S.A.A., Oni, T., Wilkinson, K.A., Wilkinson, R.J.W., Kon, O.M., Banchereau, J., Chaussabel, D., and O' Garra, A. 2011. Programmed Death Ligand 1 is over-expressed by neutrophils in the blood of patients with active Tuberculosis. Eur. J. Immunol. Jul;41(7):1941-7.
5. Lowe DM, Redford PS, Wilkinson RJ, O'Garra A, Martineau AR. 2012. Neutrophils in tuberculosis: friend or foe? Trends Immunol. 33(1):14-25.
6. Pitt JM, Stavropoulos E, Redford PS, Beebe AM, Bancroft GJ, Young DB, O'Garra A. Blockade of IL-10 Signaling during Bacillus Calmette-Guerin Vaccination Enhances and Sustains Th1, Th17, and Innate Lymphoid IFN-γ and IL-17 Responses and Increases Protection to Mycobacterium tuberculosis Infection. J Immunol. 2012 Sep 12. [Epub ahead of print].
7. Bloom, CI, Graham, CM, Berry, MPR, Wilkinson, KM, Oni, T, Rozakeas, F, Xu, Z, Rossello-Urgell, J, Chaussabel, D, Banchereau, J, Pascual, J, Lipman, J, Wilkinson, RJ, and O' Garra, A. 2012. Detectable Changes in The Blood Transcriptome Are Present after Two Weeks of Antituberculosis Therapy. PLoS One. 7 (10), e46191.

<MEMO>

〈Talk 8〉
“A new era for the therapy of autoimmune inflammatory diseases”

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Educational History:

1964	Graduated from Osaka University Medical School
1970-1973	Research Fellow, Department of Medicine, Johns Hopkins University, School of Medicine

Professional History:

1973-1974	Assistant Professor in the Department of Medicine, Johns Hopkins University, School of Medicine
1974-1979	Assistant Professor, Department of Medicine III, Osaka University Medical School
1979-1983	Professor, Department of Pathology and Medicine, Osaka University Medical School
1983-1991	Professor, Institute for Molecular and Cellular Biology, Osaka University
1991-1998	Professor and Chairman, Department of Medicine III, Osaka University Medical School
1995-1997	Dean, Osaka University Medical School
1997-2003	President, Osaka University
2003-2011	Professor of Immunology, Graduate School of Frontier Biosciences, Osaka University
2004-2006	Member, Council for Science and Technology Policy, Cabinet Office
2007-Present	Chairman of the Board of directors, Senri Life Science Foundation
2011-Present	Guest Professor, Immunology Frontier Research Center, Osaka University

Honors & Awards:

1982 Behring-Kitasato Prize
1983 Osaka Science Prize
1986 Erwin von Bälz Prize
1988 Takeda Prize
1988 Asahi Prize
1990 Prize of The Japanese Medical Association
1990 Person of Cultural Merit, Japan
1991 Foreign Associate, The US National Academy of Science
1991 Scientific Achievement Award from the International Association of Allergology and Clinical Immunology
1992 Honorary Member, the American Association of Immunologists
1992 Imperial Prize from the Japan Academy
1992 Sandoz Prize for Immunology from International Union of Immunology Society
1992 Honorary Citizen, Tondabayashi City
1995 Member, the Japan Academy
1996 The Avery-Landsteiner Prize from the German Immunology Society
1997 Foreign Associate member, the Institute of Medicine of the National Academy of Science, USA
1997 Honorary member, the American Society of Hematology
1998 The Order of Culture from Emperor
1999 The Donald Seldin Award from the International Society of Nephrology
2000 ISI Citation Laureate Award
2001 Honorary Member, International Association of Dental Research
2002 Honorary Professor, the forth Military Medical University, Xi'an, China
2002 Honorary Member, World Innovation Foundation
2003 Doctor of Science, Honoris Causa, Mahidol University
2003 Robert Koch Gold Medal
2004 Clemens von Pirquet Distinguished Professor, Medicine and Immunology, University California, Davis
2005 Member, Deutsche Akademie der Naturforscher Leopoldina
2006 Honorary Lifetime Achievement Awards, International Cytokine Society
2009 The Crafoord Prize from the Royal Swedish Academy of Sciences
2010 CIS (Clinical Immunology Society, USA) President's Award
2011 The Japan Prize

Abstract

A series of studies have revealed that IL-6 has a pleiotropic activity in various tissues and cells and its deregulated expression is responsible for several chronic inflammations and hemopoietic malignancies.

Humanized antibody against 80kd IL-6R (Tocilizumab) has shown significant therapeutic effect in RA, JIA, Castleman's diseases, several other autoimmune inflammatory diseases, such as progressive sclerosis, reactive arthritis, polymyalgia rheumatica, adult still's desease and uveoretinitis. Cytokine storm induced by hyperactivation of T cells has been shown to be controlled by Tocilizumab. Recently, Th17 is shown to be responsible for the pathogenesis of autoimmune diseases and IL-6 together with TGF-β are essential for the induction of Th17.

Therapeutic effect of Tocilizumab indicates that overproduction of IL-6 is responsible for the pathogenesis of autoimmune diseases. Then, a question to be asked is how IL-6 production regulated. In a certain stimulation such as oxidized phospholipid (OxPL), overproduction of IL-6 was observed without any increase of TNF. This suggests that post-transcriptional regulation of IL-6 is important for abnormal production of IL-6. We identified a novel molecule, Arid5a, which specifically stabilizes mRNA of IL-6, sustains its overproduction and plays an important role in the promotion of these inflammatory processes and autoimmune diseases. In mice deleted of the Arid5a gene, no EAE was observed and LPS stimulation did not induce an increase of IL-6. In contrast, as was published, in Regnase-1 knockout mice, various autoimmune diseases were spontaneously induced and all mice died. Arid5a and Regnase-1 knockout mice showed mirror image phenomena regarding with autoimmune disease.

In T cells Arid5a is induced in the Th17 inducing conditions, indicating that Arid5a stabilizes not only IL-6 mRNA but also the other mRNA required for Th17 induction. Our preliminary study showed that Arid5a stabilizes STAT3 mRNA.

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Closing Remarks

Shizuo Akira, MD.,PhD.

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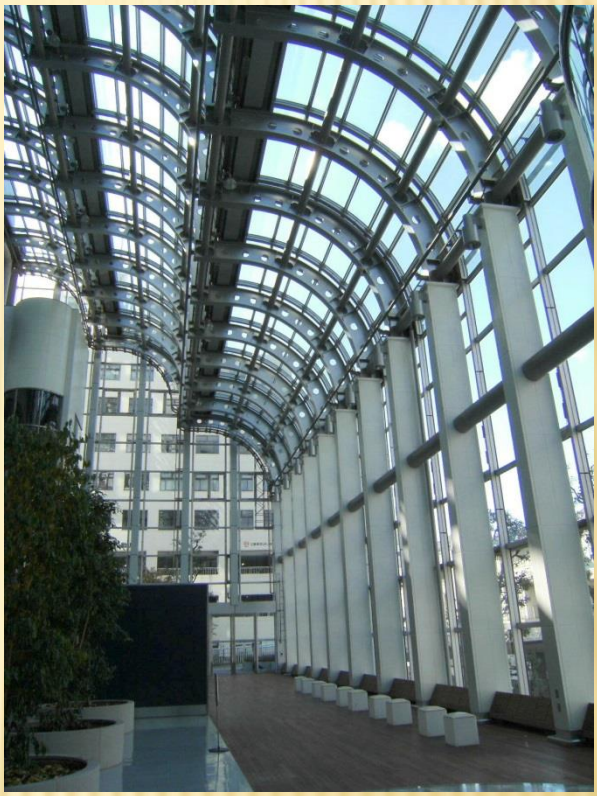

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