2009/09/01 現在

3rd Global COE Seminar
“Innate Immunity and Vaccine Adjuvants”

■Date & time **September 28, 2009　(mon) 17:00-19:10**
■Venue **Sapporo Aspen Hotel, 2F “Aspen A”**
Address/ Kita 8-jyo Nishi 4-chome, Kita-ku, Sapporo
Phone /011-700-2111
http://www.aspen-hotel.co.jp/english/frame.htm

■開催日時　9 月 28 日（月） 17:00～19：10
■開催場所　札幌アスペンホテル　2F 「アスペン A」会場
札幌市北区北 8 条西 5 丁目
tel. 011-700-2111,　http://www.aspen-hotel.co.jp/

■PROGRAM

17：00-17：05
Opening remarks
Hiroshi Kida, Graduate School of Veterinary Medicine & Research Center for Zoonosis Control, Hokkaido University

17:05-17:45
Pattern recognition receptors and their application to tumor immunotherapy: adjuvants that induce dendritic cell-mediated natural killer cell activation
Tsukasa Seya, Department of Microbiology and Immunology, Hokkaido University Graduate School of Medicine

17:45-18:25
The use of simple synthetic lipid structures for targeting different vaccine cargos to dendritic cells
David C. Jackson, Department of Microbiology and Immunology, The University of Melbourne, Australia

18:25-19:05
The role of adjuvants in vaccines for seasonal and pandemic influenza
Lorena E. Brown, Department of Microbiology and Immunology, The University of Melbourne, Australia

19:05-19：10
Closing remarks
Hiroshi Kida

■参加収容定員　100 名　先着順、参加費無料 （英語による講演、同時通訳なし。）
■主催　北海道大学グローバル COE プログラム
『人獣共通感染症国際共同教育研究拠点の創成』
http://www.vetmed.hokudai.ac.jp/gcoe/
■問い合わせ先　北大獣医学研究科グローバル COE 推進室　tel. 011-706-5294
gcoe@vetmed.hokudai.ac.jp
■懇親会予定　札幌アスペンホテル　2F 「アカシア」会場 （関係者のみ）

Pattern recognition receptors and their application to tumor immunotherapy: adjuvants that induce dendritic cell-mediated natural killer cell activation

Tsukasa Seya, Takshi Ebihara, Hiroyuki Oshiumi, Misako Matsumoto
Department of Microbiology and Immunology, Hokkaido University Graduate School of Medicine, Sapporo 060-8638, Japan. e-mail: seya-tu@pop.med.hokudai.ac.jp

Dendritic cell (DC) starts maturation in response to the complex stimuli consisting of the antigen and pattern molecule (PAMP) of the innate immunity. Recently, dendritic cells have been subdivided into a number of subsets with cell-surface markers, and they have unique differential maturation in response to pattern molecules to induce various effector cells. Here we review the pattern recognition molecules of each DC subset and outlined the mechanism of induction of the effector cells by PAMPs. In addition, we show the mechanism by which DC dependent NK activation is triggered for induction of antitumor NK activation.

Mouse dendritic cells (mDCs) express TLR3 in the endosome (1) and links the adaptor TICAM-1 (TRIF) (2). Stimulation of mDC TLR3 with dsRNA (or polyI:C) results in maturation of mDCs. A characteristic feature for activation of the TICAM-1 pathway in murine mDCs is to drive NK activation (3). The mDC potential for NK activation is typically observed in mDCs phagocytosing dsRNA-containing cell debris (4). Here we identified the transcription factor IRF-3- and a TICAM-1-inducing membrane molecule that governs the mDC-NK reciprocal activation. We named this protein IRF-3-derived NK-activating molecule (INAM) (5). We found polyI:C an adjuvant that induces INAM, therefore it activates NK cells. Using a mouse tumor-implanting model (B16D8 vs. C57BL/6), adoptive transfer of INAM-expressing mDCs but not vector control-mDCs allowed the tumor to regress in tumor-implant mice. Pre-injection of NK1.1 Ab into tumor-implant mice abrogated the INAM-mDC-mediated retardation of tumor growth. Hence, INAM facilitates adjuvant-mediated tumor regression in NK-sensitive tumor and is applicable to antitumor immunotherapy.

References

1. Matsumoto, M., and T. Seya. 2008. TLR3 : interferon induction by double-stranded RNA including poly(I:C). ***Adv. Drug Deliv. Rev.*** 60: 805-812.
2. Oshiumi, H., M. Matsumoto, K. Funami, T. Akazawa, and T. Seya. 2003. TICAM-1, an adapter molecule that participates in Toll-like receptor 3-mediated interferon-beta induction. ***Nature Immunol.*** 4: 161-167.
3. Akazawa T., M. Okuno, Y. Okuda, K. Tsujimura, T. Takahashi, M. Ikawa, M. Okabe, T. Ebihara, M, Shingai, N. Inoue, M. Tanaka-Okamoto, H. Ishizaki, J. Miyoshi, M. Matsumoto, and T. Seya. 2007. Antitumor NK activation induced by the Toll-like receptor3-TICAM-1 (TRIF) pathway in myeloid dendritic cells. ***Proc. Natl. Acad. Sci. USA***. 104: 252-257.
4. Ebihara, T., M. Shingai, M. Matsumoto, T. Wakita, and T. Seya. 2008. Hepatitis C virus (HCV)-infected hepatocytes extrinsically modulate dendritic cell maturation to activate T cells and NK cells. ***Hepatology***. 48: 48-58.
5. Ebihara, T., M. Azuma, H. Oshiumi, M. Matsumoto, and T. Seya. 2009. Identification of INAM, a polyI:C-inducible membrane protein, that participates in dendritic cell-mediated natural killer cell activation. ***J. Exp. Med.*** (in press).

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Tsukasa Seya

Professor
Department of Immunology
Graduate School of Medicine
Hokkaido University

ACADEMIC DEGREES:

Ph. D.	1984	Hokkaido University (School of Pharmaceutical Sciences)
M. D.	1987	Hokkaido University (Medical School)

PROFESSIONAL APPOINTMENTS:

1984-1987	Research Associate, Division of Rheumatology, Washington University School of Medicine (Immunology)
1987-1996	Associate Director, Department of Immunology, Osaka Medical Center for Cancer, Osaka. (Immunology)
1996- 2001	Director, Department of Immunology, Osaka Medical Center for Cancer, Osaka
1998-2004	Professor (concurrently), Nara Institute of Science and Technology.
2001-2004	Director-in-Chief, Research Institute of Osaka Medical Center for Cancer.
2002-2004	Professor (concurrently), Osaka University School of Medicine.
2004-	Professor, Hokkaido University Graduate School of Medicine (Department of Microbiology and Immunology)

RESEARCH INTERESTS:

Innate immunity, adjuvant immunotherapy, Toll-like receptor, HCV

The Use of Simple Synthetic Lipid Structures for Targeting Different Vaccine Cargos to Dendritic Cells

David C. Jackson, Lorena E. Brown, Lara Grollo & Weiguang Zeng

Department of Microbiology and Immunology
The University of Melbourne, Parkville, Victoria, Australia 3010

The rational design of vaccines becomes increasingly possible as we understand how the immune system recognises antigen and how it then responds to it. The discovery that cells of the *innate* immune system, principally the dendritic cell (DC), are amongst the first cells to encounter antigen is especially relevant and knowledge of the function and specificity of various DC surface receptors can be exploited to provide ways of delivering vaccines to these cells. Receptors of the Toll-like receptor family are particularly useful in facilitating the targeting and transport of vaccine cargo to DC. Toll-like receptor 2 has the advantage of being a plasma membrane receptor that upon ligation, triggers uptake of the ligand into the cell. Engagement of TLR-2 leads to DC activation and maturation initiated by signal transduction pathways involving MyD88 and NFkB. Activation of the DC in this way leads to its migration, bearing its antigen cargo, to the draining lymph node where it can efficiently present the processed antigen to T cells to trigger their activation.

We have exploited these properties of Toll-like receptor 2 by incorporating a synthetic version of the TLR-2 ligand, S-[2,3-bis(palmitoyloxy)-(2RS)-propyl]-[R]-cysteine (Pam2Cys), into various vaccine candidates. Our early work explored the use of totally synthetic epitope-based vaccines that incorporated a $CD4^+$ helper T cell epitope and a target epitope, capable of eliciting either an antibody or a $CD8^+$ T cell response, with Pam2Cys covalently attached between the two epitopes. By virtue of its DC targeting and activation properties the generic structure that we developed provides a *self-adjuvanting* solution to vaccines. Encouraging and persuasive results using this strategy have been obtained with a variety of vaccine candidates in a variety of animal models ranging from immunocontraceptive vaccines that elicit high titres of anti-gonadotrophin releasing hormone antibodies to those that induce protective anti-influenza $CD8^+$ T cell responses.

We have also explored the use of Pam2Cys in the context of non-synthetic peptide-based approaches where the induction of immunity against an intact protein or DNA may be more appropriate. Our results demonstrate that combination of various forms of Pam2Cys with whole protein or DNA has led to an increased immunogenicity of these vaccine candidates.

The presentation will describe some of the successes that we have had using these various approaches and will also describe some of the limitations and possible solutions of the individual methods.

Professor David C. Jackson, PhD (University of Melbourne)

2008 – present	Professor, Department of Microbiology and Immunology, University of Melbourne
2005 - present	Member Science Advisory Board of Lipotek Pty. Ltd. (honorary appointment)
2004 - present	Chief Scientist of VacTX Pty. Ltd
1999 - 2006	Member Executive Committee Cooperative Research Centre for Vaccine Technology
1998 -2000	Senior Tutor in Residence (Science) at Ormond College
1993 -1999	Member Research and Development Advisory Committee, Cooperative Research Centre for Vaccine Technology.
1993 -2006	Programme Leader Cooperative Research Centre for Vaccine Technology.
1992 -1993	Member Steering Committee for Cooperative Research Centre for Vaccine Technology.
1992 –2008	Associate Professor, Department of Microbiology & Immunology, University of Melbourne (honorary appointment)
1992 - present	Principal Research Fellow by the NH&MRC in the Dept Microbiol Immunol, UM
1984 -1991	Senior Research Fellow with the NH&MRC in the Dept Microbiol Immunol, UM
1982	Visiting Scientist to Division of Virology and Molecular Biology, St. Jude Children's Research Hospital, Memphis, Tennessee, U.S.A.
1980 -1983	Research Fellow with the NH&MRC in the Dept Microbiol, UM
1976 -1980	Senior Research Officer, Dept Microbiol, UM
1967 -1970	Medical Laboratory Technician at St. Bernard's Hospital, Southall, Middlesex and at the Central Middlesex Hospital, London, N.W.10.

The role of adjuvants in vaccines for seasonal and pandemic influenza

Lorena E. Brown

Department of Microbiology and Immunology
The University of Melbourne, Parkville, Victoria, Australia 3010

Current seasonal influenza vaccines aim to induce high-titred virus-neutralizing antibody to the viral hemagglutinin (HA) which is the best form of protection against infection, but these can be poorly efficacious in the elderly and other target groups that rely on them most. Furthermore these vaccines provide little cross-protection against significantly drifted strains and no protection against different subtype viruses with pandemic potential.

Modification of existing, antibody-based seasonal influenza vaccines to include a component that activates cross-protective T cells would not only offer an attractive strategy for improving community protection against drifted variant virus but would also reduce the impact of a novel subtype of virus at the beginning of a pandemic before highly specific vaccines are prepared. Specific vaccines to the newly emerging pandemic influenza virus strains will require about 4-6 months before the first batches are manufactured and the use of an adjuvant to decrease the amount of antigen needed will be the principle way of obtaining significant numbers of vaccine doses.

Recent advances in immunology provide an understanding of how conventional and novel vaccine adjuvants act on the innate immune system to shape and enhance adaptive immunity. Three signaling steps are required during the priming of CD4+ T cells by DC. The so called “danger signal” is provided by the adjuvant itself to the DC, either by direct interaction with Pattern Recognition Receptors or by the products of damaged cells. The cross-linking of T cell receptors by MHC class II molecules and the interaction of costimulatory molecules with their ligands provide the additional signals. The cytokine environment during priming of CD4+ T cells determines the role of these cells in supporting subsequent activation of CD8+ T cells and/or antibody-producing B cells. Data comparing the potency of two different adjuvants to stimulate highly specific protective antibody responses to pandemic H5N1 virus vaccines in ferrets will be shown and discussed in the context of how each is thought to interact with the innate immune system. A third adjuvant system, which has the capacity to directly stimulate dendritic cells to prime long-lasting cross-protective CD8+ T cell responses in mice will also be discussed and data demonstrating significant reduction in disease severity after influenza virus challenge will be shown. We also show that addition of the CD8+ T cell-inducing component to suboptimal antibody-inducing influenza vaccines results in enhanced overall protection.

Professor Lorena E. Brown, PhD (The University of Melbourne)

2007–present	Professor, Department of Microbiology and Immunology, University of Melbourne
2005–2007	Associate Professor and Reader, Dept Microbiol Immunol, UM
2001-2004	Senior Lecturer in Virology, Dept Microbiol Immunol, UM
2001-2006	Cooperative Research Centre for Vaccine Technology Education Program Leader
2001-2006	Cooperative Research Centre for Vaccine Technology Executive Committee Member
2001-2003	Biotechnology Education and Training Program Steering Committee Member
1999-2006	Key Researchers Committee Member, Cooperative Research Centre for Vaccine Technology
1996-2000	National Health and Medical Research Council Senior Research Fellow, Dept Microbiol, UM
1995-1999	Cooperative Research Centre for Vaccine Technology Influenza Program Leader
1994-1999	Cooperative Research Centre for Vaccine Technology Task Force Leader
1993-1995	National Health and Medical Research Council Research Fellow, Dept Microbiol, UM
1987-1992	National Health and Medical Research Council Senior Research Officer, Dept Microbiol, UM
1983-1986	National Health and Medical Research Council Postdoctoral Research Fellow, Dept Microbiol, UM
1981-1983	Research Fellow, Division of Virology and Molecular Biology, St. Jude Children's Research Hospital, Memphis, Tennessee, USA