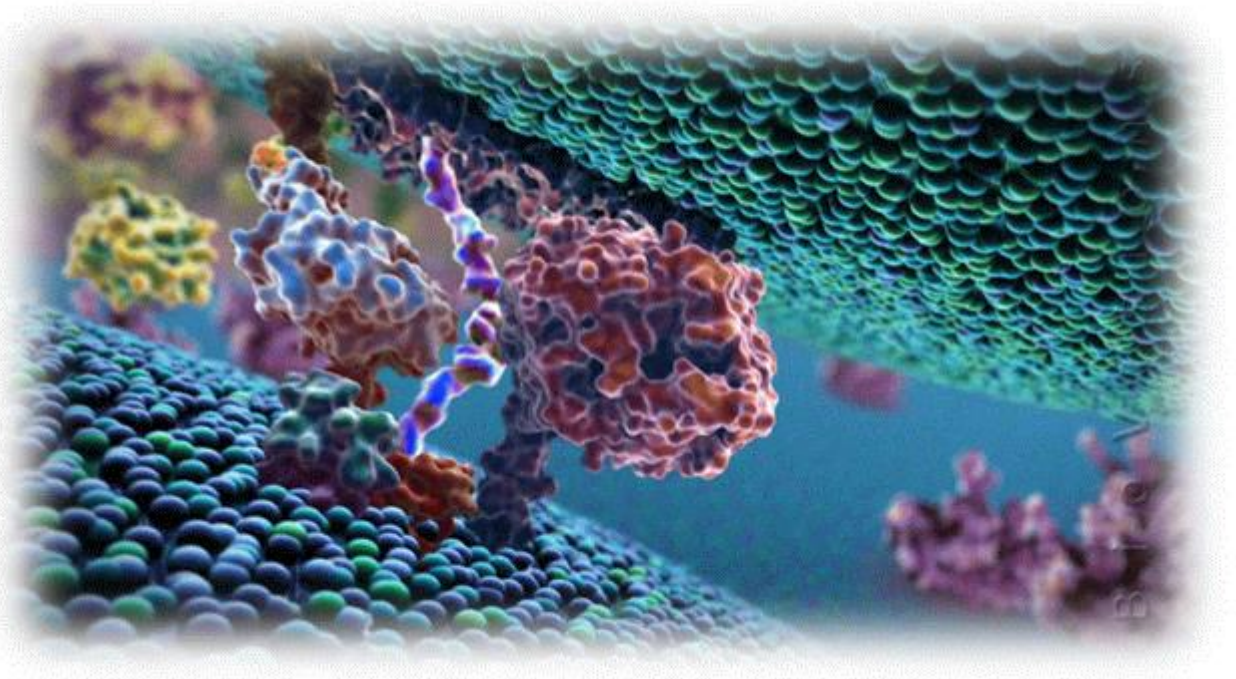
2017 노벨석학 심포지움

Functional Perspective for Membrane & Protein

일시: 2017년 3월 24일 (금) 14:30-17:40

장소: 연세삼성학술정보관 7층 장기원국제회의실



［주최］ 연세대학교
- 생명시스템대학
- BK21플러스 생체기능시스템사업단
- Y-IBS 나노의학연구단

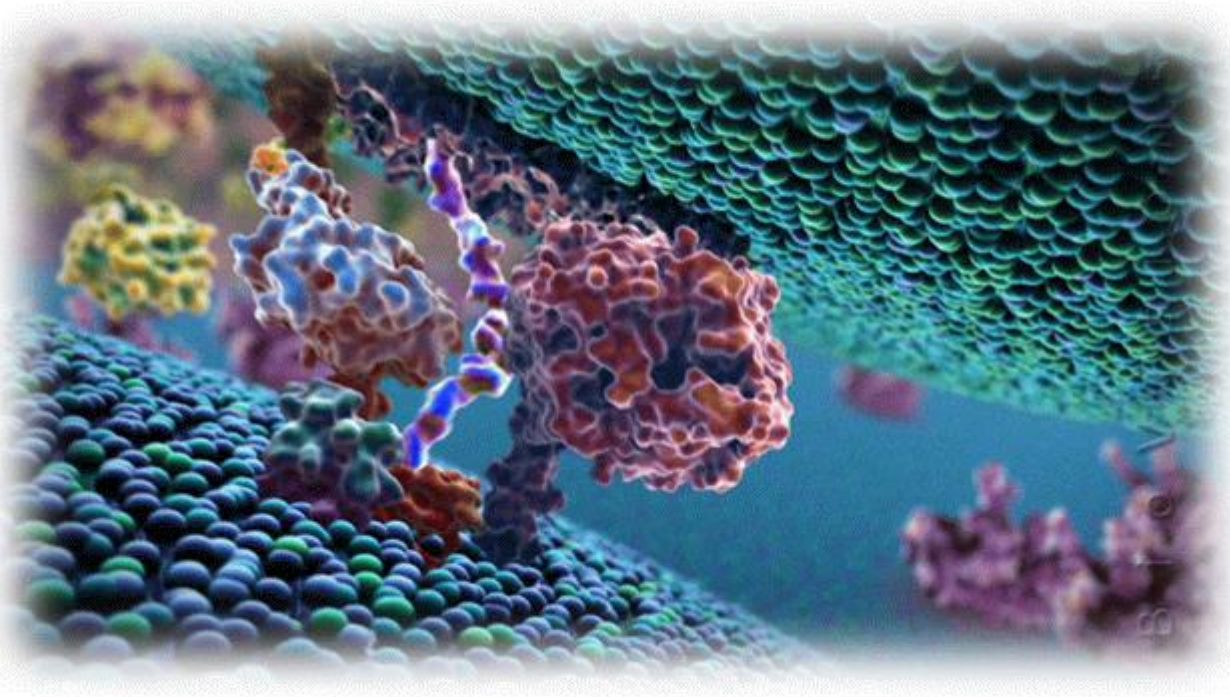
［후원］ 연세대학교 연구처, 기초과학연구원

2017 NOBEL LAUREATE SYMPOSIUM

Functional Perspective for Membrane & Protein

Date: Mar 24, 2017, 14:30-17:40

Venue: Chang Ki-Won International Conference Room
Yonsei-Samsung Library 7th floor



[Co-hosts] Yonsei University
- College of Life Science and Biotechnology
- BK21plus Initiative for Biological Function & Systems
- Y-IBS Center for Nanomedicine

[Sponsors]
- Yonsei Univ. Research Affairs
- Institute for Basic Science (IBS)

[Program]

14:30-14:50 Registration

Chair: Prof. Hyun Woo Park (Dept. Biochemistry, Yonsei U)

14:50-15:00 **Opening Remark**
Prof. Joo Hun Lee
(Dean, College of Life Science and Biotechnology, Yonsei U)

15:00-15:50 **Biogenesis and Function of the Autophagosomal Membrane**
Prof. Randy Schekman
- Howard Hughes Medical Institute Investigator
- Cell and Developmental Biology, UC Berkeley
- Graduate School of Life Science & Biotechnology, Yonsei U
- Y-IBS Center for Nanomedicine

15:50-16:20 **Cell Death through Necroptosis**
Prof. Jaewhan Song (Dept. Biochemistry, Yonsei U)

16:20-16:40 Coffee Break

16:40-17:10 **Crystal Structure of a Unique Light-driven Chloride Pump Rhodopsin**
Prof. Hyun-Soo Cho (Dept. Systems Biology, Yonsei U)

17:10-17:40 **Target Protein Identification & Validation of Bioactive Small Molecules**
Prof. Ho Jeong Kwon (Dept. Biotechnology, Yonsei U)

Randy W. Schekman, Ph.D.

Professor,
Department of Molecular and Cell Biology
Howard Hughes Medical Institute
University of California, Berkeley
Berkeley, CA 94720 USA
Phone: (510)642-5686
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Education and Appointment:

1966 – 1970	B.A., Department of Molecular Biology, University of California, Los Angeles
1970 – 1974	Ph.D.., Department of Biochemistry, Stanford University
1974 – 1976	Post-doctoral fellow, Department of Biology, University of California, San Diego
1976 – 1989	Assistant/Associate Professor, Department of Molecular and Cell Biology, University of California, Berkeley
1989 – Present	Professor, Department of Molecular and Cell Biology, University of California, Berkeley
1990 – 1994	Head, Division of Biochemistry and Molecular Biology
1990 – Present	Investigator, Howard Hughes Medical Institute
1997 – 2000	Co-chairman, Department of Molecular and Cell Biology
2002 – 2012	Chair, Chancellor's Advisory Committee on Biology, UCB
2005	Founding Director, UC Berkeley Stem Cell Center
2006 – 2010	Program Director, CIRM Training Grant
2016 – Present	Chair-Professor, Graduate School of Life Science & Biotechnology, Yonsei University, Korea
2016 – Present	Advisory Board, Yonsei-IBS Institute, Yonsei University, Korea

Academic Honors:

1970	Woodrow Wilson Fellow
1970	UCLA Zoology Department Undergraduate Research Award
1974 – 1976	Cystic Fibrosis Postdoctoral Fellow
1982 – 1983	Guggenheim Fellow
1987	Eli Lilly Research Award in Microbiology and Immunology

1994	Lewis S. Rosenstiel Award in Basic Biomedical Science
1995	Harvey Lecture
1996	The Gairdner International Award
1999	Berkeley Faculty Research Lecturer
1999	Amgen Award Lecture, Protein Society
2002	Albert Lasker Award in Basic Medical Research
2002	Louisa Gross Horwitz Prize of Columbia University
2005	Keith Porter Lecture, American Society for Cell Biology
2007	Van Deenan Medalist, Utrecht University, the Netherlands
2008	Dickson Prize in Medicine, University of Pittsburgh
2008	Inaugural Senior Fellow, Miller Institute, UC Berkeley
2010	Massry Prize, Meira and Shaul G. Massry Foundation
2010	E. B. Wilson Award, American Society for Cell Biology
2011	Inaugural Arthur Kornberg and Paul Berg Lifetime Achievement Award, Stanford University School of Medicine
2013	Otto Warburg Prize of the German Biochemical Society
2013	Nobel Prize in Medicine or Physiology
2014	UCLA Medal
2015	University Professor, University of California

Elections and Honorific Societies:

1992	Election to the National Academy of Sciences
1993	Honorary Member, Japanese Biochemical Society
1997	Docteur Honoris Causa, University of Geneva, Switzerland
1999	President, American Society for Cell Biology
2000	American Academy of Arts and Sciences
2001	Foreign Associate, EMBO
2005	Docteur Honoris Causa, University of Regensburg, Germany
2008	Elected Member, The American Philosophical Society
2010	Elected Foreign Member, Accademia Nazionale dei Lincei, Italy
2013	Foreign Associate, The Royal Society, London
2014	Elected Member, Institute of Medicine
2014	The Academia Sinica, Honorary Academician
2014	Doctor Scientiae et Honoris Causa, Pontificia Universidad Católica de Chile

2014 Doctor honoris causa, Aula Magna Facultad de Ciencias Quimicas y Farmacẻuticas, Universidad de Chile

2016 Doctor honoris causa, Chinese University of Hong Kong

Professional Activities:

[Society Member]

American Society for Microbiology, American Academy for Microbiology, American Society for Biochemistry and Molecular Biology, American Society for Cell Biology, Pew Scholars Program Advisory Committee, Natl. Inst. of Health Cell Biology Study Section

[Editorial Boards]

The Journal of Cell Biology, 1985-1992

Biochemistry, 1986-1993

Proceedings of the National Academy of Sciences, 2002-2005

The Journal of Membrane Biology, 1986-2000

Cell, 2001-2012

Chair, National Academy of Sciences Biochemistry Section, 2002-2005

Chair, National Academy of Sciences Biology Class, 2005-2008

Council, American Academy of Arts & Sciences, 2009-2012

Editor-in-Chief, Annual Review of Cell and Developmental Biology, 1999

Editor-in-Chief, Proceedings of the National Academy of Sciences, 2006-2011

Scientific Director, Jane Coffin Childs Memorial Fund, 2002-2012

Editor-in-Chief, eLife, 2011-present

Council, National Academy of Sciences, 2014-present

Specialty and Research Field of Interest:

Mechanism and control of intracellular protein transport

Selected Publications

1. Shurtleff MJ, Temoche-Diaz MM, Karfilis KV, Ri S, **Schekman R**. Y-box protein 1 is required to sort microRNAs into exosomes in cells and in a cell-free reaction. ***Elife*** 2016 5:e19276
2. Zhang M, Kenny SJ, Ge L, Xu K, **Schekman R**. Translocation of interleukin-1β into a vesicle intermediate in autophagy-mediated secretion. ***Elife*** 2015 4:e11205
3. Bajaj Pahuja K, Wang J, Blagoveshchenskaya A, Lim L, Madhusudhan MS, Mayinger P,

Schekman R. Phosphoregulatory protein 14-3-3 facilitates SAC1 transport from the endoplasmic reticulum. ***Proc Natl Acad Sci USA*** 2015 112:E3199

4. Ge L, Zhang M, **Schekman R**. Phosphatidylinositol 3-kinase and COPII generate LC3 lipidation vesicles from the ER-Golgi intermediate compartment. ***Elife*** 2014 3:e04135
5. Zhang M, **Schekman R**. Unconventional secretion, unconventional solutions. ***Science*** 2013 340:559
6. Ge L, Melville D, Zhang M, **Schekman R**. The ER-Golgi intermediate compartment is a key membrane source for the LC3 lipidation step of autophagosome biogenesis. ***Elife*** 2013 2:e00947
7. Guo Y, Zanetti G, **Schekman R**. A novel GTP-binding protein-adaptor protein complex responsible for export of Vangl2 from the trans Golgi network. ***Elife*** 2013 2:e00160
8. Choy RW, Cheng Z, **Schekman R**. Amyloid precursor protein (APP) traffics from the cell surface via endosomes for amyloid β (Aβ) production in the trans-Golgi network. ***Proc Natl Acad Sci USA*** 2012 109:E2077
9. Lam SK, Yoda N, **Schekman R**. A vesicle carrier that mediates peroxisome protein traffic from the endoplasmic reticulum. ***Proc Natl Acad Sci USA*** 2010 107:21523
10. Schindler AJ, **Schekman R**. In vitro reconstitution of ER-stress induced ATF6 transport in COPII vesicles. ***Proc Natl Acad Sci USA*** 2009 106:17775
11. Lee MC, Orci L, Hamamoto S, Futai E, Ravazzola M, **Schekman R**. Sar1p N-terminal helix initiates membrane curvature and completes the fission of a COPII vesicle. ***Cell*** 2005 122:605
12. Miller EA, Beilharz TH, Malkus PN, Lee MC, Hamamoto S, Orci L, **Schekman R**. Multiple cargo binding sites on the COPII subunit Sec24p ensure capture of diverse membrane proteins into transport vesicles. ***Cell*** 2003 114:497
13. Springer S, **Schekman R**. Nucleation of COPII vesicular coat complex by endoplasmic reticulum to Golgi vesicle SNAREs. ***Science*** 1998 281:698
14. Kuehn MJ, Herrmann JM, **Schekman R**. COPII-cargo interactions direct protein sorting into ER-derived transport vesicles. ***Nature*** 1998 391:187
15. Lyman SK, **Schekman R**. Binding of secretory precursor polypeptides to a translocon subcomplex is regulated by BiP. ***Cell*** 1997 88:85
16. Latterich M, Fröhlich KU, **Schekman R**. Membrane fusion and the cell cycle: Cdc48p participates in the fusion of ER membranes. ***Cell*** 1995 82:885

17. Latterich M, **Schekman R**. The karyogamy gene KAR2 and novel proteins are required for ER-membrane fusion. ***Cell*** 1994 78:87
18. Barlowe C, Orci L, Yeung T, Hosobuchi M, Hamamoto S, Salama N, Rexach MF, Ravazzola M, Amherdt M, **Schekman R**. COPII: a membrane coat formed by Sec proteins that drive vesicle budding from the endoplasmic reticulum. ***Cell*** 1994 77:895
19. Barlowe C, **Schekman R**. SEC12 encodes a guanine-nucleotide-exchange factor essential for transport vesicle budding from the ER. ***Nature*** 1993 365:347
20. Yoshihisa T, Barlowe C, **Schekman R**. Requirement for a GTPase-activating protein in vesicle budding from the endoplasmic reticulum. ***Science*** 1993 259:1466
21. Sanders SL, Whitfield KM, Vogel JP, Rose MD, **Schekman RW**. Sec61p and BiP directly facilitate polypeptide translocation into the ER. ***Cell*** 1992 69:353
22. Chiang HL, **Schekman R**. Regulated import and degradation of a cytosolic protein in the yeast vacuole. ***Nature*** 1991 350:313
23. Deshaies RJ, Sanders SL, Feldheim DA, **Schekman R**. Assembly of yeast Sec proteins involved in translocation into the endoplasmic reticulum into a membrane-bound multisubunit complex. ***Nature*** 1991 349:806
24. Kaiser CA, **Schekman R**. Distinct sets of SEC genes govern transport vesicle formation and fusion early in the secretory pathway. ***Cell*** 1990 61:723
25. Baker D, Hicke L, Rexach M, Schleyer M, **Schekman R**. Reconstitution of SEC gene product-dependent intercompartmental protein transport. ***Cell*** 1988 54:335
26. Deshaies RJ, Koch BD, Werner-Washburne M, Craig EA, **Schekman R**. A subfamily of stress proteins facilitates translocation of secretory and mitochondrial precursor polypeptides. ***Nature*** 1988 332:800

Abstract

Biogenesis and Function of the Autophagosomal Membrane

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Recent evidence suggests that the membrane responsible for starvation-induced autophagy originates in the ER exit site in yeast, or the ER-Golgi intermediate compartment (ERGIC) in mammalian cells (1, 2). We studied the biogenesis of the phagophore membrane by examining an early covalent event in autophagy, the lipidation of a cytosolic protein, LC3-I to form LC3-II. Using membranes from a cultured cell line deficient in lipidation, we demonstrated that the ERGIC was a major site for lipidation of LC3. Starvation induces the activation of a PI3 kinase to produce PI3P, which is required for the formation of LC3-II. We find that starved cells produce vesicles smaller than the ERGIC that are active in the formation of LC3-II even in the presence of inhibitors of PI3K. These vesicles appear to arise by a COPII budding event at the ERGIC. We suggest that these vesicles may be the immediate precursor of the phagophore membrane.

Conditions of stress induce the abundant secretion of IL-1 β from macrophages by a process that appears to be independent of the normal secretory pathway. Co-expression of IL-1β and caspase 1 reconstituted the stress-induced secretion of mature IL-1β in HEK293 cells under conditions where cell lysis was minimal. We have confirmed a published report that the secretion of IL-1β requires some aspect of the autophagy pathway (3, 4, 5). Cells deficient in the lipidation of a cytosolic protein, LC-3, required

for autophagy, accumulated mature and precursor forms of IL-1β in the cytoplasm. Using cell fractionation experiments we found that IL-1β precursor and mature forms co-isolated with phagophore membranes marked by their content of lapidated LC-3. Using a cell depleted of ATG2, a protein required for phagophore closure to produce a double-membrane mature authophagosome, we found that mature IL-1β, but not the precursor or control proteins were resistant to proteinase k, suggesting that IL-1β enters the lumen of the phagophore membrane rather than being engulfed into the cyoplasmic interior of the organelle. We have identified a targeting signal and a role for hsp90 in a translocation event that localizes IL-1β to the interior of the phagophore envelope. Fusion of the autophagosome with the plasma membrane would then result in the release of soluble IL-1β to the extracellular space.

References:

1. Ge L, Melville D, Zhang M, Schekman R. The ER–Golgi intermediate compartment is a key membrane source for the LC3 lipidation step of autophagosome biogenesis. ***Elife*** 2013 2:e00947

2. Ge L, Zhang M, Schekman R. Phosphatidylinositol 3-kinase and COPII generate LC3 lipidation vesicles from the ER-Golgi intermediate compartment. ***Elife*** 2014 3:e04135

3. Dupont N, Jiang S, Pilli M, Ornatowski W, Bhattacharya D, Deretic V. Autophagy-based unconventional secretory pathway for extracellular delivery of IL1β. ***EMBO J*** 2011 30:4701

4. Zhang M, Schekman R. Unconventional secretion, unconventional solutions. ***Science*** 2013 340:559

5. Zhang M, Kenny SJ, Ge L, Xu K, Schekman R (2015) Translocation of interleukin-1β into a vesicle intermediate in autophagy-mediated secretion. ***Elife*** 2015 4:e11205

Jaewhan Song, Ph.D.

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Education and Appointment:

1987 – 1993 B.S., Department of Biochemistry, Yonsei University, Korea
1993 – 1995 M.S., Department of Biochemistry, Yonsei University, Korea
1995 –2000 Ph.D., Northwestern University, US
2000 – 2002 Post-doctoral fellow, Northwestern University, US
2002 – 2010 Assistant/Associate Professor, Sungkyunkwan University, Korea
2010 – Present Professor, Yonsei University, Korea

Specialty and Research Field of Interest:

Tumorigenesis, senescence, metabolism, cell death

Selected Publications (within 10 papers)

1. Kim JH, Shin S, Seo J, Lee EW, Jeong M, Lee MS, Han HJ, **Song J**. C-terminus of HSC70-Interacting Protein (CHIP) Inhibits Adipocyte Differentiation via Ubiquitin- and Proteasome-Mediated Degradation of PPARγ. ***Sci Rep*** 2017 7:40023
2. Han SY, Ko A, Kitano H, Choi CH, Lee MS, Seo J, Fukuoka J, Kim SY, Hewitt SM, Chung JY, **Song J**. Molecular chaperone HSP90 is necessary to prevent cellular senescence via lysosomal degradation of p14ARF. ***Cancer Res*** 2017 77:343
3. Jeong M, Lee EW, Seong D, Seo J, Kim JH, Grootjans S, Kim SY, Vandenabeele P, **Song J**. USP8 suppresses death receptor-mediated apoptosis by enhancing FLIPL stability. ***Oncogene*** 2017 36:458

4. Seo J, Lee EW, Sung H, Seong D, Dondelinger Y, Shin J, Jeong M, Lee HK, Kim JH, Han SY, Lee C, Seong JK, Vandenabeele P, **Song J**. CHIP controls necroptosis through and lysosome dependent degradation of RIPK3. ***Nat Cell Biol*** 2016 18:291

5. Lee MS, Jeong MH, Lee HW, Han HJ, Ko A, Hewitt SM, Kim JH, Chun KH, Chung JY, Lee C, Cho H, **Song J**. PI3K/AKT activation induces PTEN ubiquitination and destabilization, accelerating tumorigenesis. ***Nat Comm*** 2015 6:7769
6. Lee EW, Seong D, Seo J, Jeong M, Lee HK, **Song J**. USP11-dependent selective cIAP2 deubiquitylation and stabilizationdetermine sensitivity to Smac mimetics. ***Cell Death Differ*** 2015 22:1463
7. Kim JH, Park KW, Lee EW, Jang WS, Seo J, Shin S, Hwang KA, **Song J**. Suppression of PPARγã through MKRN1-Mediated Ubiquitination and Degradation Prevents Adipocyte Differentiation. ***Cell Death Differ*** 2014 21:594
8. Lee MS, Seo J, Choi DY, Lee EW, Ko A, Ha NC, Yoon JB, Lee HW, Kim KP, **Song J**. Stabilization of p21 (Cip1/WAF1) Following Tip60 Dependent Acetylation Is Required for p21-Mediated DNA Damage Response. ***Cell Death Differ*** 2013 20:620
9. Ko A, Shin JY, Seo J, Lee KD, Lee EW, Lee MS, Lee HW, Choi IJ, Jeong JS, Chun KH, **Song J**. Acceleration of gastric tumorigenesis through MKRN1-mediated post-translational regulation of p14ARF. ***J Natl Cancer Inst*** 2012 104:1660
10. Lee EW, Kim JH, Ahn YH, Seo J, Ko A, Jeong M, Kim SJ, Ro JY, Park KM, Lee HW, Park EJ, Chun KH, **Song J**. Ubiquitination and degradation of the FADD adaptor protein regulate death receptor-mediated apoptosis and necroptosis. ***Nat Comm*** 2012 3:978

Abstract

Cell Death through Necroptosis

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Department of Biochemistry, College of Life Science & Biotechnology,
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Receptor-interacting protein kinase 3 (RIPK3) functions as a key regulator of necroptosis. Here, we report that the RIPK3 expression level is negatively regulated by CHIP (carboxyl terminus of Hsp70-interacting protein; also known as STUB1) E3 ligase-mediated ubiquitylation. Chip(-/-) mouse embryonic fibroblasts and CHIP-depleted L929 and HT-29 cells exhibited higher levels of RIPK3 expression, resulting in increased sensitivity to necroptosis induced by TNF (also known as TNFα). These phenomena are due to the CHIP-mediated ubiquitylation of RIPK3, which leads to its lysosomal degradation. Interestingly, RIPK1 expression is also negatively regulated by CHIP-mediated ubiquitylation, validating the major role of CHIP in necrosome formation and sensitivity to TNF-mediated necroptosis. Chip(-/-) mice (C57BL/6) exhibit inflammation in the thymus and massive cell death and disintegration in the small intestinal tract, and die within a few weeks after birth. These phenotypes are rescued by crossing with Ripk3(-/-) mice. These results imply that CHIP is a bona fide negative regulator of the RIPK1-RIPK3 necrosome formation leading to desensitization of TNF-mediated necroptosis.

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Education and Appointment:

1990 – 1996 B.S., Department of Life Science, POSTECH, Pohang, Korea
1996 – 1998 M.S., Department of Life Science, POSTECH, Pohang, Korea
1998 – 2001 Ph.D., Department of Life Science, POSTECH, Pohang, Korea
2001 – 2003 Post-doctoral fellow, Johns Hopkins University, US
2003 – 2007 Assistant Professor, Yonsei University, Seoul, Korea
2007 – 2014 Associate Professor, Yonsei University, Seoul, Korea
2014 – Present Professor, Yonsei University, Seoul, Korea

Specialty and Research Field of Interest:

Structural studies on disease-related receptors including G-Protein Coupled Receptors Using X-ray Crystallography & Cryo-EM

Selected Publications

1. Kim K, Kwon SK, Jun SH, Cha JS, Kim H, Lee W, Kim J*, **Cho HS***. Crystal structure and functional characterization of a light-driven chloride pump having an NTQ motif. ***Nat Comm*** 2016 7:12677
2. Choi Y, Yun JH, Yoo J, Lee I, Kim H, Son HN, Kim IS, Yoon HS, Zimmermann P, Couchman J, **Cho HS**, Oh ES*, Lee W*. New structural insight of C-terminal region of Syntenin-1, enhancing the molecular dimerization and inhibitory function related on Syndecan-4 signaling. ***Sci Rep*** 2016 6:39818
3. Kim JS, Choi DK, Shin JY, Shin SM, Park SW, **Cho HS**, Kim YS*. Endosomal acidic pH-induced conformational changes of a cytosol-penetrating antibody mediate endosomal escape. ***J Control Release*** 2016 235:165

4. Kim Y, Cheon S, Min CK, Sohn KM, Kang YJ, Cha YJ, Kang JI, Han SK, Ha NY, Kim G, Aigerim A, Shin HM, Choi MS, Kim S, **Cho HS**, Kim YS*, Cho NH*. Spread of mutant middle east respiratory syndrome coronavirus with reduced affinity to human CD26 during the South Korean outbreak. ***MBio*** 2016 7:e00019
5. Lim Y, Yoo J, Kim MS, Hur M, Lee EH, Hur HS, Lee JC, Lee SN, Park TW, Lee K, Chang KH, Kim K, Kang YJ, Hong KW, Kim SH, Kim YG, Yoon Y, Nam DH, Yang H, Kim DG, **Cho HS***, Won J*. GC1118, an anti-EGFR antibody with a distinct binding epitope and superior inhibitory activity against high-affinity EGFR ligands. ***Mol Cancer Ther*** 2016 15:251
6. Kim YH, Kwak MS, Park JB, Lee SA, Choi JE, **Cho HS***, Shin JS*. N-linked glycosylation plays a crucial role in the secretion of HMGB1. ***J Cell Sci*** 2016 129:29
7. Lee J, Choi HJ, Yun M, Kang YJ, Jung JE, Ryu Y, Kim TY, Cha YJ, **Cho HS***, Min JJ*, Chung CW*, Kim HS*. Enzymatic prenylation and oxime ligation for the synthesis of stable and homogeneous protein-drug conjugates for targeted therapy. ***Angew Chem Int Ed Engl*** 2015 54:12020
8. Jeong SA, Kim K, Lee JH, Cha JS, Khadka P, **Cho HS***, Chung IK*. Akt-mediated phosphorylation increases the binding affinity of hTERT for importin α to promote nuclear translocation. ***J Cell Sci*** 2015 128:2287
9. Cho YS, Yoo J, Park S, **Cho HS***. The structures of the kinase domain and UBA domain of MPK38 suggest the activation mechanism for kinase activity. ***Acta Crystallogr D Biol Crystallogr*** 2014 70:514

Abstract

Crystal Structure of a Unique Light-driven Chloride Pump Rhodopsin

Hyun-Soo Cho

Department of Systems Biology, College of Life Science & Biotechnology,
Yonsei University, Seoul 03722, Korea

Recently, light-driven sodium pump rhodopsin (NaR/KR2/NDQ rhodopsin) and chloride pump rhodopsin (ClR/NTQ rhodopsin) from marine flavobacteria were identified by metagenomics study. One of them, light-driven sodium pump rhodopsin (NaR) structure was determined. The other one we have solved the first crystal structure of a unique class light-driven chloride pump (ClR) from Nonlabens marinus S1-08, at resolutions of 1.57 Å. Like structured Halorhodopsin (HR), ClR can transfer chloride ion from extracellular to cytosol. Although both ClR and HR are same light-driven chloride pump rhodopsin, we found some evidences that ClR and HR are different in structure and mechanism. The structures reveal two chloride-binding sites, one around the protonated Schiff base and the other on a cytoplasmic loop. We identify a "3 omega motif" formed by three non-consecutive aromatic amino acids that is correlated with the B-C loop orientation. Detailed CIR structural analyses with functional studies in E. coli reveal the chloride ion transduction pathway. Our results help understand the molecular mechanism and physiological role of ClR and provide a structural basis for optogenetic applications.

Ho Jeong Kwon , Ph.D.

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Education and Appointment:

1980 – 1984 B.S., Seoul National University, Seoul, Korea
1990 – 1992 M.S., Department of Biotechnology, The University of Tokyo, Tokyo, Japan
1992 – 1995 Ph.D., Department of Biotechnology, The University of Tokyo, Tokyo, Japan
1995 – 1998 Post-doctoral fellow, Department of Chemistry & Chemical Biology, Harvard University, US
1999 – 2005 Professor, Department of Biotechnology, Sejong University, Seoul, Korea
2011 – 2012 Visiting Professor, Dept. of Chemical & Systems Biology, Stanford University, US
2005 – present Professor, Department of Biotechnology, Yonsei University, Seoul, Korea
2014 – present Adjunctive Professor, Yonsei University, Medical School, Seoul, Korea
2012 – present Scientific Advisory Committee, Institut Pasteur Korea (IPK), Seoul, Korea

Specialty and Research Field of Interest:

Chemical Biology/ Genomics/Proteomics

Selected Publications (within 10 papers)

1. **Kwon HJ**,* Owa T, Hassig CA, Shimada J, Schreiber SL. Depudecin induces morphological reversion of transformed fibroblasts via the inhibition of histone deacetylase. ***Proc Natl Acad Sci USA*** 1998 95:3356 "highlighted issue"
2. Kim MS, **Kwon HJ**, Lee YM, Baek JH, Jang JE, Lee SW, Moon EJ, Kim HS, Lee SK, Chung HY, Kim CW, Kim KW. Histone deacetylases induce angiogenesis by negative regulation of tumor suppressor genes. ***Nat Med*** 2001 7:437
3. Shim JS, Kim JH, Cho HY, Yum YN, Kim SH, Park HJ, Shim BS, Choi SH, **Kwon HJ***. Irreversible inhibition of CD13/aminopeptidase N by the antiangiogenic agent

curcumin. ***Cell Chem Biol*** 2003 10:695 "cover issue"

4. Shim JS, Lee J, Park HJ, Park SJ, **Kwon HJ**. 2004 A new curcumin derivative, HBC, interferes with the cell cycle progression of colon cancer cells via antagonization of the Ca 2+/calmodulin function. ***Cell Chem Biol*** 11:1455
5. **Kwon HJ**, Lee CH, Osada H, Yoshida M, Imoto M. Hot springs and cool natural products. ***Nat Chem Biol*** 2008 4(8):444
6. Jung HJ, Shim JS, Lee J, Song YM, Park KC, Choi SH, Kim ND, Yoon JH, Mungai PT, Schumacker PT, **Kwon HJ**. Terpestacin Inhibits Tumor Angiogenesis by Targeting UQCRB of Mitochondrial Complex III and Suppressing Hypoxia-induced Reactive Oxygen Species Production and Cellular Oxygen Sensing. ***J Biol Chem*** 2010 285(15):11584 "Faculty of 1000" selected paper
7. Jung HJ, Cho M, Kim Y, Han G, **Kwon HJ**. Development of a Novel Class of Mitochondrial Ubiquinol–Cytochrome c Reductase Binding Protein (UQCRB) Modulators as Promising Antiangiogenic Leads. ***J Med Chem*** 2014 57:7990
8. Chang J, Kim YH, **Kwon HJ**. Advances in identification and validation of protein targets of natural products without chemical modification. ***Nat Product Rep*** 2016 33:719
9. Cho YS, Yen CN, Shim JS, Kang DH, Kang SW, Liu JO, **Kwon HJ**. Antidepressant indatraline induces autophagy and inhibits restenosis via suppression of mTOR/S6 kinase signaling pathway. ***Sci Rep*** 2016 6:34655
10. Kim D, Hwang HY, Kim JY, Lee JY, Yoo JS, Marko-Varga G, **Kwon HJ**. FK506, an immunosuppressive drug, induces autophagy by binding to the V-ATPase catalytic subunit A in neuronal cells. ***J Prot Res*** 2017 16:55

Abstract

Target Protein Identification & Validation of Bioactive Small Molecules

Ho Jeong Kwon

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To explore the mechanism of bioactive small molecules, identification of target proteins of small molecules is crucial. Target identification of small molecules has usually utilized biotin or photoactivable probes linked to small molecules to effectively pull-down target proteins in the proteome based on an affinity interaction of small molecule to target protein. However, the drawback to this conventional method is that probe synthesis step is required, and the labeled small molecule may lose or change its innate activity. Here, I will introduce multi-omics based target identification and validation (MOTIV) for a target identification of label-free small molecule. By combination of DARTS (drug affinity response target stability) with LC/MS/MS method (DARTS-MS), target protein candidates of label-free small molecules were identified by using the whole cell lysate proteome. Following informatics based analysis including KEGG, STRING, and *in silico* docking verifies the engagement of small molecule to target proteins. Finally, genetic knock-down or over-expression and biochemical assays validate the biological relevancy of identified protein targets of a small molecule. Case studies of target identification for label-free bioactive small molecules such as FK506 and autophagonizer (APZ) as autophagy modulators will be presented to demonstrate this new method for target identification of bioactive small molecules with no chemical modification.