DEPARTMENT OF CHEMISTRY AND ENVIRONMENTAL SCIENCE
FALL 2017 GRAD SEMINAR SERIES

OPEN TO THE PUBLIC

DATE: WEDNESDAY, NOVEMBER 15, 2017

WHERE: CENTRAL KING BUILDING - 204
TIME: 2:30 PM

Refreshments at 2:30 pm – Seminar at 2:45 pm

GUEST SPEAKER

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TOPIC

When receptor meets ion channel

--Molecular basis of the assembly and function of the TRPP2/PKD1 complex

ABSTRACT

TRPP proteins and PKD proteins can form functionally important receptor-ion channel complexes. Mutations in the founding members of these two families, TRPP2 and PKD1, account for almost all clinically identified cases of autosomal dominant polycystic kidney disease (ADPKD), one of the most common human genetic diseases. TRPP2 functions as a cation channel in its homomeric complex and also in its complex with PKD1. In the TRPP2/PKD1 complex, we found that three TRPP2 assemble with one PKD1 through their C-terminal coiled-coil domains. This stoichiometry is shared by another homologous complex formed by TRPP3 and PKD1L. We have further evidence demonstrates that PKD subunits constitute a new class of channel-forming proteins in their complexes with TRPP proteins. Despite the importance of TRPP2 and PKD1, research in the field has been significantly delayed due to the lack of a known activation mechanism of the channels formed by them. Recently, we generated a group of constitutively active gain-of-function (GOF) mutants of TRPP2. With the platform provided by these mutants, we were able to gain insights into the molecular mechanisms of the function and regulation of the TRPP2 homomeric channel and the TRPP2/PKD1 complex.

BIOGRAPHY

My research was focused on membrane ion channel and receptors. Science 2004, I have been working on TRPP2 and PKD1, the two proteins that were found mutated in Autosomal Dominant Polycystic Kidney Disease (ADPKD). My goal is to understand the molecular mechanism of the function and regulation of these proteins and how their malfunction causes ADPKD. Previously, our work has demonstrated the 3 (TRPP): 1 (PKD) stoichiometry of the TRPP/PKD complexes and uncovered the structural and molecular basis of this stoichiometry [a, b]. We also defined that the PKD protein can function as ion channel protein by showing that PKD1L3 is involved in forming channel pore in its complex with TRPP3 [c]. The study of TRPP2 and PKD1 has been significantly delayed due to the lack of a known mechanism to active the channel. In my lab, we have recently generated a gain-of-function (GOF) mutant of TRPP2 which provided

a reliable platform for functional analysis of TRPP2 [d]. The current application builds logically on our prior work to further apply this mutant in the study of TRPP2 and PKD1.

In the past four and half years after I joined St. John's University, ten undergraduate, four Master's, and four Ph.D. students have received intensive research training in my lab. Eleven of them have authored on at least one research article from my lab. Thus, I have the expertise, techniques, publication records, and a lot student training experience to carry out the proposed experiments.

a. Yu Y., Ulbrich M.H., Li M.-H., Buraei Z., Chen X.-Z., Ong A.C. M., Tong L., Isacoff E.Y.,and Yang J., Structural and molecular basis of the assembly of the TRPP2/PKD1 complex. *Proc. Natl. Acad. Sci. U.S.A.*, 106(28):11558-11563, 2009. PMC2710685
b. Zhu J.***,** Yu Y.*, Ulbrich M. H., Li M.-H., Isacoff E. Y., Honig B. and Yang J., Structural model of the TRPP2/PKD1 C-terminal coiled-coil complex produced by a combined computational and experimental approach. *Proc. Natl. Acad. Sci. U.S.A.*, 108(25):10133-10138, 2011. PMC3121833. (*equal contribution)
c. Yu Y., Ulbrich M.H., Dobbins S., Li M.-H., Zhang K. W., Isacoff E.Y. and Yang J., Molecular mechanism of the assembly of an acid-sensing receptor/ion channel complex. *Nat Comms*, 3:1252 doi: 10.1038/ncomms2257, 2012. PMC3575195
d. Arif Pavel M., Lv C., Ng C., Yang L., Kashyap P., Lam C., Valentino V., Fung H., Campbell T., Møller S.G., Zenisek D., Holtzman N.G., and **Yu Y.**, Function and regulation of TRPP2 ion channel revealed by a gain-of-function mutant. *Proc. Natl. Acad. Sci. USA*, 113 (17) E2363-E2372, 2016

B. Positions and Honors

Academic Positions

2001- 2004 Postdoctoral Research Scientist, Center for Molecular Recognition, Columbia University
2004-2006 Postdoctoral Research Scientist, Department of Biological Sciences, Columbia University
2006-2012 Associate Research Scientist, Department of Biological Sciences, Columbia University
2012-2016 Assistant Professor, Department of Biological Sciences, St. John's University
2016-present Associate Professor, Department of Biological Sciences, St. John's University

Other Experience and Professional Memberships

2016-present Director of Graduate Studies, Department of Biological Sciences, St. John's University
2015-present Faculty advisor, ASBMB student chapter at St. John's University
2017 ad hoc grant reviewer, National Science Foundation
2013- ad hoc reviewer for *Nature Structural and Molecular Biology, Nature Communications, Scientific Report, Journal of General Physiology, Biophysical Journal, Frontiers in Pharmacology, Oncotarget, Science China - Life Science, PLOS One, Acta Pharmacologica Sinica, American Journal of Undergraduate Research*
2004-present Member, Biophysical Society
2015-present Member, American Society of Biochemistry and Molecular Biology
2013-2014 Member, American Heart Association

Editorial Boards

2015-present: Review editor, Frontiers in Pharmacology

Honors

1993-1996 First class student scholarship, Ocean University of Qingdao
1996 Excellent student model, Ocean University of Qingdao
1996 Tian-Tai Award, Ocean University of Qingdao
2000 Director Award, Shanghai Institute of Plant Physiology
2000 President Award, Chinese Academy of Sciences
2001 Research paper award, Chinese Academy of Sciences
2001 Peng Yin-Gang Award, Chinese Academy of Sciences
2013, 2014 Summer Support of Research, St. John's University
2013, 2014, 2015 Venture Capital Award, St. John's University
2015 Grants Recognition Award, St. John's University

C. Contributions to Science

1. Structural and molecular basis of the assembly of the TRPP2/PKD1 complex.

ADPKD is caused by mutations in proteins PKD1 or TRPP2. These two proteins form a receptor-ion channel complex for coupling extracellular signal into intracellular cell signaling. In our study, we uncovered that the TRPP2/PKD1 complex has three TRPP2 subunits and one PKD1 subunit, and found that the stoichiometry is determined by the assembly of the C-terminal coiled-coil domains [3a]. We have solved the crystal structure of TRPP2 C-terminal coiled-coil domain trimer and generated a structural model of the TRPP2/PKD1 coiled-coil domain complex [1a, 1b]. Recently, work from my lab showed their extracellular loops also play crucial roles in the assembly of the complex [1c]. These results shed light on the molecular mechanism of the assembly and function of the TRPP2/PKD1 complex. I am either the first author or the primary investigator of these studies.

1a. **Yu Y.**, Ulbrich M.H., Li M.-H., Buraei Z., Chen X.-Z., Ong A.C. M., Tong L., Isacoff E.Y.,and Yang J., Structural and molecular basis of the assembly of the TRPP2/PKD1 complex. ***Proc. Natl. Acad. Sci. U.S.A.***, 106(28):11558-11563, 2009. PMC2710685

1b. Zhu J.*, **Yu Y.***, Ulbrich M. H., Li M.-H., Isacoff E. Y., Honig B. and Yang J., Structural model of the TRPP2/PKD1 C-terminal coiled-coil complex produced by a combined computational and experimental approach. ***Proc. Natl. Acad. Sci. U.S.A.***, 108(25):10133-10138, 2011. PMC3121833 (*equal contribution)

1c. Salehi-Najafabadi Z.*, Li B.*, Valentino V., Ng C., Martin H., Yu Y., Wang Z., Kashyap P., and **Yu Y.**, Extracellular loops are essential for the assembly and function of polycystin receptor-ion channel complexes. ***J. Biol. Chem.***, 292(10):4210-4221, 2017. PMC5354480

2. Molecular basis of the assembly of the TRPP3/PKD1L3, an acid-sensing receptor.

Several functionally important protein complexes associated by the PKD family proteins and the TRPP family proteins have been identified. TRPP3 and PKD1L3 colocalize in a subset of acid-sensing taste cells and form a complex which responses to low pH, making this complex a good candidate for a sour taste receptor. In this study, we found that PKD1L3 functions as a channel-forming subunit in the TRPP3/PKD1L3 complex channel [2a]. We further showed that the TRPP3/PKD1L3 complex contains three TRPP3 and one PKD1L3, and a TRPP3 C-terminal coiled-coil domain trimer has a crucial role in the assembly of this complex [2a]. Together with the data of the TRPP2/PKD1 complex, our results suggest that the 3 (TRPP): 1 (PKD) stoichiometry is shared among the TRPP/PKD complexes. More importantly, these results demonstrate that PKD subunits constitute a new class of channel-forming proteins, enriching our understanding of the function of PKD proteins and the TRPP/PKD complexes. I am the first author of this study.

2a. **Yu Y.**, Ulbrich M.H., Dobbins S., Li M.-H., Zhang K. W., Isacoff E.Y. and Yang J., Molecular mechanism of the assembly of an acid-sensing receptor/ion channel complex. ***Nature Communications***, 3:1252 doi: 10.1038/ncomms2257, 2012. PMC3575195

3. Function and regulation of TRPP2 ion channel revealed by a GOF mutant

Despite the fact that the link between ADPKD and the mutations in the TRPP2 and PKD1 proteins has been discovered for more than 20 years, the roles of these two proteins in ADPKD are still largely unknown. The activation mechanism of TRPP2 is unsolved, which significantly limits the study of its function and regulation. In my lab, we recently generated a constitutively active gain-of-function (GOF) mutant of TRPP2 by applying a mutagenesis scan [3a]. We have applied this GOF mutant into the study of the channel properties of TRPP2 and its functional regulation by divalent ions. We further demonstrated that the GOF TRPP2 channel, compared to WT channel, more efficiently rescued morphological abnormalities caused by down-regulation of endogenous TRPP2 expression in zebrafish embryos [3a]. Thus, we established a reliable platform for TRPP2 function study. The GOF channel may also have potential application for developing new therapeutic strategies for ADPKD. I am the primary investigator of this study.

3a. Arif Pavel M., Lv C., Ng C., Yang L., Kashyap P., Lam C., Valentino V., Fung H., Campbell T., Møller S.G., Zenisek D., Holtzman N.G., and **Yu Y.**, Function and regulation of TRPP2 ion channel revealed by a gain-of-function mutant. ***Proc. Natl. Acad. Sci. USA.***, 113 (17) E2363-E2372, 2016. PMC4855601

4. Structural effects of open blocker binding in acetylcholine receptor channel.
Nicotinic acetylcholine (ACh) receptors are neuron neurotransmitter receptors that respond to the neurotransmitter acetylcholine. They play crucial roles in the peripheral nervous system as well as in the central nervous system. Noncompetitive inhibitors of the ACh receptors suppress ion flux directly by binding in and blocking the open channel of the receptor. With substituted-cysteine-accessibility method (SCAM), we mapped the binding site of the quinacrine in the open channel to the midway down the second membrane-spanning segment (M2) of the α subunit [4a]. We also found that channel opening involves both the opening of the resting gate at the inner end of M2 and the removal of an obstruction formed by the outer end of M1 [4a]. This work gain insight into molecular mechanism of the binding of channel blockers into the open channel and demonstrated that blocker binding causes a further change in the structure of the receptor. I am the first author of this study.

4a. **Yu Y.**, Shi L., and Karlin A., Structural effects of quinacrine binding in the open channel of the acetylcholine receptor. ***Proc. Natl. Acad. Sci. U.S.A.***, 100(7): 3907-3912, 2003. PMC153021

5. Structure and function of the extrinsic proteins in the oxygen-evolving complex of PSII
My Ph.D. thesis was focused on the photosystem II (PSII), the first protein complex in the light-dependent reactions. Life on earth depends upon the ability of the oxygenic photosynthesis to oxidize water to oxygen. This process is catalyzed by the oxygen-evolving complex (OEC) of photosystem II. Three extrinsic proteins (17 kDa, 23 kDa, and 33 kDa) bind to the lumenal side of OEC and play a crucial regulatory role in water oxidation cycle. We found that incubating the PSII under high hydrostatic pressure is a mild but efficient way to sequentially remove the three extrinsic proteins and the manganese cluster in OEC [5a]. This method allows us to explore the relationship between the extrinsic proteins and the oxygen-evolving activity. We further discovered that the tryptophan 241 is located in the hydrophobic core of the 33 kDa protein and is critical for maintaining the protein's structure and function [5b, 5c]. We then used the 33 kDa protein as a model protein to study protein unfolding under high-pressure and showed some physical-chemical conditions could modulate unfolding reaction by influencing the standard free energy [5d]. I am the first author or major contributor of these studies.

5a. **Yu Y.**, Tian S., Ruan K., and Xu C., The release of extrinsic polypeptides and manganese cluster from photosystem II membrane under high hydrostatic pressure. ***Photosynthetica***, 39: 115-117, 2001.
5b. **Yu Y.**, Li R., Tian S., Xu C., and Ruan K., The influence of NBS modification of 241Trp on the reconstitution of 33 kD polypeptide with PSII and on the recovery of oxygen-evolving activity. ***Acta Biochimica et Biophysica Sinica***, 31: 341-343, 1999.
5c. **Yu Y.**, Li R., Xu C., Ruan K., Shen Y., and Govindjee, N-bromosuccinimide modification of tryptophan 241 at the C-terminus of the manganese stabilizing protein of plant photosystem II influences its structure and function. ***Physiologia Plantarum***, 111: 108-115, 2001.
5d. Ruan K., Xu C., **Yu Y.**, Li J., Lange R., Bee N., and Balny C., Pressure-exploration of the 33-kDa protein from spinach photosystem II particle. ***European Journal of Biochemistry***, 268: 2742-2750, 2001.

Complete list of published work in my bibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1L11ar9hb6i5M/bibliography/42804541/public/?sort=date&direction=descending

D. Research Support
Ongoing Research Support
R15DK102092 Yu (PI) 09/23/2014-08/31/2018
(2017-2018: no-cost extension)
NIH Function and regulation of TRPP2, and its role in ADPKD
The goal of this project is to understand the molecular and cellular mechanisms of the function and regulation of the TRPP2 channel

Role: PI

Seed grant Yu (PI) 5/1/2017-4/30/2018
St. John's University
Molecular mechanism of the roles of the PKD1L2 in zebrafish heart development
The goal of this project was to characterize the defect on heart development when knock down PKD1L2 expression.
Role: PI

Completed Research Support
Seed grant Yu (PI) 5/1/2014-4/30/2015
St. John's University
Crystallization and structure determination of functionally important protein domains of TRP channels
The goal of this project was to crystallize and solve the structure of functional TRP channel domains
Role: PI

Seed grant Yu (PI) 5/1/2015-4/30/2016
St. John's University
Systematic study of the effects of ADPDK- causing mutations on the function and trafficking of TRPP2 channel
The goal of this project was to characterize the effects of the ADPKD pathogenic mutations
Role: PI

Seminar Series Coordinators

Dr. Yong Yan - yong.yan@njit.edu
Dr. Yuan Zhangwei - yuanwei.zhang@njit.edu