OMICS Group International is an amalgamation of Open Access publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology ‘Open Access’, OMICS Group publishes 400 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 300 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.
OMICS Group International is a pioneer and leading science event organizer, which publishes around 400 open access journals and conducts over 300 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.
UVRAG and Rubicon Regulate Cardiac Autophagy and Function

Hongxin Zhu Ph.D
Bio-X Institutes
Shanghai Jiao Tong University
April 15, 2014
Macroautophagy (Autophagy) is an evolutionarily conserved pathway that degrades cytoplasmic components in lysosomes.
Physiological Functions of Cardiac Autophagy

- Basal autophagy is required for the maintenance of homeostasis in the heart.
  - Provision of nutrient during catabolism
  - Generation of ATP in starved cells
  - Removal of damaged organelles and protein aggregates
  - Degradation of misfolded proteins
- Dysregulated autophagy contributes to many forms of heart diseases.
UVRAG

- UVRAG: The ultraviolet (UV) radiation resistance-associated gene.
  - Homologue of yeast Vps38.
  - Partially complement UV sensitivity in xeroderma pigmentosum (XP) cells.
    Monoallelically deleted in colon cancer, breast cancer and gastric cancer.
  - Tumor suppressor.
Regulation of Autophagy and Endocytic Trafficking by UVRAG and Rubicon
UVRAG Complexes

PR
C2
CCD
CEP63-BD
DNAPK-BD

p-Bif
Bax
Beclin 1
CEP63
DNA-PK

1 42 147 200 269 442 699

apoptosis
centrosome stability
DNA repair & genomic stability
UVRAG-deficient Mice Develop Age-related Cardiomyopathy

A

B

C

D

E

F

G

H

Song et al. Cardiovasc Res. 2014
Cardiac Function is Compromised in UVRAG-deficient mice

Song et al. Cardiovasc Res. 2014
Autophagosome is Accumulated in UVRAG-deficient Heart

A

+/-  PB/PB

LC3 I
LC3 II
α-Tubulin

B

LC

+/-  PB/PB

* 

D

LC3 dots per cell

+/-  PB/PB

* 

E

Song et al. Cardiovasc Res. 2014
UVRAG Deficiency Enhances Autophagic Flux in the heart

Song et al. Cardiovasc Res. 2014
Inflammatory Cytokine Expression is Up-regulated in UVRAG-deficient Heart

Song et al. Cardiovasc Res. 2014
UVRAG Deficiency Enhances Pro-inflammatory Cytokine Expression in the Heart Following LPS Treatment

**TNFα**

<table>
<thead>
<tr>
<th></th>
<th>+/+ PB/PB vehicle</th>
<th>+/+ PB/PB LPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFα/GAPDH</td>
<td>1</td>
<td><strong>2</strong></td>
</tr>
</tbody>
</table>

**IL-6**

<table>
<thead>
<tr>
<th></th>
<th>+/+ PB/PB vehicle</th>
<th>+/+ PB/PB LPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6/GAPDH</td>
<td>30</td>
<td><strong>150</strong></td>
</tr>
</tbody>
</table>
Rubicon

- Rubicon: RUN domain protein as Beclin-1-interacting and cysteine-rich containing.

What is the physiological function of Rubicon in the heart?
Genetic Characterization of Rubicon Knockout (KO) Mice

![Diagram of Rubicon gene with ATG, Intron 1, E1, E2, PB insert, GL, PB, GR, and Rubicon/GAPDH blot images.](image)

<table>
<thead>
<tr>
<th></th>
<th>+/+</th>
<th>PB/+</th>
<th>PB/PB</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>150</td>
<td>70</td>
<td></td>
<td>300</td>
</tr>
</tbody>
</table>
Genetic Characterization of Rubicon Knockout (KO) Mice

<table>
<thead>
<tr>
<th>liver</th>
<th>heart</th>
<th>kidney</th>
<th>brain</th>
<th>skm</th>
<th>lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
</tr>
<tr>
<td>−/−</td>
<td>−/−</td>
<td>−/−</td>
<td>−/−</td>
<td>−/−</td>
<td>−/−</td>
</tr>
</tbody>
</table>

- Rubicon
- GAPDH

![Genetic Characterization of Rubicon Knockout (KO) Mice](image)
Autophagic Flux is Enhanced in Rubicon KO Mouse Hearts
Rubicon KO Mice Have Normal Cardiac Morphology and Function

A

WT | KO

HE

picrosirius red

B

<table>
<thead>
<tr>
<th></th>
<th>LVEDD</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>WT KO</td>
<td></td>
<td>WT KO</td>
<td></td>
<td>WT KO</td>
</tr>
<tr>
<td>2M</td>
<td></td>
<td>8M</td>
<td></td>
<td>12M</td>
</tr>
</tbody>
</table>

C

<table>
<thead>
<tr>
<th></th>
<th>LVESD</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>WT KO</td>
<td></td>
<td>WT KO</td>
<td></td>
<td>WT KO</td>
</tr>
<tr>
<td>2M</td>
<td></td>
<td>8M</td>
<td></td>
<td>12M</td>
</tr>
</tbody>
</table>

D

<table>
<thead>
<tr>
<th></th>
<th>EF</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>WT KO</td>
<td></td>
<td>WT KO</td>
<td></td>
<td>WT KO</td>
</tr>
<tr>
<td>2M</td>
<td></td>
<td>8M</td>
<td></td>
<td>12M</td>
</tr>
</tbody>
</table>

E

<table>
<thead>
<tr>
<th></th>
<th>FS%</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>WT KO</td>
<td></td>
<td>WT KO</td>
<td></td>
<td>WT KO</td>
</tr>
<tr>
<td>2M</td>
<td></td>
<td>8M</td>
<td></td>
<td>12M</td>
</tr>
</tbody>
</table>
Rubicon Deficiency Attenuates LPS-induced Lethality and Cardiac Dysfunction

Graph showing percent survival over time with different conditions.

Bar graphs comparing stroke volume and cardiac output between WT and KO groups with vehicle and LPS treatments.
Rubicon Deficiency Enhances Autophagic Flux in the Hearts

<table>
<thead>
<tr>
<th>LPS+ Vehicle</th>
<th>LPS+ Bafilomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>+/+</td>
<td>+/+</td>
</tr>
<tr>
<td>-/-</td>
<td>-/-</td>
</tr>
</tbody>
</table>

- LC3 I
- LC3 II
- α-Tubulin

a b c d e f

+/+: LPS

-/-: LPS
Analysis of Transcripts of Autophagy-related Genes in the Heart
Summary

- UVRAG deficiency impairs autophagic flux while Rubicon deficiency enhances autophagic flux in the heart.
- UVRAG deficiency leads to cardiomyopathy accompanied by compromised cardiac function.
- Inflammatory response is enhanced in UVRAG-deficient hearts.
- Rubicon deficiency attenuates LPS-induced lethality and cardiac dysfunction, which is associated with enhanced autophagic flux in the heart.
Conclusion

UVRAG plays an essential role in autophagy and maintenance of cardiac function.

Loss of Rubicon enhances autophagic flux in the heart with no obvious impact on cardiac morphology and function at baseline, but confers protection against LPS-induced lethality and cardiac dysfunction.
Acknowledgements

Zongpei Song       Xiaohui Wu Ph.D.
Lin An             Yingyu Chen Ph.D.
Shasha Zhang       Yunzeng Zou MD
Zhenguo Zi         Lin He Ph.D.
Yong Ye
Jian Wu
Thanks' for your kind attention!!!!!!
Let Us Meet Again

We welcome you all to our future conferences of OMICS Group International

Please Visit:
www.omicsgroup.com
www.conferenceseries.com
http://cardiology.conferenceseries.com/