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FIRST PERSON

# First person – Yiwei Zhang and Hui Tu

First Person is a series of interviews with the first authors of a selection of papers published in Journal of Cell Science, helping early-career researchers promote themselves alongside their papers. Yiwei Zhang and Hui Tu are co-first authors on 'Oligopeptide transporter Slc15A modulates macropinocytosis in *Dictyostelium* by maintaining intracellular nutrient status', published in JCS. Yiwei is a PhD student in the lab of Huaqing Cai at Institute of Biophysics, Chinese Academy of Sciences, Beijing, China, where she is interested in understanding the interrelationship between cellular nutrient status and macropinocytic activity, and lipid transport. Hui is a PhD student in the same lab, investigating the mechanisms of macropinocytosis, cell migration and lipid transport.

Yiwei Zhang

**How would you explain the main findings of your paper in lay terms?**

**Y.Z. and H.T:** Macropinocytois is a specialized form of 'cell drinking'. It enables amoebae and some cancer cells to ingest extracellular macromolecules in bulk and break them down in the lysosome, creating an intracellular source of nutrients to fuel cell growth. Using the social amoeba *Dictyostelium discoideum* as a model system, we found that a membrane-dwelling oligopeptide transporter Slc15A is a novel macropinocytosis regulator. By mediating peptide transport from growth medium in the early macropinocytic pathway instead of the lysosome, Slc15A maintains the intracellular availability of key amino acids and promotes macropinocytic activity of cells. This study reveals that the lysosome might not be the only cellular compartment where internalized nutrients are extracted. Furthermore, we found that seemingly opposite strategies are taken by *Dictyostelium* and cancer cells to modulate macropinocytosis when coping with amino acid stress conditions. *Dictyostelium* cells downregulate macropinocytosis, conserve energy and enter multicellular development for survival, whereas cancer cells lacking this alternative route resort to macropinocytosis upregulation and protein-scavenging instead. How cells develop different survival strategies is fascinating.

**Were there any specific challenges associated with this project? If so, how did you overcome them?**

**Y.Z.:** I faced two major challenges. One was to establish the high-content imaging-based genetic screening system at the beginning of this project. My co-worker Yazhou Hao and I tried an array of experimental conditions for growing cells, generating mutants and characterizing phenotypes. After over a year of trial and error, we successfully got the screen to work and identified a series of candidate genes involved in macropinocytosis regulation. Another challenge was to pinpoint where Slc15A functions. I generated Slc15A-GFP/RFP knock-in cells, but the fluorescent signals of the fusion proteins were fairly low. I had to analyze the colocalization of Slc15A with multiple markers using different microscopes to eventually draw a solid conclusion. Although the process was difficult, the moments when nice results were obtained were always extremely joyful and exciting.

**When doing the research, did you have a particular result or 'eureka' moment that has stuck with you?**

**Y.Z.:** My 'eureka' moment was when I finally figured out the experimental condition to show that Slc15A modulates macropinocytosis by importing oligopeptides. This experiment

Hui Tu

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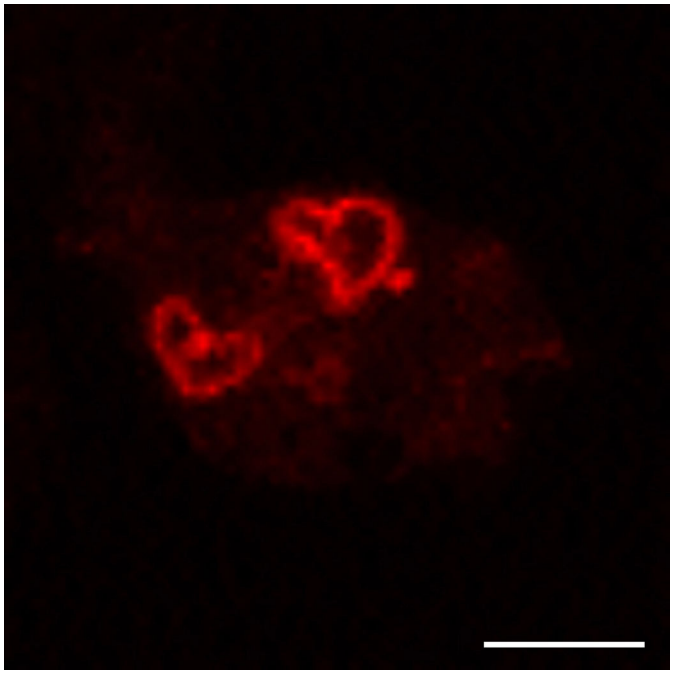

**'Love' macropinosomes.** TAPP1–RFP-labeled macropinosomes. Scale bar: 5 µm.

involves using synthetic dipeptides to replace the corresponding amino acids in the growth medium and then to compare the recovery of macropinocytosis in wild-type and *slc15A* deletion cells. Initially, I used the standard concentration but found that the added Arg-Arg and Lys-Lys dipeptides restored macropinocytosis in both cell types. This unexpected result confused me for a while until one day we guessed that the surplus dipeptides internalized into the macropinocytic pathway might be degraded into amino acids and utilized by the cells, thereby bypassing the need for Slc15A. When I reduced the concentrations of added dipeptides, I found a condition that failed to restore macropinocytosis in *slc15A* deletion cells but perfectly restored it in wild-type cells. How cells may adapt to nutrient supply really amazed me.

**H.T.:** The first step of this project required the establishment of a completely new screening system. Prior to this work, no one in our lab, including our supervisor, had experience in high-throughput screening. During the process, we designed and tried many experiments and learned different techniques. These efforts laid a good foundation for the laboratory's following works.

**Why did you choose Journal of Cell Science for your paper?**

**Y.Z. and H.T:** We know Journal of Cell Science is a classic scientific journal with a long history. There have been a lot of important discoveries in cell biology published in this journal.

**Have you had any significant mentors who have helped you beyond supervision in the lab? How was their guidance special?**

**Y.Z.:** I was very fortunate to have completed my PhD under the guidance of Prof. Huaqing Cai. In a relaxed and pleasant research environment, I not only learned scientific knowledge but also developed critical thinking skills. I became more and more interested in scientific research and fell in love with it. To enjoy the process of learning and exploring is the greatest wealth that Huaqing has brought me.

**H.T.:** My grandmother Baofeng Li is my life mentor. She is an ordinary Chinese rural woman with no educational experience, but she encourages each of her children to pursue knowledge and truth. She experienced many setbacks when she was young, but she worked hard to break the shackles. She never held grudges against those who hurt her and never forgot everyone who helped her. She has always taught us that we should help others.

**What motivated you to pursue a career in science, and what have been the most interesting moments on the path that led you to where you are now?**

**H.T.:** My uncle passed away from lung cancer when I was in high school, and it saddened my family for a long time. I decided to do scientific research and try to unravel the basis of disease. I hope that one day my work can help more people. Whenever I discover new biological phenomena, they inspire me to keep going.

**Who are your role models in science? Why?**

**H.T.:** I really admire my PhD supervisor Huaqing Cai. She is smart, kind, rigorous and passionate about science. She not only cared about my research project but also my personal life. Dr Yoshinori Ohsumi is also my role model in science. He conducted a series of groundbreaking experiments that led to the discovery of autophagy, and has devoted 50 years to basic research.

**Tell us something interesting about yourself that wouldn't be on your CV**

**Y.Z.:** One of the perks working in our lab is its close proximity to the Olympic Forest Park. In my spare time, I like to go for a walk in the park or sit by the lake watching fishes and tadpoles. Spring is coming and it's kite-flying season again.

**H.T:** I love to collect beautiful hats even though I rarely wear them, and I also like photography.

**Reference**

**Zhang, Y., Tu, H., Hao, Y., Li, D., Yang, Y., Yuan, Y., Guo, Z., Li, L., Wang, H. and Cai, H**. (2022). Oligopeptide transporter Slc15A modulates macropinocytosis in *Dictyostelium* by maintaining intracellular nutrient status. *J. Cell Sci.* **135**, jcs259450. doi:10.1242/jcs.259450