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FIRST PERSON

First person – Yohan Kim

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. Yohan Kim is first author on 'Tau interacts with SHP2 in neuronal systems and in Alzheimer's disease brains', published in JCS. Yohan conducted the research described in this article while a graduate student in Gloria Lee's lab at the University of Iowa Carver College of Medicine, IA, USA . He is now a postdoctoral fellow in the lab of Efrat Levy at the Center for Dementia Research, Nathan S. Kline Institute, NY, USA, investigating the pathogenesis of Alzheimer's disease and developing therapeutic strategies.

Yohan Kim

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

The main problem with current Alzheimer's disease (AD) research is that we still do not know when AD exactly begins, what causes AD, and how this disease develops as individuals age. Thus, it is very important to better understand the pathogenic mechanisms of AD in order to make any progress in the development of AD treatment. The main finding of our paper is the interaction of two proteins, tau and SHP2, in neuronal cells, mouse brain and human brain, where the level of this interaction specifically increases in brains of patients with AD. Although tau protein is well-known to be important in making a track in neuronal cells to facilitate the trafficking of several key proteins necessary for maintaining cell fitness, there is no doubt that tau also plays a critical role in signal transductions relevant for neuronal development, survival and more. Interestingly, SHP2 is also involved in signaling pathways where tau is involved. Tau is also known to play a neurotoxic role in AD by engaging in signal transduction events relevant to the progression of AD. However, the involvement of SHP2 in AD has never been studied. Because we found that (i) tau and SHP2 associate and the levels of this complex change in developing neurons and AD brains, and (ii) there is a resemblance between the signal transduction pathways of developing and AD brains, our findings thus suggest that tau–SHP2 complexes have a role in AD pathogenesis, providing further insight into the disease mechanism of AD.

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

Since I was studying protein–protein association of the tau–SHP2 complex, obtaining rigorous data proving this association was very important. While using biochemical approaches to study the protein interaction was useful, there was a clear limitation when we attempted to investigate and visualize the localization of the protein complex within intact brain sections and neurons. In order to overcome this technical issue, we looked through several approaches in the literature and fortunately found the proximity ligation assay (PLA), which allows for detection of endogenous protein complexes by amplifying signals from associated proteins. Since there were only a few articles that applied PLA to tau, I had to optimize the assay before finally being able to utilize it for my study and obtain great data. As tau protein has numerous binding partners that play critical roles in physiological and pathological signal transductions, adapting cutting-edge techniques such as PLA has a huge potential to advance the tau field.

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

Tau protein is both a microtubule-associated and phospho-protein. Phosphorylation in tau regulates its function in terms of microtubule-binding and association with other proteins. Since I was interested in the effect of phosphorylation at threonine 231 (pT231-tau) on the association with SHP2, I examined whether pT231-tau affects its affinity to SHP2. When I obtained the results (both *in vitro* and in the cell) showing a significant increase in the association between pT231-tau and SHP2, relative to normal tau and SHP2, I was very excited because pT231-tau is known to increase in AD brain. Interestingly, we also observed an increased level of the tau–SHP2 complex in AD brain. This suggests that increased phosphorylation at T231 of tau might contribute to the increase in the level of tau–SHP2 association in AD brain.

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?

In my last year of veterinary school, I had the chance to think deeply about my future – how can I live my life in a more meaningful way, how can I contribute to making the world better, and what can and should I then do? Since I enjoy reading, studying and performing

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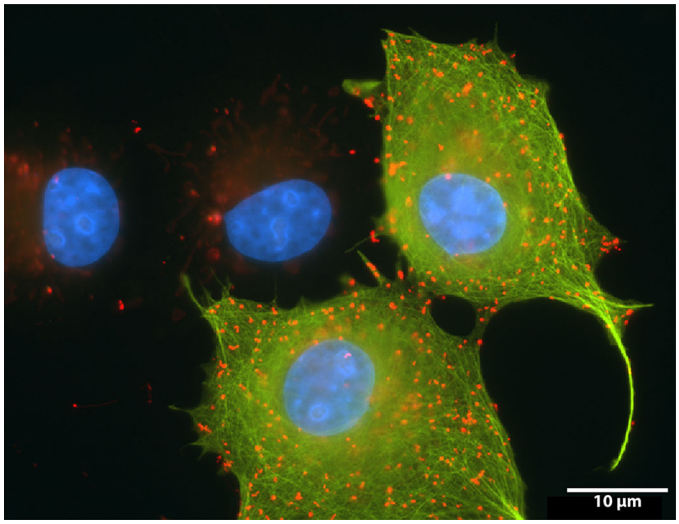

tau–SHP2 complexes (red puncta) are shown in COS7 cells expressing transiently transfected tau protein, which labels microtubules (green).

experiments, I decided to put these skills to good use, committing myself to science (in any way and in any kind of research because I only had a vague idea at the time). While studying in my PhD program, I was able to work in several labs, learning a variety of basic research topics. When I joined the lab studying AD, I realized that AD research is it for me, as if I was already destined. Currently, the biggest problem in AD research is that all the clinical trials performed to date were not successful, even though they were all based on numerous experimental data. This clearly indicates that we have attempted to develop AD therapies based on an incomplete understanding of neuropathogenic mechanisms; specifically, we don't understand the causes and events underlying the disease at a molecular level. Such clinical failure not only increases the economic burden, but also adds to the social cost of caring for patients with AD. Thus, when I noticed that my data was adding to our knowledge of the underlying mechanisms for AD pathogenesis, I was very excited and further motivated to help elucidate AD pathologies. This has finally led me to another chapter of my AD research as a postdoctoral fellow, and I will continue to pursue the development of therapeutic strategies to cure AD and look for early diagnostic markers for the disease.

What's next for you?

As a postdoctoral fellow, I still conduct research on AD, but instead of focusing on the tau protein I am now investigating the involvement of amyloid-beta associated with exosomes (a part of extracellular vesicles) in the disease mechanism. This research has really helped me to expand my knowledge and technical skills leading to better understanding of the pathomechanism of AD. As my career goal is to become a good scientist making a big step forward for AD research, no matter where I work, either in academia or in industry, my next chapter of research will be taking place where therapeutic strategies for AD are being practically pursued, in addition to basic AD research.

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

I love music: listening, singing and playing instruments. I used to serve as a conductor in church choirs.

Reference

Kim, Y., Liu, G., Leugers, C. J., Mueller, J. D., Francis, M. B., Hefti, M. M., Schneider, J. A. and Lee, G. (2018). Tau interacts with SHP2 in neuronal systems and in Alzheimer's disease brains. *J. Cell Sci.* **132**, 229054. doi:10.1242/jcs.229054