Researchers Discover a Key Protein Involved in Sensing Small Rapid Movement of Limbs and Body

Dr. Chih-Cheng Chen, an Associate Research Fellow at the Institute of Biomedical Sciences (IBMS) in collaboration with Dr. Guy Bewick at University of Aberdeen, UK have identified a protein named Acid-sensing ion channel 3 (ASIC3) that is involved in the so-called "position-movement" sensation—the "sense" of the relative position of neighboring parts of the body through which we know our body exists and ensures we do not easily fall. Dr. Chen's team used novel genetic mouse models to reveal the role of ASIC3 in detecting small and rapid movements through which the brain is informed where our limbs are and what they are doing. Understanding the role of ASIC3 in this sense, which is known to specialists as "proprioception", provides new insight into movement control and will inform research into therapeutic strategies for movement disorders, and hopefully eventually benefit people with fall problems due to aging, diabetes, spinal injury, and cerebral palsy. The research was published in *Nature Communications* on May 10, 2016.

Mechanical senses (e.g., proprioception) are important for control of body movements, but far less is known about them than the other senses through which the body perceives the outside world, such as temperature, sight, smell, taste, and pain. The mechanical sense of movement is very complicated and approaches to identify specific roles for the proteins involved in the mechanical senses are challenging. Therefore, the molecular mechanism underlying this sense is largely unknown. In 2009, Dr. Chen's team developed a key technique to detect a specific model of mechanical senses—the tether mode. In the current research they used this technique to discover a role for ASIC3 in the tether mode of mechanical sense and proprioception.

To probe the role of ASIC3 in the mechanical senses, the team first developed several genetic mouse models to detect and manipulate the expression of ASIC3. They tried to block ASIC3 function in the tether mode, in which the mechanical force acts on a group of tethering proteins from both the inside and outside of the cell membrane to open a hole in the membrane called an ion channel. Opening such channels in the nerve ending is how the cell detects such types of movement. When ASIC3 was blocked, a series of tests (in cell culture, isolated tissue, and in walking behavior) revealed that cells no longer detected very gentle movements, isolated muscles were hypersensitive to rapid movements, and fine foot placement while walking was clumsy.

Dr. Chen's team concluded that ASIC3 is involved in the detection of small and rapid movement of the limbs and the whole body, and thus is essential for proprioception. This is the first time that an ion channel (ASIC3) has been proved to be involved in tether mode of mechanical senses in vertebrates. The finding will facilitate further research to discover more proteins involved

in tether mode, not only in walking but perhaps also in detection of blood pressure and mechanical pain, which are also part of the mechanical senses.

The first author Dr. Shing-Hong Lin was a postdoctoral fellow in the Institute of Biomedical Sciences at the time of the study; he has since moved to Harvard University as a postdoctoral researcher, from this April. The research project was supported by Academia Sinica and grants from the Ministry of Science and Technology of Taiwan.

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The full article entitled “Evidence for the involvement of ASIC3 in sensory mechanotransduction in proprioceptors” is available at the *Nature Communications* website at: http://www.nature.com/ncomms/2016/160510/ncomms11460/full/ncomms11460.html