proteinspotlight
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Issue 89, December 2007

www.proteinspotlight.org

Ear of stone

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The end of December is a time of year when many lose their balance. This, however, is usually due to the numbing of the senses by an exaggerated consumption of alcohol. There are many other ways of losing your balance, and one of them can be caused by an altered architecture of the inner ear. Besides bearing the intricate machinery which allows animals to perceive sound, the inner ear is also responsible for our sense of movement. Those who are stricken with sea-sickness know all too well what this means. Very small regions known as the saccule and the utricle detect both gravity and acceleration, two forces we spend our time dealing with. Deprived of the capacity to perceive them, the simple act of moving our head would prove to be an awesome experience. At the heart of this perception are small stones. And one protein, otopetrin 1, is proving to be essential for their formation.

Ocean perch (*Sebastes mentella)* otoliths

Source : Wikipedia

Keeping our balance is not such a simple task. You may think that it's all a question of a little concentration and crafty positioning of the body. But it's not. There is more to it than that. We have built-in devices which we need not only to keep an upright posture but also to sense movement. These devices are known as otoconia and are located in the darkest recesses of our inner ear. Otoconia are a mixture of organic and inorganic material. In humans, their size ranges from 3 to 30µm and they are bathed in an extracellular gelatinous matrix. The otoconia themselves have an organic protein core cloaked with calcium carbonate (CaCO3) crystals – a bit like the sweets our grandmothers gave us, which were hard on the outside and filled with a soft centre.

Otoconia synthesis is completed shortly after birth. Caught in an extracellular gelatinous matrix, itself packed full of protein, this peculiar biomineral cum protein mass forms a jelly-like membrane which rests on tiny hairs. These hairs are embedded in two small organs of the inner ear, known as the utricle and the saccule. Any movement of our head – with respect to acceleration or gravity – makes the otoconia move. And since they are resting on the hairs, their movement will, in turn, cause the hairs to move. The perception is then relayed to nerves which will make a point of telling the brain. The utricle is largely horizontal and will register any movement in the horizontal plane, such as acceleration. The saccule, on the other hand, lies in a vertical plane and registers movement due to the pull of gravity.

Otoconia are formed during embryogenesis and their final design is completed shortly after birth. Otoconia seedlings are probably secreted into the extracellular matrix, and are most likely to involve a core protein matrix which is calcium-friendly. Calcium and carbonate concentration must also be heightened in the seedlings' vicinity, so that the calcium carbonate crystal envelope can be shaped. Otopetrin 1 is part of the gelatinous extracellular matrix in which the otoconia float.

When otopetrin 1 is deficient, the formation of otoconia is impaired. As a result, the perception of acceleration and gravity is confused, and mice carry tilted heads or zebrafish swim upside down.

Otopetrin 1 has all the characteristics of an integral membrane protein, yet it is found in the extracellular gelatinous matrix. This has led scientists to believe that the protein is most probably imbedded in the membranes of vesicles which bud off epithelium cells. In zebrafish, otopetrin 1 seems to be involved in protein transport, and in particular the trafficking and localization of a protein known as Starmaker. Starmaker is proving to be essential both for the fashioning of the fish biominerals – known as otoliths – and the crystal lattice on which they grow. Otoliths are of the same nature as otoconia, only far bigger. While we own many otoconia, fish only have three. But they are large, mainly because the deposit of calcium carbonate only stops when a fish doesn't need a sense of balance anymore. Though a role in protein trafficking has not yet been witnessed in humans, otopetrin 1 does seem to be involved in calcium regulation in response to ATP. However, otopetrin 1 itself doesn't sport domains that, until now, have been known to interact with ATP or calcium. Consequently, either otopetrin 1 activates proteins that do, or its sequence contains atypical domains that can! Whatever the outcome, otopetrin 1 is certainly essential for the formation of calcium carbonate crystals, and hence otoconia.

Otoconia – or the lack of them - can be the source of trouble. The passing of time can cause the structures to degenerate or change position. The sensation perceived is known as benign paroxysmal positional vertigo (BPPV) and, though harmless, those concerned suffer from dizziness or loss of balance. The elderly are prone to falling which frequently results in broken bones or even, sometimes, accidental death. Certain drugs can also be the cause of otoconia degeneration and patients suffer from the same disorders. Research on otoconia and otholiths is now focused on finding therapies which could improve their stability over time as well as enhance the biomineralization of remaining otoconia. Otoconia regeneration is also being considered. Furthermore, getting to know the mechanisms involved in otoconia synthesis could lead to a better understanding of how bone (CaCO4) is made – and without bone or otoconia, how could we fully enjoy a balanced life?

Cross-references to Swiss-Prot

Otopetrin 1, *Danio rerio* (Zebrafish): Q7ZWK8
Otopetrin 1, *Homo sapiens* (Human): Q7RTM1
Otopetrin 1a, *Mus musculus* (Mouse): Q80VM9

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