Regenerating cells in the inner ear

6/18/15

The hair cells present in the auditory portion of the inner ear - the organ of Corti in the cochlea - are indispensable to the transmission of sound to our brain. Unfortunately, when these cells are destroyed they are not replaced resulting in hearing impairments or even deafness. Brigitte Malgrange and her team are working on an important line of research involving the regeneration of hair cells in the cochlea: they have discovered that when the expression or function of Ephrin-B2 protein is inhibited, the cochlear supporting cells transdifferentiate into hair cells. This enabled them to create new hair cells at the right place in the organ of Corti.

More than 5% of the world's population suffer from a debilitating hearing impairment according to the World Health Organisation (WHO). Therefore, around 360 million people including 328 million adults and 32 million children are affected by this condition. In the case of people over the age of 65, the figures increase dramatically with more than one third of this elderly category being affected by a debilitating loss of hearing. It is certainly true that this can sometimes be compensated for by using devices such as hearing aids or cochlear implants etc. However, this is not always possible for medical or financial reasons.

In a general sense, hearing impairment or deafness can be due to genetic factors or to complications that arise during pregnancy or childbirth. These are known as congenital reasons and could involve, for example, an infection such as the German measles or syphilis or the inappropriate use of medicine during pregnancy. In the case where hearing impairment does not occur around childbirth, it is classed as having been "acquired". In these cases also, there may be numerous causes: infections, medicines that are specifically "ototoxic" (such as certain types of antibiotics or an anti-carcinogens widely used in clinical treatment), acoustic trauma or ageing…
Hair cells and sensorineural deafness

According to the type of structure affected within the ear, there are two kinds of deafness, conductive or sensorineural. Conductive deafness more particularly concerns the external or middle ear while sensorineural deafness is caused by damage to the inner ear or the auditory nerve. Professor Brigitte Malgrange's team have therefore focused their attention on these structures and on sensorineural deafness in particular. Professor Malgrange is the head of the Developmental Neurobiology Research Unit of the GIGA. "The objective of our research is to better understand the development of the auditory portion of the cochlea, the hearing organ", explains Brigitte Malgrange. "Inside the cochlea there is an organ called organ of Corti which is the sensory element involved in hearing". The organ of Corti is composed of two main types of cells: supporting cells and hair cells. "The hair cells directly transmit auditory information to the neurones to enable this information to reach the brain", continues the researcher. The hair cells are therefore of capital importance
for sound perception. When these cells are destroyed, they do not regenerate and this leads to sensorineural deafness. In the context of his PhD, Jean Defourny studied how these cells are generated. "Understanding the underlying mechanisms involved in the development of the hair cells should enable us to use these same mechanisms to combat deafness", continues Brigitte Malgrange.

**Ephrin-B2 protein, a key factor in cell identity in the inner ear**

The research of Jean Defourny and Brigitte Malgrange has resulted in a promising discovery. The results of this study have been published in the journal *Nature Communications* (1). "We identified a signaling pathway involving the Ephrin-B2 protein and its specific receptor EphA4. These play a very important role in the maintenance of the identity of the cells in the organ of Corti", explains Brigitte Malgrange. The scientists used various methods and experiments with knockout mice whose coding gene for the protein Ephrin-B2 was invalidated by means of soluble inhibitors of the protein or interfering RNAs. "The Ephrin-B2 protein is only present in supporting cells, not in hair cells. When we inhibit the expression of the coding gene for this protein or its function, the supporting cells transdifferentiate into hair cells", explains the researcher. This very interesting discovery makes it possible to induce new hair cells directly at the right place within the inner ear. While the researchers from Liege would seem to be on the right path with regard to combatting sensorineural deafness linked to the loss of hair cells, other steps remain necessary before this can be achieved. "We must now verify that these newly generated hair cells connect correctly to the sensory nerves of the inner ear. This is the only way that sound can be transmitted to the brain", explains Brigitte Malgrange. This research is currently under way at GIGA-Neurosciences.

**A small step towards finding an alternative to hearing aids**

Currently, there is no medical procedure to correct problems of sensorineural deafness. "The only possible solution are hearing aids, but only in the case where there is some residual hearing" explains Brigitte
Malgrange. External hearing aids make it possible to amplify the sound that reaches the ear. Cochlear implants are used in case of profound deafness, when the patient's inner ear is no longer capable of analyzing the sound that reaches him. Cochlear implants do this work in place of the cochlea and stimulate the residual neurones. The line of research involving the regeneration of hair cells that is currently being followed by Brigitte Malgrange's team is both innovative and promising given the results that they have recently obtained. It only remains for science to succeed in finding a medical application for this discovery.