The mysteries of the Broken Ear

11/25/10

How about if it became possible to prevent the destruction of the cells or neurones which, in our inner ear, are responsible for deafness? Or even to regenerate these cells? In attempting to one day be able to do so, Brigitte Malgrange and her team have been tracking down, amongst other things, the role of the Sox10 gene.

Seventeen per cent of the world's population are deaf or hard of hearing. After the age of 65 this problem affects 50% of us. In the years to come, given the ageing of the population but also due to the multiple ways in which our ears are exposed to inappropriate noise, there is a risk that this proportion will rise drastically. To try to counter such possibilities the team led by Dr Brigitte Malgrange, a Doctor of Pharmacy, a FNRS Research Director and the head of the University of Liège's Giga Neurosciences unit, is trying to penetrate the secrets of the inner ear. Within this organ certain molecular mechanisms are involved both in the development of cells which will be linked to hearing and deafness and in the regeneration of these cells. One of the driving ideas of the two studies she has just published with her team consists of studying the factors involved in development. And to discover within them new therapeutic avenues.
Within the inner ear

Hearing losses are classed into two categories: so called forms of conduction deafness and those of perception deafness. The former, due to a lesion of the middle or of the external ear, are also the least common forms, for which there exist surgical treatments or support techniques for the auditory function, which range from lip reading to sign language and from hearing aids to cochlear implants. As for forms of perception deafness, they are almost always the consequence of lesions to certain cells within the inner ear, either the acoustic hair cells of the Organ of Corti (the auditory section of the inner ear) and/or auditory neurones located in the spiral ganglion. In effect they are neither repaired nor replaced.

Forms of perception deafness involve people who receive medicinal ototoxic treatments (toxic for the ear) such as, for example, antineoplastic (anti cancer treatment) or even, amongst other products, certain antibiotics. But deafness can also result from certain diseases (meningitis, mumps, multiple sclerosis, etc.) or arise from a slow and progressive degenerative disease specifically affecting the ear and linked, for example, to ageing and/or unreasonable exposure to noise.

As Brigitte Malgrange explains, there exists no treatment which can enable the restoration of the auditory function for forms of perception deafness (only inserting a cochlear implant, as long as there still exist
functioning spiral ganglions, can sometimes be considered). 'Research into the inner ear is difficult,' she observes. 'At the present time we are still faced with a large number of unknowns. They concern, for example, the development of this organ and the role of the different factors which contribute to it. Yet a better understanding of these factors would allow us to develop new therapeutic pathways against deafness. In effect we could make use of these molecular mechanisms and make them the targets medicinally based on cell regeneration.' And that is why, even if the two studies recently published under her leadership could be taken for highly specialised research in neurosciences (which they indeed are), they could nonetheless lead, in the mid or long term, to clinical research into innovative therapies. They could improve the quality of life of a very large number of people affected by a hearing problem.
The embryo, but what about afterwards?

In mammals the regeneration of acoustic hair cells and neurones seems to be restricted to the period of embryo development. What is one of the key thought processes behind the research of Brigitte Malgrange’s team? It is that it has not settled for this notion of irreversibility and has attempted to adapt it. To do so it has thus sought to identify the molecular actors which allow progenitor cells (or stem cells) to be differentiated into acoustic hair cells and/or spiral ganglion neurones, as well as their proliferation. Identifying such heavyweight actors is nevertheless not an easy task.

Nearly all the cells of the inner ear derive from the otic placode, which gathers together a group of identical cells. A large number of genes and factors are involved in this development. In the organ of Corti they drive a cell proliferation phase, and then cellular differentiation into two types of cell: acoustic hair cells (or sensory cells) and non sensory cells (or support cells). Other research - carried out previously by Brigitte Malgrange - has revealed the presence of the progenitors of acoustic hair cells in the neonatal organ of Corti. Yet the persistence of these immature precursors suggests the possibility of their being developed in the postnatal period. But in order to take advantage of such an opportunity it is first of all necessary to determine the molecular signals which, in the sensory epithelium of the inner ear, control the number of these progenitor cells, their differentiation into two cell types and their organisation. Without this knowledge, how could one imagine one day stimulating these progenitors? And how could one raise hopes of preventing or blocking cell degeneration in human beings, or even of being able to regenerate these cells, essential to hearing?

‘We split the research work into two,’ points out Brigitte Malgrange. ‘Morgan Bodson, who was doing her doctorate, and Dr. Ingrid Breuskin were very involved in carrying out these two studies. One of the articles is specifically devoted to the Organ of Corti. In this auditory organ acoustic hair cells - also called sensory cells - allow the transmission of auditory information. The second publication was centred on the auditory neurones, or spiral ganglion neurones. They constitute the major nerve relay between the organ of Corti and the central nervous system.’

A bet on Sox10

In effect, the researchers have focused on progenitor differentiation factors. ‘We in particular chose to study the role of one these transcription factors, that of the Sox10 gene,’ points out Brigitte Malgrange. ‘The Sox family has over twenty members. They play important roles in various processes over the course of development and more especially in cell differentiation. Yet Sox10 is very strongly expressed at the embryo stage in the otic placode, from which nearly all the cells of the inner ear subsequently derive: this gene fixes on the promotors of a whole series of factors involved in differentiatiation and the survival of the cells in the inner ear. We wanted to understand its role better, and we succeeded.’

The research was carried out on mice in which the Sox10 gene had been invalidated. These mice were provided by Professor Wegner's laboratory, at the University of Erlangen in Germany. The study showed that Sox10 was necessary in the organ of Corti for the survival of the progenitors of acoustic hair cells. In the absence of Sox10 the researchers noted a drastic shortening of the organ of Corti, an increase of cell death and a significant drop in progenitor cells. ‘On the other hand, we confirmed the fact that Sox 10 was not necessary for the survival of glial cells which accompany the neurones in the ganglion. The new factor unearthed by our research? In the other ganglions of the peripheral nervous system, the neurones deprived of glial cells do not survive, whilst they do so in the inner ear. In fact, the glial cells then secrete trophic factors
which are indispensable for neurone survival, and especially for one of them, the Brain-Derived Neutrophic Factor, BDNF. In this case neurone survival is thus quite specific to the inner ear. All in all our two studies have allowed us to conclude that Sox 10 well and truly constitutes a fundamental factor for the development of the auditory section of the inner ear,' explains Brigitte Malgrange.

Another new factor springs from the Liège team's work. The Sox 10 gene is involved in an orphan disease (or rare disease), Waardenburg-Shah syndrome, and deafness is one of the symptoms linked to this condition. 'Up until now, it was thought that this deafness was connected to the absence of melanocytes (an epithelial cell of the epidermis' basement membranes) in the structures of the inner ear. Melanocytes are in effect essential for hearing: they recycle the potassium which allows the transmission of electrical sound information. Our work does not categorically rule out this idea, but nevertheless, in bringing to light the role of Sox 10 in the development of the inner ear we have opened up another possible interpretation. In the people affected the absence of Sox 10, and the impact of this absence on progenitors and on glial cells, might add to the melanocyte problem, or even supersede it,' points out the researcher.

**For a quality of life**

In the end, Brigitte Malgrange's team did not settle for merely identifying, on its own scale, the role and place of an important actor in the development of the inner ear. 'In the long term, the objective consists of being able to modulate Sox 10 in order to be allow the survival of the progenitors of the organ of Corti,' specifies Brigitte Malgrange. 'In over expressing Sox 10, and thus curbing the death of the progenitors, we could for example stop progressive auditory degeneration, a disease which is poorly understood and which leads to the deafness of numerous aged people.'

Brigitte Malgrange is not expecting to tomorrow - or even the day after - see the appearance of a miracle molecule which would resuscitate or protect against the impairment of acoustic hair cells and of neurones, all the more so in that research into and clinical studies...
of the inner ear remain difficult and that there not so many of them. Her team has nonetheless opened up a new avenue to explore: that of a product which 'boosts' or modulates the progenitors, and thus protects or regenerates acoustic hair cells and neurones. This product could, for example, be introduced during the insertion of a cochlear implant: the effectiveness of these sophisticated implants would be improved, as their performance depends on the neurone pool in which it is placed. Deafness is not necessarily a huge problem, but a lessening or a stabilisation of this handicap would nevertheless improve the lives of a significant number of people.