

The Japanese horseshoe crab and deafness

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The human ear is an elegant and intricate organ that consists of an outer, an inner and a middle ear, and converts mechanical signals into electrical signals with great precision. The outer ear is relatively simple in structure and functions as a sound-collecting funnel which directs sound waves to the middle ear. The middle ear transmits sound waves to the inner ear via three small bones: the malleus, the incus and the stapes. The inner ear is the ear's boiler room; this is where sound waves are processed into electrical signals and sent – via the auditory nerve – to the brain.

The inner ear is an intricate meshwork of bones and cavities bathed in fluid. There is an intimate structural arrangement where many components interact with one another in an elegant and precise way to process sound waves and control balance. And because of this high level of complexity, the task of unravelling key proteins important for sound processing is a huge challenge. As it goes, recent genetic studies have helped enormously.

These studies were performed on families with late onset dominant hearing loss and resulted in the localisation of a gene to human chromosome 14. The gene – *COCH* – codes for a 550 amino-acid protein that shares 94% and 79% amino-acid identity with the mouse and chicken sequences, respectively. Seven families with hereditary hearing loss have been reported as having non-conservative amino-acid changes in this protein, making *COCH* a major player in the pathogenesis of late onset hearing loss. All the pathogenic changes reside in a 100 amino-acid stretch of the protein, suggesting that this domain plays a pivotal role in the functioning of *COCH* in the inner ear.

Furthermore, this particular domain bears significant homology with a Factor C domain in the ancient invertebrate *Limulus* or Japanese horseshoe crab. Factor C (FC) is a serine protease-clotting factor – activated by lipopolysaccharide binding – and initiates a clotting cascade. The role of this domain in *COCH* is unclear but in *Limulus* it is located in the H chain of factor C that has been shown to bind to lipopolysaccharides. The FC domain contains four cysteine residues that may form disulfide bonds which could be important for the correct folding of the protein. Amino-acid

changes in this domain could disrupt disulfide bond formation and thus result in a poorly folded protein.



The living fossil

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The three dimensional structure of *COCH* is not yet known but information on its putative function can be deduced from a few key features found in the amino-acid sequence. The N-terminal region of the human and mouse proteins are predicted to contain a signal peptide domain suggesting that *COCH* is a secreted protein. Supporting this is the absence of any transmembrane spanning domains and the presence of two domains with homology to von Willebrand factor (vWF) type A domains. Type A domains are present in a variety of proteins involved in homeostasis, the immune system and the extracellular matrix. With the exception

of integrins, all “type A domain” containing proteins are secreted.

Clearly, there is strong predictive evidence that COCH is secreted. But what happens to it after that? Some have suggested that COCH may interact with other extracellular proteins and play a structural role in the inner ear. The presence of two type A domains – which in vWF have been shown to bind fibrillar collagens type I and III – supports this suggestion. Additionally, there is a high expression of two other proteins, *COL1A2* and *COL3A1*, in the cochlea – the spiral structure within the inner ear. So there may indeed be some kind of interaction involved with extracellular proteins though it has to be supported by experimental evidence.

An interesting clinical finding in hearing impaired individuals with pathological mutations in the COCH gene is the presence of acidophilic materials, possibly glycosamines, in the cochlea. These deposits accumulate in channels that accommodate nerve fibres, thus causing nerve degeneration. This accounts for the late onset and progressive nature of hearing impairment in these individuals. It could be that COCH plays a role in the formation of these acidophilic deposits either directly, by the accumulation of the defective protein or indirectly, by abnormal interactions of the altered COCH with other extracellular components. So, though the exact role of COCH in the inner ear is yet to be fully elucidated, it is already providing some tantalising insights into how the inner ear functions.

Cross-references to Swiss-Prot

Cochlin, *Gallus gallus* (chicken) : O42163

Cochlin, *Homo sapiens* (human) : O43405

Cochlin, *Mus musculus* (mouse) : Q62507

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