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Assembly of the cochlear gap junction macromolecular complex requires Connexin26

(コネキシン 26 による蝸牛ギャップ結合巨大分子複合体の集積)

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Abstract

Hereditary deafness affects ~1 in 2,000 children. The mutations in connexin26 (Cx26), a cochlear gap junction protein, represent a major cause of pre-lingual, non-syndromic deafness, as they are responsible for as many as 50% of such cases of deafness in certain populations. Connexin-associated deafness has been believed to be triggered by a functional defect resulting from mutated connexins. There has been, however, a discrepancy in that Cx26 deficiency was not compensated for by Cx30, which is abundantly expressed in the same cochlear cells. Here we demonstrate that Cx26-dependent gap junction plaque (GJP) disruption occurs as the earliest change during embryonic development, resulting in a drastic reduction in the GJP area, and is associated with excessive endocytosis with increased expression of Caveolin1 and Caveolin2 in models of two major forms of Cx26-associated deafness. GJP disruption with the functional defects was also clearly reproduced with human Cx26 and Cx30 clones in vitro.

This is the first report demonstrating that a mutation in Cx26 induces macromolecular degradation of large gap junction complexes, accompanied by an increase in caveolar structures, which may lead to excessive membrane retrieval and result in a drastic reduction in the GJP area. This may represent a new molecular pathology for hereditary sensorineural deafness and for the general formation of gap junctions, and thus this machinery could be an effective target for drug design and chemical screening to reinforce the assembly of the other cochlear connexins, such as Cx30.