A checkerboard pattern of inner ear cells enables us to hear

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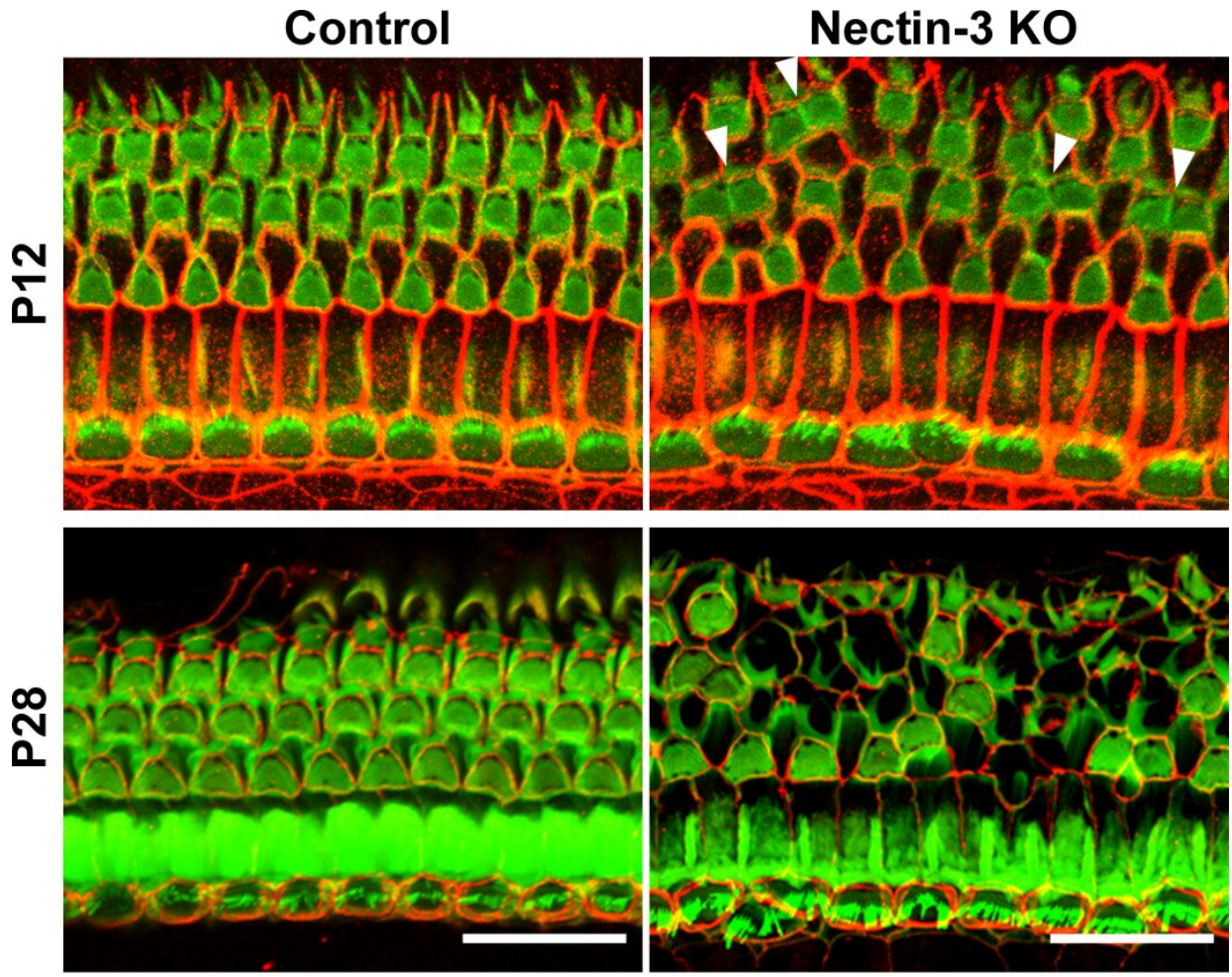

Nectin KO mice went deaf due to the loss of hair cells. Left: The organ of Corti from a normal (control) mouse. The hair cells and their support cells are lined up in an alternating, checkerboard-like pattern. Right: The organ of Corti from a nectin KO mouse. The top row of images were taken at 12 days old, the bottom row at 28 days old. 2 weeks after birth, the hair cells in nectin KO mice

disappeared due to apoptosis (cell death). The white arrows indicate where hair cells became attached to each other. Credit: *Frontiers in Cell and Developmental Biology* (2022). DOI: 10.3389/fcell.2022.1073830

A Japanese research group has become the first to reveal that the checkerboard-like arrangement of cells in the inner ear's organ of Corti is vital for hearing. The discovery gives new insight into how hearing works from the perspective of cell self-organization and will also enable various hearing loss disorders to be better understood.

The research group included Assistant Professor Togashi Hideru of Kobe University's Graduate School of Medicine and Dr. Katsunuma Sayaka of Hyogo Prefectural Kobe Children's Hospital.

These research results were published online in *Frontiers in Cell and Developmental Biology* on December 8, 2022.

The inner ear cochlea is necessary for hearing sound, and located inside it is the organ of Corti. When the organ of Corti is viewed from above with a microscope, two types of cells arranged in a precisely ordered layout resembling a chess or checkerboard can be seen. Hair cells that convey sound waves to the brain are separated by support cells, which prevent the hair cells from touching each other. Although it has been thought that this checkerboard arrangement is necessary for the organ of Corti to function properly, the relationship between this pattern and hearing function has long remained unclear.

This research group previously revealed that this inner ear checkerboard is formed by a cellular segregation mechanism that enables the hair cells and support cells to move into line correctly. Hair cells and support cells each express a different type of the cell adhesion molecule nectin. This

results in a hair cell and a support cell adhering more strongly to each other than two hair cells or two support cells would.

This property is what causes hair cells and support cells to be arranged in a checkerboard pattern. In a mouse model where one of these nectin molecules is not functional, the properties change and the checkerboard pattern cannot form correctly. In this study, the researchers used these mice to investigate the connection between the checkerboard arrangement of cells and hearing functionality.

The research group compared regular (control) mice to mice with one type of nectin not functioning correctly (nectin-3 KO mouse, referred to as nectin KO mouse below). No difference between the mice was observed in the number of hair cells and support cells in the organ of Corti immediately after birth. However, there was a difference in how easily the two types of cell adhere to each other; in the nectin-3 KO mice hair cells adhere together (which does not normally happen) resulting in abnormalities in the checkerboard pattern.

At this point, the researchers hypothesized that testing the hearing of these mice might reveal the relationship between hearing and the checkerboard pattern. They measured the hearing of over one month-old nectin KO mice using the auditory brainstem response (ABR) method. This test revealed that the nectin KO mice were moderately deaf, demonstrating that this hearing loss was caused by the abnormalities in the inner ear.

The researchers then examined the organs of Corti of the nectin KO mice that underwent the ABR test and found that the number of hair cells had decreased by approximately half. Next they set out to find out why only the hair cells (and not the support cells) had disappeared. They discovered that after two weeks of age, hair cell apoptosis occurred. In addition, examination of the traces of apoptosis revealed that cell death

occurred in many cells that had adhered to each other. This led the researchers to suppose that the hair cells adhering to each other (which does not normally happen) caused the apoptosis.

In the epithelial tissue, which also includes the organ of Corti, there are tight junctions between each cell. These tight junctions not only connect the cells, they also prevent various molecules (including ions) from passing between the cells. If the organ of Corti doesn't have these tight junctions, hair cells cannot function properly, cells die and hearing loss occurs. In nectin KO mice, tight junctions were not formed properly in the places where hair cells adhered together.

However, tight junctions did correctly form in between hair cells and support cells. As long as two hair cells were not adhered together, normal cell function remained. In other words, hair cell apoptosis was induced only in the places where hair cells were abnormally adhered to each other and tight junctions did not form correctly. These results revealed for the first time that the checkerboard pattern of hair cells and support cells found in the organ of Corti functions as a fundamental structure, which protects hair cells and their functionality, by preventing hair cells from becoming attached to each other.

Nectin is the causal gene for Margarita Island ectodermal dysplasia. In addition to a cleft lip or palate and intellectual disabilities, deafness has also been reported in some cases of this genetic disorder. Therefore, the results of the current study might provide a new explanation for some cases of deafness where the cause is unclear.

This study focused on hearing and demonstrated the physiological significance of the checkerboard-like mosaic pattern of cells in the organ of Corti. However, other sensory cells that respond to outside stimuli and their respective supporter cells are also arranged in the same kind of alternating mosaic pattern. These mosaic patterns are found in sensory

organs, such as the olfactory epithelium that is responsible for the sense of smell and the retina which is responsible for vision.

The fact that these mosaic patterns are not only found in mammals but also in a variety of other organisms suggests that they are functionally important. The mosaic patterns in sensory tissues are created by self-organization due to the differences in adhesiveness between cells. Therefore, focusing research on cellular self-organization in sensory organs will increase our knowledge of the functions of sensory organs and advance our understanding of various related diseases.

More information: Sayaka Katsunuma et al, Hearing loss in mice with disruption of auditory epithelial patterning in the cochlea, *Frontiers in Cell and Developmental Biology* (2022). DOI: 10.3389/fcell.2022.1073830

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