Title:	In search of biophyscial model for age-related hearing loss (ARHL) for precision therapeutic studies
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Abstract:	Aging is an inevitable and involuntary process, associated with gradual deterioration of health. Age-related hearing loss (ARHL) is one of the most frequent sensory disabilities which advances with age. ARHL is a multifactorial aging disorder and is mostly affected by environmental, lifestyle, genetic factors, and fluctuation in the inner ear fluid composition with age. These factors irreversibly and slowly damage the integrity of the auditory machinery present in the inner ear. Auditory machinery is precisely composed of tiny hair cells along with the stereocilia which are projected vertically in a stairway manner. The deflection of these stereocilia helps in decoding sound from mechanical stimuli to electrical signals. The top of the consecutive stereocilia is anchored through thin filamentous proteins called tip links. These tip links are held together by two proteins, protocadherin-15 (Pcdh15) from the bottom and cadherin-23 (Cdh23) from the top. These proteins interact in a handshake conformation and act as a gating channel for mechanotransduction of sound. Out of these two proteins, the Cdh23 is mapped with the ARHL phenotype, and mutations in the Cdh23 are marked with congenital as well as progressive hearing loss (PHL). PHL is an accelerated state of ARHL that marks the early onset of hearing loss and drives towards complete hearing loss at a relatively faster rate compared to ARHL. The lack of any biophysical models deciphering the molecular basis of senile deafness is the major bottleneck in designing the precise therapeutic remedy. Here, in search of molecular origins for ARHL, we dissect the conformational behavior of Cdh23 along with the PHL mutant (S47P) that progresses the hearing loss drastically. Using an array of ensemble and single-molecule experimental, and computational approaches, we highlight lower thermodynamic stability, significant weakening in the hydrogen-bond network, and loss of cross- correlated motions among β-strands, due to mutation. This loss in coherence adverse the force adaptations from mechanical stimuli and slow down the folding of the mutant. As an antipode to the PHL mutant, we measured superior thermodynamic stability and correlated motions in another natural variant of tip-link protein, where serine is replaced by valine (S47V) found in vertebrates with a superior organ of Corti and presumably no ARHL. We thus propose that loss in correlated motions within cadherin-23 with aging may trigger ARHL, a molecular feature that likely holds true for other disease mutations in β-strand-rich proteins.
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