Title:	Deciphering the force-dependent lifetime dynamics of tip-links in inner-ear
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Abstract:	Hearing is a mechanotransduction process where sound as mechanical stimuli is converted into electrical signal by a gating-spring. Tip-link, a filamentous element in the inner-ear proposed to act as gating spring. Tip-link is a heterotetrameric complex of two calcium-binding, non-classical cadherin family proteins, Cadherin-23 (Cdh23) and Protocadherin-15 (Pcdh15). In the process of hearing, this proteinaceous spring is exposed to varying intensity of tensile forces as input in the range of 10-100 pN. Tip-links transduce this force to the ion-channels, located at their bottom end. However, for opening of the ion-channel only 4-8 pN force is enough. How tip-link successfully conveys a threshold force which is sufficient to open the ion channel while simultaneously protect the sensory machinery from overexcitation is not yet clear. In this work, we studied the force-responsive behavior of tip-links employing Atomic Force Microscopy based single-molecule force spectroscopy and in-silico tools. Using force-clamp experiments we report that the heterotetrameric tip-link follows slip-ideal-slip bonds with increasing force. While in slip, the complex dissociates monotonously; the ideal-bond interface responds indifferently to mechanical forces. Insensitivity of the tetrameric complex-interface to a range of tensile forces implicates a cut-off in the force-propagation, characteristic of gating- springs. At extreme loud sound, tip-links detach. Individual tip-link interface, however, forms slip- catch-slip bonds under tension. While catch bonds turn stronger with force from loud sound, our Langevin dynamics indicated the transition from slip-catch-slip to slip-ideal-slip bonds as cooperative effect of individual binding interfaces in the atypical tip-link architecture
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