Abstract

Cadherins mediate the cell-cell junctions in multicellular organisms. Essential cellular functions like cell-migration, differentiation, and morphogenesis that require tailoring of the cell-cell junctions are achieved by regulating the expression of cadherins. Among cadherins, non-classical cadherins comprise ~80% of cadherin proteins in the family. However, little is known on their participation in cell-adhesion. Cadherin-23 (Cdh23), long non-classical cadherin with 27 extracellular (EC) domains has recently been known to mediate cell-cell junctions through homophilic interactions, and its expression is regulated during cancer metastasis. Data from The Cancer Genome Atlas indicated a key correlation between Cdh23 expression and patient survival, lower the expression poor is the survival of patients. Further, in-vitro studies have measured a stronger aggregation-propensity of Cdh23 than one of the typical cadherins. While the mechanism of homophilic interaction for classical cadherins is known, the homodimer structure for Cdh23 is not yet resolved. We deciphered the unique trans- homodimer structure of Cdh23 which consists of two electrostatic-based interfaces extended up to two terminal domains (EC1-2). This unique interface is robust with a dissociation constant, 18±4 μM and an off-rate of ~8x10-4 s -1 . Next, we measured the role of the remaining 25 non-interacting EC-domains on the homophilic trans-interactions. With the help of domain deletion mutants, we showed that the flexibility exhibited by EC-domains increases with the number of domains. In-cellulo aggregation assays also showed faster aggregation of cells with increasing domain numbers. From single-molecule force spectroscopy studies, we also observed that lifetime for the trans-interactions increases with the number of domains.