Title:	Functional and Molecular Aspects of Cadherin-23 in the Context of Cell-Cell Adhesion
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Abstract:	Cell-cell adhesion is the fundamental element responsible for the generation of tissues, organs, and multicellular organisms. Cadherin superfamily cell adhesion proteins are identified as crucial for the structural integrity of tissues in vertebrates and invertebrates. Besides mediating cell-cell adhesion, cadherins involve several other cellular processes, such as signaling, polarity, differentiation, and migration. Till now, the studies have extensively narrated the minority classical type cadherins in terms of structure and function. However, the comprehensive understanding of the non-classical cadherins, the major stockholders (> 80%) of the superfamily, in physiology remains elusive. In this thesis, we worked on the functional aspects of cadherin-23 (Cdh23), a giant non-classical cadherin recognized for its participation in the hearing process. Cdh23 possesses 27 extracellular (EC) domains, a single transmembrane domain, and a cytosolic domain in its structure. Mutations in Cdh23 are associated with pathological phenotypes like usher syndrome, hearing loss, and cancer metastasis. The cell-cell junction mediated by Cdh23 is composed of adhesive trans interactions and lateral cis interactions. The terminal two domains (EC1-2) of Cdh23 from adjacent cells interact to form the trans binding, and the rest of the EC domains from the same cell surface laterally interact to form the cis binding. In this work, we deciphered the physiological role of Cdh23-mediated cell-cell adhesion using an array of in silico tools, in cellulo assays, and imaging techniques. Cdh23 expression is remarkably downregulated in most solid cancers, including lung adenocarcinoma (LUAD) and esophageal squamous cell carcinoma (ESCC). We identified an inverse correlation between Cdh23 expression and the survival of patients. Next, we delineated the nature of molecular interactions inducing the cis-clustering of Cdh23 using a series of in vitro experiments, in cellulo assays, and photobleaching experiments. The weak, nonspecific, multivalent, and transient interactions among EC domains (other than trans-interacting) of Cdh23 induced phase-separated liquid droplets in the solution phase, can be responsible for the cis-clustering of Cdh23 on the two-dimensionally confined cell membrane. Further, we deciphered the functional relevance of cis-clustering in the context of cell- cell adhesion. Collectively, this work implicated the role of Cdh23 as a prognostic marker in metastasis and disclosed that the cis-clustering of Cdh23 kinetically enhanced cell-cell adhesion.
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