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Cadherins: A View into Its Structure and Function

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Cadherins are a multigene family of transmembrane glycoproteins. Importantly involved in calcium dependent homophilic cell-cell adhesion (Takeichi et al., 1981; Angst et al., 2001). Cadherins are involved in organization of epithelial cell polarization and the formation of robust cell-cell contacts, which are commonly known as '*zonula adherens'*. They also play important role in cell proliferation as well as for the transfer of signals for cell differentiation (Takeichi, 1995; Geiger and Ayalon, 1992). The name cadherin is composed from two words 'calcium' and 'adhesion'. Cadherins were initially defined for their aspect in 'COMPACTION' by moderating adhesion between blastomeres of an early developing mouse embryo (Hyafil et al., 1981). The cadherins are expressed in the crucial stages of tissue formation, collective tissue migration and multicellular organization (Takeichi, 1995; Becker et al., 2012). Any disfunction or mutation in cadherin signaling or adhesion activity leads to metastasis, tumor invasion or congenital defects in organogenesis (Berx and van Roy, 2009; El-Amraoui and Petit, 2010).

Cadherins can be segregated into four various subtypes: classical cadherins (type I and type II), protocadherins, desmosomal and atypical cadherins. They are divided based on their structure and role in the development process. Cadherins possess three domains with separate characteristic features and functions. First is the extracellular domain, which is involved in mediating cell-cell adhesion through zipper like mechanism. Second domain is hydrophobic transmembrane domain and finally highly conserved cytoplasmic tail (Takeichi, 1990). The extracellular domain consists of multiple cadherin-specific repeats that are 110 amino acids long. In regard to different cadherin subfamily members, these cadherin repeats vary in number from four to more than thirty (Suzuki, 1996).

The classical cadherins are divided into type I and type II, based on their amino acid sequence (Tanihara et al., 1994). The analysis of sequence exhibit that classical cadherins consist of 723 to 748 amino acids with a sequence similarity of 50-60% amongst the subclasses (Takeichi, 1988). The extracellular domain is equipped with five subdomains (EC1 - EC5), which are bridged by calcium ions. The calcium ions play important role in providing stability of the protein and rod-like structure to it (Haussinger et al., 2002).

Cadherins can dimerize in *cis*-orientation (between molecules of the same cell) or also in *trans*-orientation (molecules of different cells). The two cadherins communicate in trans-orientation that is guided via their EC1 repeats by strand swapping. The strand swapping is characterized by the insertion of the aromatic side chain of tryptophan-2 (W2) into the hydrophobic pockets of the EC1 repeat of the different cadherin (Shapiro et al., 1995). The

hydrophobic pocket possesses highly conserved alanine-residue (Ala-80) in the HAV motif (type I) or the QAV motif (type II) (Blaschuk et al., 1990; Nose et al., 1990).

In type II classical cadherins, the homophilic cell-cell adhesion is mediated via tryptophan-2 and tryptophan-4. Further to it, any disfunction in the hydrophobic pocket or in the tryptophan residue leads to the loss of the cadherins adhesion function (Patel et al., 2006). The trans-interaction between the cadherins is important for cell-cell adhesion but moreover this adhesion is reinforced by cis-dimerization. *Cis*-dimerization is formed through cooperation of the EC1 backbone with the EC2 domain of the neighboring cell. This phenomenon is different to earlier models where *cis*-dimerization was shown to contain the complete EC domains. But mechanistic aspects of *cis*-dimerization are still to be studied in detail (Niessen et al., 2011). Both the *trans*- and *cis*- interactions are equally required for mediating cell-cell adhesion (Boggon et al., 2002; Harrison et al., 2011). The replacement of tryptophan-2 and alanine-80 residue present in hydrophobic pockets with alanine and leucine respectively, result in a loss of *trans*-interaction, but *cis*-dimerization remains intact (Pertz et al., 1999; Boggon et al., 2002).

The transmembrane domain of cadherins is a single-span and this domain possess the highest homology, with few exceptional members such as flamingo. It is atypical cadherin family member that consists of seven-pass transmembrane domain (Huber et al., 1999; Usui et al., 1999). The interactions between transmembrane domain are necessary for oligomerization (Lemmon and Engelman, 1994). Specifically in E-cadherin, transmembrane domain mutations result into the loss of the adhesive function. The transmembrane domain self-assembly is damaged by the introduction of a proline amino acid residue. Point mutations in the transmembrane domain (L568P, L569P, L570P, L571P, I570G/L571P and L571P/L572G) of E-cadherin leads to decreased adhesive function indicating that the interplay between the transmembrane segments is required for the lateral association of E-cadherin molecules required for cell-cell adhesion. The membrane localization and interaction with catenins and the cytoskeleton is not affected as observed from control experiments (Huber et al., 1999). A similar mechanism is detected for N-cadherin, where it communicates with arcadlin or PAPC via its transmembrane domain. By introducing point mutations at L561P or L561P/M562G in the N-cadherin transmembrane domain a reduced interaction to arcadlin can be observed (Yasuda et al., 2007).

The classical cadherins communicate with cytoplasmic proteins through their highly conserved cytoplasmic domain. This in turn regulates the actin filaments (Gumbiner, 2000). The cytoplasmic domain of classical cadherins binds β- catenin at its C-terminal region and regulates connection to the actin cytoskeleton through α-catenin (Aberle et al., 1994; Stappert and Kemler, 1994). As β-catenin and F-actin attaches to the N-terminus and C-terminus of α-catenin, respectively (Pokutta et al., 2008), it was also disclosed that α-catenin do not bind to β-catenin and F-actin at the same time implying dynamic interaction of cadherins to the actin cytoskeleton. The cadherin-catenin complex connection to the actin cytoskeleton is very dynamic (Yamada et al., 2005). β-catenin plays crucial role in the canonical Wnt signaling pathway (Behrens et al., 1996). p120 binds to the juxtamembrane domain and mediates the cadherin turnover, as well as its transport and the stability of the protein at the cell membrane.

p120 mediates the dynamics of the actin cytoskeleton by triggering RhoGTPases family members (Yap et al., 1998; Anastasiadis and Reynolds, 2001; Reynolds and Carnahan, 2004). α-catenin connects cytoskeleton directly to the cadherins. And it also binds to F-actin via proteins such as myosin VI, vinculin and EPLIN indirectly (Abe and Takeichi, 2008; Ratheesh and Yap, 2012).

The interactions between integrins and cadherins are function and they share various signaling molecules. They possess importance in downstream functions like cell growth and survival. The adhesive synergy is regulated through three different mechanisms. These adhesive interactions mainly rely on cellular signaling and physical bonding. The mechanisms are: (a) Input-output signaling: in which adhesive signals occurring at one point can result into the functional changes at the other part of the cell. (b) Convergent signaling: where in cadherins and integrins possess similar downstream signaling effectors like Rho GTPases. (c) Lateral coupling: which exist of short-range associations. Here interactions do not require cell-cell or cell-extracellular matrix adhesion (Weber et al., 2011).

The interactions are also regulated via different transmembrane proteins such as tetraspanins or the insulin-like growth factor 1 (IGF1) receptor (Chattopadhyay et al., 2003; Canonici et al., 2008). It is reported that fibroblast growth factor receptor (FGFR) interacts with N-cadherin, while epidermal growth factor receptor (EGFR) interacts with E-cadherin (Jawhari et al., 1999; Andl and Rustgi, 2005). Growth factor receptors such as vascular endothelial growth factors (VEGF) and epidermal growth factor (EGF) play crucial role in integrin mediated adhesion to the extracellular matrix (Giancotti and Ruoslahti, 1999; Schwartz and Baron, 1999).

Overall cadherins are important class of proteins, which are crucial for cell-cell and cell-extracellular matrix adhesion during the development.

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