Cosmos Multidisciplinary Research E-Journal
Online Available at www.cmrj.in
Recognized International Peer Reviewed Journal
ISSN No. 2456-1665

Synergistic Role of Cadherin-11 and Syndecan 4 in Cell Adhesion and Migration

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Cadherins are calcium-dependent cell-cell adhesion proteins known to play important role in tissue movements during development. Cadherins are typically involved in cell migration, cell polarization and invagination. Specifically, Cadherin-11 is known to play crucial role in cell migration. Cadherin-11 bonds with proteoglycan, Syndecan 4 to form a complex that allows cell-extracellular adhesion and migration. This is an important function, which could be observed in process such as tumour progression. Here, I highlighted the synergistic relation between cadherin-11 and Syndecan 4 in cell migration.

These transmembrane glycoproteins are important class of dynamic cell-cell adhesion proteins and specifically they formulate cell mobility via signaling cascade. Cadherin-11 belongs to the family of type II classical cadherins and was first identified in humans (Tanihara et al., 1994). Cadherins consist of three domains, an extracellular domain (EC) mediating cell-cell adhesion via a zipper like mechanism, a hydrophobic transmembrane domain and a highly conserved cytoplasmic tail (Takeichi, 1990). The EC domain consists of five subdomains (EC1 - EC5) that are bridged by calcium ions. The calcium ions are necessary for the rod-like structure and stability of the protein (Haussinger et al., 2002). Cadherins consist of a single-span transmembrane domain. Through their highly conserved cytoplasmic domain, classical cadherins interact with cytoplasmic proteins, which are known to regulate or recruit actin filaments (Gumbiner, 2000; Jamora and Fuchs, 2002). The cytoplasmic domain of classical cadherins binds β-catenin at its C-terminal region and mediates connection to the actin cytoskeleton via α-catenin (Aberle et al., 1994). Via the activation of members of the RhoGTPases family, p120 can regulate the dynamics of the actin cytoskeleton (Anastasiadis and Reynolds, 2001; Reynolds and Carnahan, 2004). Cadherins are connected to the actin cytoskeleton directly or indirectly.

Cadherin-11 is highly expressed in prostate and breast cancer cells, where it leads to an accelerated invasion of malignant cells into healthy tissues, illustrating a promoting function of cadherin-11 in cell migration (Pishvaian et al., 1999; Bussemakers et al., 2000). During *Xenopus* embryogenesis cadherin-11 (Xcad-11) is mainly expressed in migrating cranial neural crest (CNC) cells. The important role of Xcad-11 in CNC cell migration was first shown by transplantation analysis. Overexpression of full length Xcad-11 or Xcad-11 Δc, which lacks the cytoplasmic domain containing the p120 and β-catenin binding site, blocks CNC migration. Surprisingly, besides its localization at cell-cell contacts Xcad-11 is also localized in CNC protrusions towards the leading edge and at the cell-substrate surface (Kashef et al., 2009). Interestingly, this novel mechanism of cadherin mediated cell migration was shown in breast cancer cells, where cadherin-11 facilitates cancer cell migration also through GTP exchange factor Trio and small GTPase such as Rac, pointing to a general function of cadherin-11 in promoting cell migration (Li et al., 2011).

Basically, cell adhesion is crucial for cell migration and signaling (Thiery et al., 1985). Cells either bind directly with each other to form cell-cell adhesion or they bind to the extracellular matrix (ECM), which is termed cell-substrate adhesion. Cell-substrate adhesion is the process in which cells adhere at specific sites of extracellular matrix proteins through cell surface receptors (Bidanset et al., 1992). The ECM provides support to the cells along with directionality for their migration. ECM components involved in cell-substrate adhesion are fibronectin, collagen, laminin and proteoglycans (Alberts et al., 2007; Schaefer and Schaefer, 2010). Among these, the most important ECM component is fibronectin. Fibronectin possesses binding sites for (1) integrins (arginine-glycine-aspartic acid – RGD binding motif) and (2) syndecans (heparin II binding motif) through which cell adhesion is mediated (Singh et al., 2010). Particularly on Syndecans that are transmembrane cell-surface proteoglycans, which act as cell surface receptors mediating cell adhesion, motility and proliferation (Kwon et al., 2012). The syndecan family consists of four members: syndecan-1, syndecan-2, syndecan-3 and syndecan-4. To focus on Syndecan 4, its cytoplasmic domain possesses three subdomains: C1, V and C2. C1 links the proteins to the cytoskeleton. The variable region (V) binds to phosphatidylinositol-4, 5-bisphosphate and activates protein kinase Cα (PKCα). C2 interacts with the PDZ domain of the binding proteins. The extracellular domain consists of heparan sulfate chains, which interact with growth factors like FGFR and fibronectin (Carey et al., 1992; Multhaupt et al., 2009).

It is demonstrated that knockdown of the cell-cell adhesion molecule Xcad-11 led surprisingly to a loss of cell-substrate adhesion of CNC cells. This might be due to an indirect effect of Xcad-11 in regulating the gene expression of proteins, which are involved in cell-substrate adhesion, or Xcad-11 is directly involved in mediating cell-substrate adhesion. Since Xcad-11 promotes CNC cell migration, it would be more likely that Xcad-11 directly facilitates cell-substrate adhesion. Indeed, through high resolution TIRF microscopy imaging resolved that Xcad-11 is localized at the cell-substrate surface of CNC cells in three different subpopulations: in focal adhesions, in adhesion plaques and in cell protrusions. Xcad-11 is also localized in CNC adhesion plaques at the membrane facing the substrate. At these plaques, surprisingly, Xcad-11 is mainly localized with β-catenin and partially with paxillin. Adhesion plaques are formed at the region where cells adhere most tightly to the substrate beneath. The cell-cell adhesion molecule Xcad-11 is co-localized at the cell-substrate with molecules like paxillin and vinculin, which are involved in mediating cell-substrate adhesion (Ziegler et al., 2006; Iioka et al., 2007). Therefore, the recruitment of these proteins to the cytoplasmic domain of Xcad-11 could be important for mediating cell-substrate adhesion. The knockdown of Xcad-11 led to loss of cell-substrate adhesion. The cytoplasmic domain of Xcad-11, which is essential to mediate cell-substrate adhesion, contains binding sites for adaptor proteins like p120 catenin and β-catenin (Aberle et al., 1994; Yap et al., 1998). The transmembrane domain of Xcad-11 is also crucial to mediate cell-substrate adhesion. The mutated transmembrane domain of Xcad-11 where the valine (V506P) and leucine (L507G) amino acid residues were replaced by proline and glycine respectively, failed to rescue the adhesion to fibronectin. Hence only the cytoplasmic and transmembrane of cadherin-11 are important form adhesion, whereas extracellular domain is not required for Cell-ECM adhesion.

Cell-substrate adhesion is mediated through fibronectin receptors like integrins and syndecans (Longley et al., 1999). Syn-4 is expressed in migrating CNC (Munoz et al., 2006) and the loss of Syn-4 leads to disturbed migration of CNC cells *in vivo* (Matthews et al., 2008). Loss of Syn-4 led to reduction of focal adhesion formation and cell-substrate adhesion on fibronectin. As knockdown of Syn-4 and Xcad-11 resulted in loss of focal adhesion formation and cell-substrate adhesion, it can be predicted that both proteins could act synergistically in mediating CNC cell adhesion. The extracellular domain of Xcad-11 was not sufficient for mediating the adhesion to fibronectin. Syn-4 is known to bind to fibronectin via its extracellular domain. The chimera construct including the extracellular domain of Syn-4 and the transmembrane and cytoplasmic domain of Xcad-11 was able to rescue Syn-4 and Xcad-11 loss of function phenotypes, and promoted cell adhesion to fibronectin. Hence the extracellular domain of Syn-4 and the transmembrane and cytoplasmic domain of Xcad-11 are crucial for cell-substrate adhesion (Langhe et al., 2016).
This exhibits unexpected role of a classical cadherin-11 in synergy with proteoglycan Syndecan 4 in cell–matrix adhesion during cell migration.

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