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E-cadherin: Its dysregulation in carcinogenesis and clinical implications

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ABSTRACT

E-cadherin is a transmembrane glycoprotein which connects epithelial cells together at adherens junctions. In normal cells, E-cadherin exerts its tumour suppressing role mainly by sequestering β-catenin from its binding to LEF (Lymphoid enhancer factor)/TCF (T cell factor) which serves the function of transcribing genes of the proliferative Wnt signaling pathway. Despite the ongoing debate on whether the loss of E-cadherin is the cause or effect of epithelial-mesenchymal transition (EMT), E-cadherin functional loss has frequently been associated with poor prognosis and survival in patients of various cancers. The dysregulation of E-cadherin expression that leads to carcinogenesis happens mostly at the epigenetic level but there are cases of genetic alterations as well. E-cadherin expression has been linked to the cellular functions of invasiveness reduction, growth inhibition, apoptosis, cell cycle arrest and differentiation. Studies on various cancers have shown that these different cellular functions are also interdependent. Recent studies have reported a rapid expansion of E-cadherin clinical relevance in various cancers. This review article summarises the multifaceted effect E-cadherin expression has on cellular functions in the context of carcinogenesis as well as its clinical implications in diagnosis, prognosis and therapeutics.

1. E-cadherin and its biological role

The type I cadherin family comprises transmembrane glycoproteins which bind to various cell types, and are vital in normal animal tissue morphogenesis and development (Halbleib and Nelson, 2006; Lagendijk and Hogan, 2015; West and Harris, 2016). The E-cadherin gene (*CDH1*), of approximately 100 kb long, is housed on chromosome 16q22.1. The gene region comprises 16 exons, sized between 115 and 2245 bp and intervened by 15 introns in total. Comparison of the human *CDH1* exon borders across different species and different cadherin types revealed noteworthy conservation of their splice sites, implying gene duplication or conversion along the coevolution process between cadherin types. E-cadherin is the protein member discovered earliest by Takeichi (Takeichi, 1977) which connects epithelial cells together at adherens junctions (AJs). Its related cadherin family members which differ in terms of spatial and temportal expression were subsequently discovered (van Roy and Berx, 2008).

E-cadherin protein is transcribed from *CDH1* gene into a precursor polypeptide of 135 kDa. The precursor segment carries a prosequence harbouring the consensus protease cleavage site (Arg-Arg-Gln-Lys-Arg) which facilitates its proteolytic processing into a mature and functional protein with adhesive properties (Fig. 1). The mature E-cadherin protein is a 120 kDa, Ca^{2+}-dependent transmembrane glycoprotein which binds normal and polarized epithelial cells together at lateral surface via AJs (Ogou et al., 1983; Jiang, 1996; Wheelock and Johnson, 2003; Capaldo et al., 2014). The amino terminal of E-cadherin houses five extracellular cadherin domains between which Ca^{2+} ions bind and its adhesive activity lies (Pećina-Šlaus, 2003). Ca^{2+} ions binding then induces the stiffening of the entire span of the extracellular domain (Nagar et al., 1996; Harrison et al., 2011) and promotes protease resistance (Leckband and Prakasam, 2006). The stiffening of the extracellular domain provides a vital role for three-dimensional domain swapping which is at the core of E-cadherin's homophilic *trans* dimer formation between apposed cells (Fig. 2).

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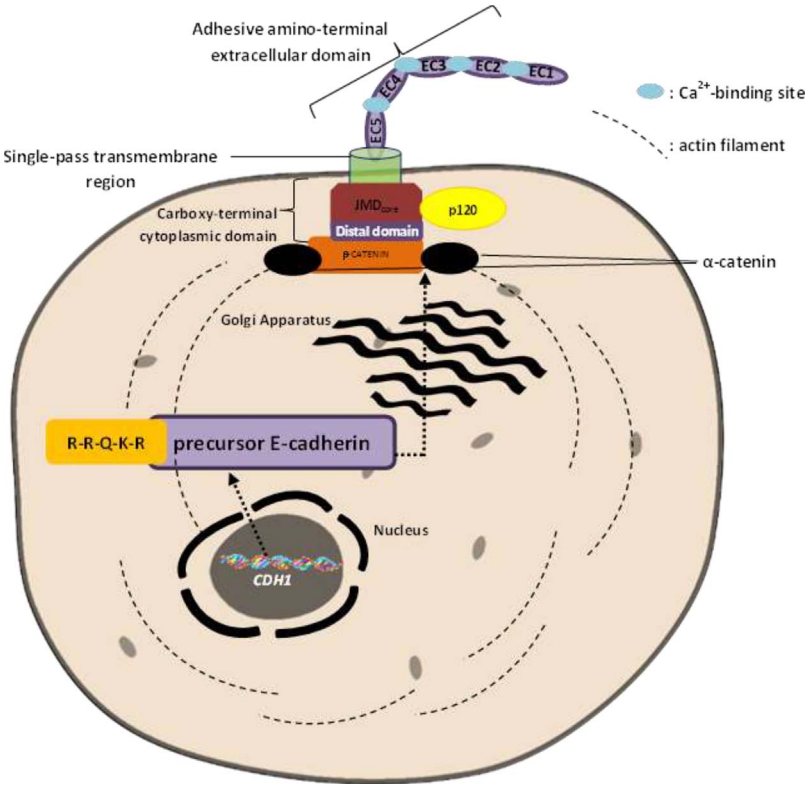

Fig. 1. The schematic illustration of E-cadherin production through the central dogma. The *CDH1* gene is transcribed into a precursor polypeptide of E-cadherin carrying the prosequence which has a cleavage site of Arg-Arg-Gln-Lys-Arg (R-R-Q-K-R) for its subsequent removal in the Golgi apparatus. The mature E-cadherin is then transported to the plasma membrane. The E-cadherin-β-catenin complex is linked to the actin filaments via association with α-catenin.
JMD_{core}: juxtamembrane core domain; EC1-EC5: Extracellular cadherin/EC subdomains of E-cadherin

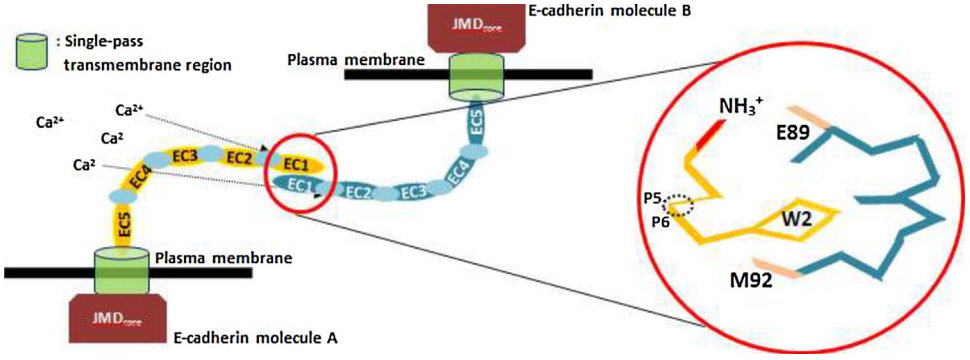

Fig. 2. The schematic representation of the E-cadherin-mediated homophilic cell–cell adhesion mechanism. The domain swapping happens between EC1s of two E-cadherin molecules from two apposed cells. Upon binding of calcium ions to the calcium binding sites between the EC subdomains, the extracellular domain is stiffened and this conformation is favourable towards domain swapping. As shown in the inset (red circle), the positively charged tryptophan (W2) from E-cadherin molecule A is balanced by the net negative charge of glutamine (E89) and methionine (M92) from the acceptor pocket of E-cadherin molecule B to which it has been inserted. The binding is of low affinity and highly specific due to the conformational strain placed by the proline–-proline motif (P5-P6) (dotted circle) on the molecule, hindering the formation of unusually tight and non-specific binding. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Mature AJs are formed between cells by E-cadherin binding to β-catenin via its distal cytoplasmic domain, forming an E-cadherin-β-catenin complex which then links to the actin cytoskeleton via α-catenin and its interacting protein, α-actinin (Hulsken et al., 1994; Jou et al., 1995; Nieset et al., 1997). In addition, p120 interaction with the juxtamembrane core domain (JMD_{core}) also forms part of the mature AJs (Ishiyama et al., 2010). p120-JMD_{core} interaction blocks the dileucine endocytosis motif on E-cadherin, thereby preventing its endocytosis and prolonging its functionality on the cell surface (Davis et al., 2003; Fujita et al., 2002). These structural entities are collectively involved in the core function of E-cadherin as the adhesion protein in epithelial cells in maintaining the stability of AJs (Fig. 1).

2. E-cadherin in normal cells

During embryonic development, E-cadherin expression starts as early as the two-cell stage (Larue et al., 1994; Riethmacher et al., 1995). It plays an important role in the adhesion of blastomeres and the compaction of early embryos (Fleming et al., 1992) as shown by E-cadherin −/- embryos' failure to polarize, compact and form the trophectoderm epithelium (Pećina-Šlaus, 2003). Morula compaction is initiated by E-cadherin-mediated filopodia adhesion and their traction on neighbouring blastomeres induced by myosin (Fierro-González et al., 2013). This E-cadherin-mediated adhesion has been shown to be regulated by proprotein convertase 7 (PC7) and related PCs, Furin and Pace4, during blastocyst formation (Bessonnard et al., 2015).

In normal epithelial tissues with high expression of E-cadherin, β-catenin is sequestered at the membrane, preventing it from being released into the cytoplasm and entering the nucleus (Jeanes et al., 2008). This prevents β-catenin from binding to a member of the DNA binding protein family LEF (Lymphoid enhancer factor)/TCF (T cell factor) in the nucleus. Hence, the Wnt signaling pathway is not activated and cancer initiation is prevented (Pećina-Šlaus, 2003). It has been documented that *wnt* genes and other components of the Wnt signaling pathway can cause cancer (Peifer and Polakis, 2000).