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A Conserved Phosphorylation Switch Controls the Interaction between Cadherin and β-Catenin In Vitro and In Vivo

Highlights

- Conserved phospho-Ser1212 in *C. elegans* cadherin is required for binding to β-catenin
- Loss of HMR-1 Ser1212 phosphorylation produces severe adhesion defects
- Sequence differences in β-catenin homologs define roles in adhesion and Wnt signaling

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In Brief

Choi et al. identify a phosphoserine in the tail of the *C. elegans* cadherin HMR-1 required for strong binding to the β-catenin homolog HMP-2 during cell adhesion. Structural analysis allows the authors to define sequence differences among worm β-catenin homologs that explain their separate roles in adhesion and Wnt signaling.

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A Conserved Phosphorylation Switch Controls the Interaction between Cadherin and β-Catenin In Vitro and In Vivo

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SUMMARY

In metazoan adherens junctions, β-catenin links the cytoplasmic tail of classical cadherins to the F-actin-binding protein α-catenin. Phosphorylation of a Ser/Thr-rich region in the cadherin tail dramatically enhances affinity for β-catenin and promotes cell-cell adhesion in cell culture systems, but its importance has not been demonstrated in vivo. Here, we identify a critical phosphorylated serine in the *C. elegans* cadherin HMR-1 required for strong binding to the β-catenin homolog HMP-2. Ablation of this phosphoserine interaction produces developmental defects that resemble full loss-of-function (Hammerhead and Humpback) phenotypes. Most metazoans possess a single gene for β-catenin, which is also a transcriptional coactivator in Wnt signaling. Nematodes and planaria, however, have a set of paralogous β-catenins; for example, *C. elegans* HMP-2 functions only in cell-cell adhesion, whereas SYS-1 mediates transcriptional activation through interactions with POP-1/Tcf. Our structural data define critical sequence differences responsible for the unique ligand specificities of these two proteins.

INTRODUCTION

Cell-cell adhesion is fundamental to the generation and structure of multicellular tissues. The classical cadherin cell adhesion molecules mediate homophilic adhesion and are linked to the actin cytoskeleton through the catenins (Pokutta and Weis, 2007). β-Catenin binds to the cytoplasmic tail of classical cadherins, and to α-catenin, an F-actin binding protein. β-Catenin is a highly conserved metazoan protein that functions in cell-cell adhesion and as a transcriptional coactivator in the Wnt/β-catenin pathway. β-Catenin has an N-terminal region of roughly 150 amino acids, followed by 12 armadillo (arm) repeats, each comprised of three α helices, and a C-terminal acidic tail that mediates interactions with components of the general transcription apparatus. Structural studies have shown that the different partners of β-catenin involved in adhesion (the classical cadherin cytoplasmic domain) and in Wnt signaling (TCF transcription factors, ICAT, the Adenomatous Polyposis Coli protein, and Axin) interact similarly with the arm domain (Pokutta and Weis, 2007).

In most metazoans, a single gene encodes a β-catenin that functions in both cadherin-based adhesion and transcriptional coactivation via Wnt signaling. An exception is *C. elegans*, a nematode that expresses four distinct β-catenin paralogs, only one of which, HMP-2, functions in cell adhesion. It is therefore of interest to understand how these different paralogs have evolved to mediate distinct functions by binding to partners involved in adhesion versus signaling. *C. elegans* also expresses the cadherin HMR-1, whose cytoplasmic domain bears significant sequence homology to that of mammalian classical cadherins, and the α-catenin homolog HMP-1 (Costa et al., 1998; Cox and Hardin, 2004).

Studies in cell culture have revealed that interactions among adherens junction (AJ) components can be regulated by phosphorylation. A serine-rich region of the classical cadherin tail is phosphorylated (Stappert and Kemler, 1994), and in vitro phosphorylation of the purified cadherin tail by glycogen synthase kinase 3β (GSK-3β) and casein kinase II (CKII) strengthens its affinity for β-catenin ~800-fold by creating an additional interaction surface (Choi et al., 2006; Huber and Weis, 2001; Lickert et al., 2000). Mutation of the phosphorylated serines to alanine reduced cell-cell adhesion when these constructs were transfected into NIH 3T3 cells (Lickert et al., 2000). Gottardi and colleagues recently narrowed these phosphorylation sites to three residues that are required for high-affinity β-catenin binding, cell adhesion, inhibition of cell migration, and surface stability of cadherin in cultured cells (McEwen et al., 2014). In contrast, Src-mediated phosphorylation of β-catenin Tyr654 reduces affinity for cadherin (Roura et al., 1999), and CKII phosphorylation of β-catenin regulates its interaction with α-catenin (Bek and Kemler, 2002).

Although there are strong correlations between dysregulation of AJ assembly and disease such as metastatic cancers (Benjamin and Nelson, 2008; van Roy, 2014), the functional