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CD44 regulates Wnt signaling at the level of LRP6

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Abbreviations: ERM, ezrin-radixin-moesin, Fz, Frizzled, LEF, lymphoid enhancer factor, LRP6, low-density lipoprotein receptor-related proteins, TCF, T-cell factor

Wnt/β-catenin signaling is activated upon binding of Wnt ligands to both Frizzled (Fz) receptors and low-density lipoprotein receptor-related protein 5/6 (LRP5/6) co-receptors (reviewed in 1). This activation results in the inhibition of β-catenin degradation and its cytosolic accumulation. Subsequent β-catenin translocation to the nucleus leads to T-cell factor/lymphoid enhancer factor (TCF/LEF)-driven transcription. Among the Wnt target genes are regulators of cell proliferation, growth, differentiation, and migration. Hence, Wnt/β-catenin signaling plays key roles in development (reviewed in 1). This pathway also regulates homeostasis of bones, hematopoiesis, and renewal of tissues such as the intestine or the skin, and therefore remains essential throughout life. Consequently, misregulation of Wnt/β-catenin signaling leads to developmental defects, malformations, degenerative and metabolic diseases, and cancer (reviewed in 1). A tight regulation of Wnt signaling involves feedback control mechanisms in which the expression of several Wnt-signaling components is regulated by Wnt/β-catenin signaling itself (reviewed in 1).

The cell adhesion molecule CD44 was identified as a canonical Wnt target in the intestine, where it is highly expressed in intestinal stem and proliferative progenitor cells. Loss of CD44 in ApcMin/+ mice significantly reduced the tumor number in the small intestine, thus indicating an involvement of CD44 in Wnt-induced tumorigenesis.2 Furthermore, increased CD44 expression correlates with late stages and poor prognosis of colorectal cancer.3 However, considering CD44 solely as a Wnt target gene might only be part of the story. In fact, our recent paper4 shows that CD44 also acts as a positive Wnt feedback regulator. In several cell lines, silencing of all CD44 isoforms suppressed Wnt-induced activation and nuclear translocation of β-catenin, as well as TCF/LEF-driven transcription. Conversely, overexpression of CD44 isoforms enhanced Wnt signaling regardless of the isoform, suggesting the involvement of a function common to all CD44 isoforms in the regulation of this pathway. A CD44 isoform with deletion of the cytoplasmic domain of CD44 and its binding to F-actin via Ezrin. Finally, experiments in Xenopus laevis demonstrated an in vivo requirement of CD44 for Wnt/β-catenin signaling in CNS development, as indicated by reduced expression of the Wnt-target genes tcf-4 and engrailed-2 in CD44 morphants.

The activity of the Wnt cascade is regulated at each step from the cell surface to the nucleus (reviewed in 1). What could be the additional contribution of CD44? One important characteristic of CD44 is its ability to bind to the cytoskeleton through ERM proteins. This network formed by the CD44–ERM–actin complex might provide a platform necessary for the tight association between LRP6 and kinases such as glycogen synthase kinase 3β and casein kinase 1y. Additionally,
trafficking of the LRP6-containing vesicles from the Golgi to the membrane might take place within the F-actin rich cortex. These F-actin tracks might be tethered to the plasma membrane through the CD44-ERM complex. Although these hypotheses are highly speculative one should note that CD44 can be found on coat protein complex 1 (COP1) vesicles involved in vesicle trafficking. Additionally, CD44 was shown to co-localize with soluble NSF attachment protein receptors (SNAREs) that play important roles in the fusion of vesicles with the plasma membrane.

CD44 is not the only Wnt-target gene providing positive feedback regulation in Wnt/β-catenin signaling. Other positive regulators like LEF1 or Fz-receptors have been shown to be upregulated upon activation of canonical Wnt signaling.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.