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Requirement of Wnt/β-catenin signaling in pronephric kidney development

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ABSTRACT

The pronephric kidney controls water and electrolyte balance during early fish and amphibian embryogenesis. Many Wnt signaling components have been implicated in kidney development. Specifically, in *Xenopus* pronephric development as well as the murine metanephroi, the secreted glycoprotein Wnt-4 has been shown to be essential for renal tubule formation. Despite the importance of Wnt signals in kidney organogenesis, little is known of the definitive downstream signaling pathway(s) that mediate their effects. Here we report that inhibition of Wnt/β-catenin signaling within the pronephric field of *Xenopus* results in significant losses to kidney epithelial tubulogenesis with little or no effect on adjoining axis or somite development. We find that the requirement for Wnt/β-catenin signaling extends throughout the pronephric primordium and is essential for the development of proximal and distal tubules of the pronephros as well as for the development of the duct and glomus. Although less pronounced than effects upon later pronephric tubule differentiation, inhibition of the Wnt/β-catenin pathway decreased expression of early pronephric mesenchymal markers indicating it is also needed in early pronephric patterning. We find that upstream inhibition of Wnt/β-catenin signals in zebrafish likewise reduces pronephric epithelial tubulogenesis. We also find that exogenous activation of Wnt/β-catenin signaling within the *Xenopus* pronephric field results in significant tubulogenic losses. Together, we propose Wnt/β-catenin signaling is required for pronephric tubule, duct and glomus formation in *Xenopus laevis*, and this requirement is conserved in zebrafish pronephric tubule formation.

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1. Introduction

Tubule formation occurs in many developmental contexts, yet many of the underlying signaling processes driving differentiation and morphogenesis are incompletely understood. A classic system for studies of inductive interactions and mesenchyme-to-epithelial transitions, inclusive of tubule formation, has been the vertebrate kidney (Saxén, 1987).

Mammals progress through three developmental kidney stages: the pronephros, the mesonephros and the metanephros (Vize et al., 1997). Amphibian and fish embryos do not form the third stage but generate an embryonic pronephros, followed by formation of a mesonephros in adults (Vize et al., 1997). These kidney forms have similar architecture: they have the same basic unit of filtration, the nephron. Additionally, similar inductive events, signaling cascades and gene products drive their differentiation and morphogenesis (Brandli, 1999; Hensey et al., 2002; Vize et al., 1997). The pronephros, which is as functionally complex as later kidney forms, is experimentally attractive because of its simpler structure. It is composed of a single nephron, inclusive of tubules, a duct and a glomus (Carroll et al., 1999a; Vize et al., 1997, 2003). Various constructs, including mRNAs coding for native or mutant proteins of interest, can be targeted to the pronephros by injecting them into blastomeres that will ultimately give rise to this structure. Thus, development can be altered by activating or interfering with chosen developmental pathways. Early markers of nephron formation, such as *lhx-1* and *pax-8*, have been shown to be active in the nephrogenic mesenchyme prior to epithelialization, morphogenesis, and tubule maturation in both the pronephros and metanephros (Vize et al., 1997, 2003). Later, the conversion of nephrogenic mesenchyme to polarized nephric epithelia requires the action of Wnt signaling components. Many Wnt signaling components have been implicated in kidney development including Wnt-2b, Wnt-4, Wnt-6, Wnt-9b, Wnt-11, Frz4, Frz8, LRP6, Dkk1, CK2, GSK3, Tcf2, Pygo1 and Pygo2 (Carroll et al., 2005; Dressler, 2006; Itaranta et al., 2002; Kuure et al., 2007; Kyuno et al., 2008; Lin et al., 2001; Majumdar et al., 2003; Satow et al., 2004; Saulnier et al., 2002; Schedl, 2007; Schwab et al., 2007; Stark et al., 1994b, 2000; Valerius et al., 2002). Wnt-4 in particular has been shown to be important in both the *Xenopus* pronephros and murine metanephros (Saulnier et al., 2002; Stark et al., 1994b). In both systems, loss of Wnt-4 inhibits mesenchyme condensation and thus the epithelialization of nephric tubules (Saulnier et al., 2002; Stark et al., 1994a). In *Xenopus*, expression of Wnt-9a, Wnt-9b and Wnt-11b have also been observed in the pronephric kidney (E.A. Jones, unpublished results).

In mice, several Wnts participate in kidney formation, with Wnt-9b also contributing to metanephric tubulogenesis (Carroll et al., 2005). Unlike Wnt-4, which is expressed in the metanephric mesenchyme, Wnt-9b is expressed in the stalks of the invading ureteric bud (Carroll et al., 2005). Wnt-9b knockouts do not undergo metanephric mesenchymal to epithelial transition, and markers of nephron formation, such as *pax-8*, *lhx-1*, and *wnt-4* are not expressed (Carroll et al., 2005). Wnt-6, which is also expressed in the murine ureteric bud, induces tubulogenesis from mesenchyme *in vitro* (Itaranta et al., 2002). Other Wnts include Wnt-11, expressed in the ureteric epithelium and needed for ureteric branching (Majumdar et al., 2003), as well as Wnt-2b, expressed in the perinephric mesenchyme and likewise is involved in ureter formation (Lin et al., 2001).

Wnts may affect kidney development via canonical and/or non-canonical signaling trajectories. Wnts activating the canonical pathway bind both Frizzled (Fz) and LRP receptors resulting in activation of the transcription factor β-catenin. In the absence of Wnt signals, β-catenin is marked for degradation by a multiprotein complex that includes GSK-3β, APC, and Axin (Huang and He, 2008; Sokol and Wharton, 2007; Widelitz, 2005; Willert and Jones, 2006). In the presence of canonical Wnt signals, Dishevelled and LRP sequester the degradation complex, allowing β-catenin to accumulate (Schwarz-Romond et al., 2007; Zeng et al., 2005). β-Catenin then enters the nucleus to associate with and relieve Lef/Tcf-mediated transcriptional repression, resulting in target gene activation (Widelitz, 2005). Wnt signaling that does not act through the canonical β-catenin signaling trajectory is by definition considered non-canonical Wnt signaling. The two primary non-canonical Wnt signaling pathways are the planar cell polarity (PCP) pathway, involving Rho GTPases and JNK, and the calcium pathway, involving PKC and CAMKII (Wallingford and Habas, 2005; Widelitz, 2005).

Growing evidence suggests that canonical Wnt/β-catenin signals act in kidney development. Mice bearing a β-catenin-responsiveTcf/βGal reporter transgene reveal canonical Wnt activity in the nephrogenic mesenchyme during tubulogenesis (Iglesias et al., 2007), removal of β-catenin from metanephric progenitors reduces nephron number and organization (Park et al., 2007), and β-catenin deficiencies in the ureteric bud produce abnormal ureteric branching (Bridgewater et al., 2008). In organ culture, constitutive β-catenin signaling in epithelial progenitors induces Tcf/Lef-dependent epithelial transcripts (Schmidt-Ott et al., 2007), and in cultured Madin–Darby Canine Kidney (MDCK) epithelial cells, Wnt-4 activates canonical Wnt/β-catenin signals (Lyons et al., 2004). While suggestive, each of these studies has either been conducted *in vitro* or *ex vivo*, or has reduced β-catenin function using an approach that could have perturbed cell–cell adhesion in addition to canonical Wnt target gene expression. This latter concern arises from the fact that in addition to its signaling roles, β-catenin is an essential component of cadherin complexes present at cell–cell adhesive junctions, where it contributes to the indirect dynamic association of cadherins with the underlying cortical actin cytoskeleton (Brembeck et al., 2006; Nelson, 2008).

Here, using amphibian and zebrafish pronephric model systems, we test the hypothesis that Wnt/β-catenin signaling, specifically, is required for kidney development. We show that inhibiting this pathway inhibits formation of pronephric epithelial tubules, duct and glomus, reducing expression of both early and late pronephric markers. We thus demonstrate the requirement of canonical Wnt/β-catenin signals in multiple components and stages in pronephric development.

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