

VEGF Mediates a Mesenchyme:Angioblast Interaction During Early Kidney Development That Induces a State of Competence in the Nephrogenic Mesenchyme

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Most studies on kidney development have considered the interaction of the metanephric mesenchyme and the ureteric bud to be the major inductive event that maintains tubular differentiation and branching morphogenesis. The mesenchyme produces GDNF, which stimulates branching, and the ureteric bud stimulates continued growth of the mesenchyme and differentiation of nephrons from the induced mesenchyme. Here we describe the role of a third cell type, the angioblast. FLK-1-expressing angioblasts have previously been identified in the periphery of the induced mesenchyme and adjacent to the stalk of the ureteric bud. Using a novel system for microinjecting and electroporating plasmid expression constructs into murine organ cultures, it has been demonstrated that VEGF-A expression in the induced mesenchyme is regulated by WT1. VEGF-A appears to act on the angioblast population to elicit an as yet unidentified signal that acts back on the mesenchyme to induce and maintain a state of competence that permits induction of the mesenchymal to epithelial transformation by the ureteric bud. Blockade of signaling through Flk-1 decreases branching of the ureteric bud and expression of several markers of the induced mesenchyme, including Pax2. Flk-1 blockade also inhibits tubulogenesis. At least one target of the angioblast-derived signal appears to be the regulation of Pax-2 mRNA stability in the mesenchyme.