Renal ontogeny in the rhesus monkey (Macaca mulatta) and directed differentiation of human embryonic stem cells towards kidney precursors.

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Public Summary:
The development of the metanephric kidney was studied immunohistochemically across gestation to identify markers of cell specification, and to aid in developing experimental paradigms for renal precursor differentiation from human embryonic stem cells (hESC). PAX2, an important kidney developmental marker, was expressed at the tips of the ureteric bud, in the surrounding condensing mesenchyme, and in the renal vesicle. Vimentin, a mesenchymal and renal marker, was strongly expressed in the metanephric blastema then found to be limited to the glomerulus and interstitial cells of the medulla and cortex. Spontaneous hESC differentiation revealed markers of metanephric mesenchyme that increased over time, followed by upregulation of kidney precursor markers. Directed hESC differentiation was also evaluated with the addition of retinoic acid, Activin-A, and BMP-4 or BMP-7, and using different culture substrate conditions. Of the culture substrates studied, gelatin most closely recapitulated the anticipated directed developmental pattern of renal gene expression.

Scientific Abstract:
The development of the metanephric kidney was studied immunohistochemically across gestation in monkeys to identify markers of cell specification, and to aid in developing experimental paradigms for renal precursor differentiation from human embryonic stem cells (hESC). PAX2, an important kidney developmental marker, was expressed at the tips of the ureteric bud, in the surrounding condensing mesenchyme, and in the renal vesicle. Vimentin, a mesenchymal and renal marker, was strongly expressed in the metanephric blastema then found to be limited to the glomerulus and interstitial cells of the medulla and cortex. A model of gene expression based on human and nonhuman primate renal ontogeny was developed and incorporated into studies of hESC differentiation. Spontaneous hESC differentiation revealed markers of metanephric mesenchyme (OSR1, PAX2, SIX2, WT1) that increased over time, followed by upregulation of kidney precursor markers (EYA1, LIM1, CD24). Directed hESC differentiation was also evaluated with the addition of retinoic acid, Activin-A, and BMP-4 or BMP-7, and using different culture substrate conditions. Of the culture substrates studied, gelatin most closely recapitulated the anticipated directed developmental pattern of renal gene expression. No differences were found when BMP-4 and BMP-7 were compared with baseline conditions. PAX2 and Vimentin immunoreactivity in differentiating hESC was also similar to the renal precursor patterns reported for human fetal kidneys and findings described in rhesus monkeys. The results of these studies are as follows: (1) provide additional data to support that rhesus monkey kidney development parallels that of humans, and (2) provide a useful model for hESC directed differentiation towards renal precursors.