

# Reciprocal Induction of the Kidney

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The occurrence of reciprocal induction has been known for a long time. This event is typically part of organogenesis. It occurs in many places in the body such as the lungs and kidneys. The kidneys are the major focus for this paper. The basic idea behind reciprocal induction is differing tissues causing changes in each other due to signals and receptors in each. Even though this is a simple concept, the process or mechanism is quite complex and precise. The basic process of kidney reciprocal induction is <sup>2,4,8</sup>:

i. Binding/invasion between the ureteric bud (UB) and the metanephric mesenchyme (MM) of the blastema. This occurs in week four.

ii. Preventing apoptosis of the metanephric mesenchyme. This is the first step in the formation of mesenchymal condensations, which epithelialize into nephrons.

iii. Branching and proliferation of the ureteric bud into the collecting duct system.

iv. Progression of steps ii and iii, which leads to a fully functional kidney at week 16.

Mistakes in reciprocal induction result in agenesis or hypoplasia of the organ. Mishaps with signals and receptors are typically the cause of such problems. Since the tissues induce each other, proper organ development relies on both. A problem with one signal/receptor in one of the tissues leads to problems in the other. There are a number of genes and molecules being studied to figure out the exact mechanism. Because there is so much codependency and over 50 genes associated with kidney development it is difficult to determine the exact mechanism. <sup>1,5</sup> However, a few have been identified to a specific event in reciprocal induction.

In order for reciprocal induction to occur the ureteric bud and the metanephric blastema, that originate from intermediate mesoderm, must come together and adhere for several hours. <sup>8,14</sup> Factors that have been shown to assist in this event are: Sall1, WT-1, and cadherins. Sall1 is the mouse form of the human SALL1. <sup>10</sup> However, most

experiments have been performed on mice. Sall1 is expressed in the metanephric blastemal area closest to the UB and is essential for UB invasion. <sup>10</sup>

Without Sall1 mesenchymal cells do not attract the UB. <sup>10</sup> There are other factors that lead to the initial attraction between the UB and MM, so Sall1 mutations do not typically lead to agenesis of the kidneys. Townes-Brock Syndrome, an autosomal dominant disease, occasionally has kidney abnormalities that are associated with Sall1 mutations. <sup>10</sup> Wilm's tumor suppressor gene (WT-1) is a transcription factor, without it the UB does not invade the blastema. <sup>12</sup> This is because the MM cannot respond to the UB signals. <sup>12</sup> Once the UB and MM join, they adhere for proper kidney development. Cadherins are a group of cell-adhesion molecules that accomplish this. <sup>10</sup> There are two types of cadherin molecules (I and II). <sup>10</sup> Type I are typically found in epithelial (UB) while type II is found in specific cells throughout embryogenesis. <sup>10</sup> Cad-11 (type II) is expressed in the uninduced MM and E-cad (type I) is in the UB. <sup>10</sup> This expression changes by switching expressed cadherins, which is essential for UB and MM remodeling. <sup>10</sup> Mutations in the genes producing cadherins result in a decreased number of nephrons. After the tissues adhere for a while changes occur in the MM and UB.

The next step in reciprocal induction is to prevent apoptosis of the MM, which epithelializes and induce UB. <sup>1</sup> Assuming that invasion and adherence occur without problems BMP7/OP1, FGF2, and bFGF prevent apoptosis of the MM. All are expressed in the ureteric bud. Basic fibroblastic growth factor (bFGF) is known to prevent apoptosis of several specific tissues that are necessary for mesenchymal condensation development. <sup>1,5</sup> These tissues are: tubular epithelial and capillary precursors, and the cells that induce the UB to grow. <sup>1</sup> The receptor for bFGF is flgIIIc, which is expressed in embryonic mesenchyme often. <sup>1</sup> Without bFGF the kidneys are hypocellular and

have fewer nephrons than normal.<sup>1</sup> Bone morphogenetic protein 7 (BMP7) or osteogenic protein 1 (OP-1), is expressed in a number of places in development (eye, limbs, and notochord) but in mutants problems only occur in the eyes and kidneys.<sup>15</sup> The exact tissues that are saved are unknown but BMP7 is known to prevent apoptosis. It has two types of receptors (I and II) known.<sup>16</sup> OP-1 has been shown to be expressed in the UB epithelium before mesenchymal condensations form.<sup>15</sup> Its exact target and receptor are still unknown. In BMP7 mutants the size and patterning are highly abnormal.<sup>5</sup> The mutations usually result in decreased amounts of mesenchyme, hypoplasia (under developed) and hydronephrosis (accumulation of urine in the ureter).<sup>16</sup> FGF2 is a more recent find in preventing apoptosis, its exact mechanism is still unknown.<sup>8</sup> After apoptosis is prevented mesenchymal condensations form. These condensations transform into the epithelial cells of nephrons.<sup>1</sup>

There are several genes and molecules associated with epithelialization or tubulogenesis: Pax2, BF2, LIF, Wnt-1 and Li<sup>+</sup>. Pax2 is a transcription factor gene that is expressed initially in the Wolffian duct and later in its UB and MM (after induction by UB).<sup>8</sup> Mutations in this gene typically lead to renal hypoplasia, dysplasia and agenesis.<sup>8</sup> BF2 is another transcription factor, which is expressed in the mesenchymal cells that later become the stromal cells (supporting cells) of the glomeruli.<sup>12</sup> BF2 mutants fail to form nephrons or has smaller ones because epithelialization does not occur.<sup>12,16</sup> Leukemia inhibitory factor, (LIF) is secreted by the UB.<sup>8</sup> It has been shown to regulate mesenchyme-to-epithelial transition.<sup>11</sup> In LIF mutations, nephrogenesis is decreased.<sup>11</sup> Wnt-1 is a gene that produces a glycoprotein.<sup>4</sup> Its expression is apparent only in embryonic central nervous system, which accounts for the spinal cords inducing effects on MM.<sup>4</sup> Li<sup>+</sup> was also an important molecule that was found to induce MM to epithelial cells.<sup>2</sup> However, Li<sup>+</sup> can only initiate early stages of epithelialization, development is halted around the comma-shaped stage.<sup>2</sup> While epithelialization is occurring the UB is also being induced to branch, proliferate, and differentiate into the collecting duct system.

Glial-cell derived nephrotrophic factor (GDNF) aids in bud branching, and is produced by mesenchyme.<sup>14</sup> It has two receptor c-ret (tyrosine kinase receptor) and GFR-1 (co-receptor), without GDNF renal agenesis and dysplasia occur.<sup>14</sup> Pleiotrophin is a protein secreted by MM and has the UB basement membrane as a target.<sup>13</sup> The concentration gradient of pleiotrophin aids in the shaping and direction of UB development.<sup>13</sup> Proteoglycans have been suggested in having an involvement with UB branching.<sup>6</sup> Little is known of its target or mutation.

A few molecules are believed to help regulate the reciprocal induction. Pod1, which is expressed in podocytes of the glomeruli has been shown to be essential in regulation.<sup>12</sup> BMP4 is an inhibitory growth factor for bud branching.<sup>8</sup> The extracellular matrix (ECM) regulates morphogenic features and controls growth factor concentration in the areas of the cell.<sup>9</sup> WT-1 regulates in a way also, without its rare childhood cancers form.

Despite the complexity of reciprocal induction a lot is known about it. There are probably a lot of genes and molecules that have yet to be identified. It is also possible that the current ideas are wrong as well. It will most likely be years before the exact mechanism is known.

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