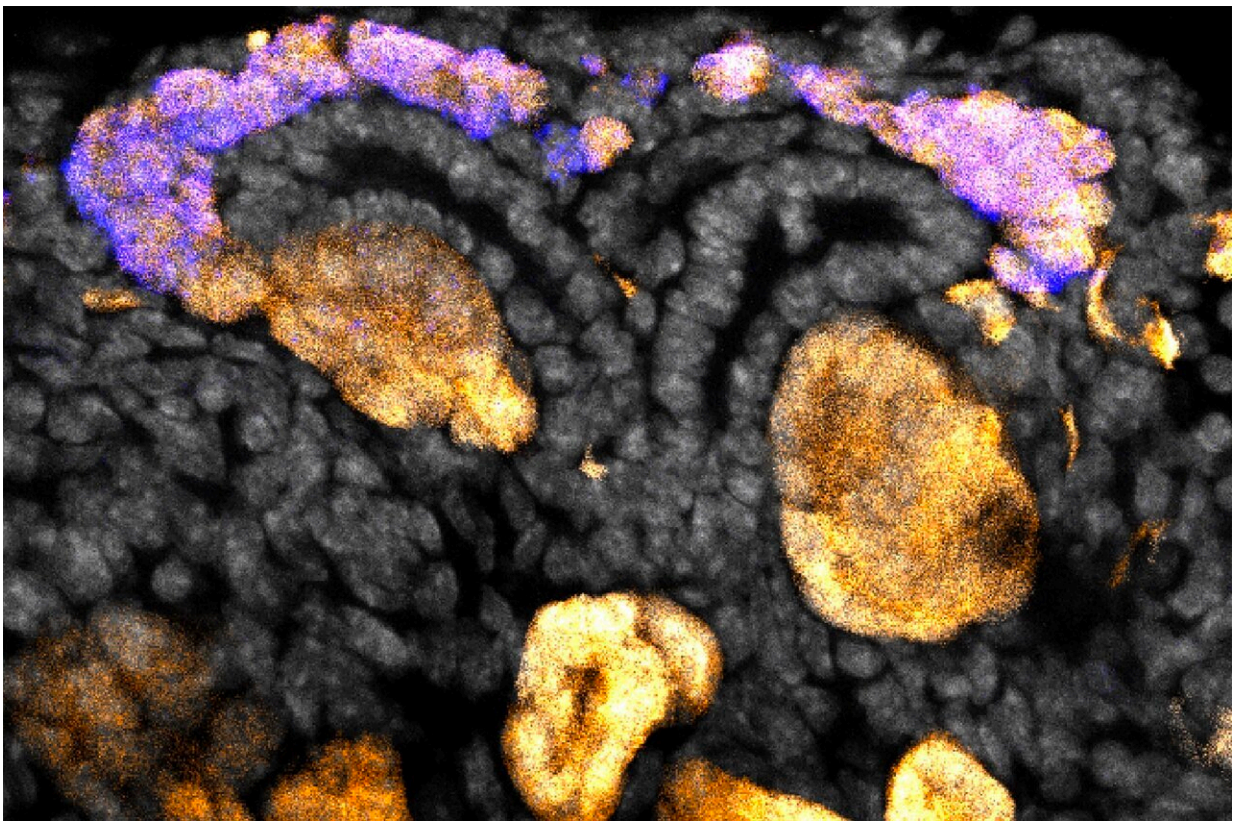
Stem cell studies detail how progenitor cells self-renew, differentiate and aggregate into early kidney structures

October 1 2024, by Cristy Lytal



Mouse kidney nephron progenitor cells (purple) forming the developing nephron tubules (yellow) of the kidney's filtering units, the nephrons. Credit: Helena Bugacov/McMahon Lab

A group of essential signaling molecules known as the Wnt pathway emerged early in the evolution of multicellular life. Scientists have been studying Wnt actions for four decades to comprehend its complex roles in development and disease.

In the development of the mammalian kidney, USC Stem Cell scientists from Andy McMahon's lab undertook a pair of complementary studies, published in the journal *Development*, that provide new insight into the critical role of Wnt signaling in initiating the development of the mammalian kidney.

"Many stem and progenitor cells require Wnt signaling, and the kidney is a particularly interesting example, because the level of signaling may have profoundly different outcomes," said corresponding author McMahon, who is the W.M. Keck Provost and University Professor of Stem Cell Biology and Regenerative Medicine, and Biological Sciences at the Keck School of Medicine of USC.

"By enhancing our knowledge of how Wnt signaling acts in the developing kidney, these two papers provide insights that can guide efforts among USC collaborators in the Synthetic Kidney Consortium to build kidneys from stem and progenitor cells as a new treatment option for patients."

Both studies focus on the progenitor and stem cells that form the kidney's filtering units, known as nephrons, in embryonic mice.

"Nephron progenitor cells cease to exist by the time humans are born," said Helena Bugacov, who is a first author on both studies and a Ph.D. graduate from the McMahon Lab now pursuing her MD at the Icahn School of Medicine at Mount Sinai in New York.

"Without NPCs, postnatal kidneys are unable to form new

nephrons—hence the need for kidney transplantation once nephron function declines. However, there are simply not enough kidneys available for those that need them.

"Therefore, understanding the signals required to promote the self-renewal, differentiation, and formation of the precursors to nephrons from their progenitor cells is pivotal to the creation of stem cell-based artificial kidneys."

The scientists isolated and grew nephron progenitor cells, or NPCs, in the lab and then exposed them to different amounts of a chemical called CHIR, which alters the activity of the Wnt signaling pathway.

To explore Wnt pathway actions, the researchers focused on how Wnt signals regulate genes, a process mediated by proteins involved in DNA binding. In addition to its essential role in Wnt-induced gene regulation, beta-catenin is a key mediator of the cell adhesion processes that engineer and hold together a type of tissue known as epithelium.

To investigate the actions of these Wnt pathway components, Helena Bugacov pioneered a technique for genetically manipulating NPCs.

In the first study, Bugacov and colleagues applied the genetic modification technique to study responses to different levels of Wnt pathway activation.

The scientists found that low signaling levels regulate NPC self-renewal, critical to generating the full number of NPCs necessary to form the 14,000 nephrons of the mouse kidney. Higher levels initiate the differentiation of NPCs into mature kidney cell types. In line with earlier studies from the McMahon Lab and others, the levels of beta-catenin determine different NPC outcomes.

Induction of kidney formation in response to high levels of Wnt signaling results in a critical cellular transition: isolated NPCs aggregate and cooperatively form a small cluster of cells, called the renal vesicle. Each renal vesicle is a precursor for a single nephron. One million renal vesicles generate the one million nephrons of the human .

In the second study, the first authors—postdoc Bálint Dér, MD, and Bugacov in the McMahon Lab—studied how the Wnt signaling pathway directs NPC aggregation to form the condensed clusters that become the precursors of nephrons.

Dér, Bugacov, and their co-authors found that activating Wnt prompts NPCs to adhere to each other, transforming from a mobile and loosely organized collection of cells into a stationary and organized arrangement of cells that goes onto form the renal vesicle.

This process, known as the mesenchymal-epithelial transition, is a hallmark of embryonic development in the kidney, as well as in many other developmental and disease processes throughout the body. The reverse process, an epithelial-mesenchymal transition, underlies the spread of many cancers from the primary tumor to distant sites during tumor metastasis.

To achieve this cellular aggregation that enables the nephrons to begin to take shape, beta-catenin links adhesive proteins at the surface of NPCs, known as cadherins, through another protein, alpha-catenin, with a structural scaffold within the cell.

"It's been a pleasure and an honor to work on these research projects in a lab that has been investigating the Wnt signaling pathway since the first identification of Wnt genes and their developmental actions in mammals—and to be able to combine the power of developmental biology, stem cell science, and genetic engineering to one day advance

treatment options for people with kidney disease," said Bugacov.

Dér, who is currently specializing in urological surgery at Semmelweis University in Budapest, Hungary, added, "Because the Wnt signaling pathway plays a role in so many organ systems throughout the body, our studies are important not only for understanding the development of the kidney, but also for gaining relevant insight into development of other organs.

"Furthermore, it was an honor to work in the McMahon Lab, and I am grateful for the people I have met along the way."

More information: Helena Bugacov et al, Dose-dependent responses to canonical Wnt transcriptional complexes in the regulation of mammalian nephron progenitors, *Development* (2024). DOI: 10.1242/dev.202279

Balint Der et al, Cadherin adhesion complexes direct cell aggregation in the epithelial transition of Wnt-induced nephron progenitor cells, *Development* (2024). DOI: 10.1242/dev.202303

Provided by Keck School of Medicine of USC

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