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Brca2/Fancd1 is Necessary for the Formation of the Pronephros, According to the Zebrafish Kidney Mutant Zeppelin

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Abstract

Because the kidneys filter the blood, reabsorb necessary metabolites and solutes, and collect remaining waste products for eventual excretion, the renal system is essential to homeostasis. During the development of a vertebrate species, up to three kidneys of varying complexity are formed. These kidneys can be functional or merely relics, as these forms gradually deteriorate and vanish when the next organ form appears. The pronephros, mesonephros, and metanephros are the three renal iterations that emerge from the intermediate mesoderm (IM). Nephrons are the individual excretory units that make up each of these kidney types. Nephrons typically have three parts: a glomerular blood filter, a tubule, and a duct. However, there are some exceptions, such as aglomerular fish.

Keywords: Zeppelin • Metabolites • zebrafish kidney

Introduction

The embryonic zebrafish kidney is a functioning pronephros with two nephrons that connect at the cloaca and a single fused glomerulus in the anterior and posterior regions, respectively. The segmental organization of the pronephros is relatively conserved with other vertebrate species, making it possible to utilize zebrafish genetics for nephrogenesis research and renal disease modeling as well, despite the fact that this form of the kidney is significantly less complex than the metanephric kidneys that are found in amniotes. Zebrafish pronephric tubule segments, for instance, are distinguished by the expression of a particular group of solute transporter proteins that also characterize the same region in mice and humans [1].

Literature Review

Additionally, the zebrafish pronephric blood filter shares many of its components with mammals, including podocyte-like epithelial cells, specialized glomerular basement membrane (GBM), and capillaries with a fenestrated endothelium. The podocytes surrounding the capillaries extend intricate cellular extensions known as foot processes, which interdigitate to form unique cell junctions known as the slit diaphragm. These parts are anatomically located within the glomerulus. Nephron filtration relies on these junctions, which will express Nephrin and Podocin in mature podocytes. The podocytes and the GBM form a fine molecular sieve that keeps cells, platelets, and large molecules like albumin in circulation while allowing small compounds and solutes to enter the tubule [2].

Clinical studies have shown that podocyte dysfunction is the root cause of about 80% of end-stage renal disease (ESRD). This is because podocyte dysfunction compromises nephron function and starts a chain reaction of cellular and molecular changes that cause nephron damage. Because differentiated podocytes do not proliferate normally, podocyte dysfunction or loss has such a significant impact on kidney health and individual health. All podocytes in mammals are formed during development, and these cells cannot be replenished as they get older. It has been discovered through extensive research that when podocytes are lost, the podocytes that are nearby hypertrophy to take their place. As a result, developing therapies that encourage podocyte renewal may benefit from learning more about the early development of podocytes [3].

Discussion

The expression domains of the Wilms tumor 1 (WT1) paralogs, wt1a and wt1b, overlap in a region where podocytes develop as two bilateral clusters of cells adjacent to the paraxial mesoderm that forms the third pair of trunk somites in the zebrafish embryo. These groups of cells congregate and migrate toward the midline during the early stages of development, enlisting the vasculature and creating a fused glomerulus. Several transcription factors and signaling molecules, including lhx1a and mafba, are known to be expressed in podocytes. Additionally, wt1a, wt1b, foxc1a, lmx1bb, osr1, and the Notch pathway effector rbpj have been found to play important roles in podocyte development. Additionally, a variety of renal defects and disease states are linked to these essential genetic factors. Wilms Tumor disease, a kidney cancer in children, is caused, for instance, by mutations in the human WT1 gene [4].

Biochemical studies have suggested that a large, multimeric protein complex that controls podocyte differentiation is formed when a number of these integral factors interact. Nephrin, Podocin, CD2AP, and -actinin4 are among the slit diaphragm proteins that must be expressed by podocytes as they mature for glomerular assembly to take place correctly. Not only are the aforementioned proteins involved in the development of vertebrate podocytes, but also the following: During the proximo-distal pattern formation of the zebrafish IM, the morphogen retinoic acid (RA) is also necessary for proper podocyte genesis because it specifies the podocyte lineage.

In order to regulate the transcription of target genes, RA binds retinoic acid and retinoid X receptors (RARs, RXRs) in DNA and interacts with RA response elements (RAREs). In order to form signaling gradients, RA synthesis and degradation enzymes establish distinct RA sources and sinks. Treatment with exogenous all-trans RA proximalizes the nephron during zebrafish pronephros formation, while inhibition of RA biosynthesis distalizes the nephron, resulting in podocyte loss or reduction depending on the severity of RA deficiency. Intriguingly, subsequent research revealed a functional RARE in both human WT1 enhancers and zebrafish wt1a.

A group of cells that gives rise to the interrenal gland, which forms adjacent to the pronephric glomerulus, is closely mingled with the developing podocytes in the zebrafish embryo. Similar to the adrenal gland in mammals, the interrenal gland secretes steroids. The interrenal lineage is thought to come from the wt1a-expressing field, just like podocytes do. However, it comes from a subset of this field that is made to express the steroid hormone receptor encoded by nuclear

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receptor subfamily 5, group A, member 1a. Previous research has shown that the specification of these lineages must remain in a delicate balance: The number of podocytes and interrenal cells both decrease when wt1a expression is low or Notch signaling is reduced. These results suggest that the podocyte and interrenal lineages share a precursor, or that depending on the combination of internal and external cues, one fate may transdifferentiate from the other [5-9].

Using the chemical mutagen N-ethyl-N-nitrosurea (ENU), we isolated the novel zebrafish podocyte mutant zep in a F3 forward genetic screen, where families with congenital edema were further examined for kidney defects. We discovered through expression and functional analyses that podocyte loss results in a dysfunctional glomerulus in zep mutants. Interestingly, zep embryos had larger interrenal glands, whereas wild-type (WT) embryos did not differ in terms of cell death or proliferation in the IM or the pronephros that followed. We discovered through the use of WGS that zep have a defect in the gene for breast cancer 2, early onset (brca2)/fancd1, which is expressed extensively during embryogenesis and is also inherited from the mother [10].

Conclusion

We show through knockdown experiments that embryos lacking brca2 mimic zep in the development of edema, a decrease in the number of podocytes, and an increase in the number of interrenal cells. The combination of these genetic defects in zep and brca2ZM_00057434 -/- fish, which have an insertional mutant allele, resulted in an increase in the size of the interrenal glands, despite the fact that podocyte development was unaffected. We discovered that brca2 overexpression was sufficient to partially restore podocyte formation in zep through rescue experiments. These results lend credence to the hypothesis that brca2 deficiency alone is sufficient to cause the zep phenotype. This study is the first to show that podocyte development can be altered when brca2 is disrupted; making this gene an important renal factor that needs more research.

Acknowledgement

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Conflict of Interest

None.

References

1. Miltoft, Caroline Borregaard, Line Rode, Charlotte Kvist Ekelund and Karin Sundberg, et al. "Contingent first-trimester screening for aneuploidies with cell-free DNA in a Danish clinical setting." *Ultrasound Obstet Gynecol* 51 (2018): 470-479.
2. Petersen, Olav Bjørn, Ida Vogel, C. Ekelund and J. Hyett, et al. "Potential diagnostic consequences of applying non-invasive prenatal testing: Population-based study from a country with existing first-trimester screening." *Ultrasound Obstet Gynecol* 43 (2014): 265-271.
3. Persico, Nicola, Simona Boito, Benedetta Ischia and Adalgisa Cordisco, et al. "Cell-free DNA testing in the maternal blood in high-risk pregnancies after first-trimester combined screening." *Prenat Diagn* 36 (2016): 232-236.
4. Iqbal, Corey W, Shawn D. St Peter, Kuojen Tsao and Daniel C. Cullinane, et al. "Operative vs nonoperative management for blunt pancreatic transection in children: Multi-institutional outcomes." *J Am Coll Surg* 218 (2014): 157-162.
5. Beres, Alana L, Paul W. Wales, Emily R. Christison-Lagay and Mary Elizabeth McClure, et al. "Non-operative management of high-grade pancreatic trauma: Is it worth the wait?." *J Pediatr Surg* 48 (2013): 1060-1064.
6. Paul, Michael D and David P. Mooney. "The management of pancreatic injuries in children: Operate or observe." *J Pediatr Surg* 46 (2011): 1140-1143.
7. Wood, James H, David A. Partrick, Jennifer L. Bruny and Angela Sauaia et al. "Operative vs nonoperative management of blunt pancreatic trauma in children." *J Pediatr Surg* 45 (2010): 401-406.
8. Kazantzis, Nikolaos, Craig Whittington, Leah Zelencich and Michael Kyrios, et al. "Quantity and quality of homework compliance: A meta-analysis of relations with outcome in cognitive behavior therapy." *Behav Ther* 47 (2016): 755-772.
9. Perkusich, Mirko, Lenardo Chaves e Silva, Alexandre Costa and Felipe Ramos, et al. "Intelligent software engineering in the context of agile software development: A systematic literature review." *Inf Softw Technol* 119 (2020): 106241.
10. Benn, Peter, Antoni Borrell, Rossa WK Chiu and Howard Cuckle, et al. "Position statement from the chromosome abnormality screening committee on behalf of the board of the international society for prenatal diagnosis." *Prenat Diagn* 35 (2015): 725-734.

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