

# The cellular mechanisms of kidney fibrosis: A hitherto understudied aspect of Polycystic Kidney Disease

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**In this exclusive Q&A session with Dr. Andras Kapus, we unravel the complexities of chronic kidney disease in general and Polycystic Kidney Disease (PKD) in particular, and delve into the ongoing research efforts aimed at combatting kidney fibrosis**

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Dr. Kapus shares valuable insights into the molecular mechanisms driving PKD and the broader implications of understanding fibrosis in the world of medical science. Let's dive into this enlightening conversation.

**Can you provide an overview of your research and your specific focus on the molecular mechanisms underlying Polycystic Kidney Disease?**

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Our lab primarily explores cellular and molecular mechanisms related to cell stress, with a specific emphasis on fibrosis, chronic scarring, a common feature in numerous diseases.

“It is believed that 45% of all deaths in the Western world are due to some form of fibrosis.”

Our research explores the molecular and cellular aspects of fibrosis, with a keen interest in the cytoskeleton, a vital cellular framework. The cytoskeleton was long known to be essential for normal cell structure and movement; research in the past 20 years showed that it is also critical for gene expression.

We investigate how the cytoskeleton plays a crucial role in various diseases, especially those involving fibrosis. This is one aspect of PKD as well, and this has attracted our research effort in this direction.

**Could you explain what Polycystic Kidney Disease is and why it's considered significant in the field of kidney health?**

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Normal kidney function is vital for maintaining overall health, as it helps eliminate waste and maintain chemical balance in the body. However, around 12% of people develop chronic kidney disease (CKD), which is often a consequence of prevalent common conditions like diabetes and hypertension. Thus, CKD is a very significant concern in kidney health.

Unfortunately, there is currently no cure for this condition, and the available treatments, such as transplantation, or dialysis, are costly and challenging.

Polycystic kidney disease (PKD) is the most common inherited kidney disease, affecting approximately one person in 500. PKD presents unique challenges; it involves the absence of normal function of one of two critical proteins (so called polycystins) that regulate cell division, metabolism and regeneration.

PKD exhibits two major features when examined via a microscope:

1. The formation of large fluid-filled cysts that develop as a consequence of abnormal cell division;
2. The occurrence of chronic scarring, known as fibrosis.

Both the presence of cysts and the persistent fibrosis disrupt the normal kidney architecture, and are primary factors contributing to the long-term fatality of this disease. In short, PKD is a genetic cause for CKD. While there's a considerable understanding of the molecular mechanisms behind cyst formation, relatively little is known about the processes driving the fibrotic component of the disease.

## **What motivated you to delve into this area of research?**

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As I mentioned previously, 45% of people in the West are dying from some form of fibrosis. It's worse than cancer in many a way. It is a disease that is unstoppable with no real cure that affects every organ, from the lung to the heart to the liver to the kidney.

The underlying cell biology is incompletely understood. 12% of the people live with chronic kidney disease, making it a modern "epidemic". Therefore research has to catch up. It is because of these reasons that I continue to work in this area.

You were involved in the "Advancing Discovery Research in Nephrology in Canada" conference. Could you tell us about the conference's focus and its significance in the field of nephrology?

Canadian nephrologists have always formed a very coherent group for addressing different types and causes of kidney diseases. Although The Kidney Foundation of Canada, a funding organization specifically dedicated to supporting kidney research has always played a key role in advancing the field, Canadian researchers felt that it was very important to share information through different channels – basic science-minded conferences – as well.

That's the novelty here, basic researchers and clinician scientists sharing information together during a concise and intensive event, with lots of opportunities to discuss new findings.

## **How do insights and discussions from conferences like these influence your ongoing research and its potential applications in clinical settings or medical advancements?**

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Greatly. For example, in addition to the mentioned Canadian initiatives, in the United States there is the Polycystic Kidney Disease Research Resource Consortium. This excellent organization provides anybody in this field with necessary reagents for research, advice, and exchanges of ideas.

It also is responsible for organizing conferences which not only scientists and clinicians are participating but also patients. This gives patients the opportunity to learn about what efforts have been made in order to address their problems. Conversely, it also helps researchers to focus on the main concerns of patients.

### **You've researched epithelial-mesenchymal transition (EMT) and its role in tissue fibrosis. Could you elaborate on how EMT contributes to the development of fibrosis in organs like the kidney?**

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Polycystic kidney disease actually is the number one inherited reason for kidney fibrosis and it involves EMT.

EMT, which stands for Epithelial- Mesenchymal Transition, is a critical process in fibrosis. It involves a transformation where epithelial cells take on more mesenchymal characteristics. This process holds significant importance in diseases like Polycystic Kidney Disease

Cellular research by others and us has revealed that in the context of PKD (and CKD in general), partial EMT occurs. This means that instead of a complete transformation from a normal kidney tubular cell into a fibroblast, which produces a large amount of matrix resulting in scar tissue (fibrosis), there is a partial shift. In this partial form of EMT, the normal epithelial cells, which are the functional units of the kidney, start to lose their typical characteristics and gradually acquire features that make them scar-inducing cells.

One key aspect of this process is the reorganization of the cell's skeleton in response to cellular injury or stress. This reorganization triggers changes in gene expression, which ultimately leads to the development of fibrotic tissue. Although the epithelial cells do not become scar-forming fibroblast themselves, they activate connective tissue cells, through partial EMT, to produce large amounts of extracellular matrix. Perhaps the more appropriate term to use is epithelial mesenchymal communication, wherein the altered – i.e. diseased-epithelium activates mesenchymal cells like fibroblasts to induce fibrosis.

### **How does understanding the mechanisms of EMT contribute to our understanding of kidney fibrosis and related conditions such as liver cirrhosis and lung fibrosis?**

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As mentioned earlier, the process known as epithelial-mesenchymal transition (EMT), or rather the partial form of EMT, is intricately linked to the underlying causes of various fibrotic diseases, including lung, kidney, and liver fibrosis. Research from multiple laboratories, including our own, has demonstrated that partial EMT serves as a driving force behind the

formation of scar tissue in these conditions. In essence, while partial EMT represents just one aspect of these diseases, its importance spans across various fibrotic conditions, making it a crucial area of study.

PKD is a new aspect of our research, recently added to the broader frame of our CKD work. However, it is important to note that there is strong tradition of PKD research in Canada. We collaborate with Dr York Pei at the Toronto General Hospital, a world-renowned expert in PKD, who brings valuable clinical and scientific insights. Additionally, researchers like Marie Trudel, who focus on theoretical aspects and animal models of these diseases, greatly contribute to our comprehensive understanding through ongoing conversations.

### **Are there any collaborations or interdisciplinary efforts that your research is part of? How do these collaborations enhance the scope and impact of your work?**

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In our research efforts, collaboration plays a pivotal role. Notably, as mentioned, we collaborate with esteemed experts in the field, such as York Pei, a renowned international expert in PKD.

Within our institution, the Keenan Research Centre at St. Michael's Hospital's Research Institute, I lead one of its scientific pillars called 'Organ Injury and Regeneration.' This pillar facilitates numerous collaborations with eminent scientists and clinicians. We have long-term collaborations with Katalin Szaszi focusing on the role of cytoskeleton-reorganizing pathways, and with Boris Hinz, a leading expert in fibrosis research. Excellent, kidney-focused clinician-scientists in our institution include Richard Gilbert and Darren Yuen.

In the Toronto area, there's a larger fibrosis group led by Chris McCulloch at the University of Toronto. We also have a university-wide cytoskeleton group, organized by Andrew Wilde. Additionally, we maintain international links with a diverse group of scientists. Furthermore, we collaborate with researchers at the American Polycystic Kidney Consortium.

These collaborations are essential as we collectively address the challenges of our field.

### **What are your future plans or directions for your research in the field of kidney diseases and cellular responses to stress?**

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Our research primarily focuses on understanding how normal epithelial cells transform into scar-inducing cells, with a focus on critical factors and mechanisms. Our goals are twofold: to deepen our understanding of these critical mechanisms and to explore innovative therapies.

We receive financial support from organizations like the Canadian Institute of Health Research, the Kidney Foundation of Canada, and the Thor Eaton Professorship, a collaborative initiative between the Keenan Research Centre and the University of Toronto to help further our research.

Additionally, we plan to develop new disease models like organoids and we have expanded our research to include mitochondrial energy metabolism. Besides critical contributions of my students, I would like to mention by name two excellent colleagues in my lab, Michael Kofler and Zsuzsanna Lichner, with key roles in spearheading our research efforts.

All these facets are integrated to form a comprehensive molecular understanding of the diseases we study. We hope to contribute to the difference, which is bound to happen in our understanding and treatment of kidney diseases.

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