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University of Nevada, Reno

Polycystic Kidney Disease: Literature Review on the Mechanism of Mammalian Target of Rapamycin (mTOR) Inhibitors in the Reduction of Cyst Growth in Patients with ADPKD and a Clinical Case Study

A thesis submitted in partial fulfillment
of the requirements for the degree of

BACHELOR OF SCIENCE IN BIOCHEMISTRY AND MOLECULAR BIOLOGY

By

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prepared under our supervision by

Niraj Gandhi

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**Polycystic Kidney Disease: Literature Review on the Mechanism of Mammalian
Target of Rapamycin (mTOR) Inhibitors in the Reduction of Cyst Growth in
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Abstract

Polycystic Kidney Disease (PKD) is a genetic disorder characterized by a growth of multiple cysts in the kidney which, in most cases, culminates in end stage renal failure. A clinical case study was done to highlight the clinical manifestations and the progression of Autosomal Dominant Polycystic Kidney Disease (ADPKD). Currently there are no treatments or cures for PKD with the exception of dialysis and kidney transplantation for patients in kidney failure. Exploration of the role of PKD1 and PKD2 in cystogenesis had yielded potential treatment alternatives for ADPKD such as the use of mammalian target of rapamycin (mTOR) inhibitors to reduce cyst growth and preserve kidney function.

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Table of Contents:

• Abstract.....	i
• Acknowledgements.....	ii
• Table of Contents.....	iii
• List of Tables.....	v
• List of Figures.....	vi
• Introduction.....	1
○ Pathogenesis.....	2
○ Epidemiology.....	6
○ Genetics.....	6
○ Clinical Feature and Diagnosis.....	8
○ Treatment.....	9
○ Body of Review and Conclusions.....	11
• Literature Review.....	13
○ Introduction: mTOR Pathway.....	13
○ Methods and Results: Use of mTOR inhibitors.....	21
○ Discussion and Conclusion.....	26
• Clinical Case Study.....	28
○ ID and Chief Complaint.....	28
○ History of Present Illness.....	28
○ Social/Family History.....	29

- Review of Systems.....30
- Physical Exams.....30
- Diagnostic Work.....32
- Assessment.....36
- Treatment Plan39
- Prognosis.....40
- Works Cited.....42

List of Tables

Table 1: Receptor Affinity and actions of various Vascular Endothelial Growth Factors	7
Table 2: mTOR Signalling in Polycystic Kidneys.....	10

List of Figures

Figure 1: PC1/PC2 role in cell signaling of renal cell and its effects.....	10
Figure 2: The effect of RAAS on the development of hypertension in ADPKD patients.....	13
Figure 3: Overview of mTOR Pathway	15
Figure 4: Han:SPRD Rat Model Studies	24
Figure 5: Han:SPRD Rat Studies Quantitative	25
Figure 6: Orally fed Rapamycin on Han:SPRD Rat Models	27
Figure 7: Renal Ultrasound of patients left kidney	30

Introduction: Overview of Disease

Polycystic Kidney Disease is a common genetic disorder characterized by the growth of multiple cysts in the kidney that can potentially culminate in end stage renal failure. If intervention is not taken, PKD eventually will result in death.

There are two main types of Polycystic Kidney Disease. The more common Autosomal Dominant Polycystic Kidney Disease (ADPKD) occurs with an incidence of 1:1000 individuals, and is generally characterized by cyst growth in kidneys, liver, pancreas and other organs. The disease is slow progressing and usually results in end stage renal disease around the age of 50³. The second and less common, Autosomal Recessive Polycystic Kidney Disease (ARPKD) occurs with an incidence of 1:20000 individuals, and is an infantile disease characterized by renal cyst formation and congenital hepatic fibrosis³.

The process of renal cyst growth in ADPKD patients is called cystogenesis. Although the exact mechanism of cyst growth is not known, it is commonly believed that mutations in the PKD1 or PKD2 genes are the underlying cause. Cystogenesis in ADPKD patients is similar to tumor growth: they both exhibit traits such as increased cell proliferation, changes in apoptosis and angiogenesis².

Currently the only options available for ADPKD patients are constant monitoring of cyst growth, renal function and blood pressure. In cases of end stage renal disease, kidney transplants or dialysis treatment are needed. Understanding the role of PKD1 and

PKD2 mutations in cystogenesis is very important in that it can potentially yield a possible alternative treatment option for PKD patients. Currently, studies are being done on alternative treatments that focus on altering or inhibiting angiogenesis of cyst growth in order to slow or even halt the progression of the disease. These alternative therapies include using vasopressin V2 receptor antagonists, mTOR inhibitors and the drug ocreotide to treat ADPKD. These treatments, although promising, still need more research to be conducted before they can be used ⁴.

Pathogenesis

Mutations in PKD1, PKD2 and PKHD1 are the underlying cause of cyst growth on PKD patients. The mutant proteins resulting from these mutations are implicated in altering normal cell processes in order to accelerate cyst growth. Polycystin-1 (PC1) and Polycystin-2 (PC2), proteins encoded by the PKD1 and PKD2 gene, negatively regulate the signaling molecules that elevate cellular growth rate. PKHD1 is the gene that encodes fibrocystin, and its mutation is implicated in ARPKD. Figure 1 highlights the role of PC1 and PC2 on signaling pathways in renal cells.

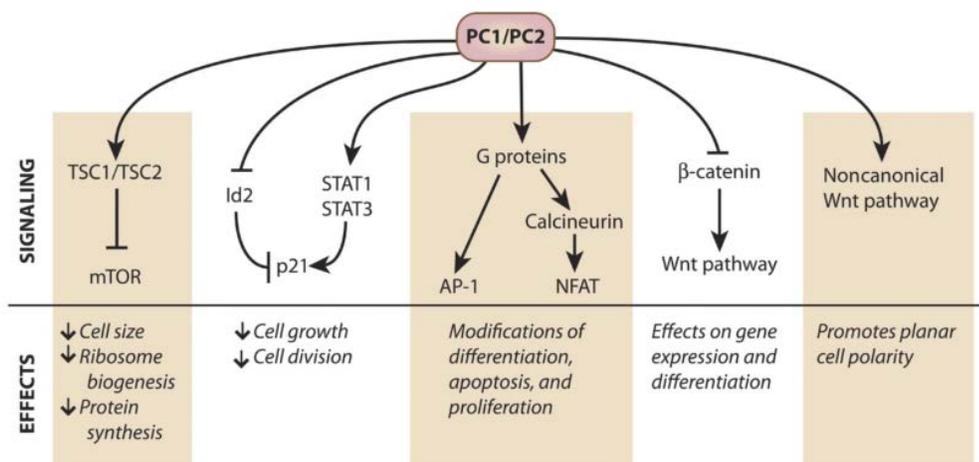


Figure 1: PC1/PC2 role in cell signaling of renal cell and its effects⁵

Source: *The Cell Biology of Polycystic Kidney Disease*

PC1 and PC2 are integral in regulating cell growth in kidneys. In PKD patients, these proteins are defective therefore cell growth is unregulated.

One of the key characteristics of PKD is the gross enlargement of kidneys due to the growth of multiple cysts. Cyst growth is similar to tumor growth in that both are highly active processes that require oxygen and nutrients to provide energy¹. New blood vessels and other supplementary structures need to be formed to support the requirements for cyst growth. These new blood vessels are formed by a process called angiogenesis. Angiogenesis is defined “by sprout formation or by splitting of a pre-existing blood vessel”². There are a number of growth factors that regulate angiogenesis. These include vascular endothelial growth factors (VEGF), angiopoietin-1 (ANG-1), angiopoietin-2 (ANG-2) and other various chemokines². These growth factors work together to ensure that angiogenesis occurs appropriately. Table 1 highlights some various VEGFs and their function.

Family Member	Receptor	Action
VEGF A	VEGFR-1/Flt-1 and VEGFR-2/Flk (with lower affinity)	Angiogenesis Endothelial cell migration Mitosis Permeability Chemotactic for macrophages and granulocytes
VEGF B	VEGFR-1/Flt-1	Embryonic angiogenesis
VEGF C	VEGFR-3/Flt-4	Mitosis, Migration, Differentiation, Survival of lymphatic endothelial cells
VEGF D	VEGFR-3/Flt-4	Lymphatic vasculature around broniole in lung
PlGF	VEGFR-1	Vasculogenesis Angiogenesis in ischaemia, Inflammation, Wound healing, Cancer related angiogenesis

Table 1: Receptor Affinity and actions of various Vascular Endothelial Growth Factors²
Source: *Angiogenesis and the Pathogenesis of Autosomal Dominant Polycystic Kidney Disease*

The process of angiogenesis is initiated by the binding of HIF-1 (hypoxia inducible factor) to an angiogenesis growth factor such as VEGF-A⁶. This usually occurs in regions of the body that are in a hypoxic (oxygen deprived) state. In PKD patients, the growing cysts restrict the oxygen flow to the kidneys thereby inducing a hypoxic state which promotes angiogenesis. VEGF is up regulated in hypoxic states due to the increased HIF-1 α levels.

According to Huang et al, the VEGF-A levels in ADPKD patients were found to be six times greater than age matched individual with normal renal function. Upon further examination, VEGF-A was detected in cyst epithelial cells. This finding shows that the growth factors are found primarily in the regions where cyst growth is evident. The study also showed a positive correlation with VEGF-A levels to the number of renal cysts and renal volume¹.

ANG-1 and ANG-2 are regulators in the angiogenesis process. ANG-1 is an agonist which down regulates angiogenesis whereas ANG-2 inhibits ANG-1 when VEGFs are not present. Hypertension results in an improper balance of ANG-1 and ANG-2 resulting in organ damage². This is extremely prevalent in PKD patients. Many novel treatment techniques for PKD is aimed at restoring the angiogenesis growth factor imbalance thereby inhibiting and/or retarding cyst growth in the kidney in hopes of preserving renal function.

One of the hallmark manifestations of PKD is hypertension. Numerous studies have shown that hypertension is more prevalent in PKD patients than in patients with any other renal disease⁷. Hypertension in PKD patients stem from the increased activation of the renin angiotensin-aldosterone system (RAAS).

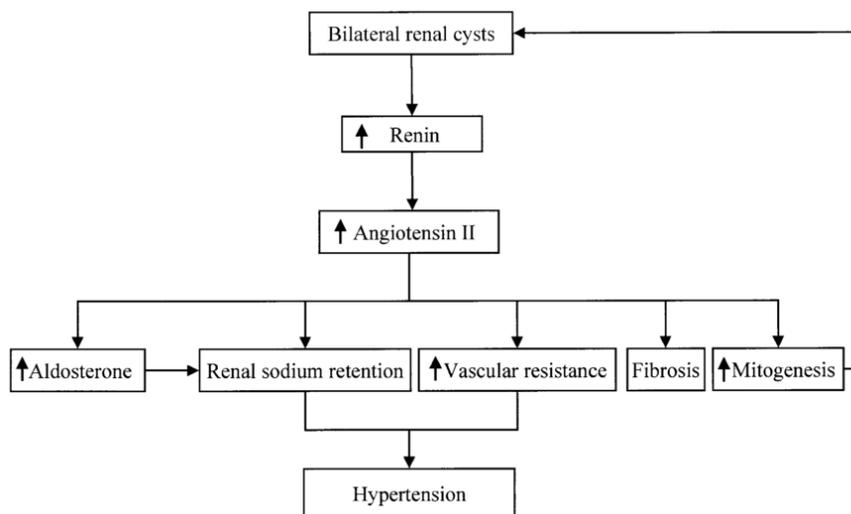


Figure 2: The effect of RAAS on the development of hypertension in ADPKD patients
 Source: *Hypertension in Autosomal-Dominant Polycystic Kidney Disease: Early Occurrence and Unique Aspects*

As seen in Figure 2, increased activity of RAAS not only affects blood pressure, it also promotes mitogenesis (increases mitosis) of the cysts. As cysts grow, renal arterioles start to compress leading to ischemia (restriction of blood supply to tissues⁷) which leads to hypertension and the up regulation of angiogenesis.

As PKD progresses, renal function is diminished. According to Dr. David Woo, this is a result of apoptosis of the nephrons in PKD patients. This was determined by noticing the presence apoptotic DNA fragmentation in polycystic kidneys. This DNA fragmentation was not seen in normal kidneys. It is believed that DNA fragmentation could have resulted from a mutation⁸. Although the exact mutation that resulted in the apoptotic DNA fragments is not known, this discovery provides a reasonable explanation to loss of renal function as PKD progresses.

Epidemiology

PKD affects both children and adults, with ADPKD affecting 1 in 1000 individuals and ARPKD affecting 1 in 10000 neonates and children. ADPKD accounts for about 3-4% of end stage renal disease cases; which ranks fourth among all kidney disease⁹. There is no known pattern of PKD in certain races or ethnicities.

Genetics

ADPKD is a dominant genetic disorder resulting from mutations in PKD1 or PKD2 genes. PKD1 and PKD2 encode for polycystin-1 and polycystin-2 respectively. PKD1 is located on the short arm of chromosome 16 and PKD 2 is located on the long

arm of chromosome 4. The majority of ADPKD cases result from PKD1 mutation. These patients often exhibit more cyst growth and more rapid deterioration of renal function⁴.

ARPKD is a recessive disorder resulting from mutation in the Polycystic Kidney and Hepatic Disease 1 gene (PKHD1). PKHD1 encodes for fibrocystin, which is “found to localize in the primary cilium and basal body of the renal and bile duct epithelium”⁴.

ARPKD is typically seen in younger patients and often results in congenital hepatic fibrosis. Unlike that of ADPKD, the majority of the ARPKD patients die from respiratory failure or sepsis⁴.

Symptoms

There are numerous symptoms associated with ADPKD, the most common being pain in the abdomen and/or lower back, hematuria (blood in urine), high blood pressure, increased size of abdomen and kidney failure¹⁰. The pain in abdomen region and the increased abdomen size is associated with the increased size of the kidney due to the growth of multiple cysts. The increased kidney size starts to push other internal organs, resulting in pain. The blood in urine is due to the occasional bursting of cysts in the kidney. Other symptoms seen in ADPKD patients include kidney/urinary tract infections and kidney stones¹⁰.

Symptoms associated with ARPKD include noticeably larger kidneys seen in neonates, hypertension, hematuria and proteinuria (abnormal amount of protein in urine). There are also a number of deformities of the face and spine⁴.

Clinical Features and Diagnosis

Patients are not usually diagnosed with ADPKD until the fourth or fifth decade of life. Before then, these individuals are usually asymptomatic. There are about 1-2% of cases where the patient has developed an early onset form of the disease. These individuals are characterized as exhibiting symptoms prior to the age of 15⁴. During this asymptomatic time, the kidney function tends to be stable and does not start to deteriorate until the kidney reaches a critical size. Once critical size is reached, kidney function rapidly declines⁴. When the kidney reaches critical size, patients tend to start feeling pain in the lower back/abdomen region, and exhibit occasional blood in urine.

ARPKD is diagnosed at much younger ages than ADPKD. Often diagnosed during the neonatal period, these patients tend to display symptoms of respiratory distress or noticeably large kidneys⁴. Many of these patients develop congenital hepatic fibrosis, which is characterized by increased fibrosis of portal tracts and the abnormal development of biliary ducts. These patients often die of respiratory complications rather than renal complications⁴. Abnormal lab finding indicative of ARPKD include elevated creatinine levels, hematuria, proteinuria and enlarged kidneys⁴. According to Halvorson et al, the later the onset of ARPKD symptoms in a particular patient, the better the outcome of the patient. Studies show survival rates for ARPKD patients that start to exhibit symptoms at age 9 rather than as an infant have been as high as 80%⁴.

Hypertension is a clinical feature especially important in PKD patients. Hypertension, defined as having a resting systolic/diastolic blood pressure of above 160/100 mmHg⁷, is prevalent in PKD patients. According to Ecker et al, increased blood

pressure commonly precedes loss of renal function. Furthermore, it has been found that hypertension is more prevalent in patients with PKD than patients with other renal diseases. Therefore, hypertension is a good indicator to determine if a patient has PKD and also an indicator for level of kidney function⁷.

In order to confirm that a patient has PKD, an ultrasound, computerized tomography (CT) scan, or a magnetic resonance imaging (MRI) scan is performed. These scans allow the physician to see the enlarged kidney and the presence of multiple cysts¹⁰. These scans also allows for the nephrologist to monitor the progression of the disease⁴. The patient's family history can also be referenced.

Treatment

There are currently no cures for PKD. The current treatments for PKD rely on treating symptoms and the clinical features of the disease. For cases of end stage renal failure, dialysis and/or kidney transplantation are needed.

Often fatalities due to PKD result not from the polycystic kidneys themselves but from numerous other complications resulting from the eventual buildup of toxic wastes in body. Therefore treatments for PKD are focused on preserving kidney function. The most common recommendations made by nephrologists include stopping smoking, restricting the consumption of caffeine and maintaining a healthy blood pressure⁴. Essentially, the healthier the individual, the better chance he or she will have with maintaining stable kidney function.

Treating hypertension is very important in preserving the function of the kidney. Severe hypertension can lead to ischemia in the kidney resulting in up regulation of angiogenesis. This leads to increased cyst growth which leads to hypertension and so on (Refer Figure 2). ACE inhibitors, such as Enalapril, inhibit RAAS and have been shown to be especially effective⁷. Other blood pressure medications, such as Norvasc, a calcium channel blocker, and atenolol, a β -blocker, are also effective in slowing the progression of the disease⁴.

There are a number of options to treat pain associated with the enlarged kidneys. Non-steroidal anti-inflammatory drugs (NSAIDs) should not be taken due its side effects on the kidney. Therefore narcotics usually are used, but only during minor episodes of severe pain. This is done to minimize addiction to the narcotics⁴. There are also surgical options that can potentially reduce pain. Cyst decortication is a surgical procedure that removes cysts. This surgery is usually performed laparoscopically. Though effective in the short term, this procedure has numerous side effects including worsened hypertension, post-operative bleeding, arrhythmia and even death⁴. This procedure is usually used in cases of severe pain. Another surgical option that is very effective in treating pain is renal artery embolization. This surgical procedure essentially blocks the renal artery by purposely forming an embolism. The procedure effectively renders the kidney useless, eliminating any remaining renal function (glomerular filtration rate is zero). Therefore, this procedure is primarily done on patients who are on dialysis and where transplantation is not possible. Unlike that of cyst decortication, this procedure is

very effective in treating pain and hematuria. It also has minimal side effects which include nausea, vomiting and temporary flank pain⁴.

In cases of urinary tract infections, antibiotics are prescribed. Cyst penetrating antibiotics such as trimethoprim-sulfamethoxazole and fluoroquinolone are commonly prescribed specifically to PKD patients⁴.

In cases of renal failure, dialysis and/or kidney transplantation is required. Dialysis is a machine that filters blood from all the toxins that a healthy kidney would usually filter. In essence the dialysis machine takes over the role of the kidneys. Dialysis treatment is often very restrictive on one's lifestyle. There are numerous dietary and fluid restrictions. Transplantation is often the best option for PKD patients in kidney failure. Post-transplantation, renal function improves significantly⁴. Furthermore kidney transplantation allows for the patient to essentially live a normal life with little to no restrictions, unlike those on dialysis. Kidney transplant recipients are usually placed on immunosuppressive drugs indefinitely to deter organ rejection.

Body of Review and Conclusions

Polycystic Kidney Disease is a prevalent disorder that afflicts millions of people worldwide. Currently there are no cures to the disease only treatments that help alleviate symptoms or to slow progression of renal failure. According to the US Department of Health and Human Services, as of November 2013 there are about 100,000 individuals waiting for a kidney transplant, and more and more people are being added every day as a result of PKD. Developing a cure for this disease is very important for these patients and

the many that have yet to find out they have the disease. Understanding cell signaling and processes involved in cyst development has shed light on possible treatments that can potentially cure the debilitating disease.

The use of mTOR inhibitors have been a promising alternative to the current therapies for PKD patients. Chapter 2 highlights the mTOR pathway in renal epithelial cell proliferation and how the use of mTOR inhibitors disrupts the progression of PKD.

Literature Review

The majority of Polycystic Kidney Disease cases result from a mutation in the PKD1 gene which encodes for the protein polycystin-1. The resulting defective polycystin-1 protein inappropriately interacts with another protein, tuberin, thereby up regulating the mTOR pathway in cyst lining epithelial cells of PKD patients¹¹. The mammalian target of rapamycin (mTOR) is a protein that regulates cell growth and protein synthesis via direct and indirect phosphorylation¹². Currently, studies have shown that the use of mTOR inhibitors such as sirolimus (rapamycin) are effective in slowing cyst growth, preserving renal function and inhibiting cell proliferation in PKD patients. The use of mTOR inhibitors offers us a better treatment option for PKD patients and also offers us a better understanding of the mechanism behind the abnormal cyst growth.

INTRODUCTION

The mTOR Pathway

Mammalian target of rapamycin (mTOR) is a signaling protein belonging to the serine/threonine kinase family that regulates cell growth, metabolism and survival. Its improper activation has been observed in numerous medical disorders including cancer and the aforementioned polycystic kidney disease¹³. mTOR signaling utilizes numerous intracellular and extracellular signals to promote cell proliferation.

mTOR is found in two major protein complexes: mTORC1 and mTORC2. These distinct classes both support cell growth and survival. mTORC1 specifically stimulates

anabolic processes such as protein and lipid synthesis. The overall function of mTORC2 is not well known but it has been noted that it promotes cell metabolism and cytoskeleton organization¹³. Due to their different interactions with rapamycin, mTORC1 is considered rapamycin sensitive and mTORC2 is considered rapamycin insensitive. Despite mTORC2 being rapamycin insensitive, it can still be inhibited by large amounts of rapamycin¹³.

Composition of mTOR complexes

mTORC1 is composed of five parts: mTOR, Raptor, mammalian lethal with Sec13 protein 8 (mLST8, also known as GbL), proline- rich AKT substrate 40 kDa (PRAS40), and Deptor. mTOR is the principle component, Raptor is the regulatory associated protein, mLST8 is another associated protein whose role is not known and PRAS40 and Deptor are down regulatory proteins of mTORC1¹³.

mTORC2 is comprised of six different proteins: mTOR, rapamycin-insensitive companion of mTOR (Rictor), mammalian stress-activated protein kinase interacting protein (mSIN1), protein observed with Rictor (Protor-1), mLST8 and Deptor. As with mTORC1, mTOR is the principle component and Deptor is the inhibitory protein. Rictor and mSIN1 interact together for protein stabilization. The role of Protor-1 is not entirely known, except for that it interacts with Rictor. Unlike with mTORC1, mLST8, though not entirely understood, is essential for the entire complex to function. In mTORC1, mLST8 seems to not be necessary for protein function¹³.

mTOR Signaling

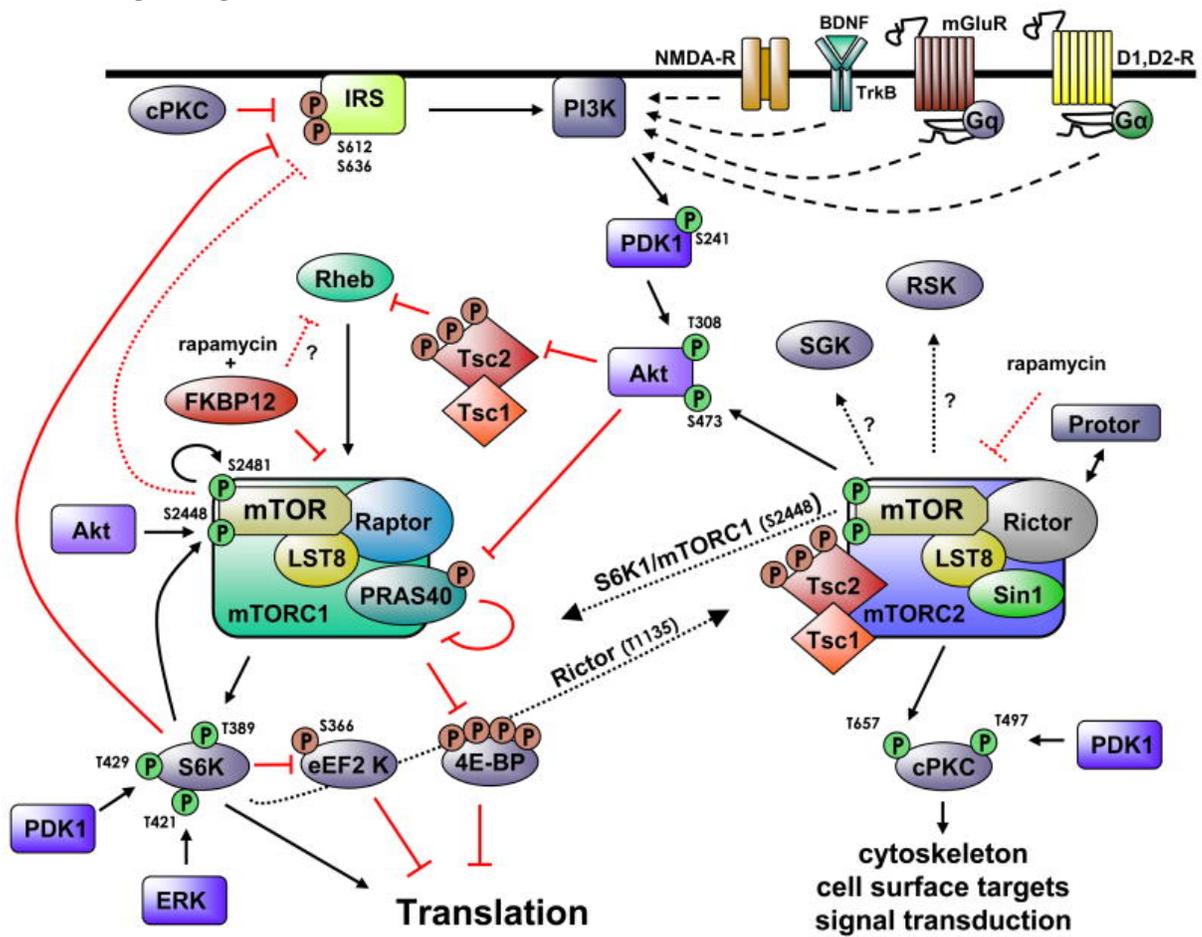


Figure 3a: Overview of mTOR Pathway – Highlights the activation of mTORC1 and the end results of its activation¹⁴.

Source: <http://www.anti-agingfirewalls.com/2011/03/04/the-many-faces-of-mtor-and-rapamycin/>

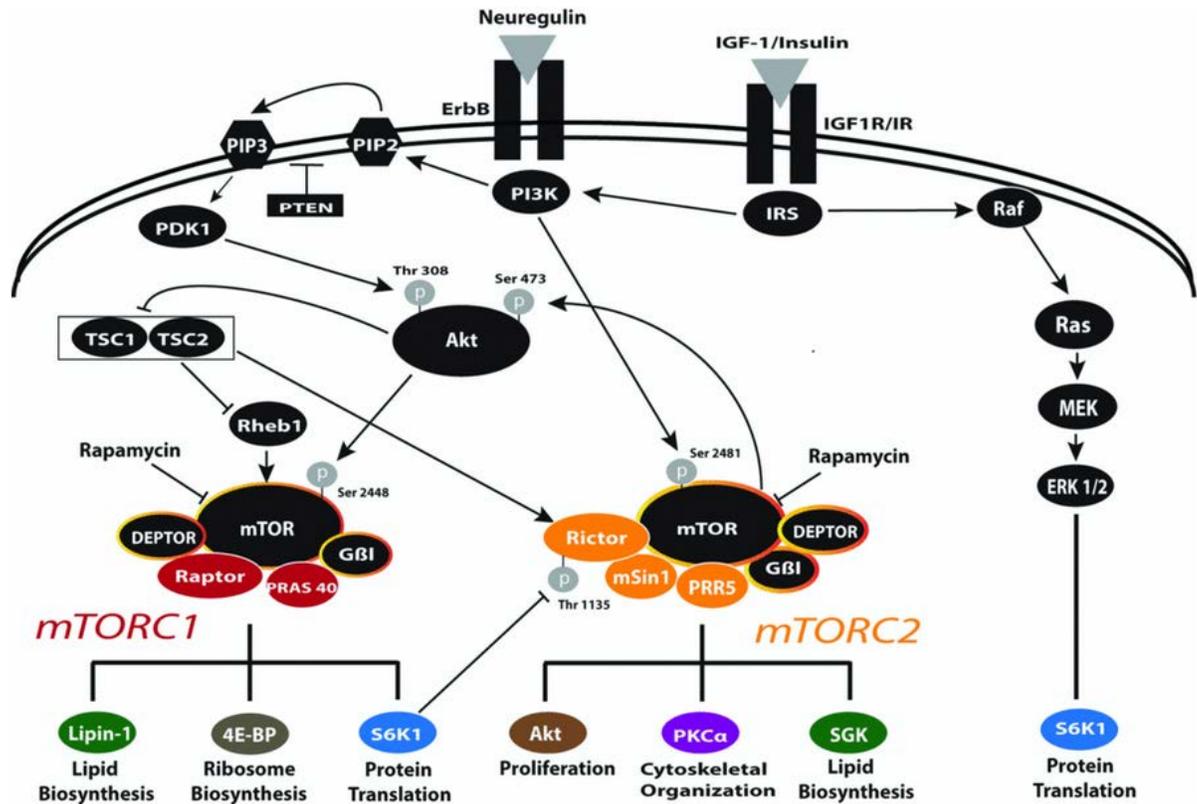


Figure 3b: Overview of mTOR pathway – Highlights how mTOR activation is initiated via IGF-1/insulin receptors and the various phosphorylations of downstream targets¹⁵

Source: <http://www.asnneuro.org/an/005/e108/an005e108f01.htm?resolution=HIGH>

Amino acid availability, presence of growth factors, states of hypoxia and energy stress regulate mTORC1 activity³. Through the use of various downstream regulators, mTORC1 promotes protein and lipid synthesis. One of the most important regulators for mTORC1 is the tuberous sclerosis complex (TSC). TSC is composed of two subunits, hamartin (TSC1) and tuberlin (TSC2)¹³. The TSC complexes act as down regulators for mTORC1. This is accomplished via the dephosphorylation of the GTP bound Rheb protein. Though the exact mechanism of Rheb and mTORC1 interaction is not known, it has been shown that the dephosphorylated Rheb protein fails to interact with mTOR1 thereby not activating it. When the TSC complexes are not present or are abnormal,

tuberous sclerosis occurs. Tuberous sclerosis is characterized by the presence of numerous benign tumors and a large number of disorganized cells¹³.

Growth factors such as insulin receptor substrates and insulin like growth factor-1 (IGF-1) strongly promote mTORC1 activity. These growth factors stimulate the insulin receptor pathways which in turn phosphorylates TSC2 via protein kinase B (PKB also known as AKT), which inactivates TSC2 (Figure 1a, 1b). This activates mTORC1. In addition, growth factors also activate mTORC1 in a TSC1/2 independent manner. This is accomplished by the growth factors directly activating AKT, which promotes phosphorylation and dissociation of PRAS40. PRAS40 is an inhibitor of mTORC1 activity therefore its removal results in mTORC1 activation¹³. As seen in Figure 1b, when insulin binds to the insulin receptor, the insulin receptor substrate (IRS) is activated and tyrosine kinase activity of the receptor is stimulated. As a result, phosphoinositide 3-kinase (PI3K) and AKT activity is increased thus resulting in mTORC1 activation. The activated mTORC1 represses the PI3K-AKT activity via a negative feedback mechanism¹³.

The energy level of the cell also plays a role in mTORC1 activity. When energy is low, AMP-activated protein kinase (AMPK), which is “a master sensor of intracellular energy status,” phosphorylates TSC2, thereby increasing GAP activity towards the Rheb protein, eventually resulting in reduced mTORC1 activity¹³. This is done to divert energy resources to other vital cell functions rather than cell growth and proliferation.

Oxygen deprived states restrict mTORC1 activity. The reduction of ATP which often results from hypoxia activates AMPK and follows the process stated above.

Hypoxia also down regulates mTORC1 via regulation of DNA damage 1 (REDD1).

REDD1 restricts mTORC1 by releasing TSC2 from growth factor associated proteins¹³. It is believed that this process evolved to save energy in conditions where growth factors are present but oxygen is not¹³.

Presence of amino acids up regulate mTORC1, however it is done independent of TSC1/2 activity. Leucine, which is critical for mTORC1 stimulation, is transported into the cell via the export of glutamine. In the presence of amino acids such as leucine, Rag proteins interact with mTORC1. The Rag proteins bind to Raptor of mTORC1 which causes the entire complex to relocate near its activator Rheb protein¹³.

Protein synthesis is up regulated by phosphorylating the eukaryotic initiation factor 4E (eIF4E)- binding protein 1 (4E-BP1) and the p70 ribosomal S6 kinase 1 (S6K1)¹³. This then inhibits the binding of 4E-BP1 to eIF4E which allows for ribosomal translation. Furthermore, the activated S6K1 stimulates mRNA formation, elongation, and the translation of ribosomal proteins (Figure 1a)¹³.

mTORC1 also limits autophagy. According to Laplante et al, autophagy is “catabolic process that is important in organelle degradation and protein turnover.” Autophagy is a natural process that often occurs when resources are limited in order for the cell to continue anabolic processes such as protein synthesis. Autophagy inhibition is the result of the interaction of the activated mTORC1 with unc-51-like kinase 1 (ULK1), autophagy-related gene 13 (ATG13) and focal adhesion kinase family-interacting protein of 200 kDa (FIP200). Though the exact mechanism is not known, studies have shown

that ULK1 and ATG13 is phosphorylated by mTORC1 thereby inactivating them and the autophagy process¹³.

mTORC1 positively regulates lipid synthesis. mTORC1 up regulates transcription factors involved in genes that encode proteins for lipid and cholesterol synthesis. Sterol regulatory element binding protein 1 (SREBP1) and of peroxisome proliferator-activated receptor-g (PPARg) are two transcription factors specifically regulated by mTORC1¹³. Furthermore, lipin-1, a protein involved in lipid synthesis is phosphorylated by mTORC1 thus stimulating lipid biosynthesis (Figure 1b)¹³.

mTORC2 activity is essential for cell survival, metabolism and proliferation. It activates AKT via the phosphorylation at two sites: first by PDK1 at the Thr308 site, and second by mTORC2 at the Ser473 site¹³. Once phosphorylated, the activated AKT inhibits the TSC1/2 complex which promotes mTORC1 activity. mTORC2 activity is also important in cytoskeletal organization. Though the exact mechanism is not known, it has been shown that mTORC2 phosphorylates protein kinase C α (PKC α) and paxillin, a signal transduction adapter protein, both of which are important in cytoskeletal organization¹³. mTORC2 activity is exemplified in Figure 1b.

mTOR activity in Polycystic Kidney Disease

It is well known that in PKD, mTOR activity is significantly up regulated. A number of studies show that the defective polycystin-1 (PC1) inappropriately interacts with TSC2, a natural inhibitor of mTORC1, thereby restricting its activity.

In healthy renal cells, the cytoplasmic tail of PC1 forms a complex with tuberlin which functions to repress mTOR activity^{11,16}. Studies show that PC1 protects TSC2 from inactivation from AKT and that it interacts with TSC2 independent of AMPK activation of TSC2¹⁶. In PKD patients, the PC1 is defective; therefore, it cannot form the complex with TSC2 and repress mTOR activity.

Further studies indicate the increase levels of IGF-1 in cysts of polycystic kidneys¹⁷. As seen in Figure 1b, IGF-1 activates the IGF1/insulin receptor which initiates the downstream phosphorylation of various targets ultimately stimulating mTOR activity.

Table 1 highlights the effects of aberrant mTOR signaling in polycystic kidneys and the model organisms used to determine the end results. All of these problems contribute to epithelial cyst growth and proliferation in polycystic kidneys.

Signal	Model
Increased IGF-1 mRNA	Pcy mouse
Increased IGF-1 protein	Han:SPRD rat
Increased p-Akt protein	PKD-1 ^{-/-} mice Han:SPRD rat
Cytoplasmic tail of polycystin-1 co-localizes with mTOR and co-localizes and interacts with tuberlin	MDCK cell clones
Phospho-mTOR and p70S6K are induced in cyst-lining epithelial cells	Human kidneys
Increase in p70S6K protein and total S6K is reduced by rapamycin	Han:SPRD rats

^amTOR, mammalian target of rapamycin.

Table 2: mTOR Signalling in Polycystic Kidneys – Numerous studies were done on various model organisms to determine the negative effects of abnormal mTOR activation in PKD patients. The negative consequences are shown in the table above.

Source: Edelstein, Charles L., *Mammalian target of rapamycin and caspase inhibitors in polycystic kidney disease*

METHODS AND RESULTS

Effects of Rapamycin on PKD

Rapamycin is a known inhibitor of the mTOR pathway. It is derived from the soil bacteria *Streptomyces hygroscopicus*. Rapamycin directly inhibits mTORC1 activity and possibly can even inhibit mTORC2 activity at higher doses (refer Figure 1a, 1b)¹³.

Therefore, it has been proposed that the use of rapamycin can be used to slow down the progression of PKD by inhibiting the mTOR pathway. This hypothesis has been shown somewhat valid by various experiments on rat models.

Han:SPRD rat model study

Three studies were done on Han:SPRD rats in order to determine the effects of inhibiting the mTOR pathway in rats with PKD. In the study there were four experimental groups: the first group consisted of wildtype male rats (+/+), the second group consisted with wildtype male rats treated with rapamycin (+/+ rapa), the third group consisted of male rats with PKD that did not receive rapamycin treatments (Cy/+) and the fourth group consisted of male rats with PKD that received rapamycin treatment (Cy/+ rapa). The first two groups served as controls. The rats had free access to tap water and food^{12,17,18}.

The first experiment determined rapamycin effects on rats when injected intraperitoneally (injected directly into body cavity)¹⁸. The rapamycin treated groups were administered with 0.2 mg drug/kg body weight per day of rapamycin intraperitoneally from 4 – 8 weeks of age. The other two groups were injected with only

ethanol vehicle. After 8 weeks the kidneys from the mice were examined¹⁷. Both kidneys were removed and weighed. The left one then was “fixed in 4% paraformaldehyde in PBS for 120 min and then put into 70% ethanol and embedded in paraffin for histologic examinations”¹⁸. The resulting kidneys are shown in Figure 2.

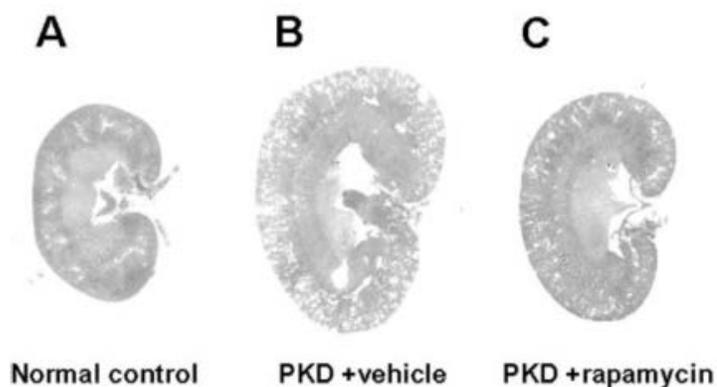


Figure 4: Han:SPRD Rat Model Studies – The kidneys from the mice in each of the three experimental groups. A is a kidney from the normal control group. B is a kidney from the PKD mice that were not treated with rapamycin. It shows significant cyst growth in the renal tubular cells as seen by the increased size of the kidneys and the presence of increased growth (cysts) surrounding the kidney. C is a kidney from the PKD mice that were treated with rapamycin. It is clearly evident that rapamycin slowed the growth of cysts in the kidneys as seen by the decrease of cysts surrounding the kidney. Source: Edelstein, Charles L., *Mammalian target of rapamycin and caspase inhibitors in polycystic kidney disease*

Rapamycin treatment in these rats showed significant effects on polycystic kidneys.

Rapamycin treated rats clearly showed repressed renal growth. Specifically it showed a 65% decrease in total kidney/total body weight ratio, 40% decrease in cyst volume density as compared to the polycystic kidneys without rapamycin treatment. The decrease in total kidney/total body weight ratio and cyst volume is evident of suppressed cystogenesis. It is clear that rapamycin treatment decreased the number of cysts in the renal tubular and epithelial cells of the polycystic kidneys which accounts for the

decrease in cyst volume density and total kidney/body weight ratio. In addition, the blood urea nitrogen (BUN) of the kidneys was tested using a Beckman autoanalyzer¹⁸. The rapamycin treated polycystic kidneys showed 59% decrease in BUN¹⁷. This decrease in BUN is indicative of improved renal function. These results are showed in Figure 3 below.

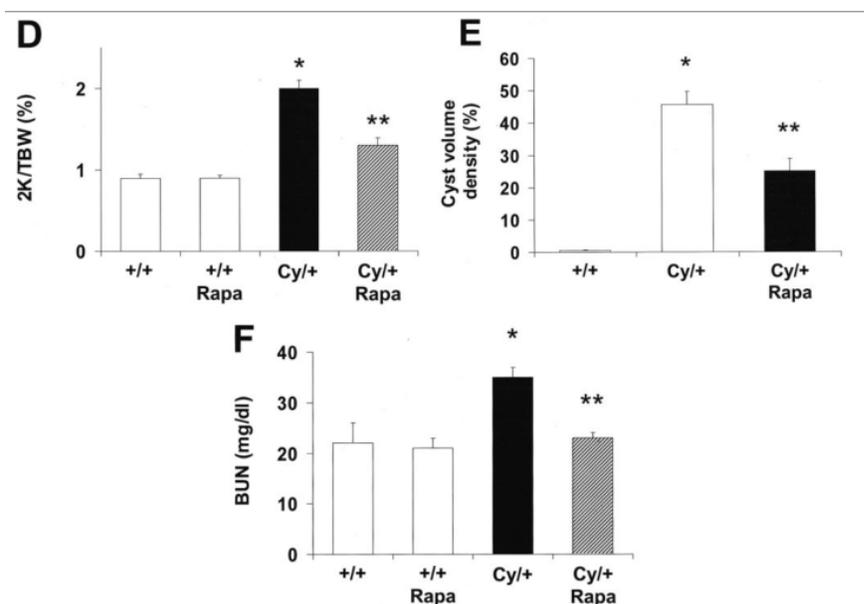


Figure 5: Han:SPRD Rat Studies Quantitative Analysis – The above figures (D-E respectively) show the total kidney/body weight ratio (2K/TBW), cyst volume density and BUN levels for all groups tested. +/+ is control group and the Cy/+ is the PKD afflicted group. Rapamycin treated groups are indicated on the figures (rapa). (D) The total kidney/total body weight ratio was unaffected by rapamycin in +/+ rats. Cy/+ rats had a more than doubling of kidney size compared with +/+ controls. Rapamycin reduced the kidney enlargement in Cy/+ rats by 65%. (E) The cyst volume density was significantly increased in vehicle-treated Cy/+ rats. Rapamycin reduced the cyst volume density by 40%. (F) BUN was unaffected by rapamycin in +/+ rats. Cy/+ rats exhibit kidney failure like symptoms as indicated by almost a doubling in BUN levels. In the Cy/+ rats treated with rapamycin, BUN levels were not nearly as increased as in Cy/+ rats without rapamycin treatment¹⁸.

Source: Tao et al., *Rapamycin Markedly Slows Disease Progression in a Rat Model of Polycystic Kidney Disease*

A second study was done on the same types of rats, except this time rapamycin was fed orally. The experimental group was given 2 mg drug/kg body weight orally per day via drinking water for three months¹². The results were similar to the first experiment in that there was an overall decrease in BUN, kidney size and cyst volume density. According to Edelstein, “there was a 39% decrease in BUN, a 34% decrease in serum creatinine, a 26% decrease in kidney size, and an 18% decrease in cyst volume density in PKD rats that were treated with rapamycin” orally. The results are displayed in Figure 4.

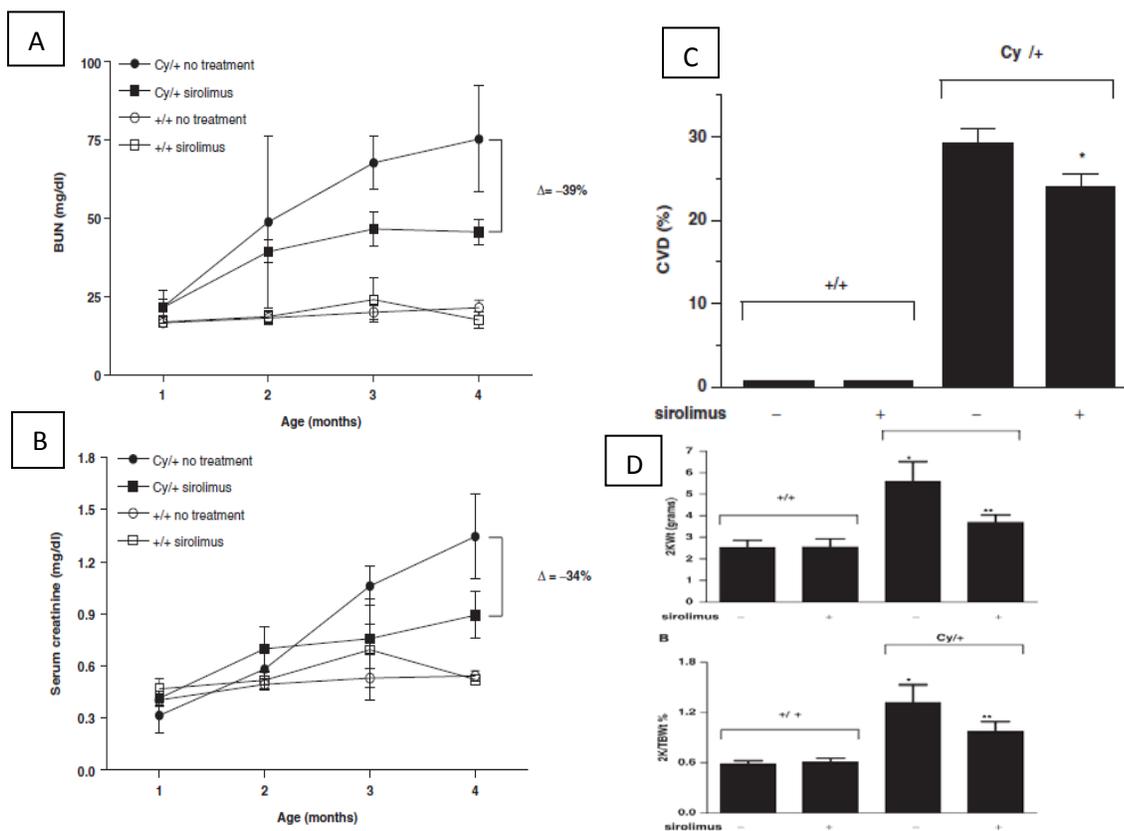


Figure 6: Orally fed Rapamycin on Han:SPRD Rat Models – A and B show BUN and serum creatinine levels from the four groups respectively, C and D show the cyst volume density (CVD) and total kidney/body weight ratio of the four groups respectively. Sirolimus (rapamycin) treatment is indicated on the graphs.

A shows a 39% difference in the BUN in Cy/+ without rapamycin treatment when compared to the Cy/+ with rapamycin. B shows a 34% difference in in serum creatinine levels in Cy/+ without rapamycin treatment when compared to the Cy/+ with rapamycin. In both graphs, it is evident that BUN and creatinine levels were much higher in Cy/+ rats than the +/+ rats. C shows that CVD in +/+ rats were essentially unaffected with rapamycin treatment. Cy/+ rats showed increased CVD with the rapamycin treated rats showing a 18% smaller CDV that the untreated rats. D shows that the 2k/TBW ratio in +/+ rats were much smaller than the Cy/+ rats. Rapamycin treatment did not affect the ratio in +/+ rats. Cy/+ rats with rapamycin exhibited kidneys that were 26% smaller than the untreated rats¹².

Source: Wahl et al., *Inhibition of mTOR with sirolimus slows disease progression in Han:SPRD rats with autosomal dominant polycystic kidney disease (ADPKD)*

A third study was done on these rats, except this time everolimus was used instead of rapamycin. This study was done to determine whether other mTOR inhibitors would cause the same effects as rapamycin. Everolimus is a derivative of sirolimus (rapamycin) and follows a similar mechanism as sirolimus in inhibiting the mTOR pathway. The experimental PKD rats were given 3ng drug/kg body weight per day for 5 weeks. Edelstein reports that “there was a 48% decrease in cyst volume density, a 30% decrease in BUN, and a 24% decrease in body weight in PKD rats that were treated with everolimus.”

No matter the method of ingestion of mTOR inhibitors or the type of mTOR inhibitor used, the PKD rats treated with mTOR inhibitors showed significant benefits from these drugs. However, treatment with rapamycin did not completely suppress the progression of the disease but rather slow the progression and prolong renal function (Figures 2 – 4).

DISCUSSION AND CONCLUSION

The studies on Han:SPRD rats showed the potential benefits of the use of mTOR inhibitors for PKD treatments. These results, though promising, still are not enough to become a viable treatment option for PKD patients. The results from the use of mTOR inhibitors in humans with PKD are not as impressive as in mice or rats. Sirolimus and similar drugs are immunosuppressants often prescribed to organ transplant recipients¹¹. The immunosuppressive effects can cause other numerous problems such as the emergence of opportunistic pathogens. Therefore, the amount of mTOR inhibitors needed to retard the progression of PKD might be too great for patients to tolerate. In addition, the overall decline of total kidney volume does not necessarily correlate with improved glomerular filtration rate (GFR) in humans¹⁹. As a result it is hard to determine whether mTOR inhibitors directly improve GFR or if it affects a supplemental mechanism that may or may not improve overall renal function. Furthermore, PKD progresses much more slowly in humans than in mice or rats (decades compared to weeks). As a result, the effects of mTOR inhibitors on PKD kidneys in humans are hard to distinguish¹⁹.

The mTOR pathway is a highly complex and intricate system important in the pathogenesis of PKD. Hypothetically, inhibiting this pathway potentially can impede the progression of this disease. Unfortunately more studies need to be conducted in order to determine its efficacy in treating the disease.

Future research includes treatments targeting other underlying causes of PKD; for example targeting the fluid secretion in renal cysts. It is believed that fluid secretion into the cyst lumen is mediated by the CFTR chloride channels which is stimulated by

cAMP⁵. A possible therapy that could be researched is the use of mTOR inhibitors in conjunction with drugs that regulate cAMP levels.

*Clinical Case Study***Chief Complaint:**

Max Powers is a 29-year-old Caucasian male that works in health care and presents for an annual evaluation and a new complaint of persistent high blood pressure as measured by himself on several occasions.

History of Present Illness:

Mr. Powers is a 29-year-old Caucasian male that presented to the office for his annual exam and a new complaint of persistently elevated blood pressure on multiple occasions. He works in a local hospital as a nurse and began to measure his blood pressure periodically 2 months ago after developing headaches several times per week. He notes that his blood pressure ranges from 130-150/80-100 every day and does not correlate with stress, time of day, or whether he is on or off shifts at the hospital. Mr. Powers states that he has not been evaluated or seen a physician for several years but does remember being told that his blood pressure was somewhat elevated in the past and opted to try improving his blood pressure through a low sodium-healthy diet and exercise. He states that while he has been able to somewhat improve total weekly exercise, he has only made some minor improvements to his diet, which primarily included cutting out fast food and take out foods.

On further questioning, he denies any visual changes/deficits, chest pain, palpitations, diaphoresis (sweating), shortness of breath, flank pain/dysuria/hematuria, dizziness/lightheadedness, weakness/fatigue. He also denies any illicit drug use, does not

smoke, and drinks only occasionally in moderate amounts. His only medications include Claritin 10mg a day only during allergy season. When he feels really miserable he may take an additional one to two capsules of 25mg Benadryl (diphenhydramine). He states that this treatment for his seasonal allergies is working.

Medications: Claritin (10mg a day) only during allergy season, occasional Benadryl (25mg) only if necessary

Allergies: No known drug allergies (NKDA)

Past Medical History: Prior hypertension diagnosis (opted to manage with diet and exercise), seasonal allergies

Social and Family History:

As noted above, he denies smoking or any illicit drug use. He drinks alcohol only occasionally and usually at parties or social functions. However, he denies ever drinking over his limit. Max Powers is an otherwise healthy individual who habitually works out every day. He works in the local hospital as a nurse. He lives with his girlfriend of two years in an apartment in the suburbs. He primarily has a Pescetarian diet, however he occasionally eats other meat products.

For family history he stated that his father died at the age of 62 due to a heart attack and vaguely remembers that his father had kidney cysts. His mother has a history of hypertension. He has a younger sister that is healthy. There is no history of any forms of cancer or diabetes.

Review of Systems:

General: No fever or chills

HEENT: No irritation or photophobia, ringing in ears (tinnitus), sore throat or dysphagia

Cardiovascular: no shortness of breath or chest pain

Respiratory: Denies coughing or trouble breathing

Gastrointestinal: Denies irregular bowel movements or abnormal appetite

Genitourinary: denies hematuria, dysuria or incontinence

Musculoskeletal: denies any joint or muscle pain

Psych: No mood swings, anxiety or depression. Some stress due to work

Neuro: occasional mild headaches

Physical Exam:

Max's vital signs, as recorded by the nurse, are as follows:

Height: 72"	Weight: 169lbs	Blood Pressure (systolic/diastolic):
152/91	Temperature: 98.4 °F	BMI: 23
	HR: 74	RR: 14

Physical exam findings for Max are as follows:

General: Patient appears healthy and alert. No apparent distress.

HEENT: Pupils are round and reactive to light, sclera are clear, No apparent ocular discharge, no visual or hearing deficits. No nasal obstruction or discharge, no apparent nosebleeds or hoarseness of voice. Fundoscopic exam was normal, no signs of Arterio-venous nicking.

Neck: supple, no carotid bruits, trachea midline, no lymphadenopathy

Respiratory: No shortness of breath, no wheezing or crackles or rhonchi (clear to auscultation bilaterally)

Cardiovascular: Normal heart rate and rhythm, normal S1 and S2, no murmurs, rubs or gallops. No peripheral edema

Gastrointestinal: Normal bowel sounds, no tenderness to palpation, no rebound or guarding, no masses or hepatosplenomegaly.

Back: Mild costovertebral angle tenderness on left greater than right, no midline tenderness

Genitourinary: no rash, erythema, swelling or lesions noted, no scrotal or testicular masses, no penile discharge

Musculoskeletal: no restriction in movement, all limbs have complete range of motion. No cyanosis or clubbing

Skin: No visible rashes, lesions or ulcerations

Neurological: Normal proprioception and gait. All reflexes are normal. Cranial nerves 2-12 are intact. Motor and sensory are grossly intact.

Diagnostic Work:

HEMATOLOGY:

<u>CBC</u>	<u>Actual</u>	<u>Normal Range</u>
WBC	7.0	4.0-10.5 K/ μ l
RBC	4.7	4.14-5.8 M/ μ l
Hemoglobin	13.9	12-16g/dL
Hematocrit	40.3	37-47%
Mean Corpuscular Volume (MCV)	86.2	77-97fL
Mean Corpuscular Hemoglobin (MCH)	27.5	37-33pg
MCHC	32.3	30-35g/dL
Red Cell Distribution Width (RDW)	14.0	12.0-16.2%
Platelet Count	188	150-400k/ μ L
<u>Differential:</u>		
Neutrophils	67.3	44-72%
Abs Neutrophils	6.0	1.8-7.7K/ μ L
Lymphocytes	29.7	22-41%
Abs Lymphocytes	3.2	1-4.8K/ μ L

Monocytes	2.0	1-9%
Eosinophils	0.4	0-6.0%
Basophils	0.5	0.5-1.0%

CHEMISTRY:

Comprehensive Metabolic Panel:

Sodium	138	135-145mmol/L
Potassium	4.6	3.6-5.5mmol/L
Chloride	108	96-112mmol/L
CO ₂	25	20-33mmol/L
Anion Gap	5.0	
Glucose	98	65-99mg/dL
Blood Urea Nitrogen (BUN)	32	6-24mg/dL
Creatinine	1.5	.76-1.27mg/dL
GFR Non-African American	58	>59ml/min/1.73
Calcium	9.8	8.4-10.2mg/dL
Aspartate Amino trans	18	12-45U/L
Alanine Amino trans	17	2-50U/L

Alkanine Phosphatase	79	30-99U/L
Bilirubin Total	0.8	0.1-1.5mg/dL
Albumin	4.1	3.2-4.9g/dL
Total Protein	6.8	6.0-8.2g/dL
Globulin	2.7	1.9-3.5g/dL
A/G ratio	1.52	
Phosphorus	3.0	2.5-4.5mg/dL
Magnesium	1.7	1.5-2.5mg/dL
LIPIDS		
Cholesterol	151	<200mg/dL
Triglycerides	135	<150mg/dL
HDL	49	>40mg/dL
LDL	75	<100mg/dL
URINALYSIS:		
Color	slight yellow	
Appearance	clear	
Specific Gravity	1.015	<1.035

pH	6.0	5.0-8.0
Glucose	Negative	Negative
Ketones	Negative	Negative
Bilirubin	Negative	Negative
Blood	Trace	Negative
Protein	Trace	Negative
Nitrites	Negative	Negative
Leukocyte Esterase	Negative	Negative
WBC	2-5/hpf	none
RBC	20-30/hpf	none
Epithelial Cells	none	none
Bacteria	none	none
Dysmorphic Red Cells	none	none

RENAL ULTRASOUND REPORT:

Findings: Enlarged kidneys (14-16cm in length, 8-10cm in width), with three bilateral renal cysts on the left kidney (sizes varying from 2-5cm). The cysts are non-communicating and the kidneys do not have smooth contours. There are no cysts on liver or spleen. No renal artery stenosis was noted.



Figure 7: Renal Ultrasound of patients left kidney – There is a presence of 3 renal cysts on his left kidney which points to possible ADPKD.

Assessment

Max is a 29 year old male with past medical history of persistent hypertension. For a relatively healthy individual at such a young age, this raised numerous red flags. A hypertension workup was done in order to figure out the cause of his hypertension. The workup included a complete blood count with chemistry panel and lipid panel, urine analysis, and a renal ultrasound. His blood test indicated possible renal dysfunction due to abnormal BUN, creatinine and GFR. The urine analysis showing trace amounts of blood further confirmed this theory. The renal ultrasound showed the presence of multiple cysts which are likely contributing to his renal dysfunction. Furthermore the ultrasound noted no renal artery stenosis. A lipid panel was done in order to assess cardiovascular disease risk in a new patient with Stage 1 hypertension. His lipid values were within normal ranges.

Differential Diagnosis

- Autosomal Dominant Polycystic Kidney Disease
- Multiple Benign Cysts
- Acquired Renal Cystic Disease
- Tuberous Sclerosis
- Medullary Cystic Disease
- Autosomal Recessive Polycystic Kidney Disease

Multiple Benign Simple Cysts – Multiple benign cysts is relatively common in the adult population. This is not likely the case with Max because it is not common in a patient under the age of 30 and it is generally found in a more elderly population ²⁰.

Acquired Renal Cystic Disease – Characterized by the developments of many fluid filled cysts in patients with no history of hereditary cystic disease ²¹. This is probably not the case with Max due to the presentation of his kidneys. Kidneys of Acquired Renal cystic disease are usually small and of normal size with smooth contours, whereas Max's kidneys are abnormally large and does not have smooth contours ²⁰.

Tuberous sclerosis – Disease characterized by the growth of numerous benign tumors in the brain and other vital organs such as the kidneys, eyes or skin. Many patients with tuberous sclerosis often present with multiple cysts in the kidney. Diagnosis of tuberous sclerosis “requires two major features (renal angiomyolipoma, facial angiofibromas or forehead plaques, nontraumatic unguinal or periungual fibroma, three or more hypomelanotic macules, shagreen patch, multiple retinal nodular hamartomas, cortical

tuber, subependymal nodule, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangioleiomyomatosis) or one major plus two minor features (multiple renal cysts, nonrenal hamartoma, hamartomatous rectal polyps, retinal achromic patch, cerebral white matter radial migration tracts, bone cysts, gingival fibromas, "confetti" skin lesions, multiple enamel pits)"²⁰. In Max's case, the presence of multiple cysts is the only symptom; therefore he does not have tuberous sclerosis.

Medullary Cystic Disease – condition where cysts grow in the medulla of the kidney eventually leading to end stage renal failure. Kidneys usually are normal sized. Patients with medullary cystic kidney disease tend to also have hyperuricemia and gout²⁰. Max probably does not have this disease because he does not have gout like symptoms.

Autosomal Recessive Polycystic Kidney Disease (ARPKD) – Polycystic kidney disease found primarily in infants or children. It is caused by a mutation in the PKDH1 gene. Patients with ARPKD often present with other complications as well including congenital hepatic fibrosis⁴. Unlike in ADPKD, extrarenal cysts are not as common. Severe systemic hypertension is prevalent in young patients, however the hypertension seems to subside as the patient ages with some patients even returning to normotensive states⁴. Due to the age of Mr. Power's is experiencing his symptoms, and the lack of symptoms Max is experiencing, ARPKD does not seem likely.

Diagnosis

After careful review, Mr. Powers was diagnosed with Autosomal Dominant Polycystic Kidney Disorder. According to Max's CMP work up, he had elevated BUN

and creatinine levels which indicated renal dysfunction. Furthermore, the urine analysis which showed trace amounts of blood which also led me to believe that there were some kidney complications. According to Halvorson et al, the presence of three or more cysts either unilaterally or bilaterally is adequate to diagnose ADPKD in patients between 15-30 years of age. Similarly patients aged 40-59 require the presence of at least two cysts on each kidney, and patients aged 60 or above require at least four cysts in each kidney (2010). As seen on the ultrasound report, Mr. Powers has three bilateral renal cysts on his left kidney. Furthermore, Max mentioned that he does vaguely remember that his father did have cysts in his kidneys. The presentation of Max's kidneys and the test results make all the other diagnoses unlikely. Genetic testing could also be used to solidify the diagnosis and also determine whether Max has a PKD1 or PKD2 mutation.

Treatment Plan

Unfortunately, there is no cure for ADPKD. The best treatment plan is to prolong renal function as long as possible and if Max develops end stage renal disease (Stage 5 CKD), he will need to be placed on dialysis and eventually need a renal transplant.

The most important step that we can take with regards to prolonging renal function is to keep Max's hypertension in check. According to the JNC 8, in patients with chronic kidney disease and older than 18 years of age, treatment with ACE inhibitors or Angiotensin II receptor blockers (ARB) is needed if the patient has a blood pressure greater than 140/90²². To do this, an ACE inhibitor such as Lisinopril was prescribed. According to Halvorson et al, some studies have shown that ACE inhibitors with ARB

can retard the progression of renal dysfunction in ADPKD patients (2010). Therefore, drugs like Valsartan can also be prescribed.

Usually in ADPKD patients, statins are also prescribed to protect cardiac function, however in Max's case, since his cholesterol is in check, statins do not seem necessary²³. However, if his cholesterol levels start to increase, a statin will be prescribed.

In addition, treatment of ADPKD also involves the treatment of symptoms such as pain in the abdominal region. For dull and minor pain or discomfort, Tylenol is recommended. If pain becomes too unbearable for Max, a short course of narcotic analgesic should be prescribed. NSAIDS should be avoided due to their negative effects on the kidneys and its reducing effect on ACE inhibitors. In extremely severe cases, cyst decortication may also be considered⁴.

With regards to his mild headaches, hopefully treatment of his hypertension will resolve the issue. Also he was asked to improve his sleeping as it may also be a contributing factor. If he wants, Tylenol can be used to alleviate pain.

Prognosis

Max's renal function will need to be regularly monitored. His kidney function will need to be tested regularly by following his BUN, creatinine and GFR levels. Many ADPKD patients die not from the defective kidneys, but rather from secondary complications with the most common being heart disease. Therefore cardiac function should also be regularly monitored. Currently he is in Stage 3 Chronic Kidney Disease

based off of his GFR (within GFR 30-59ml/min)²⁴. If he enters Stage 4 CKD (GFR 15-30ml/min), it is recommended that he sees a nephrologist. If he starts to go into end stage renal disease (GFR <15ml/min), his name will be placed on the kidney transplant list. He will also be placed on dialysis. He will need a kidney transplant.

Lifestyle steps Max should take are to consume a low salt and protein diet, and exercise regularly⁴. He should also increase fluid intake. Furthermore he should constantly monitor his blood pressure and let us know if it does not decrease. In addition, he may want to start talking to friends and family about his situation and the need for a possible kidney transplant.

Furthermore, Max may want to consult a genetic counselor. Since ADPKD is an autosomal dominant disease, he has 50% chance of passing it on, should he decide to have kids. Furthermore, since his father is believed to have kidney cysts, there is a strong possibility that he had ADPKD and died from a heart attack that was induced by his failing kidneys. His sister might also want to be tested for ADPKD so she can start taking the necessary precautions if needed. She can obtain a genetic test in which the PKD mutation in Max is determined and then test to see if she has the mutation as well.

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