

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



# Angiogenesis and the Pathogenesis of Autosomal Dominant Polycystic Kidney Disease

Berenice Reed and Wei Wang

*University of Colorado Anschutz Medical Campus,  
USA*

## 1. Introduction

Occurring with an incidence between 1/400 – 1/1000 live births autosomal dominant polycystic kidney disease (ADPKD) is the most common potentially lethal genetic disorder affecting the kidney (Eccer et al., 2007). The disease results from mutation in either of two genes *PKD1*, located on chromosome 16p13.3 or *PKD2*, located on chromosome 4q21 and is inherited in an autosomal dominant manner (European Polycystic Kidney Disease Consortium, 1994; Mochizuki et al., 1996). The resulting disrupted expression of the respective encoded proteins polycystin 1(PC1) and polycystin 2(PC2) leads to development of multiple fluid filled cysts in the kidney. As the cysts continue to grow throughout life the normal kidney parenchyma is gradually lost and ensuing decrease of renal function occurs. ADPKD accounts for 4-10% of end-stage renal disease (ESRD) worldwide (Freedman et al., 2000; Konoshita et al., 1998). In 50% of cases loss of renal function, necessitating renal replacement therapy occurs by age 60 (Gabow et al., 1992). Renal cysts are often evident on ultrasound or magnetic resonance imaging (MRI) in children, who typically do not become symptomatic until reaching young adulthood (Chapman et al., 2003; Fick-Brosnahan et al., 2001; Seeman et al., 2003). While renal cysts are an invariable characteristic of ADPKD, cysts may also occur in other organs with differing degrees of severity. Hepatic cysts are found in 75% of patients with ADPKD by age 60, while pancreatic, arachnoid, seminal vesicle, and prostate cysts occur with a lower frequency (Eccer et al., 2007). ADPKD is a systemic disorder with abnormalities occurring in several organs and a significantly increased risk for cardiovascular complications among affected patients. The reader is referred to several comprehensive reviews on the clinical and genetic determinants of ADPKD for more detailed description of disease attributes (Chapin & Caplan, 2010; Eccer et al., 2007; Pei, 2011).

The process of cystogenesis involves proliferation of the epithelial cells that line the kidney tubules. This process initially results in localized dilation of the tubule. Continued epithelial cell proliferation and fluid secretion into the cyst results in cyst growth, until the cyst pinches off from the tubule. While the development and growth of renal cysts is the key feature of this disorder, the exact mechanism and identity of the factors influencing this process remain to be determined. However, it is apparent that vascular changes including expansion and remodeling of the existing vascular network must occur in order to support the structural changes occurring in the ADPKD kidney. Accordingly, it is not surprising that

cyst growth in ADPKD has been likened to growth of a benign tumor (Grantham & Calvet, 2001). Indeed, there are many similarities between tumor growth and cyst growth, both processes being marked by increased cell proliferation, changes in apoptosis, and angiogenesis. In this chapter we will focus on the process of angiogenesis, defined as the growth of new blood vessels by invasion and sprouting of the existing vessels, as distinct from embryonic vasculogenesis or de novo growth of blood vessels.

## 2. Angiogenesis

In order to understand the various signals and processes that define angiogenesis it is necessary to consider the main function of blood vessels, namely the supply of oxygen and nutrients to all the cells in the body. Much of our current knowledge of angiogenesis stems from studies of tumor biology. The fact that the diffusion limit of oxygen is approximately 100µm indicates that all blood vessels must be located within 100-200 µm of mammalian cells to ensure viability (Torres Filho et al., 1994). Subsequent studies by Judah Folkman et al. determined that tumor growth beyond 1-2-mm was angiogenesis dependent (Folkman, 2006). In health the endothelial cells that line the blood vessel lumen and the pericytes that surround the outer surface of the endothelial cells are in a “quiescent” state. This state is maintained by a balance of “pro” and anti-angiogenic growth factors that include vascular endothelial growth factor (VEGF), angiopoietin-1 (Ang-1), angiopoietin-2 (Ang-2), and various other chemokines and growth factors. Angiogenesis in the adult is defined by sprout formation or by splitting of a pre-existing blood vessel (Persson & Buschmann, 2011). The process of angiogenesis proceeds in several distinct stages and is initiated by a decrease in partial pressure of oxygen, which is detected by oxygen sensors on the endothelial cell. In the ADPKD kidney the growing cysts compress the renal vasculature resulting in decreased oxygenation. Hypoxia results in stabilization of the hypoxia-inducible factor (HIF-1). The HIF family, which in addition to HIF-1, also includes HIF-2 and HIF-3 are transcription factors. Structurally the HIF's comprise of a heterodimer of a regulatory  $\alpha$  subunit and a constitutively expressed  $\beta$  subunit (Wang & Semenza, 1995). Angiogenesis is initiated by binding of HIF-1 to a hypoxia response element in the promoter of an angiogenic growth factor such as VEGF as reviewed by Hoeben et al. (Hoeben et al., 2004). In the case of new vascular sprout formation, when an angiogenic signal is detected by a quiescent blood vessel, the pericytes detach from the blood vessel wall and from the basement membrane. This is mediated by metalloproteinase (MMP) induced proteolytic degradation (Persson & Buschmann, 2011). Endothelial cells undergo several changes, loosening their cell junctions and allowing dilation of the vessel. VEGF increases endothelial cell permeability allowing escape of plasma proteins and formation of a provisional extracellular matrix (ECM). Endothelial cells next migrate onto the ECM surface mediated by integrin. Degradation of the ECM by proteases releases additional angiogenic growth factors from the ECM providing an angiogenic gradient that mediates migration and proliferation of the endothelial cells. One endothelial cell called a “tip cell” is instrumental in leading the migration, ECM degradation and consequent direction of growth of the vascular sprout. Maturation of the vessel requires return of the endothelial cells to a quiescent state, pericytes to attach and cover the vessel and down regulation of proteases by expression of tissue inhibitors of metalloproteinases (TIMP's). These changes are mediated by downregulated expression of VEGF and increased levels of Ang-1, transforming growth factor  $\beta$  (TGF- $\beta$ ), and platelet derived growth factor (PDGF) (Chung et al., 2010).

3. Angiogenic growth factors

In this section we will describe some of the most important angiogenic growth factors and their respective receptors with emphasis on the role of VEGF, Ang-1, and Ang-2 in the kidney in health and disease.

3.1 Vascular Endothelial Growth Factor (VEGF)

VEGF is a central mediator of angiogenesis inducing endothelial cell proliferation, sprouting and promoting vascular leakiness (Otrock et al., 2007). The VEGF family includes VEGF A, VEGF B, VEGF C, VEGF D and placenta growth factor (PlGF) each coded by a separate gene (Table 1).

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 VEGF family members.

The gene encoding VEGF A comprises of eight exons which by differential splicing encodes seven transcript variants that give rise to isoforms of differing amino acid length, VEGF-A<sub>206</sub>, VEGF-A<sub>189</sub>, VEGF-A<sub>183</sub>, VEGF-A<sub>165</sub>, VEGF-A<sub>148</sub>, VEGF-A<sub>145</sub> and VEGF-A<sub>121</sub> respectively (Bevan et al., 2008; Hoeben et al., 2004). A further variant VEGF-A<sub>110</sub> is derived by proteolytic cleavage. The major circulating isoform VEGF-A<sub>165</sub>, is also abundant in the extracellular matrix. The VEGF polypeptides are homodimers although heteodimeric forms of VEGF-A and PlGF have also been described (DiSalvo et al., 1995). The biological functions of VEGF are mediated by binding to the tyrosine kinase receptors, VEGF receptor-1/ fms-like tyrosine kinase-1 (VEGFR-1/Flt1), VEGF receptor-2/fetal liver kinase-1 (VEGFR-2/Flk-1) and VEGF receptor-3/ fms-like tyrosine kinase-4 (VEGFR-3/Flt4) (Ortega et al., 1999). The various members of the VEGF family bind to different VEGF receptors as shown in Table 1. VEGF-A (also referred to as VEGF) is expressed by mural cells including vascular smooth muscle cells and pericytes. In addition, in the kidney VEGF is expressed by both glomerular epithelial cells (podocytes) and by tubular epithelial cells (Robert et al., 2000).

The VEGF receptors are expressed on vascular endothelial cells as well as on a range of non-endothelial cells including monocytes and macrophages in the case of VEGFR-1 (Koch et al., 2011). In the kidney, glomerular endothelial cells express VEGFR-1 and VEGFR-2 (Thomas et al., 2000). Expression of VEGF is upregulated in response to hypoxia through upregulation of HIF-1 $\alpha$  transcription factors. In addition, VEGF activity is modulated by binding to heparin sulfate and through interaction with the co-receptors neuropilin 1 and neuropilin 2, although the molecular mechanisms involved at present remain unclear (Koch et al., 2011). Both animal and human studies have shown that VEGF is essential for vascular repair and maintenance of normal glomerular function in the kidney (Dumont et al., 1995; Kitamoto et al., 2001; Satchell et al., 2004; Sugimoto et al., 2003). However, over expression of VEGF is also associated with glomerular disease, indicating that maintenance of normal VEGF level is essential for renal function (Veron et al., 2010). Significantly, a link between cystogenesis and VEGF was demonstrated in an animal study showing that increased expression of VEGF in renal tubules resulted in cyst formation (Hakrrouch et al., 2009).

Several recent studies have supported a role for an imbalance of angiogenic growth factor levels in disease processes including tumor growth, diabetes, chronic kidney disease (CKD), and cardiovascular disease (Futrakul et al., 2008; Guo et al., 2009; Persson & Buschmann, 2011; Lim et al., 2005; Nadar et al., 2004; Nadar et al., 2005). Endothelial dysfunction is a feature of patients with ADPKD (Schrier, 2006). VEGF has been shown to play a crucial role in preservation of the microvasculature, promoting vascular proliferation and repair in experimental renal disease (Chade et al., 2006; Iliescu et al., 2009; Zhu et al., 2004). Increased plasma levels of the VEGF inhibitor, soluble VEGF receptor (sFlt1) were recently demonstrated in CKD patients supporting an imbalance of the VEGF pathway in CKD (Di Marco et al., 2009). Tubulointerstitial hypoxia and capillary rarefaction are common features of progressive renal disease. In a study of patients with progressive or stable proteinuric renal disease attenuated VEGF-A expression by proximal tubular cells, despite activation of the intracellular response signalling pathway, was shown to distinguish those patients with progressive disease (Rudnicki et al., 2009).

Patients with ADPKD are at an increased risk for development of left ventricular hypertrophy (LVH) which is a significant risk factor for sudden death (Chapman et al., 1997). Increased plasma VEGF levels have been demonstrated in patients with target organ damage, defined as stroke, previous myocardial infarction, angina, LVH, and mild renal failure (Nadar et al., 2005). Mice expressing a *vegfb* transgene develop cardiac hypertrophy, further indicating that VEGF may also play a potential role in cardiac pathology associated with ADPKD (Karpanen et al., 2008).

### 3.2 Angiopoietins

The members of the angiopoietin family including Ang-1, Ang-2 and Ang-4 together with their soluble Tie-2 (tyrosine kinase with immunoglobulin-like and EGF-like domains 2) receptor are endothelial cell regulators with a role in the remodeling/maturation phases of angiogenesis. In addition to expression in endothelial and vascular smooth muscle cells Ang1, Ang2 and Ang-4 are also expressed in kidney (Fiedler and Augustin, 2006; Yamakawa et al., 2004; Yuan et al., 1999). Ang-1 is a Tie-2 agonist while Ang-2 in the absence of VEGF inhibits Ang-1/Tie-2 signaling as reviewed by Fiedler et al. (Fiedler and Augustin, 2006). Conversely, under conditions of adequate VEGF, or under hypoxic conditions as may exist in and around the growing renal cysts, Ang-2 stimulates angiogenesis (Lobov et al.,



2002). The activity of Ang-4 is similar to Ang-1 as it is a Tie-2 agonist and is expressed in human kidney proximal tubule epithelial cells. Activation of Tie-2 results in a downstream activation of P13K-Akt in endothelial cells leading to a survival pathway and cell chemotaxis (Makinde and Agarwal, 2008).

The plasma level of Ang-2 is elevated in patients with diabetes and is associated with indices of endothelial damage and dysfunction (Lim et al., 2005). Likewise, abnormal levels of serum Ang-1 and Ang-2 in hypertension have been linked with target organ damage (Nadar et al., 2005), thus indicating a potential role for angiopoietins in exacerbation of the extrarenal complications associated with ADPKD including left ventricular hypertrophy (LVH). LVH is a major risk factor for cardiac arrhythmias, sudden death, heart failure and ischemic disease in ADPKD (Schrier, 2006). Prevention of LVH in ADPKD is consequently a key factor in patient management. The expression of Ang-1, Ang-2 and Ang-4 in different tissues including human kidney proximal tubule cells is regulated by various factors including hypoxia, VEGF, angiotensin II and estrogen (Ardelt et al., 2005; Kitayama et al., 2006; Yamakawa et al., 2004).

#### **4. Similarities between tumor growth and cyst growth in ADPKD**

The polycystin proteins PC1 and PC2 have been likened to tumor suppressors associated with many types of neoplasia (Grantham, 2001). Thus, when polycystin function is impaired as in ADPKD, cells revert to a more de-differentiated state marked by high proliferative capacity (Song et al., 2009). It has been recognized for many years that angiogenesis is necessary to support tumor growth (Folkman, 1971). Moreover, many non-neoplastic diseases including macular degeneration, arthritis and endometriosis are angiogenesis dependent (Folkman, 2006). Thus a facilitative role for angiogenesis in ADPKD cyst growth is suggested. Tumor cell expression of angiogenic growth factors including VEGF is mediated by hypoxia (Pugh and Ratcliffe, 2003). Central to the hypoxia response pathway are HIF-1 and 2. HIF-1 $\alpha$  is targeted for destruction via the ubiquitin pathway regulated by Von Hippel Lindau (VHL) protein. Inactivation of VHL results in an increase of HIF-1 $\alpha$  and VEGF level (Na et al., 2003). In progressive renal disease human proximal tubular epithelial cells demonstrate activation of intracellular hypoxia response pathways and VEGF signaling despite attenuated expression of VEGF-A (Rudnicki et al., 2009). Growth of renal cysts results in compression of the surrounding blood vessels. Significantly, an up-regulation of hypoxia-angiogenic pathways has been reported based on a systems biology approach in ADPKD (Song et al., 2009). A further key mediator of angiogenesis is the tumor suppressor gene phosphatase and tension homolog deleted on chromosome 10 (PTEN) which is frequently deficient or inactivated in human cancers (Mirohammadsadegh et al., 2006; Ohgaki & Kleihues, 2007; Tam et al., 2007). Activation of mammalian target of rapamycin (mTOR) is a feature of ADPKD and this pathway is regulated by PTEN (Boletta, 2009; Rosner et al., 2008; Shillingford et al., 2006). Thus the literature supports similarities between tumorigenesis and ADPKD and underscores a potential role for angiogenesis in ADPKD cyst growth.

#### **5. Evidence for angiogenesis in ADPKD kidneys**

Abnormalities of the renal vasculature in polycystic kidneys have long been recognized based on early angiographic studies of the kidney (Cornell, 1970, Ettinger et al., 1969) Bello-

Reuss et al. presented evidence of angiogenesis in human ADPKD kidneys based on angiographic studies (Bello-Reuss et al., 2001). These studies illustrated development of a well-defined vascular capsule around human renal cysts in ADPKD. Many morphological malformations were shown in the cyst wall vessels including presence of spiral, tortuous, and dilated vessels. This aberrant morphology is also typical in tumors further illustrating similarities between ADPKD cyst growth and growth of a benign tumor. A later study by the same group using corrosion cast studies of human ADPKD kidneys confirmed the occurrence of angiogenesis (Wei et al., 2006). This study also reported loss of the normal kidney vascular architecture in addition to evidence of microvascular regression. The pathological changes related to angiogenesis in ADPKD may also result in increased vascular permeability thus facilitating fluid secretion into cysts (Wei et al., 2006).

## 6. Angiogenic growth factors in ADPKD kidneys

Angiogenesis is mediated by a shift in the balance towards expression of pro-angiogenic growth factors with concomitant decrease in anti-angiogenic factors. VEGF expression by renal cystic tubular epithelial cells and VEGFR-2 expression in endothelial cells in the small capillaries surrounding the cysts was demonstrated by Bello-Reuss et al. (Bello-Reuss et al., 2001). This contrasts with normal adult kidney where only weak expression of VEGF and VEGFR-2 are present in the collecting duct and surrounding capillaries (Simon et al., 1995). The demonstration of MMP-2 and integrin  $\alpha_v\beta_3$  on the endothelial surface of blood vessels in ADPKD kidneys by the same authors further affirms the presence of components necessary for angiogenesis in ADPKD kidneys. Subsequent studies in a rat model of polycystic kidney disease demonstrated increased expression of VEGF in the kidneys and sera of the cystic animals compared to control animals (Tao et al., 2007). Similarly, increased expression of both VEGF receptors, VEGFR1 and VEGFR2 was demonstrated in renal tubular epithelial cells in the polycystic kidneys of these animals. We have also demonstrated expression of Ang-2 and the Tie-2 receptor by cyst lining epithelial cells of human polycystic kidneys as illustrated in Figure 1 (unpublished data).

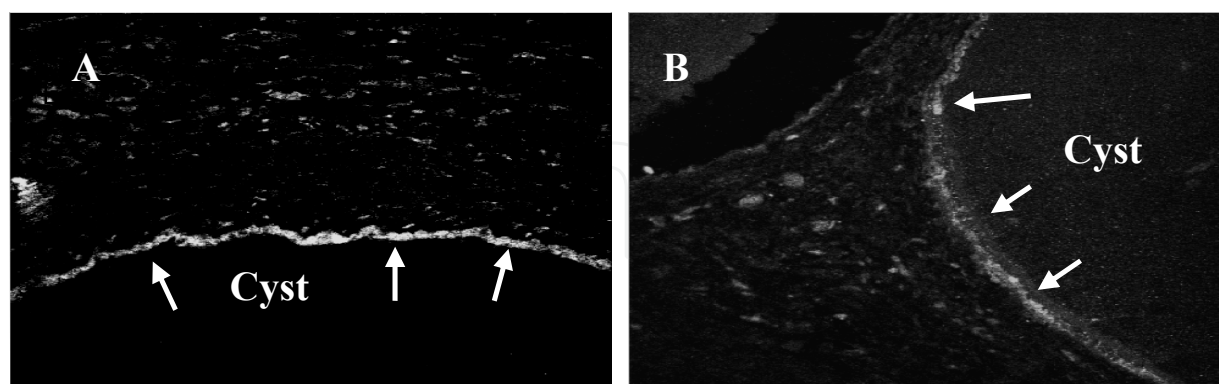


Fig. 1. Expression of Ang-2 (A) and Tie-2 (B) by ADPKD cyst lining cells. Arrows indicate cyst lining cells with Ang-2 staining shown by lighter shading in A and Tie-2 staining by lighter speckled shading in B.

These observations suggest a mechanism whereby secretion of pro-angiogenic growth factors by the cyst lining epithelial cells may result in stimulated growth of the blood vessels surrounding the cysts thus facilitating cyst growth as illustrated in Figure 2.

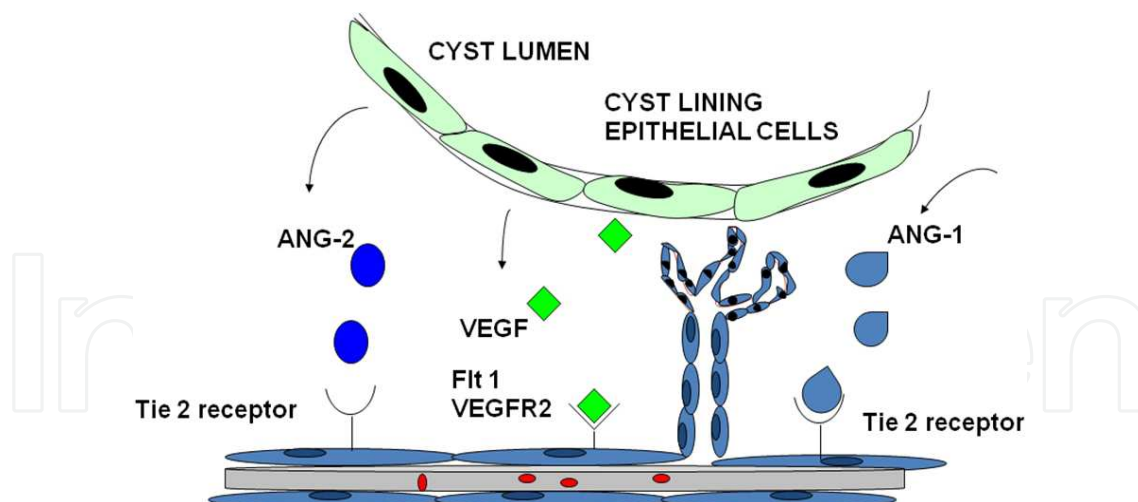


Fig. 2. Release of angiogenic growth factors by cyst lining and other cells in response to hypoxic stimulus stimulates angiogenesis.

However, the nature of renal injury in ADPKD is complex, apoptosis and loss of endothelium occurs which correlates with the severity of glomerular sclerosis and interstitial fibrosis (Wei et al., 2006). Thus both indication of angiogenesis and destabilization of the existing vasculature are apparent in ADPKD kidneys. This is supported by demonstration that changes in renal blood flow parallel increase in total kidney volume and precede decline in renal function measured by change in glomerular filtration rate (GFR) in ADPKD (Torres et al., 2007).

## 7. Angiogenic growth factors in ADPKD liver

Expression of angiogenic growth factors have also been demonstrated in cystic liver from human ADPKD patients and also in animal models of PKD. Upregulated expression of Ang-1, Ang-2 and their Tie-2 receptor has been demonstrated in the cholangiocytes that line hepatic cysts in ADPKD, supporting a role for angiogenic growth factors in liver cystogenesis (Fabris et al., 2006). Moreover, cyst fluid from hepatic cysts has been shown to contain VEGF (Amura et al., 2008; Nichols et al., 2004). In a subsequent animal study factors secreted by liver cyst epithelia were shown to promote endothelial cell proliferation and development (Brodsky et al., 2009).

## 8. Serum levels of angiogenic growth factors are increased in ADPKD

We have previously reported that serum levels of VEGF and Ang-2 are elevated in children and young adults with ADPKD compared to age, sex, and renal function matched young subjects with diabetes as shown in Table 2 (Reed et al., 2011). In these children and young adults renal function was normal, mean eGFR 128 ml/min/1.73m<sup>2</sup>. The level of VEGF detected in renal cyst fluid was comparable to the mean serum level. The plasma levels of the soluble VEGF receptor (sFlt1), an antagonist of VEGF, rise progressively with declining renal function in patients with CKD (Di Marco et al., 2009). The same study demonstrated an association between plasma sFlt1 level and endothelial dysfunction. In our own study we found that serum levels of sFlt1 ranged between <13-320 pg/ml in ADPKD patients, however normal healthy serum values were not available for comparison (unpublished data) (Table 2). It is important to note that both the circulating level of VEGF and level of the VEGF antagonist sFlt1 may play a role in implementing disease progression in ADPKD.



VEGF	Mean± SD or range (N)
Adult ADPKD patients (serum)	5910 ± 6188 pg/ml (N=46)
Children and young adults with ADPKD (serum)	2997 ± 5326 pg/ml (N=71)
Healthy adults (A) (serum)	249 ± 46 pg/ml (A) (Saito et al.,2009)
Healthy children (C) (serum)	306 ± 39 pg/ml (C) (Heshmat & El Kerdany, 2007)
Urine adults with ADPKD	82.7-277.2 pg/ml (N =8) 183.9 - 469.2 ng/24h (N=8)
Renal cyst fluid	5940 ± 6757 pg/ml (N=5)
Soluble VEGF Receptor 1 (sFlt1)	
Adult ADPKD patients (serum)	93.8 ± 63 pg/ml (N =38)
Adult ADPKD patients (urine)	Not detected
Angiopoietin 1	
Adult ADPKD patients (serum)	37.54 ± 19.54 ng/ml (N=85)
Children and young adults with ADPKD (serum)	35.53 ± 21.03 ng/ml (N=71)
Healthy adults (A) (serum)	39.0 ± 9.9 ng/ml (A) (Park et al., 2009)
Healthy children (C) (serum)	64.4 (23.5-101 ng/ml) (C) (Lovegrove et al., 2009)
Renal cyst fluid	None detected
Angiopoietin 2	
Adult ADPKD patients (serum)	3002 ± 1379 pg/ml (N=85)
Children and young adults with ADPKD (serum)	2352 ± 962 pg/ml (N=71)
Healthy adults (A) (serum)	1270 ± 494 pg/ml (A) (Park et al., 2007)
Healthy children (C) (serum)	68 (68-1330 pg/ml) (C) (Lovegrove et al., 2009)
Renal cyst fluid	1657 ± 1035 pg/ml (N=5)

Table 2. Mean serum, urine or cyst fluid levels of angiogenic growth factors.

Several recent studies have supported a role for an imbalance of angiogenic growth factor levels in disease processes including tumor growth, diabetes, CKD and cardiovascular disease (Augustin et al. 2009; David et al., 2009; Lim et al., 2005; Nadar et al., 2004; Nadar et al., 2005). Endothelial dysfunction is a common feature of patients with CKD and VEGF has been shown to play a crucial role in preservation of the microvasculature promoting vascular proliferation and repair in experimental renal disease (Chade et al., 2006; Iliescu et al., 2009; Zhu et al., 2004). The plasma level of Ang-2 is elevated in patients with diabetes and is associated with indices of endothelial damage and dysfunction (Lim et al., 2005). Likewise, abnormal levels of serum Ang-1 and Ang-2 in hypertension have been linked with target organ damage (Nadar et al., 2005), thus indicating a potential role for angiopoietins in exacerbation of the extrarenal complications of ADPKD, including LVH.

As the growing cysts in ADPKD kidneys result in compression of the vasculature with attendant ischaemia (Ecdet al., 2007) these conditions are conducive for upregulated angiopoietin expression. Furthermore, kidney expression of Ang-1 and Ang- 2 is known to be upregulated by angiotensin II in addition to hypoxia (Kitayama et al., 2006., Yamakawa et al., 2004). Thus, as activation of the renin-angiotensin-aldosterone system (RAAS) occurs

early in ADPKD, this may increase angiopoietin production with further injurious effects on the kidney vasculature and cyst growth.

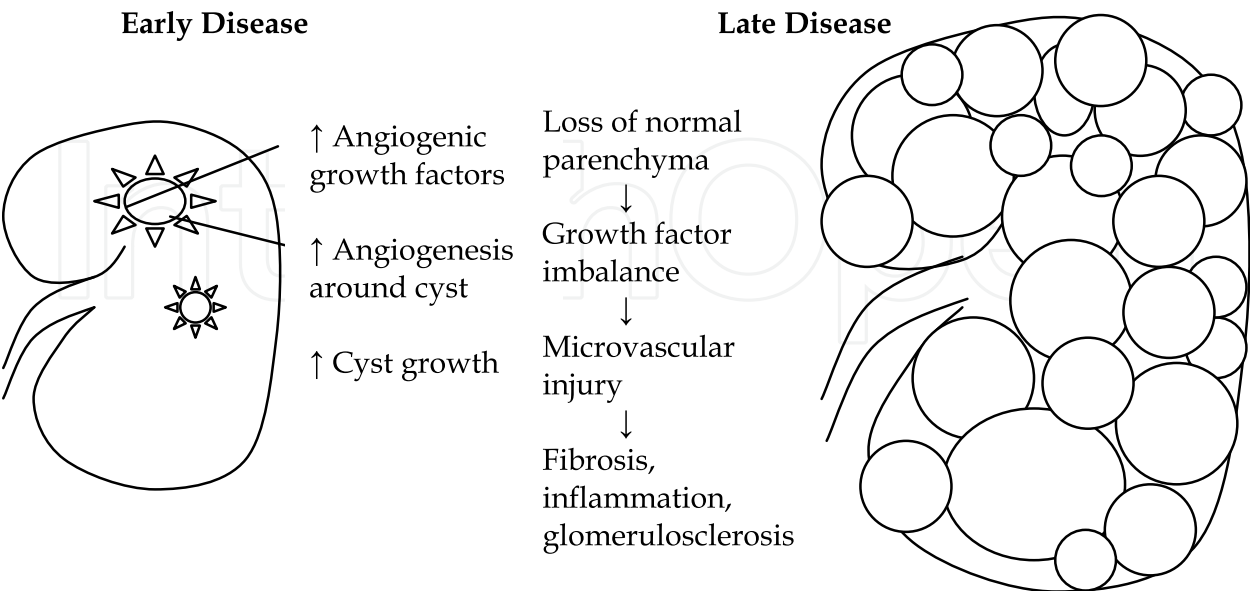


Fig. 3. Potential Role of Angiogenic Growth Factor in Renal Injury in ADPKD.

9. Serum levels of angiogenic growth factors correlate with renal and cardiac disease severity in ADPKD

Further evidence to support a role of angiogenic growth factors in the complications of ADPKD stems from our study in children and young adults (Reed et al., 2011). Measurement of VEGF, Ang-1 and Ang-2 in 71 children and young adults with ADPKD demonstrated strong correlations between log<sub>10</sub> VEGF and both log<sub>10</sub> total kidney volume and eGFR. (Table 3). In adult ADPKD patients no relationship between log<sub>10</sub> VEGF and total renal volume was found (N= 33). However, in adults there was a significant negative relationship between serum Ang-2 levels and eGFR (N = 85, p = 0. 04) that was not found in children and young adults. This indicates that VEGF may play a more significant role early in ADPKD, while Ang-2 may play a role in the progression of renal injury later in disease.

IndependentVariable	Children			Adults		
	β	SE	P	β	SE	P
	Dependent Variable					
	Log <sub>10</sub> Total Renal Volume					
Log <sub>10</sub> VEGF	0.0511	0.0183	0.0073			NS
Ang-1	0.0029	0.0014	0.0448	-0.00001	0.00001	NS
Ang-2			NS			NS
	eGFR					
Log <sub>10</sub> VEGF	-0.0229	0.0080	0.0055	-0.0583	0.0307	0.06
Ang-1	-0.0010	0.0006	0.1058			NS
Ang-2			NS	-0.1380	0.0657	0.03

Table 3. Relationship of VEGF, Ang-1 and Ang-2 with renal structure and function.

We have demonstrated significant positive correlations between LVMI and Ang-1 and VEGF in young subjects with ADPKD as shown in table 4 (Reed, et al., 2011). The relationship between LVMI and serum VEGF was apparent even in the absence of overt hypertension. This is of particular relevance as patients with ADPKD are at an increased risk for left ventricular hypertrophy (LVH) (Chapman et al., 1997). Similarly, in 33 adults a near significant relationship between LVMI and Ang-1 was observed. No relationship between VEGF and LVM was apparent in adults. However, there was a significant relationship between Log<sub>10</sub> Ang-1/Ang-2 and LVM. As Ang-2 has been reported to be both pro-angiogenic or promote vascular regression dependent upon the presence or absence of VEGF (Holash et al., 1999; Lobov et al., 2002) assessment of the Ang-1/Ang-2 ratio may be biologically relevant. Thus, angiogenic growth factor levels may help identify children at risk for cardiovascular complications. This is important because cardiac MRI and/or echocardiography are not routinely performed on young patients with ADPKD.

Independent Variable	Children			Adults		
	β	SE	P	β	SE	P
Dependent Variable						
LVM						
Log <sub>10</sub> VEGF	0.0409	0.0078	<0.0001			NS
Ang-1	0.0014	0.0007	0.04	0.0004	0.0002	0.06
Log <sub>10</sub> Ang-1/Ang-2			NS	12.2718	5.4447	0.03

Table 4. Relationship between VEGF, Ang1 and Ang-1/Ang-2 with Cardiac Structure.

10. Potential benefit of anti-angiogenic therapy in ADPKD

VEGF receptor inhibition by SU-5416 has been shown to significantly reduce liver cyst burden in pkd2(WS25/-)mice (Amura et al., 2007). Likewise, studies in the cy/+ rat model of polycystic kidney disease demonstrated that treatment with ribozymes to block VEGFR-1 and VEGFR-2 mRNA expression resulted in decreased cyst burden in the kidney (Tao et al., 2007). Metalloproteinase inhibition by batimastat in the cy/+ rat model has also been shown to significantly reduce kidney weight and cyst number in treated animals compared to untreated animals (Obermuller et al., 2001).

Several inhibitors that either target VEGF directly such as bevacizumab or those such as sorafenib and sunitinib that target receptor tyrosine kinases including VEGFR’s and platelet derived growth factor receptors have shown some success in cancer therapy. Indicating that these drugs may have a potential role in ADPKD therapy. However, there are several side effects associated with both of these drug classes including but not limited to hemorrhage, decreased wound healing and hypertension. Side effects are a significant consideration in relation to ADPKD therapy where drug use must potentially be continued for life. While most anti-angiogenic drugs are targeted towards cancer therapy, bosutinib a receptor tyrosine kinase inhibitor targeting the Src/Abl kinases which also reduces VEGF activity is currently in phase II clinical trial for ADPKD (NCT01233869).

In terms of other anti-angiogenic targets, there are several ongoing cancer clinical trials with Ang-1 or Ang-2 inhibitors. Depending on the outcome of these ongoing trials these drugs may hold some promise for future ADPKD therapy. It is also relevant that there are many

naturally occurring inhibitors of angiogenesis including angiostatin, endostatin, vasostatin, TIMPs, thrombospondins, tumstatin, prolactin (inhibits both basic fibroblast growth factor and VEGF), vasohibin-1 and sFlt1 which may also have benefit in ADPKD. The therapeutic effects of several endogenous angiogenesis inhibitors including angiostatin, endostatin, tumstatin, vasohibin-1, and the synthetic derivative of bacterial cytogenin, 1-(8-hydroxy-6-methoxy-1-oxo-1H-2-benzopyran-3-yl) proprionic acid (NM-3) have been examined in animal models of diabetic nephropathy as reviewed by Maeshima and Makino (Maeshima & Makino, 2010). These angiogenesis inhibitors have been shown to reduce renal hypertrophy/hyperfiltration and reduce albuminuria when administered during the early stages of disease (Zhang et al., 2006, Ichinose et al., 2005, Yamamoto et al., 2004, Nasu et al., 2009, Ichinose et al., 2006). However, no human studies have been performed to date. In animal models of non-diabetic renal disease angiostatin treatment has resulted in both beneficial anti-inflammatory effects while the anti-angiogenic reduction in peritubular capillaries may worsen tubular hypoxia (Mu et al., 2009). Thus, with progressive renal diseases including ADPKD angiogenic growth factors may both promote renal injury or protect from hypoxia by maintenance of the peritubular capillaries. While in the early stages of ADPKD therapeutic restoration of normal angiogenic factor balance may be more beneficial, later disease stages may need a different approach to ameliorate increasing renal hypoxia. However, further research is necessary to explore the potential disparate roles of angiogenic growth factors in progression of ADPKD.

## 11. Conclusion

In this chapter we have presented evidence that angiogenesis may be an important factor in the pathogenesis of ADPKD. We have highlighted the similarities between cyst growth and growth of a benign tumour. Significantly, as has been demonstrated in other disease conditions circulating angiogenic growth factor levels are abnormally elevated even early in ADPKD and may indicate the severity of underlying renal and cardiac disease. Lastly, the benefits of anti-angiogenic therapies which target restoration of angiogenic growth factor balance remain to be determined in ADPKD but may hold future therapeutic promise.

## 12. Acknowledgment

This research was supported by Grant numbers M01RR00051, M01RR00069, the General Research Centers Program, National Center for Research Resources (NCRR/NIH; by NCRR/NIH Colorado CTSI Grant number UL1RR025780, by Grant DK34039 from NIH (NIDDK) and by the Zell Family Foundation. The content of this publication are the authors sole responsibility and do not necessarily represent the official NIH views.

## 13. References

- Amura, C.R., Brodsky, K.S., Groff, R., Gattone, V.H., Voelkel, N.F. & Doctor, R.B. (2007) VEGF receptor inhibition blocks liver cyst growth in *pkd2*(WS25/-) mice. *Am. J. Physiol. Cell. Physiol.*, Vol.293, No.1, (July 2007) pp. C419-428, ISSN 0363-6143
- Ardelt, A.A., McCullough, L.D., Korach, K.S., Wang, M.M., Munzenmaier, D.H. & Hurn, P.D. (2005) Estradiol regulates angiopoietin-1 mRNA expression through estrogen

- receptor-alpha in a rodent experimental stroke model. *Stroke*, Vol.36, No.2, (February 2005), pp. 337-341, ISSN 0039-2499
- Augustin, H.G., Koh, G.Y., Thurston, G. & Alitalo, K. (2009) Control of vascular morphogenesis and homeostasis through the angiopoietin-Tie system. *Nat. Rev. Mol. Cell. Biol.*, Vol.10, No.3, (March 2009), pp. 165-177, ISSN 1471-0072
- Bello-Reuss, E., Holubec, K. & Rajaraman S. (2001). Angiogenesis in autosomal-dominant polycystic kidney disease. *Kidney Int.*, Vol. 60, No. 1, (July 2001), pp. 37-45, ISSN 0085-2538
- Bevan, H.S., van den Akker, N.M., Qiu, Y., Polman, J.A., Foster, R.R., Yem, J., Nishikawa, A., Satchell, S.C., Harper, S.J., Gittenberger-de Groot, A.C. & Bates, D.O. (2008) The alternatively spliced anti-angiogenic family of VEGF isoforms VEGFxxx<sub>b</sub> in human kidney development. *Nephron Physiol.*, Vol.110, No.4, (November 2008), pp. 57-67, ISSN 1660-2137
- Boletta, A. (2009) Emerging evidence of a link between polycystins and the mTOR pathways. *PathoGenetics*, Vol.2, No.1, October 2009, pp. 6, ISSN1755-8417
- Brodsky, K.S., McWilliams, R.R., Amura, C.R., Barry, N.P. & Doctor, R.B. (2009) Liver cyst cytokines promote endothelial cell proliferation and development. *Exp. Biol. Med.* (Maywood), Vol.234, No.10 (October 2009), pp. 1155-1165, ISSN 1535-3702
- Chade, A.R., Zhu, X., Mushin, O.P., Napoli, C., Lerman, A. & Lerman, L.O. (2006) Simvastatin promotes angiogenesis and prevents microvascular remodeling in chronic renal ischemia. *Faseb. J.*, Vol.20, No.10, (August 2006), pp. 1706-1708, ISSN 0892 6638
- Chapin, H.C. & Caplan, M.J. (2010). The cell biology of polycystic kidney disease. *J. Cell Biol.*, Vol. 191, No. 4, (November 2010), pp. 701-710, ISSN 0021-9525
- Chapman, A.B., Johnson, A.M., Ranguet, S., Hossack, K., Gabow, P. & Schrier, R.W. (1997) Left ventricular hypertrophy in autosomal dominant polycystic kidney disease. *J. Am. Soc. Nephrol.*, Vol.8, No.8, (August 1997), pp. 1292-1297, ISSN 1046-6673
- Chapman, A.B., Guay-Woodford, L.M., Grantham, J.J., Torres, V.E., Bae, K.T., Baumgarten, D.A., Kenney, P.J., King, B.F., Jr., Glockner, J.F., Wetzell, L.H., Brummer, M.E., O'Neill, W.C., Robbin, M.L., Bennett, W.M., Klahr, S., Hirschman, G.H., Kimmel, P.L., Thompson, P.A. & Miller, J.P. (2003). Renal structure in early autosomal-dominant polycystic kidney disease (ADPKD): The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) cohort. *Kidney Int.*, Vol.64, No.3, (September 2003), pp. 1035-1045, ISSN 0085-2538
- Chung, A.S., Lee, J. & Ferrera, N. (2010) Targeting the tumour vasculature: insights from physiological angiogenesis. *Nat. Cancer Rev.*, Vol.10, No.7, (July 2010), pp. 505-514, ISSN1474-175X
- Cornell, S.H. (1970) Angiography in polycystic disease of the kidneys. *J.Urol.*, Vol.103, No.3, (July 1970), pp. 24-26, ISSN 0970-1591
- David, S., Kumpers, P., Hellpap, J., Horn, R., Leitolf, H., Haller, H. & Kielstein, J.T. (2009) Angiopoietin 2 and cardiovascular disease in dialysis and kidney transplantation. *Am J Kidney Dis.*, Vol.53, No.5, (May 2009), pp. 770-778, ISSN 0272-6386
- Di Marco, G.S., Reuter, S., Hillebrand, U., Amler, S., Konig, M., Larger, E., Oberleithner, H., Brand, E., Pavenstadt, H. & Brand, M. (2009) The soluble VEGF receptor sFlt1 contributes to endothelial dysfunction in CKD. *J. Am. Soc. Nephrol.*, Vol.20, No.10, (October 2009), pp. 2235-2245, ISSN 1046-6673



- DiSalvo, J., Bayne, M.L., Conn, G., Kwok, P.W., Trivedi, P.G., Soderman, D.D., Palisi, T.M., Sullivan, K.A., & Thomas, K.A. (1995) Purification and characterization of a naturally occurring vascular endothelial growth factor. Placenta growth factor heterodimer. *J.Biol.Chem.*, Vol.270, No.13, (March 1995), pp. 7717-7723, ISSN 0021-9258
- Dumont, D.J., Fong, G.H., Puri, M.C., Gradwohl, G., Alitalo, K. & Breitman, M.L. (1995) Vascularization of the mouse embryo: a study of flk-1, tek, tie, and vascular endothelial growth factor expression during development. *Dev. Dyn.*, Vol.203, No.1, (May 1995), pp. 80-92, ISSN 1058-8388
- Ecder, T., Fick-Brosnahan, G.M. & Schrier, R.W. (2007) Polycystic kidney disease, In: *Diseases of the Kidney*, eighth edition, R.W. Schrier, (Ed.), 502-539, Lippincott, Williams & Wilkins, ISBN 13:978-0-7817-9307-0, Philadelphia, PA., USA
- Ettinger, A, Khahn, P.C. & Wise, H.M. (1969) The importance of selective renal angiography in the diagnosis of polycystic kidney disease. *J.Urol.*, Vol.102, No.2,(August 1969), pp. 156-161, ISSN 0970-1591
- European Polycystic Kidney Disease Consortium. (1994). The polycystic kidney disease gene encodes a 14kb transcript and lies within a duplicated region of chromosome. 16. *Cell*, 77, pp. 881-894, ISSN 0092-8674
- Fabris, L., Cadamuro, M., Fiorotto, R., Roskams, T., Spirli, C., Melero, S., Sonzogni, A., Joplin, R.E., Okolicsanyi, L. & Strazzabosco, M. (2006) Effects of angiogenic factor overexpression by human and rodent cholangiocytes in polycystic liver diseases. *Hepatology*, Vol.43, No.5, (May 2006), pp. 1001-1012, ISSN 1386-6346
- Fick-Brosnahan, G.M., Tran, Z.V., Johnson, A.M., Strain, J.D. & Gabow, P.A. (2001) Progression of autosomal-dominant polycystic kidney disease in children. *Kidney Int.*, Vol.59, No.5, (May 2001), pp. 1654-1662, ISSN 0085-2538
- Fiedler, U. & Augustin HG. (2006) Angiopoietins: a link between angiogenesis and inflammation. *Trends Immunol.*, Vol.27, No.12, ( December 2006) pp. 552-558, ISSN 0972-4567
- Folkman, J. Tumor angiogenesis: therapeutic implications. (1971) *N Engl J Med.*, Vol.285, No. 21, (November 1971), pp. 1182-1186, ISSN 0028-4793
- Folkman, J. (2006) Angiogenesis. *Ann Rev Med.*, Vol. 57, 1-18, ISSN 0066-4219
- Freedman, B.I., Soucie, J.M., Chapman, A., Krisher, J. & McClellan, W.M. (2000). Racial variation in autosomal dominant polycystic kidney disease. *Am. J. Kidney Dis.*, Vol. 35, No.1, (January 2000) , pp. 35-39, ISSN 0272-6386
- Futrakul, N., Butthep, P. & Futrakul, P. (2008) Altered vascular homeostasis in chronic kidney disease. *Clin. Hemorheol. Microcirc.*, Vol.38, No.3, (2008), pp. 201-207, ISSN (online) 1386-0291
- Gabow, P.A., Johnson, A.M., Kaehny, W.D., Kimberling, W.J., Lezotte, D.C., Duley, I.T. & Jones, R.H. (1992). Factors affecting the progression of renal disease in autosomal-dominant polycystic kidney disease. *Kidney Int.*, Vol.41, No.6, (November 1992) pp. 1311-1319, ISSN 0085-2538
- Grantham, J.J & Calvet J.P. (2001) Polycystic kidney disease: In danger of being X-rated? *Proc Natl Acad Sci U S A.*, Vol.98, No. 3, (January 2001), pp. 790-792, ISSN 0027-8424
- Guo, Q., Carrero, J.J., Yu, X., Bárány, P., Qureshi, A.R., Eriksson, M., Anderstam, B., Chmielewski, M., Heimbürger, O., Stenvinkel, P., Lindholm, B. & Axelsson. J. (2009) Associations of VEGF and its receptors sVEGFR-1 and -2 with cardiovascular

- disease and survival in prevalent haemodialysis patients. *Nephrol. Dial. Transplant*, Vol.24, No.11, (November 2009), pp. 3468-3473, ISSN 0931-0509
- Hakroush, S., Moeller, M.J., Thelig, F., Kaissling, B., Sijmonsma, T.P., Jugold, M., Akeson, A.L., Traykova-Brauch, M., Hosser, H., Hähnel, B., Koesters, R. & Kriz, W. (2009) Effects of increased renal tubular vascular endothelial growth factor (VEGF) on fibrosis, cyst formation, and glomerular disease. *Am. J. Pathol.*, Vol.175, No.5, (November 2009), pp. 1883-1895, ISSN 0002-9440
- Heshmat, N.M. & El-Kerdany, T.H. (2007) Serum levels of vascular endothelial growth factor in children and adolescents with sytemic lupus erythematosus. *Pediatr. Allergy Immunol.*, Vol.18 No.4, (June 2007), pp. 346-353, ISSN 0905-6157
- Hoeben, A., Landuyt, B., Highley, H.W., Van Oosterom, A.T. & DeBruijn, E.A. (2004) Vascular endothelial growth factor and angiogenesis. *Pharmacol. Rev.*, Vol.56, (December 2004,) pp. 549-580, ISSN 0031-6997
- Holash, J., Maisonpierre, P.C., Compton, D., Boland, P., Alexander, C.R., Zagzag, D., Yancopoulos, G.D. & Wiegand, S.J. (1999) Vessel cooption, regression, and growth in tumors mediated by angiopoietins and VEGF. *Science*, Vol.284, No.5422, (June 1999) (1994-1998, ISSN 0036-8075
- Iliescu, R., Fernandez, S.R., Kelsen, S., Maric, C. & Chade, A.R (2009) Role of renal microcirculation in experimental renovascular disease. *Nephrol. Dial.Transplant.*, Vol. 25, No.4, (April 2004), pp.1079-1087, ISSN 0931-0509
- Ichinose, K., Maeshima, Y., Yamamoto, Y., Kitayama, H., Takazawa, Y., Hirokoshi, K., Sugiyama, H., Yamasaki, Y. & Eguchi, K. (2005) Antiangiogenic endostatin peptide ameliorates renal alterations in the early stage of a type 1 diabetic nephropathy model. *Diabetes*, Vol.54, No.10, (October 2005), pp. 2891-2903, ISSN 0012-1797
- Ichinose, K., Maeshima, Y., Yamamoto, Y., Kinomura, M., Hirokoshi, K., Kitayama, H., Takazawa, Y., Sugiyama, H., Yamasaki, Y. Agata, N. & Makino, H. (2006) 2-(8-hydroxy-6-methoxy-1-oxo-1h-2-benzopyran-3-yl) proprionic acid, an inhibitor of angiogenesis, ameliorates renal alterations in obese type 2 diabetic mice. *Diabetes*, Vol.55, No.5, (May 2006), pp. 1232-1242, ISSN 0012-1797
- Karapanen, T, Bry, M., Ollila, H.M., Seppänen-Laasko, T, Liimatta, H., Kivelä, R., Helkamaa, T., Merentie, M., Jeltsch, M., Paavonen, K., Andersson, L.C., Mervaala, E., Hassinen, I.E., Ylä-Herttuala, S., Oresic, M., & Alitalo, K. (2008) Overexpression of vascular endothelial growth factor-B in mouse heart alters cardiac lipid metabolism and induces myocardial hypertrophy. *Circ.Res.*, Vol.103, No.9, (October 2008), pp. 1018-1026, ISSN 0009-7330
- Kitamoto, Y., Takeya, M., Tokunaga, T. & Tomita, Y. (2001) Glomerular endothelial cells are maintained by vascular endothelial growth factor in the adult kidney. *Tohoku, J. Exp. Med.*, Vol.195, No.1, (September 2001), pp. 43-54, ISSN 0040-8727
- Kitayama, H., Maeshima, Y., Takazawa, Y., Yamamoto, Y., Wu, Y., Ichinose, K., Hirokoshi, K., Sugiyama, H., Yamasaki, Y. & Makino, H. (2006) Regulation of angiogenic factors in angiotensin II infusion model in association with tubulointerstitial injuries. *Am. J. Hyperens.*, Vol.19, No.7, (July 2006), pp. 718-727, ISSN 0895-7061
- Koch, S., Tugues, S., LI, X., Gualandi, L. & Claesson-Welsh, L. (2011) Signal transduction by vascular endothelial growth factor receptors. *Biochem. J.*, Vol.437, No.2, (July 2011), pp. 169-183, ISSN 0939-4451

- Konoshita, T., Okamoto, K., Koni, I. & Mabuchi, H. (1998). Clinical characteristics of polycystic kidney disease with end-stage renal disease. The Kanazawa Renal Disease Study Group. *Clin. Nephrol.*, Vol.50, No.2, (August 1998), pp. 113-117, ISSN 0301-0430
- Lim, H.S., Lip, G.Y. & Blann, A.D. (2005) Angiopoietin-1 and angiopoietin-2 in diabetes mellitus: relationship to VEGF, glycaemic control, endothelial damage/dysfunction and atherosclerosis. *Atherosclerosis*, Vol.180, No.1 (May 2005) pp.113-118, ISSN
- Lobov, I.B., Brooks, P.C. & Lang, R.A. (2002) Angiopoietin-2 displays VEGF-dependent modulation of capillary structure and endothelial cell survival in vivo. *Proc. Natl. Acad. Sci.*, Vol.99, No.17, (May 2002), pp. 11205-11210, ISSN 0027-8424
- Lovegrove, F.E., Tangpukdee, N., Opoka, R.O., Lafferty, E.I., Rajwans, N., Hawkes, M., Krudsood, S., Looareesuwan, S., John, C.C., Liles, C. & Kain, K.C. (2009) Serum Angiopoietin-1 and -2 levels discriminate cerebral malaria from uncomplicated malaria and predict clinical outcome in African children. *PlosOne*, Vol.4, No.3, (March 2009), pp. e4912, ISSN 1932-6203
- Maeshima, Y. & Makino, H. (2010) Angiogenesis and chronic kidney disease. *Fibrogenesis and Tissue Repair*, online Vol.3, No.13, (online August 5, 2010), ISSN 1755-1536
- Makinde, T. & Agarwal, D.K. (2008) Intra and extravascular transmembrane signaling of angiopoietin-1-Tie-2 receptor in health and disease. *J. Cell. Med.*, Vol.12, No.3, (June 2008), pp. 810-828, ISSN 1582-1838
- Mirmohammadsadegh, A., Marini, A., Nambiar, S., Hassan, M., Tannapfel, A., Ruzicka, T., & Hengge, U.R. (2006) Epigenetic silencing of the PTEN gene in melanoma. *Cancer Res*, Vol.66, No. 3, (July 2006) pp. 6546-6552, ISSN 0969-6970
- Mochizuki, T., Wu, G., Hayashi, T., Xenophontos, S.L., Veldhuisen, B., Saris, J.J., Reynolds, D.M., Cai, Y., Gabow, P.A., Pierides, A., Kimberling, W.J., Breuning, M.H., Deltas, C.C., Peters, D.J. & Somlo, S. (1996) PKD2, a gene for polycystic kidney disease that encodes an integral membrane protein. *Science*, Vol.272, No.5266, (May 1996), pp. 1339-1342, ISSN 0036-8075
- Mu, W., Long, D.A., Ouyang, X., Agarwal, A., Cruz, W.E., Roncal, C.A., Nakagawa, T., Yu, X., Hauswith, W.W. & Johnson, R.J. (2009) Angiostatin overexpression is associated with an improvement in chronic kidney injury by an anti-inflammatory mechanism. *Am. J. Physiol. Renal Physiol.*, Vol.296, No.1, (January 2009), pp. F145-F152, ISSN 0363-6127
- Na, X., Wu, G., Ryan, C.K., Schoen, S.R., di'Santagnese, P.A. & Messing, E.M. (2003) Overproduction of vascular endothelial growth factor related to von Hippel-Lindau tumor suppressor gene mutations and hypoxia-inducible factor-1 alpha expression in renal cell carcinomas. *J. Urol.*, Vol.170, No.2.pt1, (August 2003), pp. 588-592, ISSN 0970-1591
- Nadar, S.K., Blann, A.D. & Lip, G.Y. (2004) Plasma and platelet-derived vascular endothelial growth factor and angiopoietin-1 in hypertension: effects of antihypertensive therapy. *J. Intern. Med.*, Vol.256, No.4, (October 2004), pp. 331-337, ISSN 0954-6820
- Nadar, S.K., Blann, A., Beevers, D.G. & Lip, G.Y. (2005) Abnormal angiopoietins 1&2, angiopoietin receptor Tie-2 and vascular endothelial growth factor levels in hypertension: relationship to target organ damage [a sub-study of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)]. *J Intern Med.*, Vol.258, No 4, (October 2005), pp. 336-343, ISSN 0954-6820

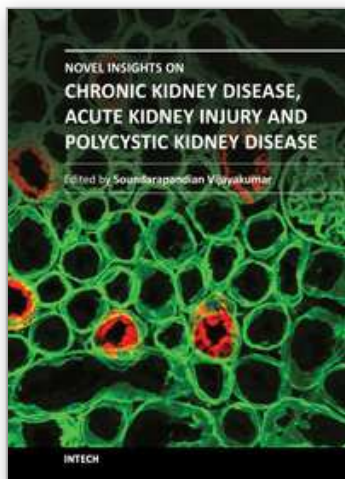
- Nasu, T., Maeshima Y, Kinomura, M., Hirokoshi-Kawahara, K, Tanabe, K., Sugiyama, H., Sonoda, H., Sato, Y. & Makino, H. (2009) Vasohibin-1, a negative feedback regulator of angiogenesis, ameliorates renal alterations in a mouse model of diabetic nephropathy. *Diabetes*, Vol.58, No.10, (October 2009), pp. 2365-2375, ISSN 0012-1797
- Nichols, M.T., Gidey, E., Matzakos, T., Dahl, R., Stiegmann, G., Shah, R.J., Grantham, J.J., Fitz, J.G. & Doctor, R.B. (2004) Secretion of cytokines and growth factors into autosomal dominant polycystic kidney disease liver cyst fluid. *Hepatology*, Vol.40, No.4, (October 2004), pp. 836-846, ISSN 1386-6346
- Obermüller, N., Morente, N., Kränzlin, B., Gretz, N. & Witzgall, R. (2001) A possible role for metalloproteinases in renal cyst development. *Am. J. Physiol. Renal Physiol.*, Vol. 280, No.3, (March 2001), pp. F540-F550, ISSN 0363-6127
- Ohgaki, H. & Kleihues, P. (2007) Genetic pathways to primary and secondary glioblastoma. *Am. J. Pathol.*, Vol.170, No.5 (May 2007), pp. 1445-1453, ISSN 0002-9440
- Ortega, N., Hutchings, H. & Plouët, J. (1999) Signal relays in the VEGF system. *Front. Biosci.*, Vol.4, (February 1999), pp. D141-D152, ISSN 1093-9946
- Otrock, Z.K., Mahfouz, R.A., Makarem, J.A. & Shamseddine, A.I. (2007) Understanding the biology of angiogenesis: review of the most important molecular mechanisms. *Blood Cells Mol. Dis.*, Vol.39, No.2, (September-October 2007), pp. 212-220, ISSN 1079-9796
- Park, J.H., Park, K.J., Kim, Y.S., Sheen, S.S., Lee, K.S., Lee, H.N., Oh, Y.J. & Heang, S.C. (2007) Serum angiopoietin-2 as a clinical marker for lung cancer. *Chest*, Vol.132, No.1, (July 2007), pp. 200-206, ISSN 0012-3692
- Park, J., Choi, H., Kim, Y., Kim, Y., Sheen, S., Choi, J., Lee, H., Lee, K., Chung, W., Lee, S., Park, K., Hwang, S., Lee, K. & Park, K. (2009) Serum angiopoietin-1 as a prognostic marker in resected early stage lung cancer. *Lung Cancer*, Vol.66, No.1-2, (December 2009), pp. 359-364, ISSN 0169-5002
- Pei, Y. (2011) Practical genetics for autosomal dominant polycystic kidney disease. *Nephron Clin. Pract.*, Vol.118, No.1, (January 2011), pp. c19-c30, ISSN 1660-8151
- Persson, A.B. & Buschmann, I.R. (2011) Vascular growth in health and disease. *Front. Mol. Neurosci.*, Vol.14, Epub., August 2011, ISSN 0892-6638
- Pugh, C.W. & Ratcliffe PJ. (2003) Regulation of angiogenesis by hypoxia: role of the HIF system. *Nat Med*. Vol.9, No.6, (June 2003), pp. 677-684, ISSN 1340-3443
- Reed, B.Y., Masoumi, A., Elhassan, E., McFann, K., Cadnapaphornchai, M. & Schrier, R.W.(2011) Angiogenic growth factors in young patients with autosomal dominant polycystic kidney disease. *Am. J. Kidney Disease*, Vol.79, No.1, (January 2011), pp. 128-134, ISSN 0272-6386
- Robert, B., Zhao, X. & Abrahamson, D.R. (2000) Coexpression of neuropilin-1, Flk1, and VEGF(164) in developing and mature mouse kidney glomeruli. *Am. J. Physiol. Renal Physiol.*, Vol.279, No.2, (August 2000), pp. F275-282, ISSN 0363-6127
- Rosner, M., Hanneder, M., Siegel, N., Valli, A., Fuchs, C. & Hengstschläger, M. (2008) The mTOR pathway and its role in human genetic diseases. *Mut. Res.*, Vol.659, No.3, (September – October), pp. 284-292, ISSN 1383-5718
- Rudnicki, M., Perco, P., Enrich, J., Eder, S., Heininger, D., Bernthaler, A., Sarközi, R., Noppert, S.J., Schramek, H., Mayer, B., Oberbauer, R. & Mayer, G. (2009) *Lab. Invest.*, Vol.89, No.3, (January 2009), pp. 337-346, ISSN 0023-6837



- Saito, T., Yamamoto, Y., Matsumura, T., Fujimura, H. & Shinno, S. (2009) Serum levels of vascular endothelial growth factor elevated in patients with muscular dystrophy. *Brain Dev.*, Vol.31, No.8, (September 2009), pp. 612-617, ISSN 0387-7604
- Satchell, S.C., Anderson, K.L. & Mathieson, P.W. (2004) Angiopoietin 1 and vascular endothelial growth factor modulate human glomerular endothelial cell barrier properties. *J. Am. Soc. Nephrol.*, Vol.15, No.3, (March 2004), pp.566-574, ISSN1046-6673
- Schrier, R.W. (2006) Optimal care of autosomal dominant polycystic kidney disease patients. *Nephrology* Vol.11, No.2, (April 2006), pp.124-130, ISSN 1320-5358
- Seeman, T., Dusek, J., Vondrichova, H., Kyncl, M., John, U., Misselwitz, J. & Janda, J. (2003). Ambulatory blood pressure correlates with renal volume and number of renal cysts in children with autosomal dominant polycystic kidney disease. *Blood Press. Monit.*, Vol 8, No.3, (June 2003), pp. 107-110, ISSN 1359-5237
- Shillingford, J.M., Murcia, N.S., Larson, C.H., Low, S.H., Hedgepeth, R., Brown, N., Flask, C.A., Novick, A.C., Goldfarb, D.A., Kramer-Zucker, A., Walz, G., Piontek, K.B., Germino, G.G. & Weimbs, T. (2006) The mTOR pathway is regulated by polycystin-1, and its inhibition reverses renal cystogenesis in polycystic kidney disease, *Proc. Natl. Acad. Sci. USA.*, Vol.103, No.14, (April 2006), pp. 5466-5471, ISSN 0027-8424
- Simon, M., Grone, H.J., Jöhren, O., Kullmer, J., Plate, K.H., Risau, W. & Fuchs, E. (1995) Expression of vascular endothelial growth factor and its receptors in human renal ontogenesis and in adult kidney. *Am. J. Physiol. Renal Physiol.*, Vol.268, No.2 pt. 2, (February 1995), pp. F240-F250, ISSN 0363-6127
- Song, X., DiGiovanni, V., He, N., Wang, K., Ingram, A., Rosenblum, N.D. & Pei, Y. (2009) Systems biology of autosomal dominant polycystic kidney disease (ADPKD): computational identification of gene expression pathways and integrated regulatory networks. *Hum. Mol. Genet.*, Vol.18, No.13, (July 2009), pp.2328-2343, ISSN 0964-6906
- Sugimoto, H, Hamano, Y., Charytan, D., Cosgrove, D., Kieran, M., Sudhakar, A. & Kalluri, R. (2003) Neutralization of circulating vascular endothelial growth factor (VEGF) by anti-VEG antibodies and soluble VEGF receptor 1 (sFlt-1) induces proteinuria. *J. Biol. Chem.*, Vol.278, No.15, (April 2003), pp. 12605-12608, ISSN 0021-9258
- Tam, K.F., Liu, V.W., Liu, S.S., Tsang, P.C., Cheung, A.N., Yip, A.M. & Ngan, H.Y. (2007) Methylation profile in benign, borderline and malignant ovarian tumors. *J. Cancer Res. Clin. Oncol.*, Vol.133, No.5, (May 2007), pp. 331-341, ISSN 0171-5216
- Tao, Y., Kim, J., Yin, Y., Zafar, I., Falk, S., He, Z., Faubel, S., Schrier, R.W. & Edelstein, C.L. (2007) VEGF receptor inhibition slows the progression of polycystic kidney disease. *Kidney Int.*, Vol.72, No.11, (December 2007), pp.1358-1366, ISSN 0085-2538
- Thomas, S., Vanuystel, J., Gruden, G., Rodríguez, V., Burt, D., Gnudi, L., Hartley, B. & Viberti, G. (2000) Vascular endothelial growth factor receptors in human mesangium in vitro and in glomerular disease. *J. Am. Soc. Nephrol.*, Vol.11, No.7, (July 2000), ISSN 1046-6673
- Torres Filho I.P., Leunig, M., Yuan, F., Intaglietta, M. & Jain R.K. (1994) Noninvasive measurement of microvascular interstitial oxygen profiles in human tumor SCID mice. *Proc Natl Acad Sci U S A.*, Vol.91, No 6, (March 1994), pp. 2081-2085, ISSN 0027-8424



- Torres, V.E., King, B.F., Chapman, A.B., Brummer, M.E., Bae, K.T., Glockner, J.F., Arya, K., Risk, D., Felmlee, J.P., Grantham, J.J., Guay-Woodford, L.M., Bennett, W.M., Klahr, S., Meyers, C.M., Zhang, X., Thompson, P.A. & Miller, J.P. (2007) Magnetic resonance measurements of renal blood flow and disease progression in autosomal dominant polycystic kidney disease. *Clin. J. Am. Soc. Nephrol.*, Vol.2, No.1, (January 2007), pp. 112-120, ISSN 1555-9041
- Veron, D., Reidy, K.J., Bertuccio, C., Teichman, J., Villegas, G., Jimenez, J., Shen, W., Kopp, J.B., Thomas, D.B. & Turfo, A. (2010) Overexpression of VEGF-A in podocytes of adult mice causes glomerular disease. *Kidney Int.*, Vol.77, No.11, (June 2010), pp. 989-999, ISSN 0085-2538
- Wang, G.L. & Semenza, G.L. (1995) Purification and characterization of hypoxia-inducible factor 1. *J. Biol. Chem.*, Vol. 270, No. 3, (January 1995), pp. 1230-1237, ISSN 0021-9258
- Wei, W., Popov, V., Walocha, J.A., Wen, J., Bello-Reuss, E. (2006) Evidence of angiogenesis and microvascular regression in autosomal-dominant polycystic kidney disease kidneys: a corrosion cast study. *Kidney Int.*, Vol.70, No.7, (October 2006), 1261-1268, ISSN 0085-2538
- Yamakawa, M., Liu, L.X., Belanger, A.J., AJ, Date, T., Kuriyama, T., Goldberg, M.A., Cheng, S.H., Gregory, R.J. & Jiang, C. (2004) Expression of angiopoietins in renal epithelial and clear cell carcinoma cells: regulation by hypoxia and participation in angiogenesis. *Am. J. Physiol. Renal Physiol.*, Vol.287, No.4, (October 2004), pp. F649-657, ISSN 0363-6127
- Yamamoto, Y., Maeshima Y., Kitayama H., Kitamura S., Takazawa Y., Sugiyama H., Yamasaki Y. & Makino, H. (2004) Tumstatin peptide, an inhibitor of angiogenesis prevents glomerular hypertrophy in the early stage of diabetic nephropathy. *Diabetes*, Vol.53, No. 7, (July 2004), pp. 1831-1840, ISSN 0012-1797
- Yuan, H.T., Suri, C., Yancopoulos, G.D. & Woolf, A.S. (1999) Expression of angiopoietin-1, angiopoietin-2 and the Tie-2 receptor tyrosine kinase during mouse kidney maturation. *J. Am. Soc. Nephrol.*, Vol.10, No.8, (August 1999), pp. 1722-1736, ISSN 1046-6673
- Zhang, S.X., Wang, J.J., Lu, K., Mott, R., Longeras, R. & Ma, J.X. (2006) Therapeutic potential of angiostatin in diabetic nephropathy. *J. Am. Soc. Nephrol.*, Vol.17, No.2, (February 2006), pp. 475-486, ISSN 1046-6673
- Zhu, X.Y., Chade, A.R., Rodriguez-Porcel, M., Bentley, M.D., Ritman, E.L., Lerman, A. & Lerman, L.O. (2004) Cortical microvascular remodeling in the stenotic kidney: role of increased oxidative stress. *Arterioscler. Thromb. Vasc. Biol.*, Vol. 24, No.10, (October 2004), pp. 1854-1859, ISSN 1079-5642



## **Novel Insights on Chronic Kidney Disease, Acute Kidney Injury and Polycystic Kidney Disease**

Edited by Dr. Soundarapandian Vijayakumar

ISBN 978-953-51-0234-2

Hard cover, 134 pages

**Publisher** InTech

**Published online** 07, March, 2012

**Published in print edition** March, 2012

This book offers novel insights on topics such as congenital obstructive nephropathy, cerebral-renal salt wasting, and the role of hemoglobin variability in clinical outcomes of CKD which are not very often discussed in the literature. With comprehensive and insightful reviews by eminent clinicians and scientists in the field, this book is a valuable tool for nephrologists.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Berenice Reed and Wei Wang (2012). Angiogenesis and the Pathogenesis of Autosomal Dominant Polycystic Kidney Disease, Novel Insights on Chronic Kidney Disease, Acute Kidney Injury and Polycystic Kidney Disease, Dr. Soundarapandian Vijayakumar (Ed.), ISBN: 978-953-51-0234-2, InTech, Available from: <http://www.intechopen.com/books/novel-insights-on-chronic-kidney-disease-acute-kidney-injury-and-polycystic-kidney-disease/angiogenesis-and-the-pathogenesis-of-autosomal-dominant-polycystic-kidney-disease>

**INTECH**  
open science | open minds

### **InTech Europe**

University Campus STeP Ri  
Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166  
[www.intechopen.com](http://www.intechopen.com)

### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen