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Implications of the PAPP-A-IGFBP-IGF-1 pathway in the pathogenesis and treatment of polycystic kidney disease

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common genetic diseases implicated in the development of end stage renal disease (ESRD). Although FDA has recently approved a drug against ADPKD, there is still a great need for development of alternative management strategies for ADPKD. Understanding the different mechanisms that lead to cystogenesis and cyst expansion in ADPKD is imperative to develop new therapies against ADPKD. Recently, we demonstrated that caloric restriction can prevent the development of cystic disease in animal models of ADPKD and through these studies identified a new role for pregnancy associated plasma protein-A (PAPP-A), a component of the insulin-like growth factors (IGF) pathway, in the pathogenesis of this disease. The PAPP-A-IGF pathway plays an important role in regulation of cell growth, differentiation, and transformation and dysregulation of this pathway has been implicated in many diseases. Several indirect studies support the involvement of IGF-1 in the pathogenesis of ADPKD. However, it was only recently that we described a direct role for a component of this pathway in pathogenesis of ADPKD, opening a new avenue for the therapeutic approaches for this cystic disease. The present literature review will critically discuss the evidence that supports the role of components of IGF pathway in the pathogenesis of ADPKD and discuss the pharmacological implications of PAPP-A-IGF axis in this disease.

Keywords

Autosomal dominant polycystic kidney disease (ADPKD); Pregnancy associated plasma protein-A (PAPP-A); Insulin like growth factors (IGFs); Insulin growth factor binding protein (IGFBP); metalloproteases

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD), one of the most common genetic diseases is caused by mutations in *PKD1* and *PKD2* genes which encodes polycystin 1 (PC1) and polycystin 2 (PC2) proteins respectively [1]. The hyperproliferation of tubular epithelial cells causes cyst formation and the cyst expansion eventually leads to the kidney enlargement which often results in ESRD [2]. Although FDA has recently approved tolvaptan drug against ADPKD to slow the progression of cystic disease, there are several adverse effects of this drug that make it unsuitable for many patients [3]. Therefore, the management strategies for ADPKD still remain largely supportive and limited. It is extremely important to understand the different molecular mechanisms that lead to cystogenesis and cyst expansion in order to develop new therapeutic strategies for management of ADPKD. Many signaling pathways have been reported to be involved in the pathogenesis of ADPKD including cyclic AMP (cAMP), MAPK/ERK, mammalian target of rapamycin (mTOR), AMP-activated protein kinase (AMPK) and growth factors [4–6]. The present review will explore the role of components of IGF pathway in ADPKD and its potential therapeutic implications. In particular, we will discuss the complexity of IGF pathway and the regulation of IGF bioavailability by the metalloproteinase, pregnancy associated plasma protein-A (PAPP-A).

The pathogenesis of ADPKD

Mutation in *PKD1* gene is responsible for about 80% ADPKD patients, whereas *PKD2* gene mutation accounts for 15% cases [7]. ADPKD patients generally carry a germline mutation in one allele of either PKD1 or PKD2, and second hits like somatic inactivation of the remaining wild-type PKD1 or PKD2 allele or loss of heterozygosity should occur in order to initiate the cyst formation [8]. The activity of the polycystins complex is thought to be necessary to prevent the cell-autonomous renal epithelial cell cystogenesis and when the level of functional PC1 or PC2 is reached below a certain critical threshold level, it leads to cystogenesis [8, 9]. The polycystins form multimeric protein complexes that are involved in regulation of components of various signaling cascades including Ca2+, cAMP and mTOR. The reduction in functional PC1 or PC2 therefore leads to several cellular alterations in cystic epithelial cells including cellular processes like fluid transport, proliferation, apoptosis, cell adhesion and differentiation [5, 10–12]. Reduction in Ca2+ influx, induction in cAMP levels, and abnormal activation of MAPK/ERK pathway in renal epithelial c ells are critical mediators of cyst growth and expansion [9]. Other mechanisms that have also been shown to be involved in cyst growth include dysregulated signaling of heterotrimeric G proteins, mTOR, phosphoinositide 3-kinase (PI3K)/Akt, AMPK, Janus kinase -signal transducer and activator of transcription (JAK/STAT) and nuclear factor-κB (NF-κB) pathway [13–16]. Additionally, metabolic alterations including defective glucose metabolism, impaired beta-oxidation, and abnormal mitochondrial activity are also shown to be associated with cyst expansion [17–22].

Therefore, cyst expansion is an important factor in the pathogenesis of ADPKD which results in compression and damage of surrounding tissue, and eventually leads to inflammation, fibrosis and kidney failure [4]. It is clear that the expansion of cysts involves

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several mechanisms including dysregulation in cell proliferation processes. Therefore, the possibility of involvement of growth factors pathways cannot be denied in pathogenesis of ADPKD. In fact, epidermal growth factors (EGF), fibroblast growth factor 23 (FGF23) and insulin like growth factors (IGFs) have been reported to be involved in ADPKD [23–26]. However, to date the specific role and mechanisms of dysregulation of growth factor pathways in ADPKD have not been elucidated. In particular, the role of components of the IGF-1 pathway in ADPKD is largely unknown.

IGF-1 pathway in ADPKD

Circulating IGF-1 is mainly produced in liver and exerts endocrine effects, but locally produced IGF-1 acts in an autocrine/paracrine manner. Therefore, IGFs can function as circulating hormones as well as tissue growth factors. The effects of both IGF-1 and IGF-2 are largely mediated through the IGF-1 receptor. Interaction of IGF-1 with IGF-1R triggers PI3K-Akt and mitogen-activated protein kinase (MAPK) pathways which regulate processes like cellular metabolism, apoptosis, cell adhesion, and angiogenesis [27, 28]. Since these pathways have also been shown to be involved in ADPKD pathogenesis, understanding the exact role of the IGF pathway and its components in ADPKD could identify potential new therapeutic targets for this cystic disease. The IGF-1 pathway is a complex growth factor pathway with multiple regulatory components [29]. It plays a key role in several physiological and pathological conditions such as aging, cancer, and tissue growth [30–34]. While it has previously been speculated that IGF-1 may play a role in ADPKD [35–40], no direct causal or mechanistic *in vivo* data implicating a role for any of the components of the IGF1 pathway in ADPKD can be found in the literature. In fact, the role of components of the IGF-1 pathway had never been directly tested in ADPKD until recently [41].

Components of the IGF pathway

As mentioned above, IGF pathway is a complex system consisting of two peptides: IGF-1 and IGF-2, two receptors: IGF-1 and −2 receptors (IGF-1R and IGF-2R), six IGF-binding proteins (IGFBP-1–6) and IGFBP proteases (Figure 1).

IGF ligands—IGFs are crucial for normal growth and development. They promote cell proliferation, differentiation and survival and also exert insulin-like metabolic effects in a wide range of cells and tissues. Although, hepatocytes are the main source of circulating IGF-1, IGFs are ubiquitously expressed on cells and have multiple endocrine, autocrine and paracrine effects [42]. IGF-I production is stimulated by growth hormone (GH) and insulin. IGF-I can also be released independent of GH. IGF-1 and IGF-2 belong to the same family and were first characterized as possessing insulin like activity [43]. IGFs share nearly 50% homology with insulin. In humans, *Igf1* gene is located on the chromosome 12q23 [44]. It has 6 exons and four transcriptional variants that are originated by alternative splicing [45], generating different isoforms for this gene, namely IGF-IEa (MGF), IGF-IEb, and IGF-IEc. These isoforms are differentially regulated, for instance, in response to exercise or muscle regeneration [46, 47]. *Igf2* gene is located on chromosome 11, possesses 9 exons and also gives rise to multiple mRNA variants and three isoforms, which have tissue specific expression [45, 48]. This transcriptional diversity contributes to IGF-1 and IGF-2 regulation, but the mechanisms involved are still mostly unknown. IGF-1 plays an important role in

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aging, fetal development, growth during childhood and adolescence, and tissue homeostasis. On the other hand, IGFs are risk factors in obesity and cancer due to the potent proliferative activity [31, 34, 49, 50].

IGF-1 receptors—IGFs exert their effects by interacting with the specific cell surface receptors known as IGF-1R and IGF-2R. IGFRs are tyrosine kinase receptors that are extensively expressed on mammalian tissues [51–53]. IGF-1R shares approximately 60% homology with the insulin receptor (IR) and a number of their downstream molecules are the same, including insulin substrate-1, PI3K, protein kinase B (PKB/Akt), mTOR and p70S6 kinase. IGF-1R is a heterotetrameric receptor comprising two α and two β subunits ($\alpha_2\beta_2$). Similar to the IR, IGFRs require a series of post-translational modifications such as glycosylation, disulfide linkage, and proteolytic cleavage before reaching their mature form consisting of two α subunits, containing the ligand biding site, and two β subunits, consisting the transmembrane and tyrosine kinase domains [54, 55]. Upon binding to IGFs, IGFR undergoes conformational changes that bring β subunits to close proximity triggering trans-autophosphorylation of the β subunits and activating the cytoplasmic tyrosine kinase domain. IGF-2 also binds to IGF-1R but with lower affinity compared with IGF-1. The IGF-2R, also known as the cation independent mannose 6-phosphate receptor, is a large single transmembrane protein with no homology with the IGF-IR. It binds to IGF-2 with higher affinity compared to IGF-1 [56]. The signaling pathways activated by the IGF-2R are not well defined. Most of the biological actions of IGF-2 are believed to be mediated by IGF-IR.

IGF-binding proteins—IGF-biding proteins (IGFBPs) are the important members of the IGF system and association between IGFs and IGFBPs is a major regulatory step in the IGF signaling pathway [57]. These proteins are present in the extracellular space as well as in the circulation and possess high affinity to IGFs [58, 59]. Over 95% of IGFs in serum are bound to IGFBPs. As the affinity of IGFBPs for IGFs is higher than the affinity of IGF to the cell - surface IGF-IR, IGFs which are bound to IGFBPs do not bind to IGF-IR. Thus, IGFBPs, in addition to stabilizing IGF by increasing its half-life in tissues and blood, play an important role in preventing the interaction between IGFs and their receptors for downstream signaling [57]. For example, in vascular smooth muscle cells (VSMCs), IGFBP-4 binds to IGF-1 and blocks its interaction with the IGF1R inhibiting IGF-1-stimulated DNA synthesis [60]. In addition, liver specific deletion of IGF-1 resulted in 80% reduction in circulating IGF-I, but did not change postnatal growth, indicating the importance of local IGF-1 [61].

Six members of IGFBP family, IGFBP-1 to IGFBP-6 have been identified [57]. IGFBPs share structurally similar features such as a three-domain structure cysteine-rich C and N-terminals, which are stabilized by multiple disulfide bounds, with a central linker domain in between [62]. Both N- and C- terminal domains are highly conserved across IGFBP family and form the IGF-binding site. Their structural domains include binding sites to components of the extracellular matrix, proteolytic cleavage sites, and sites for post-translational modifications [57, 62]. Although structurally similar, the different IGFBP proteins have distinct functions and their expression and mechanisms of regulation are cell and tissue specific. For instance, IGFBP-3, and to some extent IGFBP-5, can form a ternary complex

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of 150 kDa with IGF and the glycoprotein acid labile subunit (ALS) [63, 64]. ALS stabilizes this complex extending its half-life in the circulation; therefore this association is important to keep IGF in the circulation for a longer period of time compared to its binary complex due to its high molecular size. While the majority of circulating IGFBP-3 and IGFBP-1 are produced in the liver, IGFBP-3 and other IGFBPs are also expressed in many peripheral tissues [57]. Hepatic expression is regulated by different stimuli e.g. IGFBP-3 expression is regulated in response to GH stimulation [65, 66], whereas IGFBP-1 expression is increased by starvation, hypoxia, and glucocorticoids and decreased in response to insulin [67–70]. In some circumstances, some IGFBPs may also potentiate IGF actions. For instance, when associated with extracellular matrix components, IGFBP-5 affinity to IGF can decrease upon biding to some components of the extracellular matrix which further regulates the effects of IGF-1 [71, 72]. Interestingly, IGFBPs also have IGF-independent functions like cell migration promotion by binding to cell surface proteins such as integrins [73, 74]; antiangiogenic activity promoted by IGFBP-6 interaction with vascular endothelial growth factor (VEGF) [75]; and transcriptional transactivator functions in the nuclei [76–78].

In addition, IGFBP-related proteins (IGFBP-rP1–9) have been identified, which have several fold lower binding affinity for IGFs than IGFBPs, but their physiological and pathophysiological functions are still not clear [79].

IGFBP proteases—IGFBP proteases cleave IGFBPs into fragments that have lower affinity for IGFs. The reduced affinity of IGFBP fragments towards IGFs leads to the increased bioavailability of IGFs and thus activates IGF receptors and downstream signaling. Although, there are three major groups of proteases which cleave IGFBPs and modulate the availability of free IGF, consisting serine proteases, cathepsins and matrix metalloproteinases [80–85] (Table 1), this review will mainly focus on metalloproteinase, PAPP-A.

Pappalysins are proteases in the metzincin superfamiliy of metalloproteinases, and pregnancy associated plasma protein-A (PAPP-A), alias pappalysin-1, is the founding member of this protease family [86, 87]. PAPP-A specifically cleaves IGFBP4 in an IGF-dependent manner [88] and may be the only protease responsible for IGFBP-4 cleavage under physiological condition [89]. Although IGFBP-4 is the main substrate of PAPP-A, it has also been reported to cleave IGFBP-5 [90] and IGFBP-2 [91] in an IGF-independent manner. PAPP-A2 a paralog of PAPP-A, is the second member of pappalysin family and cleaves IGFBP-5 and IGFBP-3 in an IGF-independent manner [92].

Role of PAPP-A in regulation of local IGF signaling in tissues

PAPP-A was first identified as one of the placental proteins present at higher levels in serum of pregnant women [93, 94]. During pregnancy, it is primarily produced by placental syncytiotrophoblasts and secreted into the circulation, increasing its levels from early detection at first trimester until delivery at term. Initially, despite being recognized as a clinically relevant marker used in screening for Down’s syndrome [95], PAPP-A was considered a pregnancy protein with no physiological function. In 1990s, several studies reported the novel IGF-dependent protease activity of PAPP-A towards IGFBP-4 in cell

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culture media from various cell types [96–98], however, Lawrence et al were first to prove that PAPP-A was the protease responsible for the IGF-dependent protease activity towards IGFBP-4 [88]. Subsequently, PAPP-A was reported to specifically cleave IGFBP-4 in human, ovine, bovine, equine, and porcine ovarian follicular fluid and shown to be expressed in granulosa cells of these mammals and in culture media from osteoblasts, lung cells, smooth muscle cells [99] [100–104]. Over the past years, PAPP-A has been reported to be ubiquitously expressed in multiple tissues [86, 94] and shown to have important roles in several physiological functions outside of pregnancy [105, 106].

PAPP-A exists in two major forms. During pregnancy, it circulates as a disulfide bound 500kDa heterotetrameric complex consisting of 2 PAPP-A subunits covalently bound to two proform of eosinophil major basic protein (pro-MBP) [107] [105]. ProMBP is the endogenous inhibitor of PAPP-A, thus in this complex, PAPP-A is proteolytic inactive. proMBP recognizes cell bound PAPP-A and readily forms a complex which is unable to bind to cell surface, thus it enters the circulation [108]. On the other hand, the non-pregnant form of PAPP-A is a proteolytically active homodimer not covalently linked with pro-MBP.

Human PAPP-A sequence is comprised of 1547 amino acid residues with a distinct set of protein modules (Figure 2). In each subunit, at N-terminal, there is a 250-residue laminin G-like module with unspecified function followed by a 350 residue proteolytic domain containing the so-called elongated zinc binding consensus sequence and a short sequence for Met-turn formation, which are the characteristics of the metzincin super family of metalloproteinases [87]. The proteolytic domain is then followed by two regions M1 and M2 which are not very well characterized yet. The C-terminal module has five short consensus repeat (SCR) modules or complement control protein (CCP) modules, SCR 1–5. SCR3 and SCR4 are responsible for binding to glycosaminoglycans (GAGs) present on cell surfaces, enabling interactions between PAPP-A and cell surfaces [86]. PAPP-A also contains three Lin12-Notch repeat (LNR) modules, and each binds a calcium ion and determines the proteolytic specificity. LNR1–2 is present in the proteolytic domain and LNR-3 is in the C domain.

PAPP-A proteolytic activity cleaves IGFBP-4 at Met-135/Lys-136 in the linking domains and this cleavage only happens when IGFBP-4 is bound to IGF-1, thus showing its dependency on IGF-1. N- and C-terminal domains of IGFBPs have reduced affinity for IGFs, therefore this cleavage of IGFBP-4 by PAPP-A allows dissociation of bound IGF and increases its local bioavailability [109]. Proteolytically active PAPP-A is cell surface bound; therefore cleavage of IGFBP-4 happens in close proximity to IGF1R and released bioactive IGFs can interact with its receptors and trigger downstream signaling. This in turn enhances the effects of IGFs on cell proliferation, survival, and differentiation. Therefore, proteolysis of IGFBP-4 by cell surface bound PAPP-A is the final modulating step delivering IGF to its receptor.

The effects of PAPP-A are reported to be mainly local. For example, PAPP-A deficient mice, which are about 40% smaller than their wild-type littermates, showed no proteolytic activity against IGFBP-4 and no changes in circulating IGF levels, suggesting that PAPP-A plays a role in the regulation of autocrine/paracrine (but not endocrine) effects of IGF and local IGF

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bioavailability [89]. Furthermore, transgenic mice over-expressing PAPP-A in skeletal muscle and osteoblasts have increased skeletal muscle mass and bone formation respectively [110, 111]. However, dual overexpression of a protease-resistant IGFBP-4 along with PAPP-A completely diminished these anabolic effects of PAPP-A in mice [112] indicating that an increase in local IGF bioavailability through IGFBP proteolysis is the primary reason for the anabolic effects caused by PAPP-A. In summary, PAPP-A is not a direct inhibitor of IGF signaling, but acts as an important regulator in local bioavailability in IGF through proteolysis of IGFBP-4. PAPPA activity can be regulated by different protein binding inhibitors such as stanniocalcins (STNC). Both STNC1 and 2 have been shown to bind to PAPP-A and inhibit its proteolytic activity providing an extra layer of regulation for the IGF system [113].

PAPP-A expression in cultured cells is shown to be upregulated by proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6 [114, 115]. PAPP-A is also upregulated by TGFβ, IL-4, as well as by the cAMP-inducing agent forskolin and other factors [106].

Several lines of evidence indicate an important role for PAPP-A in a number of physiological and pathological conditions. PAPP-A plays a crucial role during pregnancy [103, 116] by regulating the IGF bioavailability. The IGFs play an important role in regulating fetal growth [117] [118], autocrine and paracrine control of trophoblast invasion of decidua and early development and vascularization of placenta [119]. Thus, during pregnancy, high levels of un-complexed PAPP-A could be required locally for placental development, whereas in circulation PAPP-A:proMBP complex inhibits the proteolytic activity of PAPP-A which would otherwise lead to unusual systemic higher IGFBP-4 proteinase activity. Low levels of PAPP-A in maternal plasma during the first trimester have been linked with Down syndrome, as well as many abnormal pregnancy outcomes including pregnancy induced hypertensive disorders, premature delivery, and still birth [120–122]. Low levels of PAPP-A in pregnancy can be associated with high IGFBPs and consequently less availability of free IGF. Therefore, reduced availability of free IGF that can interact with its receptor could lead to abnormal pregnancy outcome. Outside pregnancy, PAPP-A expression has been shown to be upregulated in vascular injury models in pigs [101], and mice [123] and also in healing skin wounds in human [124] indicating a role for PAPP-A in vascular injury and tissue remodeling. PAPP-A also plays an important role in healthy ovarian follicular development [99, 125, 126] and regulates prenatal or postnatal growth and skeletal muscle formation [110]. In addition, PAPP-A has also been implicated in the pathogenesis of many diseases like atherosclerosis and cancer, as well as age-related disorders [127–133]. Plasma PAPP-A is present at higher levels in patients on dialysis, and is an independent predictor of mortality of patients on hemodialysis [134, 135]. Elevated PAPP-A levels have also been associated with diabetes [136] and cerebrovascular diseases [137].

What is known about IGF pathway in ADPKD.

Several indirect lines of evidence over the years have indicated that the IGF-I could be involved in progression of cystic lesions in ADPKD (Table 2). Initially, a study by

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Nakamura et al [35] had reported that renal I*gf1* mRNA expression increased progressively with age in the DBA/2FG-pcy mouse model of PKD compared to the control DBA/2 mice. The authors suggested that decreased mRNA expression of renal epidermal growth factor and increased mRNA expression of IGF-l, PCNA, TGFβ, PDGF-A and PDGF-B chains as well as bFGF might be involved in progression of cystic disease in DBA/2FG-pcy mice. Later, Aukema and Housini also reported that in Han:SPRD-cy rat model of PKD, IGF-1 levels were 32 to 76% higher in kidneys of cy/+ (heterozygotes for PKD mutation) compared with control rats (+/+). Treatment with dietary soy protein delayed the progression of cystic disease and reduced the kidney IGF-1 levels in male and female cy/+ rats [36]. Both of these studies indicated that the levels of IGF-1 are increased in rodent ADPKD models.

Using the conditionally immortalized tubular epithelial cells from human ADPKD patients with defined germline *PKD1* mutations, Parker et al showed that polycystin-1 deficiency was linked to increased sensitivity to IGF-1. In cystic cells, IGF-1 stimulated cell proliferation in a dose-dependent manner (38). These authors also showed that IGF-1, as well as cAMP, stimulated proliferation in these cystic cells in a PI3K- and ERK-activity dependent manner. Higher IGF-1-stimulated GTP-Ras levels were observed in PKD1 cystic cells compared to control cells, indicating that PC1 deficiency could lower the threshold for activation of Ras-Raf-mediated signaling; leading to IGF induced hyper proliferation.

A later study employed a systems biology approach to explore the growth-modulating gene pathways in renal cyst growth in ADPKD [37]. Song et al performed global gene profiling on cysts of different sizes and minimally cystic tissues (MCT) from five PKD1 human polycystic kidneys and used gene set enrichment analysis to identify the dysregulated signaling pathways, as well as key transcription factors, between cysts and MCT. They observed that human PKD1 cysts showed downregulation of kidney epithelial differentiation genes and up-regulation of developmental and mitogenic signaling pathways. Interestingly, the up-regulation of IGF-1/IGF-1R pathway was observed along with Wnt/β-catenin, G-protein-coupled receptor signaling, and was associated with renal cystic growth. This further supported the role of the IGF axis in renal cyst growth.

In addition to these studies, Liu et al [39] also reported that in cell culture studies, IGF-1 increased the cystic epithelial cells growth by 15–20% in a dose-dependent manner compared to normal cortical tubular epithelia cells. Rosiglitazone, a thiazolidinediones (TZD) inhibited the proliferation-inducing activity of IGF-1 in cystic cells, in part by inhibiting the IGF-1-induced p70S6K activation.

In a previous study, we showed that food restriction ameliorates the cystic disease in murine models of ADPKD [40]. Interestingly, in that study we also found that food restriction, which significantly reduced the cystic disease, also reduced the serum IGF-1 levels, as well as renal *Igf1* mRNA expression, indicating a potential role for IGF-1 in the pathogenesis of ADPKD.

All these studies together indirectly support the idea that the IGF-1 pathway is involved in ADPKD. However, because the IGF system is complex and consists of several components,

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it is imperative to determine which components of the IGF pathway are involved in the pathogenesis of PKD. It wasn't until recently that a direct role for any component of the IGF pathway was clearly demonstrated in ADPKD [41] (Table 2). In fact, our recent work demonstrated that IGF-1 and other components of this pathway are upregulated in ADPKD, and reported that the metalloproteinase PAPP-A plays a crucial role in ADPKD pathogenesis by increasing the local bioavailability of IGF-1 [41].

PAPP-A as a therapeutical target in ADPKD

As mentioned above, several studies provided indirect evidences that the IGF-1 pathway is involved in pathogenesis of ADPKD. Our recent study, for the first time, evaluated different IGF pathway components in ADPKD and demonstrated that PAPP-A plays a central role in pathogenesis of ADPKD. A significant increase in gene expression of several components of IGF-1 pathway was observed in ADPKD, including *Igf1*, *Igf1r*, and *Igfbp5*. Interestingly, the greatest upregulation was observed in the expression of *Pappa*, and this increase in *Pappa* was specific to kidney [41]. The increased renal *Pappa* expression was observed in several murine models of PKD [41]. To assess if PAPP-A expression was induced in human, we analyzed cystic fluids, as well as kidney tissues from ADPKD patients. Indeed, PAPP-A was significantly higher in human cystic fluid, and kidney tissues showed stronger expression of PAPP-A in cystic epithelia and renal tubules compared to normal kidney. Additionally, ADPKD cystic epithelial cells *9–12*, derived from ADPKD patients, also showed higher PAPP-A expression compared to normal renal cortical tubular epithelial cells (RCTE), clearly showing that upregulation of PAPP-A was a common feature of several ADPKD models. Interestingly, PAPP-A expression was reduced in food restricted (FR) mice that shown reduced cystic disease. Forskolin (FSK), a cAMP inducing agent, significantly induced the PAPP-A expression in 9–12 cells in a time- and dose- dependent manner. Interestingly, we also reported that the expression of PAPP-A in these models was positively regulated by the cAMP/CREB/CBP/p300 pathway (Figure 3) [41].

Furthermore, genetic deletion of PAPP-A showed significant reduction in cyst development and significantly improved the inflammation, kidney injury and fibrosis in the $Pkd1^{RC/RC}$ mouse model. Even a single copy deletion of PAPP-A was able to improve the cystic disease, glomerular filtration rate and survival in ADPKD mice, confirming the role of PAPP-A in pathogenesis of ADPKD. PAPP-A deficiency led to the reduced expression of downstream signaling components of IGF-1R like ERK, Akt, and PCNA, whereas it also showed an induction in AMPK expression. There was no difference in the IGF levels measured in circulation. In addition, preclinical studies demonstrated that treatment with a monoclonal antibody that blocks the proteolytic activity of PAPP-A against IGFBP4 ameliorated ADPKD cystic disease *in vivo* in $Pkd1^{RC/RC}$ mice, as well as *ex vivo* in embryonic kidneys [41]. Therefore, this study demonstrated that PAPP-A–IGF-1 axis plays an important role in the cystogenesis and introduced a new therapeutic strategy for ADPKD involving the inhibition of PAPP-A (Figure 3). Moreover, there exists a cross talk between IGF and EGF receptors pathway not only on cell surface level but downstream too [138], and IGF-1 mediated transactivation of EGFR and subsequent downstream signaling have been reported earlier [139]. Therefore, although future studies are needed but it could be speculated that PAPP-A inhibition might regulate the local IGF-1 levels and thus inhibit the

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crosstalk with these receptors further inhibiting these signaling pathway responsible for cystic disease.

Pharmacological approaches to inhibit PAPP-A

Although, direct inhibition of IGF signaling targeting IGF1R has been proposed in diseases like cancer, phase III clinical trials did not demonstrate a clear benefit and shown some disadvantages due to the lack of specificity [140–142]. PAPP-A could be an alternative therapeutic target to inhibit the IGF signaling, since inhibition of PAPP-A does not inhibit the IGF-1/IGF1R signaling directly, but limits the tissue specific bioavailability of IGF. Moreover, PAPP-A is an ecto-enzyme and therefore it can be targeted by specific monoclonal antibodies that can inhibit its proteolytic activity [143]. For example, Mikkelsen et al showed the selective inhibition of PAPP-A proteolytic activity against IGFBP-4 *in vitro* by using monoclonal antibodies that target the unique substrate binding site exosite of PAPP-A [143]. Later, they also reported that IGF signaling can be targeted *in vivo* using monoclonal antibodies against PAPP-A in a murine xenograft model [144]. Similarly, these neutralizing antibodies inhibited ovarian cancer growth and ascites accumulation in human tumor avatar models in mice [145]. Recently, Mohrin et al also reported the development of a neutralizing antibody against PAPP-A (anti-PAPP-A) and demonstrated that short-term treatment with anti-PAPP-A leads to a reduction in IGF signaling in mesenchymal stromal cells (MSCs) which causes functional changes at the tissue level [146]. All these studies clearly provide the evidence that inhibition of proteolytic activity of PAPP-A using monoclonal antibodies can be utilized to modulate IGF signaling in tissues.

Therefore, the development of therapeutic monoclonal antibodies against PAPP-A will provide a novel approach to target the IGF signaling. There are several advantages in using monoclonal antibodies for therapeutical interventions. For example, monoclonal antibodies can provide highly specific targeting, therefore decreasing the potential for off- target effects and increasing its therapeutic window. In addition, antibodies have long and reliable half-lives [147].

Somatostatin analogues like octreotide and lanreotide have also been implicated in the treatment of ADPKD, and several clinical trials have been conducted with varying outcomes [148–151]. Somatostatin acts on 5 G-protein coupled receptors (GPCRs) and binding to these receptors blocks the mitogen activated protein kinase, cell proliferation and also suppresses the expression of IGF-1, as well as other growth factors [152, 153]. Thus, somatostatin analogues could block the cystic growth via multiple mechanisms, including suppression of IGF-1. Therefore, combination therapies including somatostatin analogs and PAPP-A antibodies could provide an alternative approach to treat ADPKD patients.

Conclusions

Recently, we described a direct role for PAPP-A, a component of the IGF pathway, in the pathogenesis of ADPKD. Targeting PAPP-A-IGFBP-IGF axis could provide a new avenue for the management of this cystic disease. For example, therapeutic monoclonal antibodies could be used to provide specific target engagement and higher efficacy with reduced

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toxicity. Therefore, pharmacological inhibition of PAPP-A using therapeutic monoclonal antibodies could be a novel approach to target the IGF pathway in ADPKD.

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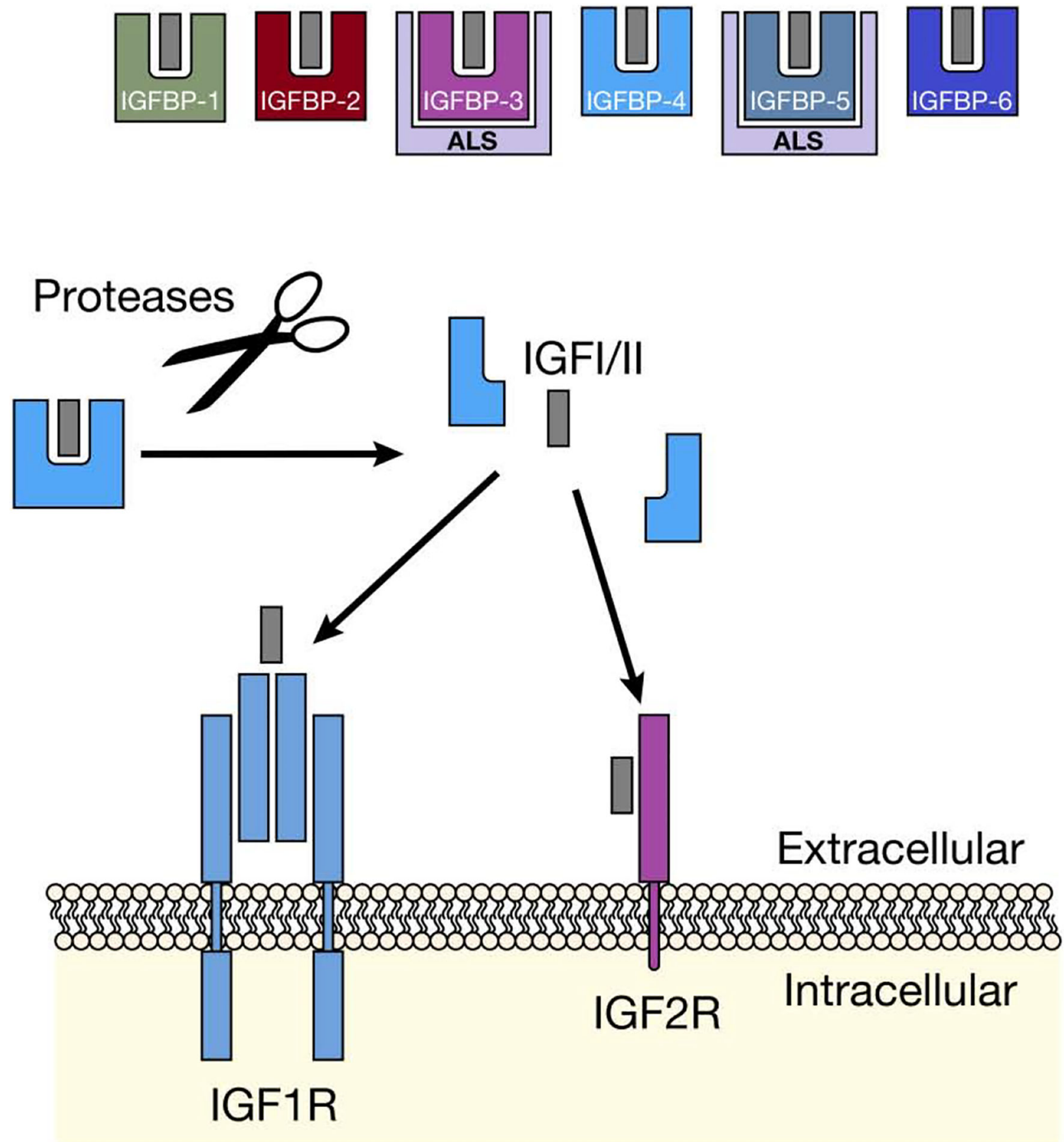

Figure-1. IGF system and its components.

IGF system consists of Insulin like growth factors (IGFs), IGF binding proteins (IGFBPs), IGF1 and 2 receptors (IGF1R and IGF2R) and proteases. ALS: Acid labile subunit.

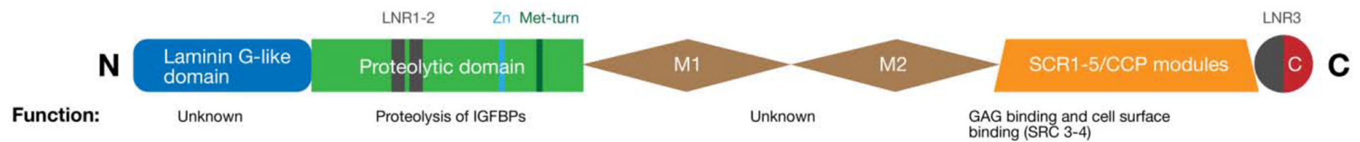

Figure-2. Schematic representation of primary structure of PAPP-A subunit.

At N-terminal, there is a 250-residue laminin G-like module with unspecified function followed by a 350 residue proteolytic domain containing the so-called elongated zinc binding consensus sequence and a short sequence for Met-turn formation. The proteolytic domain is followed by two ill-defined regions M1 and M2. The C-terminal module has five short consensus repeat (SCR) modules or complement control protein (CCP) modules, SCR 1–5. SCR3 and SCR4 are responsible for binding to glycosaminoglycans (GAGs) present on cell surfaces, enabling interactions between PAPP-A and cell surfaces. PAPP-A also contains three Lin12-Notch repeat (LNR) modules, and each binds a calcium ion and determines the proteolytic specificity. LNR1–2 is present in the proteolytic domain and LNR-3 is in the C domain.

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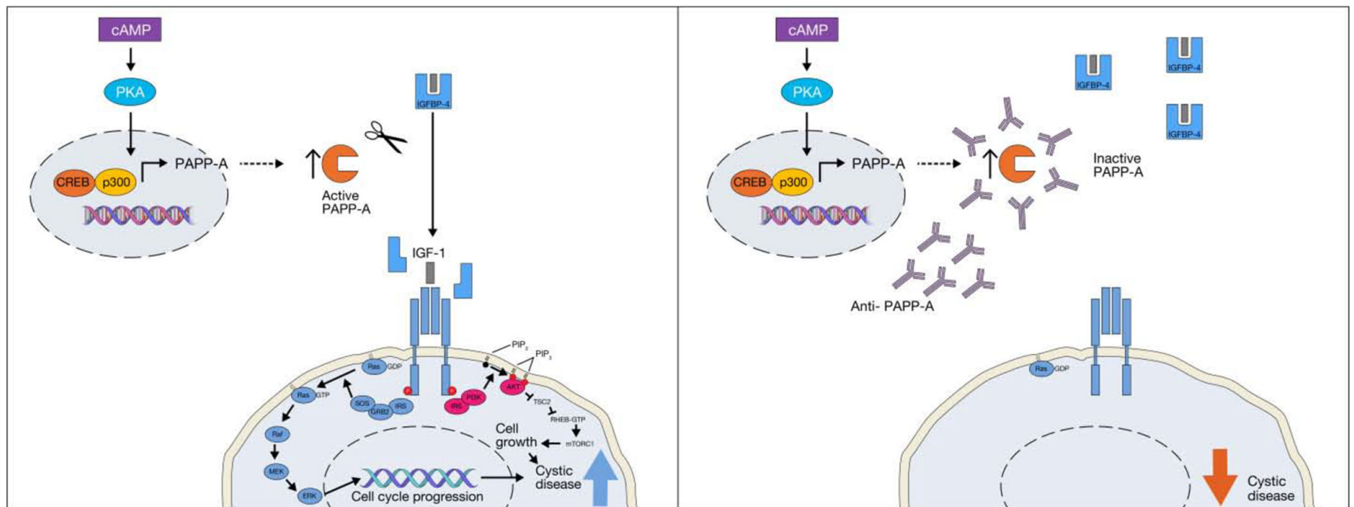

Figure 3. Role of PAPP-A in pathogenesis of ADPKD.

Higher levels of PAPP-A in ADPKD leads to increased proteolytic activity towards IGF bound IGFBP-4; which consequently results in the increased bioavailability of IGF. This free IGF leads to interaction with its receptor, IGF1R and cause the activation of downstream signaling. Inhibition of PAPP-A provides the novel therapeutic target in ADPKD. PAPP-A: pregnancy associated plasma protein, cAMP: cyclic AMP, CREB: cAMP response element-binding protein, IGF: Insulin like growth factor, PKA: Protein kinase A.

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Table 1.

Major groups of IGFBP proteases and their substrates.

<table>
<tr><th></th><th colspan="2">Enzyme</th><th>IGFBPs</th></tr>
<tr><td rowspan="5">Serine proteinases</td><td colspan="2">Prostate specific antigen (PSA) [80, 154]</td><td>IGFBP-3,5</td></tr>
<tr><td colspan="2">Kallikreinlike proteinase, Y-nerve growth factor [80, 155]</td><td>IGFBP-3,4, 6</td></tr>
<tr><td colspan="2">Plasmin [156, 157]</td><td>IGFBP-1, 3, 5</td></tr>
<tr><td colspan="2">Complement protein 1S (C1s) [83]</td><td>IGFBP-5</td></tr>
<tr><td colspan="2">Thrombin [158] [156]</td><td>IGFBP-5, 3</td></tr>
<tr><td rowspan="4">Matrix Metalloproteinases</td><td rowspan="2">Pappalysins [88, 90, 92, 159]</td><td>PAPP-A</td><td>IGFBP-2, 4, 5</td></tr>
<tr><td>PAPP-A2</td><td>IGFBP-3, 5</td></tr>
<tr><td colspan="2">Adamalysins [84, 160, 161]</td><td>IGFBP-3, 5</td></tr>
<tr><td colspan="2">Matrixins/MMPs [80, 162–165]</td><td>IGFBP-2, 3, 5,</td></tr>
<tr><td>Cathepsins</td><td colspan="2">Cathepsin D [166–169]</td><td>IGFBP 1–5</td></tr>
</table>

Table 2.

Evidences in support for the role of IGF-1 pathway in pathogenesis of autosomal dominant polycystic kidney disease (ADPKD).

Study	ADPKD model	Findings
1 Nakamura *et al.* 1993 [35]	DBA/2FG-pcy mice	• Increase in IGF-1 mRNA
2 Aukema *et al.* 2001 [36]	Han:SPRD-cy rat	• IGF-1 levels higher in cy/+ • Dietary soy protein delays the disease progression
3 Parker *et al.* 2007 [38]	Conditional immortalized cystic cells	• IGF-1 induces hyperproliferation via ras/raf pathway
4 Song *et al.* 2009 [37]	Cysts of different sizes and minimally cystic tissue from human ADPKD kidney	• Upregulation of IGF-1/IGFR1
5 Liu *et al.* 2013 (39)[170]	Immortalized epithelial cells from ADPKD patients	• Rosiglitazone inhibits IGF-1-induced cyst lining epithelial cell proliferation
6 Warner *et al.* 2016 [40]	$Pkd1^{RC/RC}$ mice	• Food restriction reduced the serum IGF-1 levels • Food restriction also reduced renal Igf 1 mRNA expression.
7 Kashyap *et al.* 2020 [41]	Human ADPKD kidney tissue sections and cystic fluids, 9–12 ADPKD tubular epithelial cells, $Pkd1^{RC/RC}$, $Pkd2^{WS25/-}$, $Pkd1^{RC/RC}$-Pappa mutant mice and metanephros	• PAPP-A significantly higher in human and experimental ADPKD • PAPP-A genetic deficiency as well as antibody treatment ameliorates the cystic disease.

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