Mesangial Cells Initiate Compensatory Tubular Cell Hypertrophy

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Key Words

Unilateral nephrectomy • Mesangial cells • Growth factors • Tubular cell • Hypertrophy • Compensatory growth • Cell cycle

Abstract

Unilateral nephrectomy results in compensatory renal growth, in which both the size and the functional capacity of the remaining kidney are increased. The functional adaptation to the removal of the contralateral kidney consists mostly of an increase in the glomerular filtration rate of the remaining kidney, and hypertrophy of cells comprising the nephron, mainly of the proximal tubular cells. Although the phenomenon of single kidney hypertrophy has been known for the past thousand years and despite intensive research over the past century, the mechanism of this process still remains unclear. The present article reviews the role of mesangial cells in compensatory renal hypertrophy.

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Introduction

Compensatory renal growth initiated by unilateral nephrectomy is a multistep adaptive process that leads to increased function of the remaining kidney. Within several weeks after unilateral nephrectomy, the remaining kidney increases in size, and begins to compensate for its missing partner. It is known that mammals having only a single kidney do not suffer from renal insufficiency. This phenomenon has been known and has fascinated physicians for more than two thousand years. Aristotle (384–322 BC) was probably the first to report that animals born with a single kidney can develop normally; he concluded that the full complement of renal tissue is not necessary for a normal animal to survive [1]. Later, Vesalius (1514–1564) found that single functional kidneys in humans were sufficient for normal life [2].

Although the phenomenon of single kidney compensatory growth is known, and despite extensive research over the past century, the mechanism responsible for this process is not yet clear.

Immediately after removal of the contralateral kidney, the remaining kidney is subject to a state of hyperfiltration [3, 4]. The changes in glomerular hemodynamics activate a sequence of growth events leading to compensatory growth of the remaining kidney.

Mesangial cells play a crucial role in glomerular functioning under both normal physiologic and pathologic conditions. Mesangial cells provide structural support for the glomerular capillary loops, and modulate glomerular capillary flow and ultrafiltration surface, thereby regulating the glomerular filtration rate [5]. In addition, the mesangium serves as a source and target of vasoactive hormones, growth factors, cytokines, and extracellular matrix proteins, and thus contributes to the pathophysiology of the variety of glomerular diseases [6]. The present review will attempt to summarize the role of mesangial cells in compensatory growth of the remaining kidney.

Cellular and Molecular Events Underlying Compensatory Renal Growth

During the first hour after nephrectomy, significantly increased expression of both positive growth control factors, including c-jun, cyclin C, cyclin E, *erg-1*, as well as negative growth control factors, such as *WT-1*, *p53*, *Rb*, and *gas-2*, is observed in the remaining kidney tissues. mRNA levels of extracellular matrix proteins such as fibronectin and collagen I, and heat shock genes *hsp70*, *hsp86*, *hsp90 β* are also increased [7]. Thus, unilateral nephrectomy induces stimuli that promote compensatory renal growth, in parallel with signals that suppress this process.

In adult organisms, compensatory growth of the remaining kidney occurs mainly through the hypertrophy of tubular cells. Hypertrophied cells increase their volume due to increased RNA and protein synthesis, without DNA replication. Studies have shown that tubular cell hypertrophy following unilateral nephrectomy is mediated by a cell cycle-dependent mechanism. This involves entry of cells into the G_1 phase of the cell cycle, initiating G_1 -related events, followed by arrest of cell cycle progression prior to the G_1/S checkpoint. Retinoblastoma protein (pRb), which is known as a suppressor of E2F transcription factor, plays a key role in the progression across the G_1/S interphase. In the quiescent, dephosphorylated state, pRb forms complexes with E2F and inhibits E2F activity. Activation of pRb proteins lead to separation of E2F from its inhibitory unit, enabling the transcription of S-phase genes [8–10]. Activation of pRb requires its serial phosphorylation first by cyclin D/CDK4/6, and then by cyclin E/CDK2 complexes. Such stepwise pRb phosphorylation is necessary because cyclin D cannot fully phosphorylate pRb, while cyclin E cannot act on the unphosphorylated

form of pRb [11–14]. Thus, progression through G_1 requires the coordinate action of both cyclin D and cyclin E kinases. The development of the hypertrophy of tubular cells was shown to occur in temporal association with increases in cyclin D/CDK4/6 kinase activities, and decreased activation of cyclin E/CDK2 complexes. Failure to activate the cyclin E/CDK2 complex could be the result of either a decrease in the formation of kinase complexes, or an increase in cyclin kinase inhibitor proteins associated with these complexes [15]. The cyclin kinase inhibitor proteins of the Cip/kip family, which include *p21^{Waf1}*, *p27^{kip1}* and *p57^{kip2}*, play an essential role in hypertrophy, because they inhibit activity of early G_1 (cyclin D/CDK4/6), late G_1 (cyclin E/CDK2), and S-phase (cyclin A/CDK2) cyclin-CDK complexes [16, 17]. Studies showed that the levels of cyclins and CDKs remain constant, while the activity of formed complexes change during the compensatory growth period. Activity of the cyclin D/CDK4/6 complexes increases at days 4, 7, and 10, and activity of the cyclin E/CDK2 increases at days 2, 4, and 7–14 after nephrectomy in the remaining kidney tissues. Thus it is conceivable that *p21^{Waf1}*, *p27^{kip1}* and *p57^{kip2}* may play essential roles in compensatory tubular cell hypertrophy [18–20].

Role of Transforming Growth Factor- β in Compensatory Renal Growth

Transforming growth factor- β (TGF- β) is a multifunctional growth factor that mediates normal cell functions and many of the pathologic changes associated with a variety of kidney diseases. These include regulation of cell proliferation, accumulation of extracellular matrix, glomerular and interstitial fibrosis, and the progression of glomerulosclerosis [21–24]. TGF- β was described as inducer of epithelial-to-mesenchymal transition in normal mammary epithelial cells, by the activation of a signaling pathway through serine/threonine kinase receptor complexes [25]. In addition, TGF- β has been suggested as one of the most important factors causing tubular cell hypertrophy. TGF- β is therefore considered to play a pivotal role in compensatory renal growth [26–29]. TGF- β induces hypertrophy of tubular cells through a cell cycle-dependent mechanism that involves entry of cells into the G_1 phase, initiating G_1 -related events, and arresting cell cycle progression prior to the G_1/S restriction point [26, 30, 31]. Moreover, moving cells from G_0 to G_1 and induction of early G_1 -associated effects by promitogenic stimuli such as EGF, IGF-I, FGF, IL-10 and HGF is a nec-

essary event, which is subsequently converted to hypertrophy by anti-proliferative effects of TGF- β in late G₁ [26, 30]. TGF- β mediates hypertrophy via inhibition of pRb phosphorylation by blocking the activity of cyclin E/CDK2 complexes, but does not affect the activity of cyclin D/CDK4/6 complexes [18, 26, 31]. In vivo and in vitro studies revealed that TGF- β -induced compensatory tubular cell hypertrophy is regulated by p57^{kip2}, but not by p21^{Waf1} or p27^{kip1} cyclin kinase inhibitor proteins [32–34].

TGF- β is synthesized and secreted by a variety of renal cells [35, 36]. Generally, TGF- β is stored as a disulfide-bonded homodimer connected to a latency-associated protein (LAP). In this state, TGF- β is maintained in its inactive, latent form. Binding of the cytokine to its receptor requires its activation, by dissociation from LAP. This process is induced by several factors, including cathepsins, plasmin, calpain, thrombospondin, integrin- α v β 6, and matrix metalloproteinases [37–39]. Most of these factors are produced by mesangial cells.

How Do Mesangial Cells Influence Compensatory Tubular Cell Hypertrophy?

Although the tubular cells are the main site at which compensatory renal growth takes place, it has been suggested that mesangial cells play an essential role in this process.

Glomerular mesangial cells play an important role in maintaining normal glomerular structure and function [5, 40–42]. Recent studies of renal tissues and isolated glomeruli showed that mesangial cells serve as both the source and the target for various growth factors, cytokines, and chemokines active in this tissue [6, 41–44]. These factors activate mesangial cells in an autocrine manner and mediate interactions with glomerular endothelial and epithelial cells, and with blood-borne inflammatory cells [6, 42]. Generally, mesangial cell proliferation is tightly regulated by the combined activity of paracrine and autocrine growth factors. Activation and/or proliferation of the mesangial cells in response to immune-mediated or non-immune injury is followed by an imbalance in the production of growth factors, cytokines and extracellular matrix proteins, leading to glomerular and interstitial damage in the setting of diabetes, hypertension, or glomerulonephritis [42–47].

Studies from our group showed that in adult rats, unilateral nephrectomy first initiates significant transient proliferation of the mesangial cells [34]. At this stage, the levels of circulating expression of growth factors and cy-

tokines, and of those expressed on the kidney tissue, such as growth hormone, IGF-I, IL-10, and others are markedly increased, leading to mesangial cell proliferation [29, 48–50]. On the other hand, concentrations of anti-proliferative mesangial cell factors, such as atrial natriuretic peptide and TGF- β , are greatly reduced relative to their baseline levels in both serum and in the remaining kidney tissue [29, 51].

Mesangial cell proliferation initiated by unilateral nephrectomy reaches a maximum at 24 h, and is then arrested within 72 h after surgery. Reduction in proliferation occurs in parallel with the appearance of renal tubular cell hypertrophy [29, 34].

It has been shown that cultured mesangial cells isolated from a remaining kidney secrete factor(s) that, in concert with serum obtained from unilateral nephrectomized rats, stimulates growth of cultured tubular cells [52]. As mentioned above, TGF- β is considered to be a pivotal factor in the progression of compensatory renal growth of the remaining kidney. It has been demonstrated that among the resident renal cell types studied, only mesangial cells secrete and activate TGF- β [53, 54]. Moreover, TGF- β production is regulated by factors such as angiotensin II, IGF-I, HGF, bFGF, TNF- α , EGF, PDGF, and others, all of which are produced by mesangial cells [55–58]. Another inducer of TGF- β is IL-10. In vivo studies showed that the major source of IL-10 in kidneys is the mesangial cells [29]. Following unilateral nephrectomy, plasma levels of both IL-10 and TGF- β are increased, and correlate positively with their expression in renal tissues. IL-10 expression in the remaining kidneys starts to increase within hours after surgery, reaches a maximum at 24 h and returns to normal levels by several days after nephrectomy. In contrast to IL-10, circulating and renal TGF- β levels decrease within 24 h after nephrectomy, and then start rising from 72 h, reaching a peak at 1 week after nephrectomy. Thus, upregulation of IL-10 in plasma and kidney tissues appears earlier than the increase in TGF- β . Experimental in vivo inhibition of IL-10 levels reduces circulating and renal TGF- β concentrations. This results in a 20–25% reduction in the remaining kidney weight and significantly decreases tubular cell hypertrophy [29, 34]. It is important to note that IL-10, an autocrine mesangial cell growth factor [44], apparently has no direct effect on tubular cells [59–61]. Moreover, *in situ* hybridization [62] and immunohistochemical studies [29] both demonstrated that IL-10 does not stain the tubular cells; thus the interaction between IL-10 and tubular cell hypertrophy is indirect, occurring through the mesangial cell population.

Fig. 1. Possible mechanisms involved in compensatory renal growth after unilateral nephrectomy.

Studies using inhibitors of IL-10 further emphasize the role of mesangial cells as the key regulator of the process of compensatory renal growth [29, 34]. As summarized in figure 1, nephrectomy initiates glomerular hyperfiltration, which is followed by activation and proliferation of the mesangial cells in the remaining kidney. Proliferating mesangial cells produce increased amounts of growth factors. These growth factors effect mesangial cells in an autocrine manner to prolong activation, influence conversion of latent TGF- β forms to active ones, and lead to increased TGF- β production. When TGF- β accu-

mulates in sufficient amounts, it induces tubular cells to themselves undergo hypertrophy, and, in parallel, acts on the mesangial cells to inhibit their proliferation. Inhibition of mesangial cell proliferation, in turn, reduces TGF- β levels and inhibits compensatory tubular cell hypertrophy.

The mechanisms of renal hypertrophy in response to loss of renal mass are fundamental to understanding the biology of the kidney and the progression of renal failure. Tubular cell hypertrophy occurs in several pathological conditions including diabetes mellitus. Moreover, tubular cell hypertrophy occurring after unilateral nephrectomy and the hypertrophy associated with diabetes mellitus, both occur through a process involving cell cycle-dependent mechanisms [8, 63]. The permanent and progressive loss of functioning nephrons following development of renal failure initiates a cascade of events, which are common to those in the renal compensatory growth process. Abnormal mesangial cell proliferation which is followed by generation of various growth factors, cytokines and matrix molecules in response to pathologic stimuli represent a common mechanism for the progression of a variety of renal disease leading to end-stage renal failure [42, 45, 46]. An increase in extracellular matrix deposition ultimately leads to induction of glomerular fibrosis and sclerosis, and results in the appearance and accumulation of proteinuria and a reduction in glomerular filtration rate due to loss of functioning nephrons [39, 50, 64–66]. In addition, increased secretion of chemokines by activated/proliferating mesangial cells is a necessary step contributing to inflammatory influx of leukocytes inducing proapoptotic and profibrotic lesions in the diseased kidney [43, 67].

This review summarizes our understanding of the mechanisms underlying the compensatory growth of the remaining kidney, which may shed light on the progression of renal diseases and identify potential targets for therapeutic intervention.

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