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Pathogenesis of Renovascular Hypertension: Challenges and Controversies

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1. Introduction

With an aging population, renovascular hypertension has become a major public health problem (Safian & Textor, 2001). Although various forms of fibromuscular disease of the renal arteries and/or traumatic disruption of renal vessels are the most common cause of RVH among the younger individuals, atherosclerotic renal artery disease (ARAD) is the most common lesion producing hypertension by far (Garovic & Textor, 2005). ARAD is present in over 6.8% of individuals over 65 years of age and is found in up to 49.1% of patients with coronary artery disease or aortoiliac disease (Iglesias et al. 2000; Valabhji et al. 2000; Hansen et al. 2002; Rihal et al. 2002; Weber-Mzell et al. 2002; Textor 2003). Although many patients with asymptomatic renovascular disease do not develop progressive renal dysfunction, overall morbidity and mortality is significantly increased (Chabova et al. 2000; Textor 2002; Textor 2003; Textor 2003; Foley et al. 2005; Foley et al. 2005). On the other hand, some studies suggest that from 10% to 40% of elderly hypertensive patients with newly discovered end stage renal disease and no identifiable parenchymal renal disease have significant RAS (Textor and Wilcox 2001). As in other forms of renal disease, the severity of interstitial fibrosis, tubular atrophy, interstitial inflammation, and glomerular sclerosis are important predictors of renal outcome (Wright et al. 2001). It has been postulated that this acquired tubulointerstitial injury may contribute to at least some forms of essential hypertension (Raghow 1994). Mechanisms underlying vascular and renal dysfunction in RAS have not been well delineated, despite intense study (Textor 2004). This information is essential for the development of therapies – surgical or medical – to treat RAS.

The hallmark of RVH arising from unilateral RAS is atrophy of the stenotic kidney and compensatory hyperplasia/hypertrophy of the contralateral kidney. Although this compensatory hypertrophy serves an adaptive function, this process may render the contralateral kidney more susceptible to other injuries (due to diabetes, glomerulonephritis, etc.) (Wenzel et al. 2002). Although the corresponding histologic, hemodynamic, and tubular alterations in the stenotic and contralateral kidneys have been superficially described in experimental animals, mechanisms underlying these alterations and the identification of markers that predict response to therapy have not been well defined. In particular, the stage in evolution of RAS at which the atrophic changes in the stenotic kidney preclude recovery of renal function after revascularization is not known. This lack of basic mechanistic knowledge is underscored by the variable response of RAS to surgical revascularization; significant

improvement in blood pressure control and recovery of renal function is achieved in only about half of patients, with approximately one-quarter showing no significant changes, and up to one-quarter of patients developing progressive deterioration of renal function (Textor and Wilcox 2001; Textor 2003; Textor 2004). Furthermore, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers potentiate hypoperfusion of the stenotic kidney, but have been advocated to prevent deterioration of function in the contralateral kidney (Mann et al. 2001; Schoolwerth et al. 2001). The stage during development of RVH and circumstances in which this treatment should be initiated are not known. This lack of understanding of basic mechanisms underlying the development of human RVH has prompted the development of animal models to address this issue.

1.1 Animal model of renovascular disease

The classic "Goldblatt" 2K1C rat model of RAS has been extensively used to model human RVH (Goldblatt et al. 1934). In the stenotic kidney, reduced renal perfusion stimulates renin secretion through the renal baroreceptor system, leading to increased plasma levels of angiotensin II (A-II), provoking systemic hypertension (Martinez-Maldonado 1991). A-II may increase blood pressure directly or through elaboration of other vasoconstrictors (such as endothelin, thromboxanes, etc.); aldosterone promotes sodium and water retention and secondarily suppresses renin release. Over time, secondary structural damage occurs to the kidneys, vessels, and other end organs. In this chronic phase, the role of A-II in maintaining elevated blood pressure is not clear, as this phase no longer completely responds to ACE inhibitor therapy. In this chronic phase, the renal damage and endothelial dysfunction may be associated with near-normal renin and A-II levels (Okamura et al. 1986; Carretero and Scicli 1991). Indeed, lack of response to A-II inhibition in experimental animals with sustained RVH may predict lack of response to surgical intervention to remove the RAS (Pipinos et al. 1998).

In the 2K1C model, the weight of the stenotic kidney tends to be lower than that of normal or sham-treated controls, indicating that the kidney has undergone atrophy. The weight of the contralateral kidney is higher than that of normal controls, indicative of a hypertrophic/hyperplastic response. Histopathologic alterations in this model are variable, and probably depend upon the extent of blood pressure elevation. As originally described, the "Goldblatt" 2K1C is a model of accelerated, or "malignant" hypertension, with mean systolic blood pressures >200 mmHg (Goldblatt et al. 1934; Wilson and Byrom 1939; Wilson and Byrom 1940). Under these conditions, the contralateral kidney, despite low renin expression, develops interstitial fibrosis, tubular atrophy, interstitial inflammation, glomerulosclerosis, and hyalinosis (Mai et al. 1993; Sebekova et al. 1998; Kobayashi et al. 1999; Gauer et al. 2003). These chronic tubulointerstitial alterations are associated with increased TGF-β expression (Wenzel et al. 2003). Reported histopathologic alterations in the stenotic kidney are variable, and range from minimal alterations (Eng et al. 1994) to focal interstitial fibrosis and tubular atrophy without significant glomerulosclerosis (Wenzel et al. 2002).

In a rat 2K1C model that develops moderate hypertension (mean arterial pressure 158 mmHg), atrophy of the stenotic kidney and hypertrophy of the contralateral kidney is observed. The stenotic kidney shows increased staining for renin associated with interstitial fibrosis and tubular atrophy, with minimal alterations observed in the contralateral kidney (Richter et al. 2004). In this model, COX-2 inhibitors significantly reduce interstitial fibrosis in the stenotic kidney (Richter et al. 2004).

The 2K1C model has been established in mice using a clip of 0.12 mm (Wiesel et al. 1997). Four weeks after clipping, these investigators reported that 2K1C hypertensive mice exhibited blood pressure approximately 20 mm Hg higher than their sham operated controls. We have recently defined the histopathologic alterations connected with renal artery stenosis in animal model (Figure 1) (Cheng et al., 2009) and human (Keddis et al., 2010). In a murine model of 2K1C of RVH, we found that both the clipped and the contralateral kidney underwent minimal histopathological alterations during the first two weeks following surgery. Subsequently, the clipped kidney underwent atrophy, with generalized tubular atrophy, interstitial fibrosis and focal mononuclear infiltrates, whereas the contralateral kidney underwent hypertrophy/hyperplasia with minimal histopathologic alterations (figure 2). We propose that the murine 2K1C model is a good model of renovascular disease in humans with moderate hypertension. These animal models have helped to elucidate and suggest which cytokines and pathways are involved in RVH. Of these, the renin-angiotensin-aldosterone system, long known to have effects on the hemodynamics of RAS, is becoming more interesting for the inflammatory effects it causes as well.

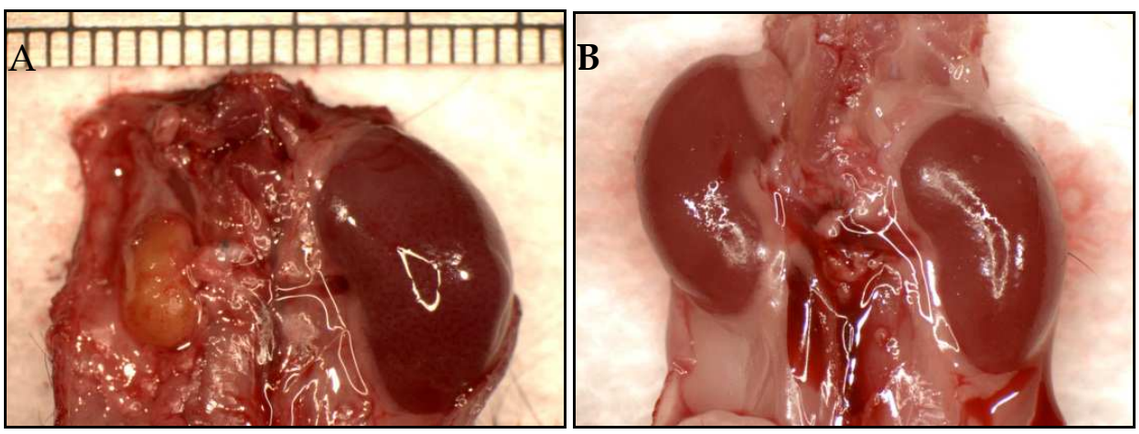

Fig. 1. Gross picture of the stenotic and contralateral kidney of mice (A) after placement of renal artery clip, the 2K1C model, compared to (B) sham procedure.

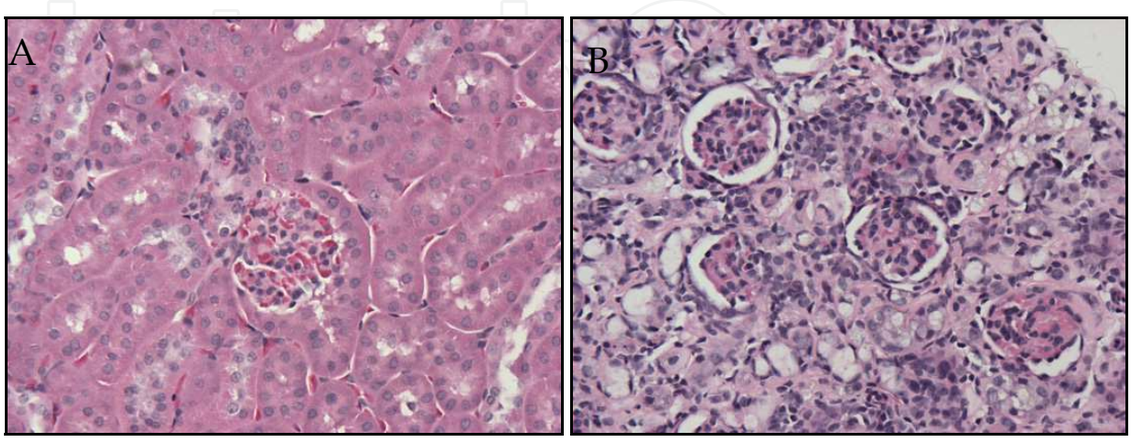

Fig. 2. Glomerular appearance of the (A) contralateral and (B) stenotic kidney with H&E staining.

1.2 The Renin-Angiotensin System and renovascular disease

Though its normal function is to preserve organ perfusion by regulating sodium and water balance, extracellular fluid volume and cardiac activity, the Renin-Angiotensin-Aldosterone System (RAAS) also plays an integral part in RVH. The RAAS has been found to be significantly activated in the presence of RAS. It is known that the increase in blood pressure caused by the RAAS has significant detrimental effects on the body, but it may also play a number of other roles in the development and progress of RVH.

Renin is made primarily by the juxtaglomerular cells in the Juxtaglomerular apparatus in response to 1) low pressure in the afferent renal artery, 2) sympathetic nervous system activity 3) A-II levels and 4) low sodium delivered to the macular densa in the distal convoluted tubule of the nephron. Other signals, such as potassium concentration, atrial natruretic peptide and endothelin also modulate renin synthesis. Renin enzymatically converts angiotensinogen, made in the liver, to angiotensin I. ACE, synthesized primarily in the lungs (though also in other tissues), then converts angiotensin I to A-II, a significantly biologically active molecule. A-II, in addition to its numerous tissue effects, induces the synthesis of aldosterone in the zona glomerulosa of the adrenal medulla, which then acts on mineralocorticoid receptors throughout the body, though when considering RAS, their most notable function is in the kidney (Laragh et al., 1992). This pathway is also located completely within other organs, including, the kidney. The proximal tubule, interstitium and medulla of the kidney have higher-than-systemic concentrations of A-II, because of local synthesis, which allows it to act in a paracrine function (Johnston et al., 1992). A-II and aldosterone can also be synthesized through an ACE-independent pathway, which is what allows for the return to normal A-II levels in the presence of ACE inhibition. This effect is also particularly prominent in the kidneys, where an estimated 40% of renally-synthesized A-II does not rely on ACE (Hollenberg, 1999).

A-II acts on 2 different receptors (angiotensin receptor type 1, or AT-1, and angiotensin receptor type 2, or AT-2) producing very different biological responses. Of these, AT-1 appears to play the most significant role in renal vascular disease (AT-2 is mostly known for its role in fetal organ development). Stimulation of the AT-1 receptor is best known for its systemic vasoconstrictive effects, and its vasoconstrictive effects on the efferent renal arteriole. The former causes general rises in systolic blood pressure, while the later decreases renal plasma flow, but increases glomerular filtration fraction. AT-1 stimulation also causes salt-retention through a number of mechanisms, increasing blood pressure even further (Dzau & Re, 1994; Liu & Cogan, 1989; Brewster & Perazella, 2004). A-II also mediates non-hemodynamic effects. A-II has the ability to promote fibrosis through a number of mechanisms, including induction of collagen synthesis, inhibition of collagen-cleaving proteases, stimulation of the secretion of platelet-derived growth factor, and, most interestingly, direct stimulation of TGF-β receptor type II(Luft, 2003; Wolf, 2000). AT-1 stimulation also has the ability to promote fibrosis by up-regulating expression and synthesis of NF-κB and thus TGF-β, as well as a number of other cytokines (Tsuzuki, 1996). Downstream, aldosterone, in addition to its hypertensive effects mediated through the mineralocorticoid receptor, also up-regulates the expression of TGF-β (Juknevicius et al., 2000). These studies have supported a widespread use of RAAS inhibitors (ACE-inhibitors, AT-1 inhibitors and aldosterone receptor inhibitors) to prevent renal disease progression. However, there is concern with the often-seen deleterious effects on renal function of the

stenotic kidney caused by these anti-hypertensive agents. With already compromised blood flow, concern about increased damage to the ischemic kidney must be weighed with the benefits to the contralateral kidney (Jackson et al., 1986). With substanstial arterial obstruction, simply reducing perfusion pressure can reduce post-stenotic blood flow beyond that required for metabolic demands in the kidney. Early experimental studies in rats emphasized the potential for irreversible damage to the clipped kidney in animals treated with ACE inhibitors, resulting in "medical nephrectomy" (Jackson, 1990). However, it is important to note that this adverse reaction can develop with any forms of antihypertensive therapy (Textor et al., 1983). The risk factors for this adverse event include older age groups, pre-existing renal dysfunction, and episodes of acute illness leading to volume depletion (such as diarrhea or reduced intake during diuretic administration) (Speirs, et al., 1988).

With the increasing evidence of the involvement of TGF-β in RAS induced damage, the role of the RAAS in RAS, especially with respect to its induction of an inflammatory response, is being re-thought. There should be careful consideration and evaluation of the role of the immunologic and cytokine-associated effects of RAAS in the pathological process and initiation of RAS induced kidney damage. Such research may shed new light on whether the benefits of RAAS inhibition outweigh the costs in patients with RAS.

1.3 TGF-β and renovascular disease

Mechanisms underlying the differential response of the stenotic and contralateral kidney during the development and progression of RVH have not been adequately defined, despite numerous studies (Goldblatt et al., 1934; Martinez-Maldonado, 1991; Carretero, 1991). TGF-β is involved in a number of processes relevant to the development of RVH, including cell cycle regulation leading to hypertrophy and/or apoptosis, MAPK activation, inflammation, and extracellular matrix synthesis (Cheng & Grande, 2002).

It is well recognized that TGF-β plays a central role in fibrotic diseases (Cheng & Grande, 2002; Border et al., 1990; Border & Noble, 1994, 1997; Border & Ruoslahti, 1992). All aspects of fibrogenesis have been shown to be regulated by TGF-β, including the initial inflammatory phase in which infiltrating inflammatory cells and macrophages set the stage for the subsequent fibrotic phase in which activated fibroblasts and myofibroblasts contribute to the pathogenic accumulation of matrix (Cheng et al., 2005). In the past few years, receptors and signal transduction pathways mediating the effects of TGF-β on cells have been identified, enabling the identification of specific pathways involved in pathogenic events dependent on this cytokine. TGF-β signals through a set of transmembrane receptor serine/threonine kinases unique to the larger superfamily of TGF-β-related proteins. The active heteromeric receptor complex is formed by binding of ligand to a type II receptor, recruitment and activation of the type I receptor kinase, and phosphorylation of intracellular mediating target proteins (Massague, 1992, 1998; Attisano et al., 1994). Increased TGF-β receptor expression is observed in experimental glomerulonephritis (Shankland et al., 1996; Tamaki et al., 1994). In experimental renal disease associated with epithelial to mesenchymal transformation, TGF-β type 1 receptor expression is increased in tubular epithelial cells (Yang & Liu, 2002). Downstream mediators are the Smad family of proteins (Piek et al., 1999). Smad2 and 3 are phosphorylated directly by the type I receptor kinase, after which they partner with Smad4 and translocate to the nucleus where they act as transcriptional regulators of target genes, including those essential for apoptosis,

inflammation, differentiation, and growth inhibition (Massague & Wotton, 2000; Derynck et al., 1998; Attisano et al., 2001). TGF-β plays a critical role in chronic inflammatory changes of the interstitium and extracellular matrix accumulation during fibrogenesis (Cheng & Grande, 2002; Grande et al., 1997, 2002). TGF-β initiates the transition of renal tubular epithelial cells to myofibroblasts, the cellular source for extracellular matrix deposition, leading to irreversible renal failure (Yang & Liu, 2001; Iwano et al., 2002; Li et al., 2002).

A predominant role of TGF-β1 in regulation of extracellular matrix deposition is highlighted in our published studies employing renal tubular epithelial cells derived from animals bearing a homozygous deletion of the TGF-β1 gene (Grande et al, 2002). Although the most direct means to test the hypothesis that T TGF-β1 plays a central role in the development of RVH would be to perform these studies in mice bearing homozygous deletion of the TGF-β1 gene, the phenotype of these animals precludes such studies. TGF-β1 KO animals have an extremely high rate of embryonic lethality, and the few surviving mice develop a systemic inflammatory syndrome, leading to their death within 2-4 weeks of age (Letterio et al, 1994; Martin et al., 1995; Kulkarni & Karlsson, 1993; Boivin et al., 1995). For this reason, more recent studies have employed mice with genetic manipulation of the Smad proteins to define potential mechanisms by which the TGF-β signaling pathway is involved in chronic tissue injury. Smad3 KO mice show accelerated healing of wounds, in association with decreased local inflammation (Ashcroft et al., 1999). Smad3-null mice have been used in several chronic injury models, including ureteric obstruction (Sato et al., 2003). In WT mice, unilateral ureteric obstruction (UUO) produces extensive interstitial fibrosis and tubular atrophy, with TGF-β1-driven epithelial to mesenchymal transformation of tubular epithelial cells, as evidenced by reduction in E-cadherin staining and de novo induction of α-smooth muscle actin (α-SMA) staining. This is associated with extensive influx of monocytes. In Smad3 KO animals subjected to UUO, there was a marked reduction in interstitial fibrosis, and epithelial to mesenchymal transformation, indicating that the Smad pathway is necessary for epithelial to mesenchymal transformation by TGF-β (Itoh et al., 2003; Yu et al., 2002).

1.4 MAPK pathways and renovascular disease

It is well recognized that cellular adaptive responses to environmental stimuli, including hypertrophy, hyperplasia, and atrophy associated with increased apoptotic activity, are transduced through the MAPK pathway(s) (Kyriakis 2000; Kyriakis and Avruch 2001). Cardiac hypertrophy in A-II dependent hypertension is associated with activation of p38, whereas ERK and JNK are preferentially stimulated in an A-II independent model of RVH (Pellieux et al. 2000). The development of hypertension is associated with persistent ERK activation in the aorta of Dahl salt-sensitive rats and stroke-prone spontaneously hypertensive rats (Kim et al. 1997; Hamaguchi et al. 2000). In human diabetic nephropathy, there is increased immunohistochemical staining for p-ERK in glomeruli which correlates with the severity of glomerular lesions and increased p-p38 staining which correlates with severity of tubulointerstitial lesions and number of CD68-positive macrophages (Adhikary et al. 2004; Toyoda et al. 2004; Sakai et al. 2005). Hypertension accelerates the development of diabetic nephropathy in a rat model of type 2 diabetes through induction of ERK and p38, as well as TGF-β (Imai et al. 2003). Similarly, the p38 and JNK pathways are activated in the early stages of experimental proliferative glomerulonephritis, whereas the ERK pathway is persistently activated (Bokemeyer et al. 1998). Both p38 and JNK are activated in

experimental anti-glomerular basement membrane antibody mediated glomerulonephritis (Stambe et al. 2003). In a variety of other human renal diseases, p-ERK expression is observed in regions of tubulointerstitial damage, within α-SMA positive myofibroblasts (Masaki et al. 2004). In cultured cells, ERK is involved in epithelial to mesenchymal transformation (Li et al. 2004; Xie et al. 2004; Yang et al. 2004). We have previously identified ERK, p38, and JNK as essential intermediates for MC mitogenesis, and ERK and p38 as essential intermediates for TGF-β stimulated collagen IV mRNA expression and MCP-1 production (Cheng et al. 2002; Cheng et al. 2004). We have also shown that ERK is significantly upregulated in a rat model of salt sensitive hypertension (Diaz et al., 2008). Others have shown that p38 activation is necessary for TGF-β stimulation of fibronectin production (Suzuki et al. 2004).

The MAPK pathways are involved in regulation of cell cycle arrest and apoptosis, which is of direct relevance to the renal atrophy which occurs in the stenotic kidney of the 2K1C RAS model. Activation of ERK is necessary for TGF-β-mediated induction of p21 and cell cycle arrest (Hu et al. 1999). High glucose promotes hypertrophy of MC through ERK mediated phosphorylation of p27 (Wolf et al. 2003). Activation of p38 or JNK is frequently associated with cell cycle arrest or apoptosis (Cardone et al. 1997; Frasch et al. 1998). Induction of apoptosis in MC requires sustained activation of JNK (Guo et al. 1998). Apoptosis and other cellular responses may be directed by a balance between ERK and JNK activation (Xia et al. 1995).

Based on these considerations, there has been intense interest in developing low molecular weight pathway specific MAPK inhibitors as therapeutic agents to treat cancer and fibroproliferative inflammatory conditions (Duncia et al. 1998; Sebolt-Leopold et al. 1999; Clemons et al. 2002; Duan et al. 2004; Sebolt-Leopold and Herrera 2004; Jo et al. 2005; McDaid et al. 2005). These agents have been employed in experimental renovascular disease, with mixed results. The ERK inhibitor U0126 was effective in reducing acute renal injury in an experimental mesangial proliferative glomerulonephritis model (Bokemeyer et al. 2002). In human renal diseases associated with injury to podocytes, p38 is induced. The p38 inhibitor FR167653 prevents renal dysfunction and glomerulosclerosis in chronic adriamycin nephropathy (Koshikawa et al. 2005) and in experimental crescenteric glomerulonephritis (Wada et al. 2001). Similarly, the p38 inhibitor NPC31145 reduced acute inflammatory injury in an experimental anti-glomerular basement membrane glomerulonephritis model (Stambe et al. 2003). On the other hand, the p38 inhibitor FR167653 increased proteinuria in a passive Heymann nephritis model of podocyte injury (Aoudjit et al. 2003), suggesting that activation of p38 protects podocytes from complement mediated injury. Furthermore, the p38 inhibitor NPC31169 exacerbated renal damage in a remnant kidney model due to in vivo induction of ERK (Ohashi et al. 2004).

1.5 The role of inflammation in renovascular disease

RVH initiates activation of the renin–angiotensin system and structural remodeling, evidenced by fibrosis and vascular deterioration in the affected kidney. Although the renin–angiotensin system tends to resolve once a stable blood pressure (BP) is reached, it has been suggested that transient elevation of plasma A-II could precipitate macrophage infiltration, thereby initiating an inflammatory response within the kidney (Ozawa et al., 2007). This inflammatory cascade may well underlie the degenerative processes within the kidney as its renal artery begins to narrow.

We performed PCR array studies of renal homogenates obtained from mice subjected to RAS or sham surgery. The results of our PCR Array studies (Table 1) implicate monocyte chemoattractant protein-1 (MCP-1) as a key chemokine in this inflammatory response. In addition to infiltrating inflammatory cells, tubular epithelial cells of the stenotic kidney of mice exposed to RAS express high level of MCP-1 (figure 3). Our findings are in accord with those of other investigators who have studied renovascular hypertension. High salt diet in DSS rats caused expression of NADPH oxidase and MCP-1 in the dilated renal tubules and resulting in interstitial inflammation and migration of mononuclear cells (Shigemoto et al., 2007). Increased MCP-1 levels also seem to stimulate TGF-β formation in glomerular cells despite the absence of infiltrating inflammatory cells (Wolf et al., 2002). Studies in the swine model of renovascular hypertension using bindarit, a selective MCP-1 blocker, show that inhibition of MCP-1 confers renal protective effects by blunting renal inflammation and reducing the level of collagen deposition, thereby preserving the kidney in chronic RAS (Zoja et al., 1998; Zhu et al., 2009). It was further indicated that MCP-1 contributes to functional and structural impairment in the RAS kidney, specifically in the tubulo-interstitial compartment.

Gene function	Gene symbol	Gene name	Fold change
Inflammation	Ccl2	MCP-1 (monocyte chemoattractant protein 2)	+43
	Ccl3	MIP-1α (macrophage inflammatory protein 1α)	+22
	Ccl4	MIP-1β (macrophage inflammatory protein 1β)	+8
	Ccl5	RANTES (regulated upon activation, normal T-cell expressed and secreted cytokine)	
	Ccl7	MCP-3 (monocyte chemoattractant protein 3)	+153
	Ccl8	MCP-2 (monocyte chemoattractant protein 2)	+149
	Ccl12	MCP-5 (monocyte chemoattractant protein 5)	+56
	Ccl20	MIP-3α (macrophage inflammatory protein 3α)	+105
	Ccl22	MDC (macrophage derived chemokine)	+41
	Ccr2	Chemokine (C-C motif) receptor 2	+30
	Ccr3	Chemokine (C-C motif) receptor 3	+35
	Ccr4	Chemokine (C-C motif) receptor 4	+6
	Cxcl2	MIP-2α (macrophage inflammatory protein 2α)	+208
	Cxcl3	MIP-2β (macrophage inflammatory protein 2β)	+7
	Cxcl5	AMCF-II (alveolar macrophage chemotactic factor)	+653
	Cxcl9	Mig (monokine induced by γ-interferon)	+5
	IL1α	Interleukin-1α	+18
	IL1β	Interleukin-1β	+11

Table 1. PCR array results of proinflammatory cytokine expression in stenotic kidneys of RAS mouse

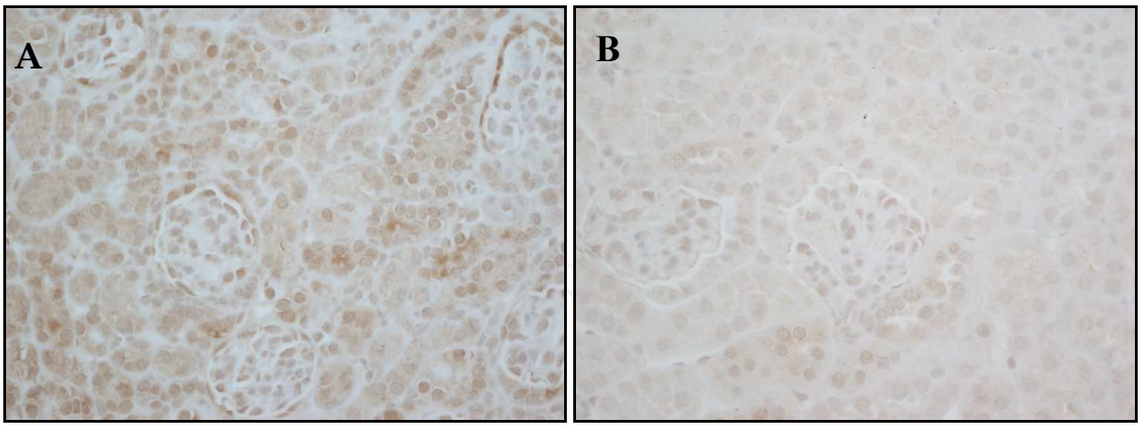

Fig. 3. MCP-1 staining in the (A) contralateral kidney and (B) stenotic kidney of C57BLKS mouse 4 weeks after placement of renal artery clip.

At a cellular level, it is apparent that the renal artery stenosis did elicit an inflammatory cascade in the kidney as evidenced by macrophage infiltration, the rise in MCP-1 and its receptor chemokine (C-C motif) receptor 2 (CCR2), NFκB, protein kinase C (PKC) and TGF-β. Remarkably, we also saw transient increase in MCP-1 and TGF-β in the contralateral kidney which indicates some inflammatory process taking place despite lack of inflammatory cells and/or tissue damage. It is apparent that blockade of the MCP-1 receptor does offer renal protection and prevents the progressive fibrosis development in renovascular hypertension. Elucidating the underlying mechanisms of this protection will allow us to develop preventive measures and novel therapeutic interventions that could possibly be applied to other renal diseases.

1.6 Therapeutic implication

Hypertension is one of the most common reasons for a visit to a physician. There are several key issues that need to be addressed during evaluation of a patient with hypertension: accurate blood pressure reading, determination of target organ damage due to hypertension, screening for other cardiovascular risk factor, stratification of cardiovascular disease, and assessment for the cause of hypertension (primary vs. secondary hypertension). Thorough assessment of the cause of hypertension is essential for determining the correct treatment approach, especially in children where atherosclerosis is not common. For children with hypertension, it is necessary to consider genetic diseases (i.e. coarctation of the aorta, primary aldosteronism) and auto-immune diseases (i.e. post-infectious-glomerulonephritis). When initiating treatment, it is important to maintain low systolic pressure as systolic pressure is a stronger predictor of cardiovascular event (Mancia et al. 2009; Cherubini et al. 2010). Maintenance of blood pressure goal should ideally be achieved within 6 to 9 months of therapeutic initiation.

2. Conclusion

Optimal management of renovascular hypertension requires an understanding of the disease process and remains an important challenge for clinicians caring for patients with hypertension. Although the pathophysiology and the consequence to human health caused

by RVH are well understood, the exact mechanism by which the stenosis of the renal artery induces the damage is not. Revascularization studies have demonstrated highly variable results, with significant improvement in a small subset of patients, but an overall lack of justification of the risks, when applied to large groups of patients (Textor et al., 2009). While parsing out why some patients benefit while others do not will be an important task in the years to come, the more significant benefit will be from determining the reasons for the continued renal damage in the majority of revascularized patients. Developing novel therapies to address these yet-unknown pathological processes will yield benefit for all RAS patients. Recent studies implicate the non-hemodynamic effects of the renin-angiotensin-aldosterone system and the inflammatory chemokines as possible initiating signals for the atrophic, inflammatory and fibrotic changes seen. Elucidating, more thoroughly, the role these pathways play in renal damage due to RAS could identify new targets for therapeutic intervention and the first biomarkers to aid in diagnosis, limiting the need for costly and damaging imaging studies. Many questions remain to understand how these pathways are initiated, how they interact and how they ultimately lead to renal damage. What cells first sense the stenosis, and how do they sense it? Which of the pathways contribute to damage and which are necessary to preserve kidney function? The answer to these and other such questions hold the possibility to further the science, diagnostics and treatment of renovascular hypertension, and to improve the lives of the millions it affects.

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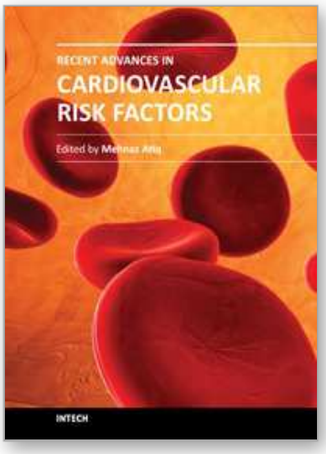

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Among the non-communicable diseases, cardiovascular disorders are the leading cause of morbidity and mortality in both the developed and the developing countries. The spectrum of risk factors is wide and their understanding is imperative to prevent the first and recurrent episodes of myocardial infarction, stroke or peripheral vascular disease which may prove fatal or disabling. This book has tried to present an update on risk factors incorporating new research which has thrown more light on the existing knowledge. It has also tried to highlight regional diversity addressing such issues. It will hopefully be resourceful to the cardiologists, general practitioners, family physicians, researchers, graduate students committed to cardiovascular risk prevention.

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