Abstract

Pericytes are cells of mesenchymal origin that are intimately involved in the development and stabilization of vascular networks. Novel studies of their role in inflammation have identified that pericytes are not only major contributors to the activated matrix depositing myofibroblast populations seen in progressive renal fibrosis but perhaps even more importantly, the detachment of renal pericytes from the vasculature contributes to the microvasculature rarefaction and subsequent hypoxia associated with chronic kidney disease. In this review, our current understanding of the functioning of renal pericytes will be considered and set in the context of the wider literature that is currently available on this neglected population of cells.

Keywords: fibrosis; pericytes; stroma; CD248

Introduction

Renal tubulointerstitial pericytes have been relatively neglected in the renal literature for the last 30 years, with few publications focussing on their structure, function and involvement in renal pathology. The last few years, however, has seen an increasing interest in the role that pericytes play in the development of renal disease [1–6]. They are emerging not only as a major contributor to the activated matrix depositing stromal cell populations seen in progressive fibrosis but perhaps even more importantly, the detachment of renal pericytes from the vasculature contributes to the microvasculature rarefaction and subsequent hypoxia associated with chronic kidney disease. In this review, our current understanding of the functioning of renal pericytes will be considered and set in the context of the wider literature currently available.

What is a pericyte?

First described by Rouget as early as 1873 [10–12], the pericyte was suggested by some authors to represent a precursor of vascular smooth muscle cells (VSMCs) that are seen in larger vessels with which they share some structural and functional similarities [13, 14]. However, VSMCs lie largely outside the basement membrane of endothelial cells, while pericytes lie in close proximity to the microvasculature [15].

In vivo pericytes can be recognized by their extensive branched processes that partially surround the albuminal side of endothelial cells [14, 16]. They are ubiquitously found throughout the microvasculature and are sheathed within a duplication of the underlying vessel’s basement membrane. Pericyte density is highly variable across vascular beds. Coverage of the abluminal surface of endothelial cells is reported to range between 10 and 50% [17] and the ratio of pericytes to endothelial cells is 1:1, 1:2.5 and 1:100 for the retina, kidney and skeletal muscle, respectively [5, 17, 18].

While pericyte processes are always enclosed within the basement membrane, the cell body is often exposed by gaps in the basement membrane thus allowing intercellular crosstalk between pericytes and the underlying endothelial cells [2]. Pericyte–endothelial crosstalk is facilitated at these sites through peg-socket contacts [17]. These represent membrane invaginations extending either from the pericyte or from the endothelial cell that permit the formation of tight, gap and adherence junctions [17, 19]. Through these connections, an individual pericyte is capable of linking to multiple endothelial cells facilitating co-ordination and integration of the corresponding endothelium [17].

Renal pericytes were first visualized using electron microscopy (EM) and described in detail by Courtoy and Boyle in 1983; their initial structural observations suggested a functional role for pericytes in modulating vessel diameter. In the kidney, pericytes are found in the tubulointerstitial space on peritubular capillaries and as specialized pericytes within the glomerulus as mesangial cells [2, 5, 20].

Identifying pericytes in vivo

Identifying pericytes in vivo is challenging and classical approaches utilizing location, morphology and surface markers have presented problems. Pericytes appear morphologically distinct across organs [16]; for example, as noted by Armulik et al. [17], in the central nervous system,
pericytes appear flattened with multiple cytoplasmic processes covering an extensive amount of the abluminal surface. In contrast, pericytes within the glomerulus are compact with minimal abluminal coverage. In view of these problems, EM has been one of the best techniques to identify and phenotype pericytes in mature tissues [21]. EM is more difficult during angiogenesis and vascular remodelling as the basement membrane is often not fully developed [22].

While no pan-pericyte markers exist, surface markers for pericytes are recognized but are not entirely specific. A selection of the markers previously used to identify pericytes in vivo are summarized in Table 1. Current markers suffer from limitations as they are dynamically expressed at different developmental stages [6], across species [17], in different organs [16] and in response to the microenvironment [6, 23]. Four of the best-described markers used to identify pericytes are alpha smooth muscle actin (αSMA), desmin, NG2 chondroitin sulphate proteoglycan and platelet-derived growth factor receptor beta (PDGFRβ).

- αSMA is expressed by pericytes but also by smooth muscle cells and myofibroblasts [16]. In pericytes, αSMA expression is restricted to sites of vascular remodelling [24].
- Desmin is expressed on pericytes in direct contact with the underlying endothelium [24].
- NG2 chondroitin sulphate proteoglycan is expressed on the surface of activated pericytes during vasculogenesis and angiogenesis [25]. High NG2 expression is retained in normal pericytes in most organs of adult organisms including the kidney.
- PDGFRβ is a tyrosine kinase receptor crucial for pericyte function and stability (see below).

**Table 1. Pericyte markers**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>αSMA</td>
<td>Intracellular marker&lt;br&gt;Restricted to expression by activated pericytes at sites of vascular remodelling&lt;br&gt;Also expressed by smooth muscle cells and myofibroblasts</td>
</tr>
<tr>
<td>Desmin</td>
<td>Intraocular marker expressed on intermediate filament proteins&lt;br&gt;Expressed on pericytes in direct contact with the underlying endothelium&lt;br&gt;Proposed as an indicator of pericyte ensheathment in underlying basement membrane</td>
</tr>
<tr>
<td>CD248 (TEM1, endosialin)</td>
<td>Recognizes pericytes and fibroblasts&lt;br&gt;Temporal expression with high levels in development and low levels in adult tissue&lt;br&gt;Implicated in PDGFRβ-mediated pericyte proliferation in vitro</td>
</tr>
<tr>
<td>NG2 chondroitin sulphate proteoglycan</td>
<td>A transmembrane proteoglycan&lt;br&gt;Expressed by nascent pericytes during the early stages of angiogenesis and persists in newly formed blood vessels</td>
</tr>
<tr>
<td>CD73</td>
<td>Pericyte and MSC marker&lt;br&gt;Expression also seen on erythropoietin-producing peritubular fibroblasts of the kidney</td>
</tr>
<tr>
<td>PDGFRβ</td>
<td>One of the most widely used pericyte markers&lt;br&gt;Plays a key role in pericyte recruitment, investment and maturation of the microvasculature</td>
</tr>
</tbody>
</table>

Fig. 1. Schema to demonstrate how pericytes contribute to CKD. (A) Normal kidney. (B) Kidney injury. In the resting healthy normal kidney, pericytes are attached to the vasculature where they act to stabilize the endothelium. In response to renal injury (B), resident fibroblasts and pericytes become activated to form matrix-depositing myofibroblasts. Pericytes detach from the endothelium (arrow Panel B), destabilizing the vasculature causing the vessel to be lost (rarefaction) and the development of tissue fibrosis.
Novel pericyte markers are emerging to help phenotype these cells further. CD248 (endosialin, TEM1) is a 175-kDa Type I transmembrane glycoprotein expressed by pericytes [23] and fibroblasts [26]. Ligands for CD248 include endothelial membrane proteins such as fibronectin and collagen Type IV [27]. We have recently used CD248 to localize renal pericytes in human and murine kidneys successfully [20] and demonstrated that CD248 is up-regulated in human renal disease [20]. Intriguingly, CD248 is thought to be crucial for pericyte PDGFRβ-mediated signalling and function [28, 29].

CD248, as with all the pericyte markers described above, is temporally and developmentally expressed by pericytes, a phenomenon reported at renal [6, 30] and non-renal sites [17, 31]. In the kidney, Lin et al. [6] have reported that at postnatal Day 12, NG2, αSMA and PDGFRβ are expressed by all pericytes but as the organ matures, expression of these markers is lost as pericytes become less active. Furthermore, in this study in response to injury, the number of NG2⁺ pericytes increased (see [6]).

Again, it must be emphasized that none of these markers are entirely specific to pericytes. NG2 is an excellent marker for oligodendrocytes and is also expressed by some macrophages [31]. CD248 is expressed by a small subset of CD8⁺ T cells [32] and PDGFRβ is expressed, at lower levels than those found in pericytes, by a variety of cell populations [16]. Consequently, one approach in identifying pericytes in vivo is to combine multiple surface markers [24]. The development in recent years of transgenic mice (reviewed in detail by Duffield et al. [4]) has taken this approach a step further. Transgenic animals allow genetic fate tracking and tagging of pericytes thus facilitating not only the in vivo localization of pericytes but also their ex vivo isolation [6, 33] and phenotyping. Isolated cells can also be used for in vitro co-culture models [34].

**Pericyte function in vessel development, maturation and stability**

Pericytes are pivotal to vascular development and remodelling. A detailed discussion of vasculogenesis and angiogenesis is beyond the scope of this article and readers are directed to several excellent recent reviews of this complex area to expand the outline described below [35, 36]. Central to vasculogenesis and angiogenesis is the process of maturation, the transition from a growing vascular bed to a fully formed stabilized vascular network. A prominent feature of maturation is the investment of pericytes in the vessel wall and defective maturation is seen in pathological settings including malignancy and fibrosis [37, 38].

Blood vessels are one of the first embryonic organs to develop and they are composed of endothelial cells and mural cells (VSMC or pericytes). During development, both these cell populations are derived from the embryonic mesoderm. The nascent vasculature is formed through the process of vasculogenesis. In the embryo, a rudimentary endothelial tube network is formed from endothelial progenitor cells [35]. This network is then branched, pruned and stabilized through the process of angiogenesis and mural pericytes are thereby embedded into the vascular wall [24].

Pericytes are important for vessel stability. *Ex vivo* coculture studies using a three-dimensional gel matrix have demonstrated that the removal of pericytes leads to loss of microvascular integrity [39]. *In vivo* pericyte coverage of endothelial cells is essential for maintenance of the blood–brain barrier [31]. An observation mirrored by similar reports across multiple vascular beds emphasizing the role pericytes play in stabilizing blood vessels [19].

Despite its importance in development, our understanding of the process whereby the vasculature is stabilized is incomplete. Generation of a functioning vascular basement membrane and recruitment of pericytes into the immature vascular network is in response to secreted growth factors [24]. Numerous growth factors are recognized but two main signalling systems appear crucial, these are the PDGFRβ/PDGFB and angiopoietin–Tie2 signalling pathways [24]. Vascular endothelial growth factor (VEGF), a key signalling molecule produced by endothelial cells to stimulate angiogenesis, is involved in both of these pathways.

PDGF-BB is secreted by endothelial cells in response to VEGF. It is crucial for the recruitment of pericytes to newly formed vessels [40]. Studies in mice demonstrate that loss of PDGFRβ or its ligand PDGF-BB (secreted from endothelial cells), results in defective pericyte recruitment and investment in the microvasculature and subsequent vascular leakage and haemorrhage [40–42]. Once pericyte recruitment to the endothelium is achieved, cell endothelial–pericyte cross-talk and anchoring involves angiopoietin–Tie2 signalling pathways. Angiopoietin (Ang) 1 and 2 both signal through the Tie2 receptor [43] but have different functional roles. Ang 1 is expressed by pericytes and is involved in reducing vessel permeability through strengthening endothelial cell–pericyte interactions [35]. Ang 2 is produced and stored by endothelial cells, antagonizes the effects of Ang 1 and is involved in the inflammatory response [16].

NG2 also plays a role in vessel development and stabilization. NG2 is an important factor in promoting endothelial cell migration and morphogenesis in the early stages of neovascularization [44]. Furthermore, NG2 null mice display altered coverage of endothelial cells by pericytes.

**Functional role of pericytes in vivo at non-renal sites**

In addition to their important role in vessel development and stabilization, pericytes have multiple functions in vivo. Pericytes synthesize matrix proteins [16] that form part of the vessel basement membrane within which they are enclosed. The capillary basement membrane is formed from Collagen IV, laminins and proteoglycans including perlecan, aggrecan and versican. Pericytes have been reported to deposit fibronectin, laminin, collagen and glycosaminoglycans [34]. Pericytes are also involved in regulating vessel tone; a property that may account for the differences in the number of pericytes observed across vascular beds [16]. Ultrastructurally, they express contractile cytoplasmic filaments and express surface receptors that regulate vessel contraction including endothelin, angiotensin II, serotonin and Bradykinin which all induce contraction in pericytes *in vitro* [16].
Pericytes can play a role in the immune response to injury. Subsets of pericytes have been reported to display macrophage-like properties and can participate in phagocytosis [16]. They express scavenger receptors and other macrophage markers such as CR3 complement receptor, Classes I and II major histocompatibility complex molecules [38]. In the brain, they are a key mediator of the immune response and are recognized to function as antigen presenting cells for primed T cells [45].

In vitro, pericytes have the capacity to differentiate into chondrocytes, osteoblasts, fibroblasts and adipocytes [9]. This pluripotency and the observation that pericytes can act as progenitor cells in vivo suggests that they are located within a MSC niche [9, 46, 47]. Furthermore, in vitro and in vivo pericytes express MSC-associated surface markers such as CD90, NG2, CD248 and CD73 [9, 48]. Interestingly, the addition of bone marrow derived-MSCs to an ex vivo co-culture model leads to stabilization of endothelial tube networks [49]. If pericytes truly represent a tissue resident progenitor cell population, this could have important implications for the development of targeted therapies to repair damaged tissue. Indeed, defective pericyte function has been implicated in a diverse array of human pathologies including hypertension [34], diabetic retinopathy [34] and tumour metastasis [50].

Resident renal pericytes

Pericytes are found within the glomerular and tubulointerstitial compartments of the kidney. There is an extensive literature on the function of mesangial cells, a specialized form of pericyte, in the pathogenesis of renal disease. This is largely due to the relative ease with which these cells can be identified, isolated and cultured in vitro from humans and mice using differential sieving techniques. In contrast, tubulointerstitial pericytes are more challenging to isolate and only relatively recently have transgenic mouse models facilitated their isolation in vitro. Here, the two renal pericyte populations will be considered separately with emphasis on the emerging novel observations regarding tubulointerstitial pericytes.

Mesangial cells (glomerular pericytes)

It was first suggested 20 years ago by Schlondorff that glomerular mesangial cells represented a specialized form of microvascular pericyte [51]. They play a central role in stabilizing and maintaining the structural architecture of the glomerulus and exhibit many of the features associated with pericytes at non-renal sites described above [16]. Mesangial cells differentiate from primitive pericytes during development and have been shown to participate in the subdivision of the capillary network during glomerulogenesis [52]. Crosstalk between mesangial cells and the glomerular endothelium is essential to maintain vascular structure, and this again involves platelet-derived growth factor (PDGF) signalling. PDGF-B and PDGFR-β null mice are non-viable and exhibit markedly abnormal glomerular structure with an absence of mesangial cells [53, 54].

In the glomerulus, mesangial cells form a central stalk and constitute ~30% of all glomerular cells [51]. They express recognized surface markers ascribed to pericytes in vitro and in vivo, such as PDGFRβ and CD90. In health, mesangial cells deposit matrix, predominately Type IV collagen, laminin and fibronectin, a process that becomes dysregulated in many of the glomerulonephropathies [51, 55]. The contractile properties of mesangial cells allow them to fine tune glomerular filtration. They can thus directly sense and respond to changes in capillary stretch which allows modulation of single nephron glomerular filtration rate [56]. They are capable of immune surveillance. Human mesangial cells are capable of acquiring a monocyte/macrophage phenotype [57]. Also, mesangial cells may represent a glomerular MSC niche since, like other pericytes, they exhibit pluripotency in vitro and can be reprogrammed to form pluripotent stem cells that form teratomas if injected into immuno-deficient mice [58].

Peritubular pericytes: the primary source of activated stromal cells in renal fibrosis?

Outside of the glomerular compartment, pericytes are aligned with the peritubular capillaries of the interstitium [59]. Our understanding of the role pericytes play in the pathogenesis of disease has expanded rapidly in recent years. Reports in the literature dating back 10 years focussed on the role pericytes play in regulating medullary blood flow [60]. While this remains an active area of research [61], more recently, a key role for pericytes in the pathogenesis of CKD has been proposed also.

CKD (defined as an estimated glomerular filtration rate <60 mL/min/1.73m² for ≥3 months) affects 10% of the population and contributes considerably to premature morbidity and mortality [62]. The dominant processes that promote progressive kidney disease, irrespective of the trigger, occur in the renal tubulointerstitial compartment where the deposition of non-functioning fibrotic matrix and microvascular rarefaction are considered hallmarks of progressive disease [8, 63]. The origin of activated renal myofibroblasts, the primary cell responsible for the deposition of fibrotic matrix, is both controversial and complex [5, 64]. Two main theories exist; firstly, myofibroblasts arise from the activation of resident stromal fibroblasts. Secondly and more controversially, myofibroblasts arise from infiltrating fibrocytes [65] and the de-differentiation of tubular epithelium via epithelial–mesenchymal transition (EMT) [6]. The idea that myofibroblasts originate from pericytes is not novel in non-renal organs, for example, in the liver, hepatic stellate cells are viewed as resting pericytes [66, 67]. However, until recently, this idea had not been examined in the kidney.

Elegant studies by Lin et al. [6] reported in 2008 used novel transgenic mouse models that allowed the tracking and phenotyping of renal pericytes in several different murine models of kidney disease. Using a mouse that expresses enhanced green fluorescent protein (EGFP) under regulation of the collagen Iα1 promoter, they demonstrated that activation of pericytes and peritubular fibroblasts contributed significantly to interstitial αSMA + activated stromal fibroblast (myofibroblast) populations in experimental renal
fibrosis. Careful tracking and kinetic modelling studies demonstrated that in response to injury, collagen1α1+ pericytes up-regulated classical pericyte markers (PDGFRβ and αSMA), up-regulated collagen deposition and detached and migrated away from the underlying endothelium. Later studies by the same group have demonstrated that this process is accompanied by microvascular rarefaction, as loss of pericytes from the vasculature destabilizes the vessel and leads to a failure of reparative angiogenesis [1]. Some fundamental limitations of these studies should be stressed. There is considerable variability in the regulation of procollagen I genes in different tissues and cell types. In particular, different cis-acting sequences acting on the collagen Type I promoter can be functional in different organs and in various fibrotic processes [68, 69]. The transgenic pro-Col1α1–EGFP reporter strain used by Duffield et al. was built after the discovery of deoxyribonuclease (DNase) I-hypersensitive sites that have been located in the distal 5′-flanking region of the alpha1(I) collagen gene and are specific to hepatic stellate cells [70]. Evidence that EGFP transgenic expression reflects endogenous pro-Col1 synthesis in the kidney is lacking. Furthermore, it is striking that high level of constitutive pro-Col1α1-EGFP expression was found in podocytes, where no fibrosis is ever found following renal injury. While there is evidence of pericytes undergoing a phenotype switch towards a myofibroblast phenotype, there is no definitive evidence that these cells then deposit fibrillar collagen in vivo.

One surprising observation from these studies was that despite severe renal injury, epithelial cells did not express the collagen transgene. Therefore, they are unlikely to be a source of myofibroblasts, questioning the process of EMT in kidney disease [6]. This assertion is supported by earlier data reported by Faulkner et al. [71], who were one of the first groups to challenge the role of EMT as the source of myofibroblasts in the kidney. They evaluated the distribution of myofibroblast markers in the renal tubulointerstitial compartment during the development of renal fibrosis induced by the administration Ang II and Habu venom to mice. These studies revealed that αSMA-positive cells were seen within interstitium but not within the tubules. Examination of staining in individual interstitial compartments showed that the predominant location of αSMA-positive cells occurred in the perivascular region.

To support their preliminary data, additional fate tracking studies were performed by Lin et al. [6]. Renal epithelial cells were genetically tagged using Six2-cre and HoxB7-cre drivers. Mesenchymal cells were labelled using the FoxD1-cre driver during embryonic development. Together Six2 and HoxB7 labelled the epithelium and collecting duct epithelium, respectively. FoxD1 was expressed by mesenchymal cells and tagged all cells destined to become pericytes. Tagged mice were then backcrossed with the appropriate reporter mice strains and the fate of the renal epithelium and pericytes in response to renal injury observed in two different models [5, 6]. FoxD1+ cells were found to represent the same population of cells as the collagen1α1-tagged cells reported previously; this population expanded rapidly to form the majority of the αSMA+ myofibroblasts seen in response to injury. No tagged epithelial cells were seen to co-express αSMA or the EMT marker fibroblast-specific protein 1 (FSP-1), within the interstitium in response to injury. In vitro, Six2-tagged epithelial cells could be induced to express αSMA and FSP-1. They also down-regulated the expression of E-cadherin in response to stimulation with the pro-fibrotic growth factor transforming growth factor beta thus suggesting that EMT may represent an in vitro phenomenon [3, 5]. These experimental findings were subsequently replicated by two independent groups [72, 73]. It should, however, be highlighted that these observations do not rule out the possibility that, regardless of EMT, epithelial cells may synthesize other types of collagen (e.g. III or IV) under pathological conditions. The studies described have generated much debate within the renal literature. The arguments by proponents and opponents of the debate will not be revisited here but readers are directed to several recent excellent reviews of the topic [74–76]. However, a number of important questions raised by the studies outlined above that are not discussed elsewhere are worthy of further consideration.

Firstly, are pericytes involved the same way following various injuries? The literature cited here relies heavily on the unilateral ureteric obstruction and ischaemia–reperfusion injury models. Protective and detrimental factors acting on pericytes and their fate may be dependent on the mechanism of insult to the kidney [77]. Secondly, what is the link between the proliferation of cells that express pericyte markers and the development of fibrosis and what are the signalling pathways involved in this process? Information on the potential pathways involved in pericyte proliferation is emerging from models of tissue injury at non-renal sites. For example, a role for NG2 is suggested during ischaemic renal neovascularization, as ectopic vessels protruding into the vitreous occur twice as frequently in wild-type animal retinas as in NG2 null animal retinas. In the NG2 knockout retina, proliferation of both pericytes and endothelial cells is significantly reduced, and the pericyte:endothelial cell ratio falls to 0.24 from the wild-type value of 0.86 [78].

Targeting endothelial–pericyte crosstalk to treat renal fibrosis

Pericytes are seen to detach from the interstitial capillary within hours of the induction of renal injury [6]. As discussed previously, pericyte investment in the endothelium is essential for the maintenance of vascular stability. Microvascular rarefaction will itself drive fibrosis by leading to tissue hypoxia [7]. Thus, pericyte detachment has a double impact for kidney disease. Not only do pericytes become myofibroblasts that deposit matrix leading to fibrosis but their detachment from the endothelium also exacerbates tissue hypoxia and damage. Stabilizing endothelial pericyte crosstalk in CKD may therefore be an effective therapeutic strategy.

Given our existing knowledge about endothelial–pericyte crosstalk, PDGF signalling is an attractive target to treat CKD [79]. Chen et al. [80] have demonstrated that PDGF receptor signalling is involved in pericyte activation, proliferation and differentiation into myofibroblasts and have shown that blockade of PDGF attenuates microvascular rarefaction and the development of renal fibrosis.
in vivo [1]. Novel pericyte markers such as CD248 which have been demonstrated to be involved in pericyte PDGF mediated signalling [28] and are up-regulated in response to renal injury [20] may represent viable treatment targets. Indeed, monoclonal antibodies against these are already in clinical trials in the treatment of renal injury [20] may represent viable treatment targets.

Conclusions

Renal interstitial pericytes are an important emerging cell population in the pathogenesis of CKD. Technological advances in murine transgenic models have overcome a number of early difficulties in identifying and tracking pericytes in vivo. Pericyte loss in response to injury in murine models leads to expansion of the myofibroblast pool responsible for deposition of pathological matrix and the development of fibrosis and destabilizes the vasculature leading to rarefication thus mirroring the clinical phenotype found in human disease. Targeted therapy aimed at modulating endothelial pericyte crosstalk promises to be a novel treatment to ameliorate renal fibrosis.

Acknowledgements. The authors would like to thank Profs Christopher Buckley and Clare Isacke for helpful advice and comments when preparing the manuscript.

Funding. This work was funded by a Wellcome Trust Clinical Training Fellowship for Dr Smith.

Conflict of interest statement. Prof. C.O.S.S. has a Consultancy with GlaxoSmithKline and Biogen Idec and has also received research grants from Talecis. All other authors: none declared.

References

24. Hellberg C, Ostman A, Heldin CH. PDGF and vessel maturation. Recent Results Cancer Res 2010; 180: 103–114
29. Demoulin JB. No PDGF receptor signal in pericytes without endothelial cell TIMP-2 and pericyte TIMP-3. Recent Results Cancer Res 2010; 265: 188–200
33. Demoulin JB. No PDGF receptor signal in pericytes without endothelial cell TIMP-2 and pericyte TIMP-3. Recent Results Cancer Res 2010; 265: 188–200
42. Bergers G, Song S. The role of pericytes in blood-vessel formation and maintenance. Neuro Oncol 2005; 7: 452–464
et al.


56. Stockand JD, Sansom SC. Glomerular mesangial cells: electrophysiology and regulation of contraction. *Physiol Rev* 1998; 78: 723–744


64. Stratuz F. How many different roads may a cell walk down in order to become a fibroblast? *J Am Soc Nephrol* 2008; 19: 2246–2248


78. Ozerdem U, Stallcup WB. Pathological angiogenesis is reduced by targeting pericytes via the NG2 proteoglycan. *Angiogenesis* 2004; 7: 269–276


Received for publication: 12.8.11; Accepted in revised form: 16.3.12