Lymphatic Microvessels in the Rat Remnant Kidney Model of Renal Fibrosis: Aminopeptidase P and Podoplanin Are Discriminatory Markers for Endothelial Cells of Blood and Lymphatic Vessels

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Abstract. Rat remnant kidney is an established model of renal tubulointerstitial fibrosis and progression to end-stage renal failure. The morphologic lesions comprise nephron loss and regenerative tubular hypertrophy, interstitial infiltration, predominately by macrophages, and progressive fibrosis. A critical role in this complex pathology was assigned to tubulointerstitial blood microvessels that regulate the supply of oxygen and nutrients to tubuli. Whereas some investigations reported a rarefaction of the vascular network in association with the degenerative cortical changes, others observed an increase in vascularization. Here these discrepant findings are addressed by reinvestigation of the vascularization of rat remnant kidneys by the use of two novel endothelial lineage specific, discriminatory markers, i.e., the membrane mucoprotein podoplanin with specificity for lymphatic endothelia, and the glycosylphosphatidylinositol (GPI)–anchored membrane enzyme aminopeptidase P that is recognized by a monoclonal antibody designated JG12 and that is specifically expressed by endothelial cells of blood vessels only. The results obtained confirm a regional rarefaction of aminopeptidase P–positive blood microvessels; they also establish major changes in the renal lymphatic vasculature. Massive proliferation of lymphatic vessels was observed in fibrotic tubulointerstitial regions, whereas in kidneys of sham-operated rats, only a few lymphatic vessels were found adjoined with arteries. The lymphatic vessels frequently contained mononuclear cells that were also encountered in the interstitial spaces and expressed relative large amounts of vascular endothelial growth factor-C mRNA by in situ hybridization. Collectively, these results indicate that a large proportion of the microvessels encountered in the cortex of remnant kidneys are of lymphatic origin and cannot be discriminated by common endothelial markers, such as CD34, that are expressed both by lymphatic and blood endothelia cells. As lymphatic endothelial cells secrete chemokines that attract dendritic cells, it is possible that the increase in lymphatic vascularization could enhance the immunologic surveillance of remnant kidneys.

In the absence of specific markers, lymphatic microvessels were difficult to distinguish from blood capillaries. Recently, several molecules that are exclusively or at least predominately expressed by lymphatic endothelial cells were discovered, such as the tyrosine kinase receptor for vascular endothelial growth factor-C (VEGF-C), VEGFR-3 (1), a CD44 homologous hyaluronic acid–binding protein designated LYVE-1 (2), the transcription factor Prox-1 (3), and the membrane mucoprotein podoplanin (4). The expression of some of these proteins is stable, so they were recently used to separate microvascular endothelial cells of dermal lymphatics (LEC) and blood vessels (BEC) (5,6), an achievement that is critical for further molecular analysis of these endothelial lineages. Most of the commonly used endothelial markers, such as CD31, von Willebrand factor, and so forth, are nondiscriminatory and are expressed both by LEC and BEC. However, BEC-specific markers are still missing. A potentially BEC-specific immunohistochemical marker in rat tissue was found in a monoclonal antibody, designated JG12, that was raised against rat glomerular membrane protein fractions and labeled intensely mi-

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crovessels of kidney and lung (7). Here we extend preliminary reports by identification of its antigen as the endothelial membrane enzyme aminopeptidase P.

These markers are of value for nephrology because they permit unambiguous identification of microvessels, particularly in renal fibrosis, that is an important factor for disease progression and chronic renal insufficiency. With antibodies to rat podoplanin and aminopeptidase P at hand, we address here the issue of vascularization of renal cortex in the rat remnant kidney model of progressive cortical fibrosis and renal failure. This rat model of disease was widely used to determine the pathogenic causes of renal fibrosis, for which the distribution of tubulointerstitial vessels is particularly critical (8,9). Whereas experiments with non-discriminatory endothelial markers have provided evidence for an overall increase of endothelial cell number in remnant kidneys, the use of JG12 and podoplanin as markers has revealed that lymphatic vessels massively proliferate within fibrotic areas and thus presumably account for the overall relative increase of endothelial markers observed previously (10).

**Materials and Methods**

**Materials**

FITC or rhodamine isothiocyanate (TRITC)-conjugated goat anti-rabbit IgG (Fab2), FITC-conjugated rabbit anti-mouse IgG, FITC-conjugated goat anti-mouse IgG (Fab2), peroxidase-conjugated sheep anti-rabbit IgG, and peroxidase-conjugated sheep anti-mouse IgG were obtained from Jaxell-Accurate (Westbury, NY). Goat anti-mouse IgG conjugated to 10 nm of gold particles was from Amersham (Auroprobe, Little Chalfont, UK), and alkaline-phosphatase (AP)-conjugated rabbit anti-mouse IgG, and peroxidase-conjugated sheep anti-mouse IgG were obtained from Promega (Madison, WI). SDS, acrylamide, N,N'-tetramethylethyleneendiamine, ammonium sulfate, high- and low-molecular-weight standards, and Tween 20 were from BioRad Laboratories (Richmond, CA). Coomassie Brilliant Blue G250 and diaminobenzidine were from Serva (Heidelberg, Germany). Nitroblue tetrazolium and 5'-bromo-4-chloro-3-indolyl-phosphosphate were from Kirkegaad and Perry (Gaithersburg, MD). Ketavet (Ketamine hydrochloride) was from Parke and Davis (Berlin, Germany), and Rompun (Xylazine hydrochloride) was from Bayer (Leverkusen, Germany). Rabbit anti-LYVE 1 antibody was produced as described (11).

**Preparation of the Monoclonal Antibody JG12**

Glomeruli were isolated from 250- to 300-g Sprague Dawley rats (all animals were obtained from the Central Animal Laboratory of the University of Vienna) by graded sieving. Isolated glomeruli were incubated in 200 mM Na2CO3 (pH 11.0); the detaching membrane vesicles were collected from the supernatant by ultracentrifugation and subjected to a phase partition using Triton X-114, as described (12). This membrane protein fraction was used as immunogen to immunize subcutaneously BALB/c mice with an emulsion of 300 ng of antigen and complete Freund’s adjuvant (Sigma). Half antigen doses in incomplete Freund’s adjuvant were used for two biweekly boosts, followed by an intravenous boost 3 d before fusion of spleen cells to P3 X 63Ag8.653 myeloma cells. Screening of monoclonal antibodies was performed by indirect immunofluorescence on unfixed 4-μm cryostat sections of normal rat kidneys, and clones that specifically immunolabeled interstitial blood vessels and glomerular capillaries were selected. Cloning was performed twice by limiting dilution, and the clone coded JG12 that secreted a monoclonal IgG1 was selected. This antibody is now commercially available through Bender MedSystems (BMS catalogue #1104; Vienna, Austria).

**Identification of the JG12 Antigen**

Membrane protein fractions of isolated rat glomeruli were separated by SDS-PAGE, transferred onto nitrocellulose membranes, and immunoblotted with monoclonal antibody JG12, as described (7). The corresponding antigen was excised from nitrocellulose membranes, reduced with dithiothreitol, carboxy methylated using iodoacetamide, and digested with trypsin. Peptides were extracted with formic acid and separated by nano-HPLC (LC Packings, Netherlands) on a PepMap C18 reversed-phase column (LC Packings). The column eluate was applied online to a LCQ ion trap (Finnigan) mass spectrometer equipped with a nanospray source (Protana Engineering, Denmark). Spectra were analyzed using MASCOT software (Matrix Science).

**Rat Remnant Kidney Model**

In this study, the same renal samples of paraffin-embedded material were used as in a previous investigation (13). Briefly, male Sprague-Dawley rats (n = 8; initial weight, 200 to 240 g) underwent a 5/6 remnant kidney surgery by subcapsular nephrectomy performed on the right kidney and resection of the upper and lower thirds of the left kidney. In controls (n = 6), a sham operation without destruction of renal tissue was performed. At 4 and 8 wk, urine samples were collected and BP was measured. All animals were fed a standard rat diet and water ad libitum.

**Immunolocalization**

Sham operated and 8-wk remnant kidneys were perfused with Eagle’s minimal essential medium via the abdominal aorta, followed by removal of a sample of the left kidneys for immunofluorescence and perfusion fixation with PLP fixative for paraffin immunohistology, immunofluorescence, and immunoelectron microscopy. Double localization of JG12 antigen and podoplanin was performed by indirect immunofluorescence on 1-μm frozen sections of PLP-fixed kidney cortex, cut on a Reichert Ultracut E ultramicrotome equipped with an F4 cryo-attachment. Sections were incubated with monoclonal antibody JG12 (1 μg/ml) and/or rabbit anti-podoplanin IgG (10 μg/ml). The bound antibodies were visualized with FITC-conjugated goat anti-rabbit (Jaxell-Accurate, Westbury, NY) and TRITC-conjugated goat anti-rabbit IgG mouse (Jaxell-Accurate).

Tissue blocks were also embedded in paraffin, and 4-μm-thick sections were stained by indirect immunoperoxidase, as described (13). Briefly, sections were deparaffinized in xylene, rehydrated, and microwave treated in citrate buffer at 600 W for 10 min. After washing in PBS, endogenous peroxidase was blocked by 3% hydrogen peroxide for 15 min, followed by incubation with PBS containing 10% normal goat serum for 30 min. For immunostaining, specimens were incubated with the polyclonal rabbit anti-podoplanin sera diluted 1:500 for 1 h. Detection was performed with biotinylated goat anti-rabbit IgG or horse anti-mouse IgG for 30 min at 20°C followed by streptavidin-peroxidase conjugate and dianamidine (Serva, Heidelberg, Germany). Slides were counterstained with hematoxylin. Double labeling by immunohistochemistry for simultaneous localization the JG12 antigen and of podoplanin on paraffin sections was performed by incubation of the autoclaved blocked sections with biotinylated monoclonal JG12 IgG that was visualized with streptavidin-horseradish peroxidase conjugate and 3-amino-9-ethyl carbazole. After washing and quenching, this first step was followed by incubation with...
rabbit anti-podoplanin IgG, biotinylated anti-rabbit IgG, alkaline-alkaline phosphatase conjugate, and Vector blue alkaline phosphatase kit III. All reagents were from Vector Laboratories. For supporting the visual impression, quantitative estimates of the relative number of lymphatic and blood vessels was made by setting the number of all vessels at 100% and expressing the relative numbers of lymphatic podoplanin positive vessels as a fraction therefrom. All counts were processed by the t test. For immunoelectron microscopy, immunogold localization of the JG12 antigen was carried out on ultrathin frozen sections, as described (13), using 10 nm of gold-conjugated anti-mouse IgG (Amersham, Auroprobe, Little Chalfont, UK).

In Situ Hybridization of VEGF-C

In Situ Hybridization of VEGF-C was performed as reported previously in detail (14). Briefly, human VEGF-C anti-sense and sense RNA probes were generated from linearized (ApaI, KpnI) pCR2.1 topo vector (Invitrogen, San Diego, CA), corresponding to nucleotides 1033 to 1593 of human VEGF-C DNA (sense, 5’-TTCCTGCGCA-CAACACTACCA-3’; antisense, 5’-CCAATATGAAAGGAGCACAAGCACA-3’). Digoxigenin-labeled antisense mRNA was synthesized using T7 RNA polymerase and (DIG)UTP, and sense mRNA was synthesized using SP6 RNA polymerase and (DIG)UTP (Boehringer Mannheim, Mannheim, Germany). In situ hybridization for VEGF-C mRNA expression was performed on 5-μm-thick formalin-fixed, paraffin-embedded tissue samples. This construct shared 82% homology with rat VEGF-C (Figure 1).

Results

Development of Interstitial Inflammation and Fibrosis in the Rat Remnant Kidney Model

As described previously in detail (8,9), surgical reduction of renal mass in rats resulted after 8 wk in several regional histologic patterns of tissue damage, including nephron loss, with focally hypertrophic, presumably regenerating, or atrophic proximal tubules and slim tubulointerstitial stroma. In other regions, atrophic tubuli and partially sclerotic glomeruli were separated by fibrotic interstitial areas. The essential clinical parameters are depicted in Table 1.

Aminopeptidase P, the Antigen of Monoclonal Antibody JG12, and Podoplanin Are Discriminatory Markers for Rat Blood and Lymphatic Vessels in Normal Renal Cortex

The mouse monoclonal antibody designated JG12 immuno-blotted a 70-kD rat glomerular membrane protein that was...
identified by mass spectroscopy sequencing of its tryptic peptides as aminopeptidase P. Aminopeptidase P was also found in microvascular endothelial cells in the lung, pancreas, and ear skin (data not shown). Podoplanin antibodies were raised against the corresponding 43-kD glomerular membrane mucoprotein, as described (4,15,16), and defined as specific marker for lymphatic endothelial cells (4).

In normal rat kidney cortex, anti–aminopeptidase P antibodies specifically labeled the entire tubulointerstitial microvasculature and the glomerular endothelial cells (Figure 2A). By immunoelectron microscopy, aminopeptidase P was found predominately on luminal endothelial membranes and only occasionally on the abluminal aspect (Figure 3). By contrast, podoplanin was expressed in lymphatic vessels that accompany large- and middle-sized interlobular arteries, as well as glomerular podocytes and the epithelia of Bowman’s capsule. Lymphatic vessels were not encountered in the tubulointerstitial spaces (Figure 2B).

The discriminatory specificity of aminopeptidase P and podoplanin was demonstrated by double immunofluorescence experiments in normal rat kidneys, in which lymphatic vessels were labeled exclusively by antipodoplanin antibodies but not by JG12, whereas the situation was reversed for blood vessels, without any overlap of labeling. Also, simultaneous double labeling by immunohistochemistry of paraffin sections using different chromophores resulted in clearly segregated signals for blood and lymphatic endothelial cells (Figure 4).

### Distribution of Lymphatic and Blood Vessels in Remnant Kidney Cortex

The paraffin sections used for immunohistochemical localizations represented large areas of the entire organ, and representative, unselected regions are documented in Figure 5. In areas of preserved cortical structure with unaffected or hypertrophic tubuli and without tubulointerstitial fibrosis, mostly JG12-positive blood microvessels were found, whereas podoplanin-positive lymphatic vessels were infrequently encountered (Figure 5, B through D). By contrast, fibrotic areas with atrophic tubuli and moderate mononuclear inflammatory cell infiltration invariably contained numerous lymphatic capillaries that were immunolabeled not only by antibodies to podoplanin but also by an alternative marker for lymphatic endothelial cells, the membrane protein LYVE-1 (Figure 6). In fibrotic

<table>
<thead>
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<th>Parameter</th>
<th>Sham Operated Controls (n = 6)</th>
<th>Remnant Kidneys (n = 8)</th>
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<tbody>
<tr>
<td>Mean body weight</td>
<td>420 ± 9 g</td>
<td>330 ± 24 g</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>120 ± 25 mmHg</td>
<td>142 ± 28 mmHg</td>
</tr>
<tr>
<td>BUN</td>
<td>16 ± 4 mg/dl</td>
<td>98 ± 29 mg/dl</td>
</tr>
<tr>
<td>Urine protein</td>
<td>18 ± 8 mg/24 h</td>
<td>130 ± 35 mg/24 h</td>
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* BUN, blood urea nitrogen.

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![Figure 2](image-url)  
**Figure 2.** Immunolabeling with monoclonal antibody JG12 specific for aminopeptidase P (A) or rabbit anti-podoplanin IgG (B) that is specific for lymphatic endothelial cells of paraffin sections of normal rat kidney. JG12 is localized on endothelial cells of glomeruli (G) and tubulointerstitial vessels. Podoplanin is observed on glomerular epithelial cells and Bowman’s epithelial cells and also in lymphatic capillaries (L) in the adventitial interstitium of an artery (A). Magnifications: ×350 in A; ×120 in B; ×450 in insert.

![Figure 3](image-url)  
**Figure 3.** Localization of aminopeptidase P by immunoelectron microscopy in ultrathin frozen sections of normal rat glomeruli. Gold particles are observed predominately on the luminal surfaces of glomerular endothelial cells. A depicts a transverse section, and B a tangential section. P, podocyte; US, urinary space; CL, capillary lumen; GBM, glomerular basement membrane. Magnification, ×3500.
regions, obvious paucity of blood vessels was noted (Figure 5A, *), whereas on other sites, occasionally also aggregates of blood capillaries were observed (Figure 6C), as reported previously (7). Some lymphatic vessels contained clusters of mononuclear cells (Figure 6A, insert).

As confirmation of the optical impression of differential densities of blood and lymphatic capillaries in double-labeled paraffin sections, a simple quantitative assessment of vascular densities that supported these significant microvascular differences was performed. When all vascular profiles in the sections were set as 100%, lymphatics amounted to 2% in normal cortex, 33% in nonfibrotic areas of remnant kidney cortex, and 65% in fibrotic areas (Table 2).

**VEGF-C is Produced by Interstitial Mononuclear Cells in Fibrotic Renal Cortex**

In normal kidneys, VEGF-C was localized by in situ hybridization primarily to smooth muscle cells of arteries, and proximal tubules were marginally positive. In sclerotic areas of remnant kidneys, by contrast, VEGF-C mRNA was expressed prominently in interstitial mononuclear cells, presumably macrophages (Figure 7), as found previously in the peritumoral stroma of human carcinomas (14).

**Discussion**

The histologic equivalents of chronic renal failure are nephron loss, interstitial infiltration by macrophages, and fibrosis. Recently, attention was focused on interstitial peritubular capillaries that form a dense network, particularly in the renal cortex, to serve the energy-demanding proximal tubular epithelial cells. Even in early stages of experimental interstitial fibrosis, the relation among intertubular capillaries, interstitial stroma, and tubuli is altered, but the interpretations of the results obtained in animal models and human kidneys remained controversial. Whereas several investigations pinpointed to focal loss of interstitial capillaries in fibrotic areas (8,9), others found an increase of their density under similar conditions (10). These conflicting interpretations were based on the use of different markers for labeling and quantification of interstitial capillaries. Specifically, a distinction between capillaries derived from the blood system and those of lymphatic origin was not possible because of the absence of specific markers. In this

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*Figure 4. Colocalization of podoplanin (green; A) and aminopeptidase P (red; B) in a 1-µM thick frozen section of rat renal cortex by double immunofluorescence. Whereas podoplanin is expressed by glomerular podocytes, epithelial cells of Bowman’s capsule, and a lymphatic vessel (L), aminopeptidase P is found exclusively on glomerular endothelial cells but not in the lymphatic endothelium. There is also no overlap of fluorescence when both pictures are merged (C). In a survey view, the distinct pattern of tubulointerstitial capillaries (red) and lymphatics (green) is apparent (D). Magnifications: ×500 in A–C; ×1200 in D.*
study, we capitalized on our discovery of two distinctive markers for rat lymphatic and blood capillaries to reinvestigate this controversial issue.

Podoplanin is a podocyte membrane mucoprotein that was named because of its apparent involvement of podocyte foot-process flattening (16). Although isoforms of podoplanin were found in several tissues, it is now established that among endothelial cells it is specifically and selectively expressed in lymphatic endothelial cells only. Evidence for this is derived from multiple recent observations, mainly in human tissues.

For example, in lymphatic endothelial cells, podoplanin was coexpressed with the CD44-related, hyaluronate-binding protein LYVE-1 (4,14) and VEGFR-3 that is specific for VEGF-C and VEGF-D, whereas the blood endothelial marker PAL-E was selectively excluded (4). Podoplanin antibodies were instrumental in our recent separation, expansion by tissue culture, and characterization of microvascular lymphatic and blood vessel–derived endothelial cell lineages (5,6). Transfection of isolated blood vessel endothelial cells to overexpress the lymphoendothelial transcription factor Prox-1 induced

Figure 5. Gallery of double localizations of podoplanin in lymphatic vessels (blue) and of aminopeptidase P in blood vessels (red) using paraffin sections of remnant kidneys 8 wk after surgery. Dilated tubuli (T) adjoin fibrotic domains of the renal cortex (A and B) that are rich in dilated lymphatic vessels. Small lymphatic capillaries (arrows) are also intermixed with blood microvessels (C and D). Tubulointerstitial capillaries remain in their original distribution in nonfibrotic areas (B; arrowheads); in other places, they are rarefied (A; asterisks). (E) In intact, nonsclerotic glomeruli, aminopeptidase P is located in endothelial cells, whereas podoplanin is expressed in podocytes and epithelia of Bowman’s capsule. Magnifications: ×200 in A and C; ×400 in B and D; ×350 in E.
massive expression of podoplanin that was consistently absent from blood vessel endothelia, as found on DNA arrays, in quantitative PCR, and by Northern and Western blotting (17). Here we show that the localization of podoplanin in rat kidney is restricted to periarterial lymphatic vessels, similar to that found in humans (Matsui et al., unpublished data). Moreover, rat podoplanin immunolabeled the same vessels in normal and remnant kidneys as anti-rat LYVE-1 antibody.

In situ hybridization to localize podoplanin mRNA in endothelial cells was not feasible, presumably because they contain only very small amounts of mRNA (Matsui et al., unpublished data). Taken together, podoplanin is an established and seemingly also the most reliable marker for lymphatic endothelia at hand.

For the specific detection of blood endothelial cells, we used here a monoclonal antibody, designated JG12, and we provide evidence that the corresponding antigen is the enzyme aminopeptidase P, a bradykinin-degrading membrane peptidase (18) that was previously associated with endothelial cells in lung, kidney, brain, and intestine by others (19). Aminopeptidase P is a glycosyl-phosphatidylinositol (GPI) membrane–linked aminoacylproline aminopeptidase specific for N-terminal Xaa-proline bonds and can inactivate bradykinin by cleaving the Arg1-Pro2 bond (18). Its precise physiologic function in this location is unknown. Using antibodies to podoplanin and to aminopeptidase P, we demonstrate in the rat remnant kidney model of progressive renal interstitial fibrosis that a large proportion of vessels within the fibrotic areas are of lymphatic lineage seem to account for high vessel counts when nondiscriminatory markers were used.

Although the focal increase in relative density of blood capillaries in fibrotic areas was explained by aggregation of preexisting tubulointerstitial vessels by atrophy and elimination of intervening structures, the lymphatic vessels must originate from a local neoangiogenic process, because in normal kidney, lymphatic vessels are restricted to the periarterial adventitia of large- and middle-sized arteries. This raised the question as to where the lymphangiogenic growth factor VEGF-C is produced in this setting (20). By immunohistochemistry and in situ hybridization, VEGF-C was localized primarily in interstitial mononuclear cells, presumably macrophages. This resembles strikingly the accumulation of CD68++ tumor-associated macrophages in human cervical carcinomas.

Table 2. Density of lymphatic versus blood vessels in normal and fibrotic renal cortex

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<tr>
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<th>Blood Vessel Density (% of Total Vessel Counts ± SD)</th>
<th>Lymphatic Vessel Density (% of Total Vessel Counts ± SD)</th>
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<tbody>
<tr>
<td>Normal rat</td>
<td>98 ± 7%</td>
<td>2 ± 0.1%</td>
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<tr>
<td></td>
<td><em>P</em> &lt; 0.0001</td>
<td><em>P</em> &lt; 0.0001</td>
</tr>
<tr>
<td>Remnant kidney</td>
<td>67 ± 23%</td>
<td>33 ± 18%</td>
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Figure 6. (A) Lymphatic microvessels (arrowheads) are labeled by antipodoplanin antibody and contain and presumably export mononuclear inflammatory cells in a remnant kidney. (B) Lymphatic vessels within an area of interstitial fibrosis are immunolabeled by an antibody specific for the CD44-related hyaluronan receptor LYVE-1, confirming the results obtained with antipodoplanin antibodies. Two arteries (A) are cross-sectioned on the left side of the picture. T, tubulus; arrowheads, lymphatic vessels. Magnifications: ×300 in A; ×1200 in insert; ×450 in B.
increased (10) in remnant kidneys could account for the discrepancy of in-
demand.

a logistic system to increase local lymphatic vessel density on
inflammatory cells, presumably macrophages, provide also in the rat
a systemic way to increase local lymphatic vessel density on

Taken together, the focal proliferation of lymphatic vessels
in remnant kidneys could account for the discrepancy of in-
creased (10) versus reduced (8,9) vascular density. Using non-
discriminatory endothelial markers, the former authors pro-
posed that blood vessel density was actually increased in
murine remnant kidneys. By contrast, immunolabeling with
endothelial lineage-specific markers confirm our previous find-
ing (8,9) of regional rarefaction of blood vessels and add the
new aspect of a sharp increase in lymphatic vessel density.
Thus, focal reduction of capillary blood flow and “starvation”
of tubuli may be associated with interstitial fibrosis and pro-
gression of renal disease. The function of newly formed lymph-
atic vessels remains to be determined. They may serve the
export of interstitial fluid and inflammatory cells, but beyond
these trivial functions, their ability to produce and secrete in a
polarized manner chemokines that attract dendritic cells (5)
suggests that they could play an as-yet-undisclosed role in the
immunosurveillance of kidneys.

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Figure 7. Predominant localization of VEGF-C mRNA by in situ
hybridization in interstitial mononuclear cells in a fibrotic intertubular
region of a remnant kidney. This region also contains two vessels that
are free of blood cells and could be lymphatic capillaries (L). T, tubulus. Magnification, ×350.


