Tubulointerstitial damage leads to atubular glomeruli: significance and possible role in progression

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Progression of renal insufficiency often continues despite the removal of the aetiological factor responsible for the renal disease. The pathogenesis of the progression is poorly understood although it is well known that quite different types of injury often lead to the same structural changes. The final stage of the renal disease often shows the same histopathologic changes, i.e. interstitial fibrosis, tubular atrophy and glomerulosclerosis.

In order to investigate further the morphological changes in chronic renal disease, the author and others have investigated a number of experimental models and human diseases with varying progression of renal insufficiency using advanced stereological, electron microscopic and immunohistochemical methods. The stereological methods included serial sectioning of the tissue in order to see whether or not atubular glomeruli were present and to estimate the glomerular volume. An atubular glomerulus is a glomerulus that is not connected to its proximal tubule (disconnected). In his elegant investigation by microdissection of the kidney in Bright’s disease, Oliver was the first to demonstrate the existence of both atubular glomeruli and aglomerular tubules [1].

Various investigations on human and animal tissue have demonstrated atubular glomeruli in many tubulo-interstitial diseases, such as lithium and cisplatin nephropathy, human chronic pyelonephritis, chronic allograft rejection and also renal artery stenosis [2–7]. In diseases other than primary tubulointerstitial diseases, such as diabetic nephropathy and experimental renal ablation, a significant number of atubular glomeruli have also been found [6,8]. The percentage of atubular glomeruli in advanced cases may reach > 35% (Table 1). A large proportion of the non-atubular glomeruli are connected to atrophic proximal tubules and only in a minority are they connected to a normal proximal tubule.

The atubular glomerulus is small, with a volume of only one-third to two-thirds that of normal glomeruli, and with a decreased number of capillaries [6,9]. The atubular glomerulus has a smaller volume if the tubulo-interstitial disease develops before adulthood, whereas it is less reduced in size if the disconnection takes place in an adult. The largest volumes are seen in the glomeruli that are connected to normal proximal tubules, and these glomeruli often enlarge due to compensatory hypertrophy. These hypertrophied glomeruli also have the greatest number of glomerular capillaries [9]. In the remnant kidney model, the atubular glomerulus also has a much smaller volume than a glomerulus connected to a normal proximal tubule [8].

In experimental settings, a good correlation has been found between the decrease in renal function and the length (or volume) of proximal tubules, on the one hand, and the percentage of glomeruli that are connected to normal proximal tubules on the other hand. This indicates that the atubular glomeruli (and glomeruli with atrophic tubules) do not contribute to glomerular filtration.

In advanced cases of renal artery stenosis, immunohistochemical methods able to distinguish between different parts of the nephron reveal that more proximal than distal tubules have vanished. In the same kidneys, as many as 50% of glomeruli may be atubular [5].

Ultrastructural investigation of the atubular glomerulus has not shown any marked changes. The mesangium is slightly increased and the basement membranes thickened, but the epithelial foot processes only show minor variation in size [6]. Scanning electron microscopy may be used to see whether the glomerulus is atubular or not and to investigate the structure of the glomerular tuft and the parietal epithelium. By these means, a number of the atubular glomeruli were found inside cystic dilated Bowman’s capsules [10].

Much evidence points toward atubular glomerulus as an important contributor to the decreased renal function seen in chronic renal diseases. Various reasons may be provided for the formation of the atubular glomerulus. First, a direct injury to the tubules (as in cisplatin-induced nephropathy or acute pyelonephritis) may result in destruction of the tubule without involving the glomerulus. Secondly, ischaemia caused by the increase in tubulocapillary distance that has
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Table 1. Stereological parameters in experimental nephropathies in rats

<table>
<thead>
<tr>
<th>Condition</th>
<th>Atubular glomeruli (%)</th>
<th>Volume of atubular glomeruli (10⁶ μm³)</th>
<th>Volume of glomeruli with normal tubular connection (10⁶ μm³)</th>
<th>Volume fraction of interstitium (%)</th>
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</thead>
<tbody>
<tr>
<td>Lithium, uninephrectomia, and high protein diet, 16 weeks</td>
<td>38 ± 12</td>
<td>0.26 ± 0.09</td>
<td>2.19 ± 0.63</td>
<td>20.9 ± 3.5 (fibrotic tissue)</td>
</tr>
<tr>
<td>Cisplatin nephropathy, 10 weeks</td>
<td>35 ± 14</td>
<td>0.68 ± 0.11</td>
<td>1.27 ± 0.23</td>
<td>40 ± 1</td>
</tr>
<tr>
<td>5/6 renal ablation, 25 weeks</td>
<td>48 ± 14</td>
<td>2.9 ± 0.9</td>
<td>5.6 ± 1.2</td>
<td>40 ± 1</td>
</tr>
<tr>
<td>Controls to the renal ablation model</td>
<td>3 ± 5</td>
<td>0.7 ± 0.7</td>
<td>2.0 ± 0.1</td>
<td>17 ± 1</td>
</tr>
</tbody>
</table>

From references [5,6,8].

been demonstrated in various chronic nephropathies may damage the tubules, leading to disconnection. Thirdly, proteinuria may have a toxic effect on the tubule. Finally, so-called ‘misuse atrophy’ of both the upstream and downstream part of the tubule may take place after tubular blockade by casts or blood.

The significance of atubular glomeruli is obvious. They are often present and do not contribute to the formation of urine. The damage done to the tubular system must be irreversible. Their possible role in progression of renal insufficiency is, however, more difficult to evaluate. Hypothetically, they may redistribute the blood in the kidney leading to tubular ischaemia and atrophy with the formation of additional atubular glomeruli. The compensatory hypertrophy of glomeruli with normal proximal tubules may also be detrimental to the kidney due to hyperfiltration injury in these hypertrophic glomeruli. Finally, Konda et al. [11] demonstrated renin-containing cells in the juxtaglomerular apparatus of atubular glomeruli, indicating that the atubular glomerulus contributes to the synthesis of renin. This means that local angiotension II production may also take place, which may promote renal scarring.

In conclusion, much evidence points strongly toward tubular destruction with glomerulo-tubular disconnection as an important and common cause of progression and irreversibility of chronic renal diseases.

References
9. Marcussen N, Nyengaard JR, Christensen S. Compensatory growth of glomeruli is accomplished by an increased number of glomerular capillaries. Lab Invest 1994; 70: 868–874