The glomerular mesangium: capillary support function and its failure under experimental conditions

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Summary. We present a structural analysis of the ability of the biomechanical unit consisting of mesangium and glomerular basement membrane to maintain normal capillary architecture in the face of mechanical challenges due to high intraglomerular pressures. Capillary support function may be considered in terms of the stabilization of local form (development of wall tension against capillary dilation) and global form (centripetal fixation of capillary loops to maintain higher order form). The pathologic consequences of the loss of this support are illustrated by way of experimental models of mechanical mesangial failure. Such failure may express itself as mesangial widening, increased transmesangial macromolecule "traffic," ballooning of capillary segments, and unfolding of capillary loops. Mechanisms are described by which these structural changes may lead to segmental glomerular sclerosis.

Key words: Kidney – Glomerulus – Mesangium – Mesangial failure – Electron microscopy – Animal models

This paper describes the anatomic organization of the glomerular mesangium together with its geometric relationship to the glomerular basement membrane (GBM), the functional relevance of this...
system in supporting the glomerular capillaries, and some of the consequences of mesangial “failure.”

**General description of the glomerular tuft**

The glomerular tuft (Fig. 1) comprises an anastomosing capillary network supported by a central mesangial stalk made up of mesangial cells and a dense fibrillar matrix \[14, 18, 28\]. The entire tuft is invested with a resilient basement membrane, the GBM. Outside the tuft but firmly attached to it by the GBM are the visceral epithelial cells (podocytes). If the capillaries are considered as tortuous endothelial cylinders wrapped about the mesangial stalk, then it must be kept in mind that along their entire length they are bordered by the mesangium over some part of their circumference. Since the GBM surrounds the combined endothelium-mesangium complex as a continuous sheet, no capillary segment is completely circumferentially surrounded by GBM.

Mesangial cells contain a contractile apparatus consisting of microfilament bundles found predominantly within the cell processes (Fig. 2). These bundles contain the usual contractile proteins such as actin, myosin, \(\alpha\)-actinin, and tropomyosin (as demonstrated by immunocytochemistry \[3\]), and cell contractility has been demonstrated in vitro \[14\]. The mesangial cells or their processes insert (either directly or via extracellular fibrils) into the GBM at the “mesangial angles” \[28\], those points where the GBM deflects from a purely pericapillary course to envelop the mesangium. Within the axial mesangium, mesangial cell processes have multiple GBM attachments. Thus, both at the mesangial angles and within the axial mesangium, the GBM is the effector site for mesangial cell contractility.

**Normal mechanical function**

An appreciation of the mechanical aspects of capillary tuft architecture is vital to an understanding of normal and deranged glomerular function \[12\]. For example, the hydrostatic pressure gradient across the glomerular capillary wall is of the order of 40 mmHg \[4\]. Such a high pressure underlies effective filtration in these capillaries, but at the same time presents a mechanical challenge which is evidently much greater than that faced by ordinary tissue capillaries, in which a transmural pressure difference of 5–15 mmHg exists.

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Fig. 2a, b. Overview of a glomerular capillary and its supporting mesangium. Most of the endothelial tube (E) is covered by the GBM; only a small portion contacts the mesangium. At the endothelium-mesangium interface, no basement membrane is developed. The mesangial cell gives rise to many cell processes which are filled with microfilament bundles (arrowheads) and attach to the GBM at the mesangial angles (arrows) as well as at sites on the perimesangial GBM. \(a \times 6800; \ b \times 18800\)