Mesangiolysis

Mesangiolysis is defined as "dissolution or attenuation of mesangial matrix and degeneration of mesangial cells" [1]. In essence, it is an injurious process which affects the glomerular mesangium without causing obvious damage to the capillary basement membranes. The matrix swells, loosens, and eventually dissolves; the mesangial cells may show only edema and vacuolization, or may undergo severe degeneration and necrosis. Mesangiolysis appears to play a significant role in a wide variety of glomerular diseases, from those caused by toxins and poisons to several forms of glomerulonephritis.

With light microscopy mesangiolysis is recognized by widening and poor staining of the mesangial areas (see Fig. 8). However, this change can be transitory and inconspicuous. A much more obvious manifestation is dilatation of the capillary lumina which attain aneurysmatic proportions and often end as a huge "blood cyst" occupying most of the glomerular space. As has been shown by electron microscopy, formation of blood cysts is secondary to the dissolution of mesangial matrix and loss of the "anchoring points" of the capillary walls. As a result, the basement membranes are no longer held in a fixed position by their attachments to the mesangium: They unfold and the adjoining capillary lumina merge.

**Historical note**

The concept of mesangiolysis was first proposed by Japanese investigators some 25 years ago. Fujimoto postulated that glomerular inflammation is often preceded by tissue damage and dissolution ("histolysis") [2, 3]. Yajima realized that histolysis primarily affected the mesangium and used the term mesangiolysis to designate this process [4]. However, some of the features of mesangiolysis, especially the formation of blood cysts, were first reported in the beginning of this century. Pearce noticed blood cysts in the glomeruli in his experiments on the hemorrhagic properties of rattlesnake venom, and attributed them to a hemorrhage into the glomerular tuft [5]. Some of the rabbits in his experiments also showed exudative lesions in the Bowman’s space, manifested by protein coagulum, fibrin, and red blood cells. Suzuki conducted similar experiments with the venom of Habu snake (Trimeresurus flavoviridis), indigenous to southern Japan, and also observed glomerular blood cysts [6]. Kitamura et al realized that the initial process of blood cyst formation was mesangial injury or mesangiolysis [7]. These observations were soon confirmed by electron microscopy [8, 9].

**Sequential histological changes in acute experimental mesangiolysis**

Experimental mesangiolysis has been produced in rabbits and rats [10–12]. Rabbits appear to be more sensitive: With the appropriate dose of snake venom, they develop blood cysts in almost all glomeruli, whereas in the rat the proportion of involved glomeruli does not exceed one third. The involvement is always focal and segmental, though a single glomerulus may have more than one lesion. Destruction of the mesangium proceeds rapidly, and what is seen by light microscopy are the effects of the damage, namely, segmental ballooning of capillaries which becomes apparent 6 to 24 hr after intravenous injection of the venom (Fig. 1). Such capillaries are packed with red blood cells which soon become mixed with fibrin and some inflammatory cells (Fig. 2). After 3 days, proliferation of cells is noted, especially at the point of attachment of the capillary to the remainder of the tuft. The cells are relatively large and have a single nucleus; they most likely represent proliferating mesangial cells or possibly transformed blood monocytes. Within a short time the cells increase to the point where they fill almost the entire ballooned loop, imparting the appearance of a segmental glomerulonephritis (Figs. 3 and 4). Silver stains demonstrate fine strands of intercellular substance between the cells (Fig. 3). After a few days, slit-like spaces, apparently lined by endothelial cells, develop in the peripheral part of the loop, particularly between points of attachment of the growing cell mass to the basement membrane (Fig. 4). These slits grow in size and assume the shape of the capillary lumina. At the same time the mesangium is reconstituted, and the capillary tuft recovers its normal structure, although a degree of cellularity persists for a long period of time, 100 days or longer. On rare occasions, crescents may be noted in the Bowman’s space.

By electron microscopy, more subtle, early changes can be seen in the mesangium and the capillary wall. The mesangium demonstrates the characteristic features of mesangiolysis, that is, progressive destruction of the matrix and cells. Proteinaceous fluid, probably derived from the capillary lumen, accumulates between and within the strands of mesangial matrix, which becomes loose and irregular (Fig. 5). Platelets may aggregate in the areas of edema, break down, and give rise to free membrane-bound granules. In a short time, most of the matrix loses its identity, dissolves, or disappears (Fig. 6). The mesangial cells are at first preserved (Fig. 6), but later, they degenerate and also disappear. The capillaries show early detachment of the endothelial cells (Fig. 5) and formation of gaps due to separation or focal loss of endothelial cells (Fig. 7). The basement membranes remain intact. With the breakdown of the mesangium the capillary lumina enlarge (Fig. 7). Platelet aggregates and free membrane-bound granules can be seen in and near the remnants of the mesangium along the capillary wall (Fig. 7), or adhering together with fibrin, to the exposed stretches of the basement membrane. In some capillaries, endothelial detachment occurs without aneurysmal lesions, but...
Fig. 1. Schematic representation of the development of a "glomerular cyst" (capillary aneurysm). A Normal glomerular lobule. The mesangial area is in the center. It consists of cells and strands of matrix. B Partial dissolution of the matrix and beginning dilatation of capillaries. Platelet accumulation is seen in the areas of dissolution. C Fully developed cyst. Abbreviations are: CL, capillary lumen; En, endothelial cell; Ep, epithelial cell; F, fibrin; MC, mesangial cell; MES, mesangium; MM, mesangial matrix; P, platelets; Mo, monocytes; PMN, polymorphonuclear leukocyte.

Fig. 2. Typical "glomerular cyst" 18 hr after intravenous injection of Habu snake venom into a rabbit. The aneurysm occupies most of the glomerulus and is filled with red blood cells and fibrin. The compressed remainder of the glomerular tuft lies toward 7 o'clock. (Hematoxylin and eosin, ×420)
Fig. 3. Seven days after injection of venom. Much of the "cyst" is filled by proliferating mononuclear cells which are separated from each other by fine strands of intercellular material. The remainder of the original tuft is in the lower part of the picture. [Periodic acid-silver methanamine (PASM), ×420]

Fig. 4. Fifteen days after injection of venom. A remnant of the original "cyst" is seen toward 3 o'clock. The mass of proliferating cells and intercellular matrix is now attached at many points to the basement membrane delineating small capillary lumina (along the top of the tuft on the right). (PAS, ×500)
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Fig. 5. Early changes in the glomerular mesangium 18 hr after injection of venom. The mesangial matrix shows progressive changes: A Edema. B Fragmentation. C Beginning dissolution. The mesangial cell (MC) on the left is preserved; that on the right shows edema of the cytoplasm. The endothelium is detached from the basement membrane at D. Abbreviations are: CL, capillary lumen; U, urinary space; MC, mesangial cell. (electron micrograph, ×16,800)

the majority of the affected loops undergo rapid dilation to form blood cysts.

By 3 days cell exudation and proliferation become apparent, and the process of restructure and reconstitution of the normal glomerular lobule evolves as outlined above. Depending on the elapsed time from injection of the venom, the histological changes can be perceived either as glomerular aneurysms or as focal proliferative glomerulonephritis.

Toxic glomerulopathy. Mesangiolysis after snake bite has also been observed in humans ([13], also C. Pirani, personal communication). Furthermore, there are occasional case reports of renal failure and focal proliferative glomerulonephritis with crescents in victims of snake bite [14, 15]. In these cases renal biopsy specimens were obtained many days or weeks after envenomation, suggesting the possibility that earlier mesangioytic lesions were missed.

Mesangiolysis and glomerular blood cysts have also been observed after the administration of several chemical poisons such as sublimate [16], croton oil [17], and monocrotaline [18]. Recently, it has been reported that cyclophosphamide produces mesangiolysis in newborn mice [19].

Mesangiolysis in glomerular ischemia and hypertension

Total acute renal ischemia induced in experimental animals by clamping of the renal pedicle, leads, if sufficiently prolonged (2.5 to 3 hr) to severe glomerular damage [20]. Mesangium appears to be very vulnerable. When the clamp is released and blood flows into the kidney, marked glomerular congestion ensues, and within 1 hr large capillary aneurysms form, indistinguishable from those caused by snake venom. Similar changes are produced by a more prolonged but incomplete occlusion (clipping) of the renal artery in experimental one kidney hypertension [21, 22]. When the artery is unclipped, the kidney is no longer protected from hypertension: Blood flows into the kidney under increased pressure, followed within 24 hr by segmental necrosis of small arteries and arterioles and the formation of “blood cysts” in the glomeruli. Though such blood cysts are a presumptive evidence of mesangiolysis, actual electron microscopic studies of the mesangial structure in renal ischemia are not yet available.

Rapidly developing severe hypertension, such as that induced by a tight clip on one renal artery, may induce arterial necrosis and glomerular aneurysms in the opposite (unprotected) kidney [21].

Mesangiolysis in thrombotic microangiopathy syndromes

Although glomerular capillary and arterial thrombosis is the striking manifestation of hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura, it is inconstant and on occasion completely absent. A much more constant change is
detachment of the endothelium from the basement membranes, as well as edema, reticulation, and dissolution of the mesangial matrix [23]. These changes are similar to those seen in the early stages of toxic mesangiolytic, except that instead of hours they apparently develop over a period of days, and involve larger areas of the glomerular tuft. On light microscopy the mesangium becomes wide and stains poorly, and the matrix is difficult to identify. The affected glomerular lobules expand, sometimes considerably so, but their general outlines remain recognizable. On occasion, however, true capillary aneurysms are formed. Healing of the lesions apparently leads to bland acellular sclerosis of the glomerular tuft.

Malignant nephrosclerosis. So-called primary malignant nephrosclerosis, that is, one occurring without a previous vascular or glomerular disease, may be accompanied by thrombotic microangiopathy and mesangiolytic, very similar to that seen in hemolytic-uremic syndrome [24]. On occasion capillary aneurysms are observed.

Transplant rejection. Rejection of a transplanted kidney frequently leads to detachment of glomerular capillary endothelium and marked widening of the subendothelial space. This may be accompanied by mesangiolytic severe enough to dissolve the mesangial areas (Fig. 8) and lead to their merger with the capillary lumina, thus creating large blood spaces. Such blood cysts have been observed in experimental animals as well as in human transplant recipients [25, 26].

Radiation nephritis. Renal glomeruli are quite sensitive to ionizing radiation. In experimental animals, glomeruli regularly demonstrate endothelial detachment and mesangiolytic, with degeneration of mesangial cells, dissolution, and homogenization of the matrix and eventual sclerosis of the mesangium [27, 28]. On occasion, glomerular cysts develop [29, 30].

Glomerulonephritis. Edema of mesangial matrix is a common phenomenon in the acute stage of glomerulonephritis. This is usually perceived as part of an acute inflammatory process, caused by injurious substances (for example, immune complexes) in the mesangium [31, 32]. Lysis of the mesangial matrix around the electron dense deposits (presumably immune complexes) may also be seen in chronic glomerulonephritis (for example, IgA nephropathy) [33]. In severe inflammation, edema and focal dissolution of matrix may progress to true mesangiolytic, with widening and poor staining of mesangial areas, marked expansion of the affected lobules and formation of capillary aneurysms. Such changes have been reported in experimental Masugi nephritis [30] and in various forms of human glomerulonephritis, including acute diffuse glomerulonephritis [34], extracapillary glomerulonephritis [35], Wegener's granulomatosis [36], Henoch-Schönlein purpura [30], subacute bacterial endocarditis [4] and echovirus infection [37]. The authors of the latter report applied the name “mesangiolytic glomerulonephritis” to the glomerular changes, which included necrosis of mesangial cells and damage to the mesangial matrix.
Fig. 7. More advanced changes in the glomerular tuft following injection of venom. A dilated capillary is filled with red blood cells and platelets. A single monocyte (Mo) and a neutrophilic leukocyte (L) are present. Platelets prominently aggregate near and in the expanded mesangial areas, most evident at M3, but also at M1 and M2. The endothelium is separated from the mesangium at M2 (arrow) and is denuded at M4. The latter area is expanded and shows a central zone of lucency. (electron micrograph, x2,700)

Fig. 8. Glomerulus in transplant rejection. The upper part of the tuft shows striking widening of the mesangial areas with edema, homogenization, and loss of staining of the matrix, and degeneration of many of the mesangial cells. Normal appearing mesangium is seen in the lower part of the tuft from 3 to 7 o'clock. The micrograph is used with permission from Dr. H. C. Hsu. (PAS, x400)
Fig. 9. Diffuse diabetic glomerulosclerosis. An early tear of the mesangium at the anchoring point leads to separation of the mesangium from the overlying basement membrane. Adherent platelets (arrows) are seen at each end of the tear. Abbreviations are: BM, basement membrane; CL, capillary lumen; MC, mesangial cell; MM, mesangial matrix; U, urinary space. The figure is used with permission from [41]. (electron micrograph, ×6,775)

Recently, specific antisera against mesangial cell antigens were shown to cause mesangiolysis [38, 39].

Diabetic glomerulosclerosis. Mesangiolysis has also been reported to occur in diabetic glomerulosclerosis, as a stage in the development of capillary aneurysms and of mesangial nodules [40—42]. The proposed mechanism involves localized lysis of the matrix and degeneration of cells at the points of attachments ("anchors") of the capillary basement membranes to the mesangium (Fig. 9): If this lysis occurs rapidly, the anchors rupture, the basement membranes uncoil and a capillary aneurysm is formed. If the change is slow, an attempt is made by the mesangial cells to repair the damage by depositing layers of fibrillar material over the accumulated masses of mesangial matrix.

The exact contribution of mesangiolysis has not been established and its role in the formation of aneurysms and nodules has not been fully assessed. The aneurysms may arise, at least in part, by a different mechanism, for example, through a decrease of the mechanical strength of the capillary wall, caused by alteration of its chemical composition. Capillary aneurysms are seen in the retina where mesangial structures are absent, although the capillaries are surrounded by pericytes, which are probably the analogues of mesangial cells. Most of the glomerular nodules (Kimmelstiel-Wilson) consist of masses of mesangial matrix and are believed to represent a more advanced stage of the "diffuse" diabetic glomerulosclerosis. However, some nodules show layered material around the core of matrix and may be produced by the process of mesangiolysis and repair mentioned in the preceding paragraph.

Formation of mesangial nodules and occasionally of capillary aneurysms and detachment of the basement membrane from the mesangium have also been reported in certain dysproteinemias (for example, Kappa light chain nephropathy [43, 44] in chronic disulfide poisoning [45] and after cortisone administration [46—49]).

Discussion

It is obvious that formation of capillary aneurysms (blood cysts) in the glomeruli initiated by mesangiolysis depends on a greater sensitivity of the mesangial matrix to injury as compared with that of the capillary basement membranes. Mesangial matrix is often referred to as "basement membrane-like material," because of the similarity in appearance under the transmission electron microscope. However, on closer inspection the mesangial matrix has a more distinct fibrillar structure, imparted mainly by the "small tubular microfibrils," 10 to 12 nm in diameter. These microfibrils are related to, or are perhaps identical with, the similar structures found in elastic fibers [50]. Furthermore, mesangial matrix contains proteoglycans, dermatan sulfate and chondroitin sulfate [51], and fibronectin [52], while basement membrane, and especially its lamina densa, contains collagen types IV and V and the proteoglycan, heparan sulfate [53].

The difference in the response of the mesangial matrix and the lamina densa of the basement membrane has been nicely demonstrated by a recent in vitro study of isolated glomeruli [54]. Immersion of such glomeruli in 60% trichloroacetic acid leads in a few hours to dissolution of the mesangium and formation of large glomerular cysts, analogous to the in vivo "blood cysts." A leaching out of mesangial cells by a detergent (Triton-X100, or sodium deoxycholate) preserves the mesangial matrix and does not alter the lobular structure of the glomerulus. A considerably more prolonged immersion in trichloroacetic acid is needed to dissolve the basement membranes, or, more specifically, their lamina densa.

The lamina rara interna and externa of the basement membrane have a much looser structure than the lamina densa. The lamina rara interna is closely related to the mesangium histogenetically and phylogenetically. In fact, in some of the lower vertebrates (for example, amphibians) the space occupied by the lamina rara interna is filled by mesangial cells and matrix which arise from the centrilobular mesangial cores and encircle the capillary [55, 56]. In humans and other higher vertebrates normal lamina rara interna lacks cells and contains mainly a ground substance (proteoglycans?), collagen types IV and V, "small" microfibrils and fibronectin. In disease, lamina rara usually mimics the changes occurring in the mesangium.
Among such changes are loosening of its structure and separation of the endothelial cells from the basement membranes. The endothelial cells sometimes degenerate and desquamate, but often they remain viable and are able to produce a new layer of basement membrane.

In acute experimental mesangiolysis it apparently matters little whether there is a primary injury to the mesangial cells, or only secondary destruction following dissolution of the mesangial matrix. The surviving cells from the nearest preserved mesangial area multiply (or perhaps are de novo formed from blood monocytes), produce mesangial matrix, and reconstitute the structure of the lobule.

The situation is more complex in human disease, where many factors weigh on the glomerular structures, including inflammation and cell proliferation, vascular thrombosis, hypertension, and ischemia. No specific information is currently available on the evolution of mesangial lesions in humans caused by snake venom. Mesangiolysis in thrombotic microangiopathy, radiation injury, transplant rejection, and various forms of glomerulonephritis is probably more apt to lead to glomerular sclerosis than to complete a return to normal, but further studies are needed in this area.

The occurrence and the role of mesangiolysis in diabetic glomerulosclerosis are less clearly defined. The suggestion that mesangiolysis plays a role in the development of glomerular capillary aneurysms and of mesangial (Kimmelstiel-Wilson) nodules, is interesting, but also needs further study.

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References

33. TAKASHI MORITA

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52. LINDER E, MIETTINEN A, TORNROTH T: Fibronectin as a marker for the glomerular mesangium in immunohistology of kidney biopsies. Lab Invest 42:70—75, 1980


54. KRAKOWER CA, MANALIGOD JR: Mesangiolysis of isolated renal glomeruli with the formation of lobular sacs or cysts. Renal Physiol 3:226—236, 1980
