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Continuity of the mesangial channel network with the glomerular basement membrane and intraglomerular subendothelial space☆

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Abstract The composition and exact structure of the non-cellular mesangial matrix in the glomerulus of the human kidney are a matter of debate. It may appear like a structure similar to the glomerular basement membrane (GBM), it has been described to contain microfilaments. The exact transport route of fluids, solvents and immunocomplexes in the mesangium is not well-known either. We know that in some glomerular diseases immunocomplexes can be found in the GBM and the mesangium at the same time in the same patient. A possible explanation of the above findings could be provided by our hypothesis, i.e. the existence of a well-defined mesangial channel network (MChN). This MChN would consist of intercommunicating channels, which were embedded into the spongy cytoplasm of the mesangial cells (MCs) and surrounded by the plasma membrane of the mesangial cells. The MChN would lead from the subendothelial space through deep mesangium to the vascular pole or the juxtaglomerular apparatus and may transport fluid and other materials such as immunocomplexes into the mesangium. It would be continuous with the GBM. Microfilaments of the MC would be anchored to the walls of the MChN regulating its diameter, thus mesangial fluid transport and pressure. The dilatation of these channels by mechanical obstruction could contribute to glomerular sclerosis. The hypothesis can be challenged by methods like electronmicroscopy, immunoelectronmicroscopy, confocal laser-scanning microscopy, and vital stain studies. We provide some

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images suggesting the existence of the channel and its connection with the GBM. If the hypothesis was true, it could contribute to understanding of mesangial transport processes, pressure regulation and pathogenesis of glomerular mesangial diseases.

Introduction

The structural relationship of glomerular basement membrane (GBM) to mesangium has been extensively studied and attempts have been made to reveal the functional significance of this relationship.

It has been demonstrated that GBM and mesangium form a functional unit, in which the mesangium physically supports the glomerular capillary loop to maintain normal capillary architecture even when challenged by increased intraglomerular pressure [1—5]. In this regard it is to be noted that the endothelial tubes of the glomerular capillaries are not completely encircled by GBM, in fact, there can be no GBM found between the endothelium and the mesangium; the GBM is only localized between podocytes and mesangium and between podocytes and endothelium [4,5]. The mesangium consists of mesangial cells (MCs) and the non-cellular mesangial matrix (MM) (Fig. 1). The latter is located between the paramesangial GBM (pmGBM) and the mesangial cell. The architecture and function of the mesangial cells are well-described [6,7], however, the composition and structure of the mesangial matrix are a matter of debate. Some authors describe it as a GBM-like material with a less compact structure and more filaments, others describe it to contain a three-dimensional network of fibers [1,3,8—10]. The material of the MM has been described to contain types III, IV, V and type VI collagen, laminin, entactin, fibronectin, fibrillin, biglycane, and decoryn [3,11—15].

Another matter of debate is the involvement of the MC and MM in intraglomerular transport processes [16]. From the pathologist's view we know that some glomerular diseases involve immunodeposits characteristically in the GBM (e.g. membranous glomerulonephritis, GN) or in the mesangium (i.e. IgA nephropathy), or in both localizations (i.e. lupus nephritis WHO Class IV, mesangiocapillary GN type III). The question arises, if there is a morphological background of the immunodeposit localization seen at the same time in the GBM and in the mesangium. Furthermore, in non-immunopathogenetic diseases such as diabetic nephropathy the GBM as well as the MM are affected, both structures expand during the course of the disease. This expansion correlates with proteinuria and subsequent deterioration of renal function.

Hypotheses

Our hypothesis is as follows: plasma-derived fluid, macromolecules and particles pass through the mesangial matrix in a well-defined, interconnecting mesangial channel network (MChN) in healthy and diseased human kidney. We believe that these channels are bordered by the cytoplasm of the MC. In fact, they are embedded into the cytoplasm of spongy MC and surrounded by the plasma membrane of the MC. The mesangium is made up of the MC and nothing else but this MChN, thus this MChN is the non-cellular MM. The channels run from the subendothelial space into deep mesangium, their branches communicate with each other, and thus they can be regarded as a continuum leading from the capillary lumen through the mesangium to the glomerular hilus. The MChN can be traced between the endothelial and the mesangial cells at the beginning, later on between the mesangial cells and they play an important role in intraglomerular transport processes.

The stability of the capillary—mesangium unit is provided by mesangial cell processes containing microfilament bundles. Microfibrils in the mesangial cell processes and in the mesangial matrix consist of contractile elements that are claimed to protect structural integrity of the glomerular tuft against distending forces and to regulate glomerular microcirculation. We believe that microfilaments inside the MC are anchored to the wall of the MChN, thus they may regulate the diameter of the channels, thus may

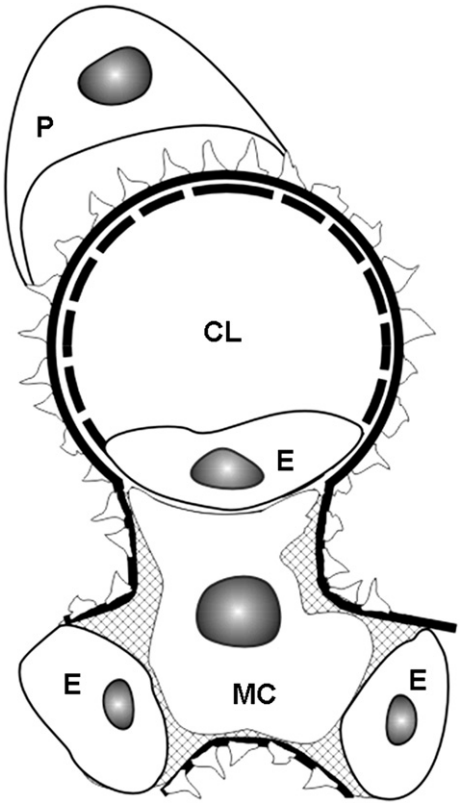

Figure 1 'Conventional view' of the structure of the glomerulus demonstrating the glomerular capillary loop (CL), the endothelial cell (E), the mesangial cell (MC), the podocyte (P), glomerular basement membrane (continuous, thick black line), the fenestrated endothelium (dashed black line) and the mesangial matrix (grey, ruled area).