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Dr Mahima Sara Mathew

Assistant professor in the Department of Dermatology

Samarkand State Medical University

"FREQUENT HISTOLOGICAL FINDINGS IN GLOMERULAR EPITHELIAL CELLS LINKED TO SECONDARY FSGS."

Abstract

In primary focal segmental glomerulosclerosis (FSGS), parietal epithelial cells (PECs) play a role in developing sclerotic lesions. By examining 60 patient biopsies, including 7 different common and uncommon glomerular diseases associated with secondary FSGS changes, this study examined the role of PECs in the more common secondary FSGS lesions. Two different quadruple staining techniques were applied to each biopsy: one targeted PECs (ANXA3), podocytes (synaptopodin), PEC matrix (LKIV69), and nuclei (Hoechst), while the other targeted activated PECs (CD44 and cytokeratin-19), PEC matrix, and nuclei. Cells expressing either podocyte or PEC markers were involved in the cellular adhesions (synechiae) that connected Bowman's capsule to the glomerular tuft in all lesions.

Keywords: chronic kidney disease, glomerulosclerosis, glomerulus, parietal epithelial cells, progression, renal biopsy.

Аннотация

В первичном очаговом сегментарном гломерулосклерозе (ФСГС) париетальные эпителиальные клетки (ПЭК) играют важную роль в развитии склеротических поражений. В данном исследовании были изучены биопсии 60 пациентов, включая 7 различных распространенных и редких гломерулярных заболеваний, связанных с вторичными изменениями ФСГС, чтобы исследовать роль ПЭК во вторичных поражениях ФСГС. К каждой биопсии применялись две разные техники четырехкратного окрашивания: одна была направлена на ПЭК (ANXA3), подоциты (синаптоподин), матрикс ПЭК (LKIV69) и ядра (Hoechst), а другая — на активированные ПЭК (CD44 и цитокератин-19), матрикс ПЭК и ядра. Клетки, экспрессирующие маркеры подоцитов или ПЭК, были вовлечены в клеточные адгезии (синехии), соединяющие капсулу Боумена с гломерулярным пучком во всех поражениях.

Ключевые слова: хроническая болезнь почек, гломерулосклероз, клубочки, париетальные эпителиальные клетки, прогрессирование, биопсия почек

Introduction

Chronic kidney disease, which affects 5–10% of the general population, has become a significant social burden. One of the biggest risk factors for cardiovascular problems is chronic kidney disease. The most frequent histological finding is focal and segmental glomerulosclerosis (FSGS).

The majority of research on the pathophysiology of FSGS to date has concentrated on "primary" or "idiopathic" FSGS, which is glomerulosclerosis without any indication of other inflammatory or degenerative glomerular pathology. But "secondary" (or "reactive") FSGS is far more prevalent, where a renal biopsy can identify the underlying glomerular disease.. The glomerular tuft and Bowman's capsule form fibrous synechiae, which are cellular adhesions containing extracellular matrix, early in the development of a classic sclerotic lesion (except collapsing FSGS). Alongside mesangial and endocapillary sclerosis, which is characterized by the obliteration of glomerular capillaries that develop in the affected tuft segments, epithelial cell hypertrophy and hyperplasia may also be observed. Significant advancements in our knowledge of the pathophysiology of glomerulosclerosis have occurred in recent years 1, 2, and 3. In general, podocyte-specific transgenic depletion studies have shown that glomerulosclerosis requires podocyte damage 4, 5 and 6. The glomerular tuft and Bowman's capsule adhere to one another (synechia), the first hallmark lesion of glomerulosclerosis. 7., 8. Segmental sclerotic lesion arises from adhesion. 9, Endocapillary sclerosis may eventually completely revert, but extra-capillary lesions are believed to be irreversible.10 Genetic cell-fate tracking in transgenic mice offered conclusive evidence for a critical role of parietal epithelial cells (PECs) in FSGS. The experiments demonstrated that PECs invade the sclerosis-affected section of the tuft where they deposit their matrix through cellular adhesions.13.PECs were segmentally "activated," meaning they expressed the de novo activation marker CD44, primarily near a sclerotic lesion.

Materials and Methods

After reviewing all 50 human biopsies, a pathologist identified 7 distinct glomerular diseases and secondary FSGS in each case (Figure S1). Normal human biopsy material from tumor nephrectomies was used to create two quadruple stainings . The first was stained with Hoechst (DNA), 10 podocytes (synaptopodin), PEC matrix (a particular but undefined heparansulfate moiety that

is synthesized in the glomerulus exclusively by PECs, LKIV69), and annexin A3 (ANXA3, characterized in17), a novel marker for all PECs.

PEC markers are found in every secondary human FSGS lesion.For every biopsy, the two quadruple stainings were used. Almost all secondary FSGS lesions had PEC markers found on the tuft. In total, periodic acid-Schiff (PAS) sections revealed FSGS in 32% of the glomeruli, and 29% (or 91% of all FSGS lesions) stained positive for LKIV69, a sensitive and specific marker for PEC matrix. Staining with the PEC marker ANXA3 produced a similar outcome . Just half of the FSGS lesions were found to be Claudin-1-positive. Using more recent batches resulted in a lower sensitivity of the claudin-1 immunostaining (data not shown).

Discussion and Results

Cellular adherences

Our first significant discovery is that cells expressing either podocyte or PEC markers, or both types of cells, can be the source of cellular adhesions between a tuft segment and Bowman's capsule (Figure 4a and b). In a number of investigations, tuft-to-capsule fibrous synechiae have been identified as a nidus for the development of sclerotic lesions in both human and experimental animal models.5. 10, 11, 12, and 13.

The development of FSGS lesions in this study was only linked to PEC marker and/or PEC matrix expression on the glomerular tuft. Therefore, any cellular adhesion may be a sign of a primary podocyte injury, while the development of sclerotic lesions may only be linked to PEC invasion of the tuft segment in question.

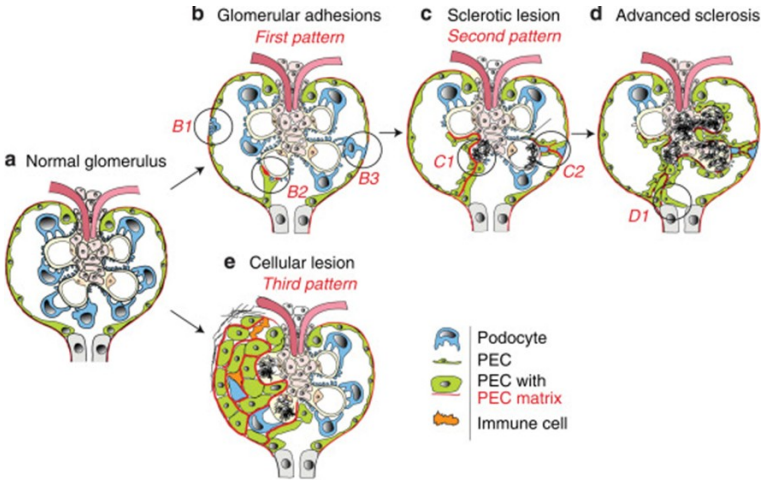

Figure 4 shows three different histological patterns of parietal epithelial cell (PEC) involvement in human focal and segmental glomerulosclerosis (FSGS) lesions. (A) Normal glomerulus with parietal epithelial cells (PECs, green) and podocytes (blue) in the extracapillary compartment, which is isolated from the endocapillary

compartment by the glomerular basement membrane (GBM). (b) PECs (B2) and/or presumed podocytes (B1) formed glomerular adhesions/synechiae. The PEC matrix beneath the parietal podocytes (B1 + B3) along the Bowman's capsule was no longer visible. At the location of adhesion to the glomerular tuft, PECs migrating onto the GBM deposited PEC matrix (B2, red). The possibility that podocytes in close proximity to cellular adhesions, unlike mice, undergo trans- or de-differentiation in situ to display PEC markers de novo cannot be ruled out. (c) Lesions of Sclerotic FSGS. There is a correlation between the development of sclerosis in the neighboring endocapillary compartment (C1) and presumed PEC migration onto the GBM. Presumptive podocytes were occasionally still visible within adhesions (C2), and cells expressing PEC markers were seen on top of podocytes that were positive for synaptopodin (arrow). Note that the formation of sclerotic lesions was not linked to podocyte migration, but rather to presumed PEC migration onto tuft segments that were impacted. Advanced sclerosis (d). Whole segments of sclerotic tufts are capped by presumed PECs. This can lead to the obstruction or loss of the tubuloglomerular outflow (D1). (e) Cells that express PEC markers almost entirely fill cellular lesions, and compared to sclerotic lesions, more presumed PECs show activation markers.

In conclusion

In our investigation, synaptopodin-positive cells on the glomerular tuft were covered by cells expressing PEC markers. This supports the theory that PECs outgrow living podocytes in situ, which may be another mechanism for podocyte loss, secondary FSGS progression, and irreversible renal function loss. As an alternative, glomerular epithelial cell layers may transdifferentiate in an orderly, outside-in fashion on the glomerular tuft.

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