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Update on Immune Mechanisms in Systemic Lupus and Lupus Nephritis

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Abstract

Lupus nephritis is a frequent complication of systemic lupus erythematosus. Multiple pathological mechanisms attribute to the pathogenesis of lupus nephritis. These mechanisms can be grossly divided into two groups, extrarenal or intrarenal pathways. A variety of genetic variants break immune tolerance to nuclear autoantigens, as evident from the existence of antinuclear antibodies. Furthermore, molecular mimicry of endogenous nucleic acids activating Toll-like receptors trigger antiviral immunity. In this review, we discuss the molecular pathomechanisms of lupus nephritis.

Keywords: Immune complex; Autoimmunity; Innate immunity; Toll-like receptors; Lupus nephritis; Molecular mimicry; Autoantigens

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease defined by immune response affecting multiple organs of which lupus nephritis (LN) is most common and a predictor of poor overall outcome of SLE patients [1-3]. The immunopathological features of SLE are based on a loss of tolerance for nuclear antigens, which becomes clinically detectable by the presence of anti-nuclear antibodies with specificities against Ro, -Sm, dsDNA, histones antibodies, etc. The presence of these autoantibodies signifies auto-immunization and can act as diagnostic marker. Of a note, a diagnosis of SLE needs further clinical signs and symptoms of autoimmune disease such as fever, fatigue, skin rashes, and arthralgia [4,5]. With the advancement of knowledge, lupus is no longer considered the 'chameleon of medicine'. Significant progress has been made in decoding the pathogenesis of SLE and lupus nephritis. Here we provide an update on the immunomolecular and pathological aspects of lupus and lupus nephritis.

Extra renal Pathomechanism of Lupus Nephritis

Dysregulation of apoptosis and dead cell opsonisation

As mentioned before SLE develops as a consequence of loss-of-tolerance to self, ubiquitous nuclear autoantigens, which could be considered as an outcome of the immunization process. Some variants in the genome can compromize the processes of immunologically silent death (apoptosis) [6,7], and dead cell clearance (opsonisation) [4], e.g. the deletion of lymphpcyte precursors during thymic-negative selection. Any impairment of these processes can lead to secondary cell necrosis, which implies rupture of the plasma and nuclear membranes and the release of nuclear autoantigens into extracellular tissue compartments and in the circulation (Figure 1). Additional factors such as trauma or sunburns enhance the burden of necrotic cells in the extracellular compartment due to which some individuals fail to clear these extracellular nuclear materials by phagocytic cells [4]. This feature also attributes to the insufficient clearance of neutrophil extracellular traps (NETs) during infections or sterile forms of inflammation [5]. Genome-wide association studies revealed a link between genetic susceptibility and LN in SLE and also demonstrates that this susceptibility varies from one individual to another individual [7]. For example, podocyte genes, primarily affecting the glomerular filtration barrier, may also incline to proteinuria, or hematuria can be affected by collagen IV gene variants [8,9].

Molecular mimicry of antiviral immunity

During the viral infection, Toll-like receptors recognizes the viral particles and elicits antiviral immunity. Dysregulation of apoptosis releases extracellular nuclear elements (nucleic acids and proteins) which mimic structural and molecular features of viruse and elicits antiviral like immunity also known as "speudo" antiviral response [10,11]. Therefore, clinical manifestations of viral infections and SLE resemble each other [12]. Release of small nuclear RNA by pathogens activates dendritic cells and macrophages [13,14]. Renal glomerular endothelial cells and mesangial cells do perceive nucleic acids and also release type I interferons, which inside the glomerulus promote podocyte loss and glomerular scarring [15-19].

Aberrant lymphocyte immunity

Dendritic cells overcome their limited lifespan by the persisting activation by endogenous RNA and DNA autoantigens via TLR7 and TLR9, which also makes them resistant to glucocorticoid-induced death [20]. These nuclear autoantigens also activate clonal expansion of the respective autoreactive T and B cell subsets, involving affinity maturation of germinal center B cells, maturation into plasma cells and immunoglobulin class switch from IgM to high-affine IgG [21]. Memory T cells and long-lived plasma cells residing in bone marrow niches assure a life-long memory that is resistant to standard immunosuppressive therapies (Figure 2). This process is conceptually identical to any immune memory obtained by previous vaccinations [22].

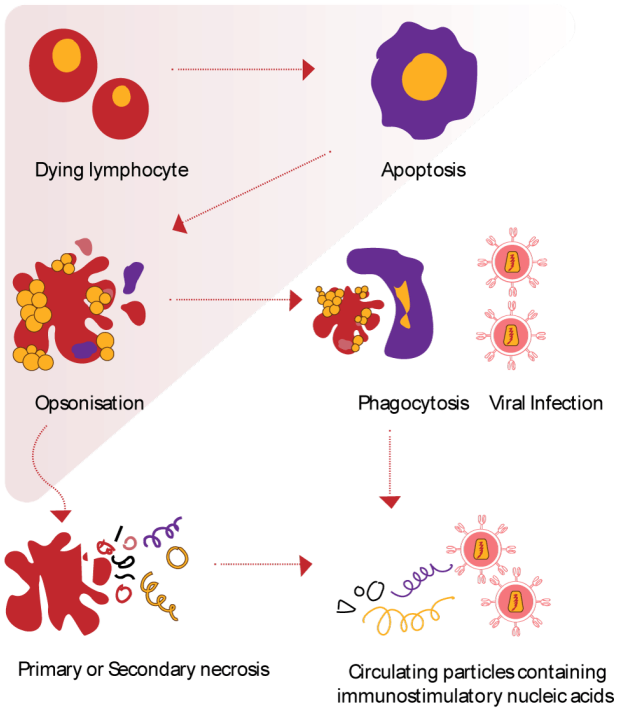

Figure 1: Extrinsic pathogenesis due to genetic variants. Various combinations of genetic variants (shown in the box) impose a genetic weakness for the loss-of-tolerance against nuclear autoantigens. These gene variants influence the mechanisms that allow a silent removal of dying cells, such as apoptosis and phagocytic clearance of apoptotic bodies or other dead cell debris. Inability of dead cell clearance leads to an accumulation of nuclear material in the extracellular space eventually causing immune system activation. These nuclear particles mimic viral particles and acts as an auto-adjuvant for adaptive immunity.

Environmental contributors of LN

The major contribution of the environment comes from viral and bacterial infections. IFN-α is the primary cytokine released upon viral infection triggering antiviral immunity and lupus activity [23]. In contrast, bacterial infections induce a nonspecific immunostimulatory effects, with transient expansion of autoreactive lymphocyte clones. Bacterial infections also contribute to proteinuria and renal damage through their products stimulating both intrarenal immune cells and other renal cell types. Ultraviolet rays act as another environmental factor contributing to SLE activity by inducing keratinocyte cell death [24]. This cell death in patients with a significant dead cell clearance defect increases the burden of extracellular nuclear antigens [2]. Drug induced SLE involves inhibition of methyl-transferases, a process that enhances the unmasking of endogenous nucleic acids and the activation of TLR7 and TLR9 [25,26]. It has been observed that hormones do play role in the manifestation of LN, progesterone and estrogens stimulate the sex hormone–dependent immunoregulatory pathways [27].

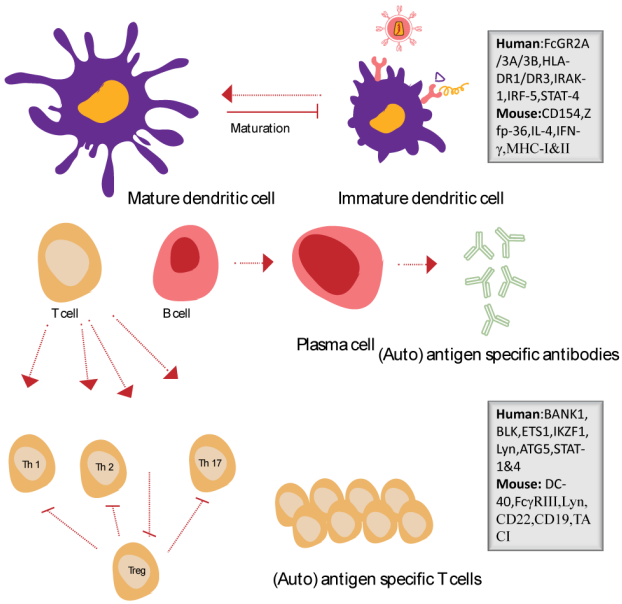

Figure 2: Extrinsic pathogenesis due to aberrant lymphocyte proliferation. Autoantigens resulting from the defective dead cell clearance will stimulate the activation of dendritic cells and B-cells. Same nuclear autoantigens also activate the clonal expansion of the respective autoreactive T and B cell subsets.

Intrarenal Pathomechanisms of Lupus Nephritis

Various intrinsic renal immunological mechanisms attribute to the development of LN. These include in situ immune complex (IC) formation, complement cascade activation, and pathological manifestations due to compartment-specific glomerular injury.

LN pathogenesis due to immune complex formation

Immune complex depositions with various components such as polyclonal autoantibodies, complement cascade contributes to the intrarenal pathogenesis of LN [28]. Compartment-specific deposition of IC determines the class and severity of the LN [29]. Mesangium being the primary site of IC deposition designates the class I and II lesions with mesangial cells injury and mesangial cell hyperplasia. Subendothelial IC classify class III and IV with endothelial cells protuberance and coalesce, which will contribute to decline in glomerular filtration rate and promotes to endstage renal disease Subepithelial IC deposits account for class V lesions contributing to podocyte injury and its related glomerulosclerosis with extensive proteinuria (Figure 3) [30].

Leukocyte infiltration and intrarenal inflammation

During the disease pathogenesis, various cytokines, chemokines, and adhesion molecules induce immune cell infiltration into the kidney namely cytotoxic T cells, Th17 T cells, macrophages and B cells [31]. The kind of cytokine or chemokine involved determines compartment-specific recruitment of leukocytes. For example, the CC-

chemokne CCL2 promotes CCR2+ proinflammatory macrophages and T cells into the glomerulus and the tubulointerstitium, whilst CCR1+ cells home to interstitial compartment only [32]. Infiltrating leukocytes also may form de novo perivascular tertiary lymphoid organs within the kidney and allow the clonal expansion and somatic hypermutation of B cells at T-cells vicinity followed by local inflammation [33-35]. Necroinflammation, a process of necrosis related inflammation or inflammation related necrosis may be initiated by these infiltrating leukocytes [36]. Extracellular histones act as an another important element in initiating necroinflammation [37]. During necrosis histones are released into the extracellular space and evoke cytotoxic effects on nearby cells by plasma membrane disruption [38]. Another important source of extracellular histones comes from the neutrophils undergoing NETosis resulting in the damage of endothelial cells, eg, in crescentic glomerulonephritis [39,40]. This process is under tight regulation. For instance, interaction of pentaxin-3 produced by renal cells with P-selectin expressed on endothelial cells regulates leukocyte recruitment [41,42].

Dual facets of fibrosis/scarring

Renal functional compartments are stabilized by mesenchyma. Glomerular tuft capillaries are stabilized by mesangial cells, the tubular part of the nephrons by interstial fibroblasts, and pericytes of mesenchymal origin protect vascular structures upon kidney injury [43]. Tissue injuries activate mesenchymal elements to proliferate and to produce extracellular matrix components to stabilize the injured tissues as a scaffold for [44]. If irreversible loss of parenchymal elements occurs, the task of refilling the injured space will be taken up by mesenchymal elements [45].

Mesenchymal healing involves multiple elements, as for instances mesangial cells, extraglomerular mesangial cells or even derived from the bone marrow [46-50]. Upon glomerular injury, mesangial hyperplasia occurs as a hallmark [51], parietal epithelial cells (PEC) contribute to scar formation when podocyte regeneration remains insufficient. Inability of PECs to replace the lost podocytes, lead to Bowman's capsule focal adhesion formation followed by PEC migration and extracellular matrix formation at glomerular tuft resulting in segmental sclerosis also known as focal segmental glomerulosclerosis (FSGS) [52]. These observations imply a dual nature of PECs [53]. Glomerular capillaries and Bowman's capsule adherence prevents the protein loss at denudated GBM by stabilizing the glomerular tuft [54]. This process promotes further podocyte loss due to additional stress by hyperfiltration and commute to global glomerulosclerosis [55].

Summary

The pathogenesis of LN is based on extra- and intrarenal mechanisms. Loss-of-immune tolerance and systemic autoimmunity against nuclear autoantigens are based on variable genetic variants, which differ from one patient to the other. These genetic variants interfere with vital aspects of cells, such as cell death (apoptosis) and dead cell clearance, resulting in loss of tolerance to self-antigens. Another important contribution to lupus nephritis comes from the pseudo viral immunity or molecular mimicry of viral immunity, which provokes innate and adaptive immunity by Toll-like receptors such as TLR-3, 7 and 9. Intrarenal inflammation and the its binding of autoantibodies to intrarenal nuclear autoantigens, complement cascade and FcR activation resulting in local inflammation, tissue scaring.

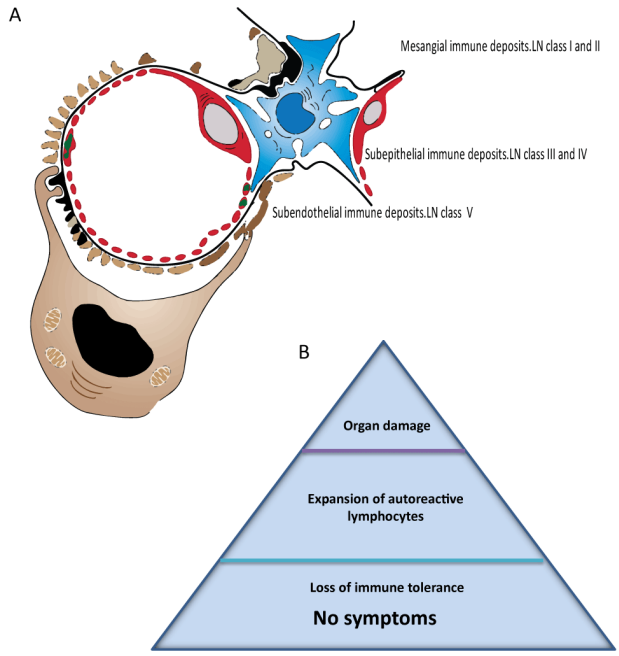

Figure 3: Schematic representation of intrinsic pathogenesis due to immune complex formation. 3A) Classification of lupus nephritis based on the location of immune complex deposition, including the subendothelial space, the mesangium, and the subepithelial space outside the glomerular basement membrane. 3B) Representation of lupus nephritis pyramid indicating various levels of mechanisms.

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References

1. Manger K, Manger B, Repp R, Geisselbrecht M, Geiger A, et al. (2002) Definition of risk factors for death, end stage renal disease, and thromboembolic events in a monocentric cohort of 338 patients with systemic lupus erythematosus. Ann Rheum Dis 61: 1065-1070.
2. Liu Z, Davidson A (2012) Taming lupus-a new understanding of pathogenesis is leading to clinical advances. Nat Med 18: 871-882.
3. Tsokos GC (2011) Systemic lupus erythematosus. N Engl J Med 365: 2110-2121.
4. Munoz LE, Lauber K, Schiller M, Manfredi AA, Herrmann M (2010) The role of defective clearance of apoptotic cells in systemic autoimmunity. Nature reviews. Rheumatology 6: 280-289.
5. Hakkim A, Fürnrohr BG, Amann K, Laube B, Abed UA, et al. (2010) Impairment of neutrophil extracellular trap degradation is associated with lupus nephritis. Proc Natl Acad Sci USA 107: 9813-9818.
6. Saxena R, Mahajan T, Mohan C (2011) Lupus nephritis: current update. Arthritis Res Ther 13: 240.
7. Migliorini A, Anders HJ (2012) A novel pathogenetic concept-antiviral immunity in lupus nephritis. Nature reviews Nephrology 8: 183-189.

8. Lennon R, Stuart HM, Bierzynska A, Randles MJ, Kerr B, et al. (2015) Coinheritance of COL4A5 and MYO1E mutations accentuate the severity of kidney disease. Pediatr Nephrol 30: 1459–1465.
9. Papazachariou L, Demosthenous P, Pieri M, Papagregoriou G, Savva I, et al. (2014) Frequency of COL4A3/COL4A4 mutations amongst families segregating glomerular microscopic hematuria and evidence for activation of the unfolded protein response. Focal and segmental glomerulosclerosis is a frequent development during ageing. PLoS One 9: e115015.
10. Hof D, Raats JM, Pruijn GJ (2005) Apoptotic modifications affect the autoreactivity of the U1 snRNP autoantigen. Autoimmun Rev 4: 380-388.
11. Huck S, Deveaud E, Namane A, Zouali M (1999) Abnormal DNA methylation and deoxycytosine-deoxyguanine content in nucleosomes from lymphocytes undergoing apoptosis. FASEB J 13: 1415-1422.
12. Leadbetter EA, Rifkin IR, Hohlbaum AM, Beaudette BC, ShlomchikMJ, et al. (2002) Chromatin-IgG complexes activate B cells by dual engagement of IgM and Toll-like receptors. Nature 416: 603-607.
13. Wen ZK, Xu W, Xu L, Cao QH, Wang Y, et al. (2007) DNA hypomethylation is crucial for apoptotic DNA to induce systemic lupus erythematosus-like autoimmune disease in SLE-non-susceptible mice. Rheumatology (Oxford) 46: 1796-1803.
14. Villanueva E, Yalavarthi S, Berthier CC, Hodgin JB, Khandpur R, et al. (2011) Netting neutrophils induce endothelial damage, infiltrate tissues, and expose immunostimulatory molecules in systemic lupus erythematosus. J Immunol 187: 538-552.
15. Ryu M, Kulkarni OP, Radomska E, Miosge N, Gross O, et al. (2011) Bacterial CpG-DNA accelerates Alport glomerulosclerosis by inducing an M1 macrophage phenotype and tumor necrosis factor-alpha-mediated podocyte loss. Kidney Int 79: 189-198.
16. Brähler S, Ising C, Hagmann H, Rasmus M, Hoehne M, et al. (2012) Intrinsic proinflammatory signaling in podocytes contributes to podocyte damage and prolonged proteinuria. Am J Physiol Renal Physiol 303: F1473-1485.
17. Flür K, Allam R, Zecher D, Kulkarni OP, Lichtnekert J, et al. (2009) Viral RNA induces type I interferon-dependent cytokine release and cell death in mesangial cells via melanoma-differentiation-associated gene-5: Implications for viral infection-associated glomerulonephritis. Am J Pathol 175: 2014-2022.
18. Hägele H, Allam R, Pawar RD, Reichel CA, Krombach F, et al. (2009) Double-stranded DNA activates glomerular endothelial cells and enhances albumin permeability via a toll-like receptor-independent cytosolic DNA recognition pathway. Am J Pathol 175: 1896-1904.
19. Migliorini A, Angelotti ML, Mulay SR, Kulkarni OO, Demleitner J, et al. (2013) The antiviral cytokines IFN-alpha and IFN-beta modulate parietal epithelial cells and promote podocyte loss: implications for IFN toxicity, viral glomerulonephritis, and glomerular regeneration. The American journal of pathology 183: 431-440.
20. Guiducci C, Gong M, Xu Z, Gill M, Chaussabel D, et al. (2010) TLR recognition of self nucleic acids hampers glucocorticoid activity in lupus. Nature 465: 937-941.
21. Allam R, Sayyed SG, Kulkarni OP, Lichtnekert J, Anders HJ (2011) Mdm2 promotes systemic lupus erythematosus and lupus nephritis. J Am Soc Nephrol 22: 2016-2027.
22. Hiepe F, Dörner T, Hauser AE, Hoyer BF, Mei H, et al. (2011) Long-lived autoreactive plasma cells drive persistent autoimmune inflammation. Nature reviews. Rheumatology 7: 170-178.
23. Theofilopoulos AN, Baccala R, Beutler B, Kono DH (2005) Type I interferons (alpha/beta) in immunity and autoimmunity. Annual review of immunology 23: 307-336.
24. Caricchio R, McPhie L, Cohen PL (2003) Ultraviolet B radiation-induced cell death: critical role of ultraviolet dose in inflammation and lupus autoantigen redistribution. J Immunol 171: 5778-5786.
25. Cornacchia E, Golbus J, Maybaum J, Strahler J, Hanash S, et al. (1988) Hydralazine and procainamide inhibit T cell DNA methylation and induce autoreactivity. J Immunol 140: 2197-2200.
26. Richardson B, Scheinbart L, Strahler J, Gross L, Hanash S, et al. (1990) Evidence for impaired T cell DNA methylation in systemic lupus erythematosus and rheumatoid arthritis. Arthritis Rheum 33: 1665-1673.
27. Hughes GC (2012) Progesterone and autoimmune disease. Autoimmun Rev 11: A502-A514.
28. Tojo T, Friou GJ (1968) Lupus nephritis: varying complement-fixing properties of immunoglobulin G antibodies to antigens of cell nuclei. Science 161: 904-906.
29. Yu F, Wu LH, Tan Y, Li LH, Wang CL, et al. (2010) Tubulointerstitial lesions of patients with lupus nephritis classified by the 2003 International Society of Nephrology and Renal Pathology Society system. Kidney Int 77: 820-829.
30. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, et al. (2004) The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney international 65: 521-530.
31. Teichmann LL, Ols ML, Kashgarian M, Reizis B, Kaplan DH, et al. (2010) Dendritic cells in lupus are not required for activation of T and B cells but promote their expansion, resulting in tissue damage. Immunity 33: 967-978.
32. Pérez de Lema G, Maier H, Franz TJ, Escribese M, Chilla S, et al. (2005) Chemokine receptor Ccr2 deficiency reduces renal disease and prolongs survival in MRL/lpr lupus-prone mice. J Am Soc Nephrol 16: 3592-3601.
33. Chan OT, Hannum LG, Haberman AM, Madaio MP, Shlomchik MJ (1999) A novel mouse with B cells but lacking serum antibody reveals an antibody-independent role for B cells in murine lupus. J Exp Med 189: 1639-1648.
34. Neusser MA, Lindenmeyer MT, Edenhofer I, Gaiser S, Kretzler M, et al. (2011) Intrarenal production of B-cell survival factors in human lupus nephritis. Modern pathology : an official journal of the United States and Canadian Academy of Pathology 24, 98-107.
35. Espeli M, Bökers S, Giannico G, Dickinson HA, Bardsley V, et al. Local renal autoantibody production in lupus nephritis. J Am Soc Nephrol 22: 296-305.
36. Linkermann A, Stockwell BR, Krautwald S, Anders HJ (2014) Regulated cell death and inflammation: an auto-amplification loop causes organ failure. Nature reviews Immunology 14: 759-767.
37. Allam R, Kumar SV, Darisipudi MN, Anders HJ (2014) Extracellular histones in tissue injury and inflammation. J Mol Med (Berl) 92: 465-472.
38. Xu J, Zhang X, Pelayo R, Monestier M, Ammollo CT, et al. (2009) Extracellular histones are major mediators of death in sepsis. Nat Med 15: 1318-1321.
39. Allam R, Scherbaum CR, Darisipudi MN, Mulay SR, Hägele H, et al. (2012) Histones from dying renal cells aggravate kidney injury via TLR2 and TLR4. J Am Soc Nephrol 23: 1375-1388.
40. Kumar SV, Kulkarni OP, Mulay SR, Darisipudi MN, Romoli S, et al. (2015) Neutrophil Extracellular Trap-Related Extracellular Histones Cause Vascular Necrosis in Severe GN. J Am Soc Nephrol 26: 2399-2413.
41. Bussolati B, Peri G, Salvidio G, Verzola D, Mantovani A, et al. (2003) The long pentraxin PTX3 is synthesized in IgA glomerulonephritis and activates mesangial cells. J Immunol 170: 1466-1472.
42. Deban L, Russo RC, Sironi M, Moalli F, Scanziani M, et al. (2010) Regulation of leukocyte recruitment by the long pentraxin PTX3. Nat Immunol 11: 328-334.
43. Schrimpf C, Xin C, Campanholle G, Gill SE, Stallcup W, et al. (2012) Pericyte TIMP3 and ADAMTS1 modulate vascular stability after kidney injury. J Am Soc Nephrol 23: 868-883.
44. Gurtner GC, Werner S, Barrandon Y, Longaker MT (2008) Wound repair and regeneration. Nature 453: 314-321.
45. Campanholle G, Ligresti G, Gharib SA, Duffield JS (2013) Cellular mechanisms of tissue fibrosis. 3. Novel mechanisms of kidney fibrosis. Am J Physiol Cell Physiol 304: C591-C603.
46. Imasawa T, Utsunomiya Y, Kawamura T, Zhong Y, Nagasawa R, et al. (2001) The potential of bone marrow-derived cells to differentiate to glomerular mesangial cells. J Am Soc Nephrol 12: 1401-1409.

47. Ikarashi K, Li B, Suwa M, Kawamura K, Morioka T, et al. (2005) Bone marrow cells contribute to regeneration of damaged glomerular endothelial cells. Kidney Int 67: 1925-1933.

48. Daniel C, Albrecht H, Lüdke A, Hugo C (2008) Nestin expression in repopulating mesangial cells promotes their proliferation. Laboratory investigation; a journal of technical methods and pathology 88: 387-397.

49. Pippin JW, Sparks MA, Glenn ST, Buitrago S, Coffman TM, et al. (2013) Cells of renin lineage are progenitors of podocytes and parietal epithelial cells in experimental glomerular disease. Am J Pathol 183: 542-557.

50. Starke C, Betz H, Hickmann L, Lachmann P, Neubauer B, et al. (2015) Renin lineage cells repopulate the glomerular mesangium after injury. J Am Soc Nephrol 26: 48-54.

51. Sethi S, Fervenza FC (2012) Membranoproliferative glomerulonephritis--a new look at an old entity. N Engl J Med 366: 1119-1131.

52. Smeets B, Kuppe C, Sicking EM, Fuss A, Jirak P, et al. (2011) Parietal epithelial cells participate in the formation of sclerotic lesions in focal segmental glomerulosclerosis. J Am Soc Nephrol 22: 1262-1274.

53. Shankland SJ, Anders HJ, Romagnani P (2013) Glomerular parietal epithelial cells in kidney physiology, pathology, and repair. Curr Opin Nephrol Hypertens 22: 302-309.

54. D'Agati VD, Kaskel FJ, Falk RJ (2011) Focal segmental glomerulosclerosis. The New England journal of medicine 365: 2398-2411.

55. Kramann R, Humphreys BD (2014) Kidney pericytes: roles in regeneration and fibrosis. Semin Nephrol 34: 374-383.