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# COMMENTARY

# Podocytes

## *Way to Go*

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An essential role of the kidney is to provide and maintain a barrier preventing the plasma proteins and other circulating macromolecules from entering the urinary ultrafiltrate. This delicate system of filtration is formed by three distinguished layers, that is, fenestrated endothelial cells, glomerular basement membrane (GBM), and podocytes (or visceral epithelial cells) from the inside out of the filter barrier. The network of these cellular structures contributes to size-selective (by keeping the molecules size of albumin or larger) and charge-dependent filtration (by restricting the passage of anionic molecules). For filtration to occur, this built-in gate system is exposed to (and should withstand) the blood pressure in the glomerulus, which represents a relatively higher pressure than any hydrostatic pressure in other capillary beds in the human body. As being highly specialized cells wrapping the outer aspect of the glomerular capillary, podocytes have been subject to keen interest when it comes to investigate glomerular permeability.[1]

Podocytes are typically described as postmitotic (ie, quiescent in the G0 phase of the cell cycle) with a limited capacity for cell division. These terminally differentiated cells do not regenerate in response to injury and loss, which is why the podocyte damage is considered to be so dire. Typically, a loss of more than 30% of these cells will lead to chronic kidney disease (CKD).[2] For decades, scientists have argued over the types of podocyte death that occurs in certain renal diseases. This is particularly important for diabetes mellitus and its major complication, diabetic nephropathy. Diagnosing the type of cell death in human biopsies could aid the proper diagnosis and improve prognosis of the disease. The article by Hara et al[3] in this issue of *The American Journal of Pathology* has intriguing implications concerning the role of mitotic catastrophe in podocyte death during diabetic kidney disease. These findings extend earlier clinical studies by contributing the podocyte biology significantly in the context of mitotic catastrophe.

Evidence for the capability of podocytes to reenter mitotic cell cycle (M phase) leading to proliferation and cell death has been reported recently.[4,5] This disastrous cycle resulting from premature entry of podocytes into mitosis is defined as mitotic catastrophe (MC), which is characterized by aberrant mitotic spindle formation and chromosomal missegregation with multicentrosomes.[6] The nuclear (eg, chromatin condensation, nuclear fragmentation and shrinkage) and biochemical events (eg, mitochondrial membrane permeabilization and caspase activation) during apoptosis include similar changes as observed in MC at the molecular level[7]; however, MC is distinguished from apoptosis by the multiple nuclei and accumulation of micronuclei (ie, round DNA aggregates) surrounding the nucleus (Figure 1). This feature of MC, on the other hand, is common to the morphological changes associated with necrosis.[8] Therefore, MC might be regarded as a genome-maintenance machinery preceding apoptosis and necrosis rather than a cell death mechanism.[6,9,10] Podocyte death can be associated with autophagy, where its own cytoplasmic material is degraded in a set of diverse lysosomal processes, or anoikis, which facilitates the podocyte detachment due to the loss of podocyte-GBM interactions (Figure 1). However, there is not much evidence to suggest that anoikis is the primary cause of podocyte death in the setting of any kidney disease.

Although superficially confusing, MC has recently been characterized in several types of nephropathies with

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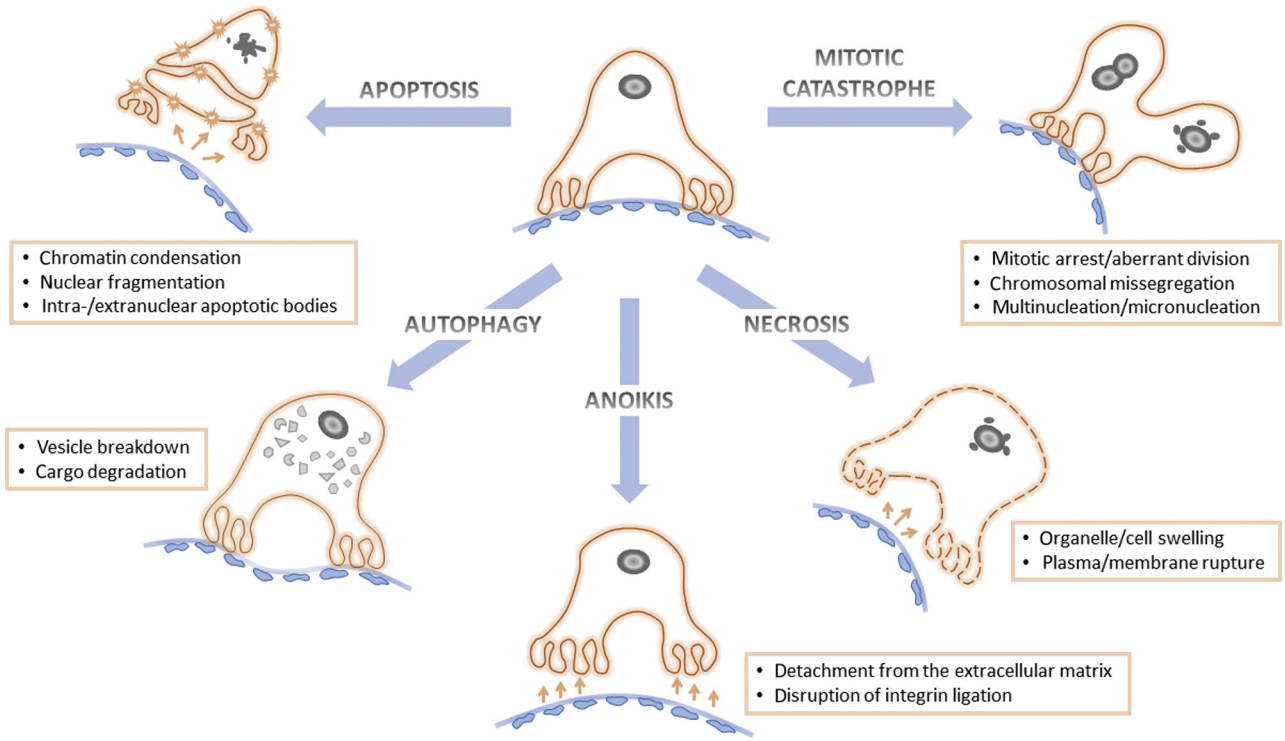


**Figure 1** Various modes of podocyte death.

marked podocyte loss such as diabetic kidney disease, IgA nephropathy, membranous lupus nephritis, focal segmental glomerulosclerosis (FSGS), and HIV-associated nephropathy (HIVAN).[11,12] The morphologic results of these clinical cases are aneuploid podocytes with two or more nuclei, which are susceptible to detachment and death.[13] Since the maintenance of the actin assembly is of utmost importance for the stable attachment of podocytes, those mitotic podocytes detach mainly due to the inability of actin assembly to form mitotic spindle and support cytoskeletal structure of FPs at the same time.[14]

Hara et al[3] now report on a clever urinary podocyte isolation and staining technique to visualize the detached podocytes (ie, podocytes in the urine) of diabetic patients. In particular, they used dual immunofluorescence staining for synaptopodin and markers of urinary podocytes, tubular and parietal epithelial cells (PECs) to confirm that the re-entry of cell cycle (mitosis) was induced in podocalyxin-positive urinary podocytes and not in other (parietal or tubular) epithelial cells. This brings us to another important implication of the earlier studies on glomerular PECs, which have been identified as podocyte reservoirs during kidney development in rodents[15] and humans.[16] The past decade have seen remarkable advances in understanding the progenitor capacity of glomerular PECs[17] and arteriolar vascular wall cells of renin lineage (CoRL),[18] which showed a transitional phenotype and committed to become podocytes as revealed by lineage tracing models. However, the magnitude of regeneration that results from these cells may be inadequate, that is, the glomerular number of these cells is far from replacing all podocytes lost in the course of any proteinuric kidney disease. Such a limited population of progenitors and other factors impairing the capacity of these cells to perform their progenitor function (such as the excess amount of filtered albumin in the urinary space,[19]) might explain the lack of PECs in the urine. Do abnormalities in podocytes due to MC have a role in the development of proteinuria? This link has not been clearly established even after the analysis of biopsies under electron microscopy since there is no statistical correlation of mitotic podocytes with proteinuria reported in this cohort.

Overall, Hara et al[3] provided evidence that majority (ie, more than half) of those podocytes had the nuclear morphologies that are hallmark of MC. Those include the pool of podocytes with large and abnormal nuclei, multinucleated podocytes with or without micronuclei, podocytes with mitotic spindles and denucleated podocytes (ie, podocytes with invisible nucleus).[3] Moreover, they investigated the apoptotic susceptibility of urinary podocytes but could not find any apoptotic cells, indicating that podocytes were stressed under the mechanism specific to MC and mitosis triggered the cell detachment in the diabetic patients.

This is the first detailed evaluation of urinary podocyte morphology in a setting of kidney disease. These data help to validate the paradigm of MC causing podocyte loss, which may explain the accompanying impairment in glomerular filtration while analyzing the experimental data and renal pathology. This study is an important step toward a category of podocyte death mechanism in a major podocyte-associated kidney disease (diabetic nephropathy); however, further studies will need to look at the many types

of renal syndromes that can develop under the umbrella of diabetes mellitus. Together with forthcoming studies, the field will continue to understand the adaptive response of podocytes to stress and eventually identify unique pathophysiologic aspects of CKD, which can be diagnosed and utilized for tailoring of therapeutic approaches.

## Supplemental Data

Supplemental material for this article can be found at *https://doi.org/10.1016/j.ajpath.2018.11.003*.

## References


1. Reiser J, Altintas MM: Podocytes [version 1; referees: 2 approved]. F1000Res 2016, 5:114
2. Wharram BL, Goyal M, Wiggins JE, Sanden SK, Hussain S, Filipiak WE, Saunders TL, Dysko RC, Kohno K, Holzman LB, Wiggins RC: Podocyte depletion causes glomerulosclerosis: diphtheria toxin-induced podocyte depletion in rats expressing human diphtheria toxin receptor transgene. J Am Soc Nephrol 2005, 16:2941−2952
3. Hara M, Oohara K, Dai DF, Liapis H: Mitotic catastrophe causes podocyte loss in the urine of human diabetics. Am J Pathol 2019, 189: 248−257
4. Mulay SR, Thomasova D, Ryu M, Kulkarni OP, Migliorini A, Bruns H, Gröbmayr R, Lazzeri E, Lasagni L, Liapis H, Romagnani P, Anders HJ: Podocyte loss involves MDM2-driven mitotic catastrophe. J Pathol 2013, 230:322−335
5. Migliorini A, Angelotti ML, Mulay SR, Kulkarni OO, Demleitner J, Dietrich A, Sagrinati C, Ballerini L, Peired A, Shankland SJ, Liapis H, Romagnani P, Anders HJ: The antiviral cytokines IFN-α and IFN-β modulate parietal epithelial cells and promote podocyte loss: implications for IFN toxicity, viral glomerulonephritis, and glomerular regeneration. Am J Pathol 2013, 183:431−440
6. Vakifahmetoglu H, Olsson M, Zhivotovsky B: Death through a tragedy: mitotic catastrophe. Cell Death Differ 2008, 15:1153−1162
7. Rogalińska M: Alterations in cell nuclei during apoptosis. Cell Mol Biol Lett 2002, 7:995−1018
8. Swanson PE, Carroll SB, Zhang XF, Mackey MA: Spontaneous premature chromosome condensation, micronucleus formation, and non-apoptotic cell death in heated HeLa S3 cells. Ultrastructural observations. Am J Pathol 1995, 146:963−971
9. Castedo M, Perfettini JL, Roumier T, Andreau K, Medema R, Kroemer G: Cell death by mitotic catastrophe: a molecular definition. Oncogene 2004, 23:2825−2837
10. Tharaux PL, Huber TB: How many ways can a podocyte die? Semin Nephrol 2012, 32:394−404
11. Nagata M, Yamaguchi Y, Komatsu Y, Ito K: Mitosis and the presence of binucleate cells among glomerular podocytes in diseased human kidneys. Nephron 1995, 70:68−71
12. Liapis H, Romagnani P, Anders HJ: New insights into the pathology of podocyte loss: mitotic catastrophe. Am J Pathol 2013, 183:1364−1374
13. Hagen M, Pfister E, Kosel A, Shankland S, Pippin J, Amann K, Daniel C: Cell cycle re-entry sensitizes podocytes to injury induced death. Cell Cycle 2016, 15:1929−1937
14. Lasagni L, Lazzeri E, Shankland SJ, Anders HJ, Romagnani P: Podocyte mitosis − a catastrophe. Curr Mol Med 2013, 13:13−23
15. Appel D, Kershaw DB, Smeets B, Yuan G, Fuss A, Frye B, Elger M, Kriz W, Floege J, Moeller MJ: Recruitment of podocytes from glomerular parietal epithelial cells. J Am Soc Nephrol 2009, 20:333−343
16. Ronconi E, Sagrinati C, Angelotti ML, Lazzeri E, Mazzinghi B, Ballerini L, Parente E, Becherucci F, Gacci M, Carini M, Maggi E, Serio M, Vannelli GB, Lasagni L, Romagnani S, Romagnani P: Regeneration of glomerular podocytes by human renal progenitors. J Am Soc Nephrol 2009, 20:322−332
17. Shankland SJ, Smeets B, Pippin JW, Moeller MJ: The emergence of the glomerular parietal epithelial cell. Nat Rev Nephrol 2014, 10:158−173
18. Altintas MM, Reiser J: Bridges to cross, burn and mend: cells of renin lineage as podocyte progenitors. Am J Physiol Renal Physiol 2015, 309:F499−F500
19. Shankland SJ, Pippin JW, Duffield JS: Progenitor cells and podocyte regeneration. Semin Nephrol 2014, 34:418−428