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COMMENTARY

APOL1—miR-193 Axis as a Bifunctional Regulator of the Glomerular Parietal Epithelium



Maintaining Parietal Cell Phenotype versus Promoting Podocyte Differentiation

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In the current issue of the *American Journal of Pathology*, Kumar et al¹ report on novel and surprising new roles for apolipoprotein (APO)-L1. The *APOLI* gene arose during the course of primate evolution, and until now its physiologic role has been largely considered to be a component of innate immunity. *APOLI* is unique to a few Old-World primates, including gorillas and baboons (the latter has a homologous protein).² Orangutans and macaques possess an *APOLI* pseudogene that is not expressed; usually the process of pseudogene formation occurs when a gene is not needed or is actually toxic. Other mammals, such as mice, lack *APOLI* altogether.

Genetic variants in *APOLI* were identified in 2010 as the major driver of linkage between this region of chromosome 22 and kidney disease among African Americans.^{3,4} The association of these variants with kidney disease among individuals with sub-Saharan African ancestry is surprisingly strong. The odds ratios for being a carrier of two *APOLI* kidney-risk alleles are as follows: HIV-associated nephropathy, 29 in the United States⁵ and 89 in South Africa⁶; focal segmental glomerulosclerosis, 17 in the United States⁵; and arterionephrosclerosis, 7 in the United States⁷ with additional associations for lupus nephritis, deceased donor transplant and living donor kidney transplant outcomes, and outcomes for living donors themselves. *APOLI* is expressed in podocytes, and the variants induce podocyte injury by several cellular and molecular pathways.⁸

miRNAs (miRs) comprise a large set of noncoding RNA species, encoded by at least 585 genes in humans, which are processed to (typically) 22 nucleotides in length. The miR transcripts fold into short hairpin turns, and, via sequence

complementarity, bind specific mRNAs. miRs may alter (generally suppressing) mRNA function by various mechanisms, including the induction of mRNA cleavage; shortening of the polyA tail (leading to shortened mRNA half-life); and compromise of translational efficiency on the ribosomes, among other mechanisms.

Kietzmann et al⁹ previously demonstrated that miR-193a down-regulates transcription of the Wilms tumor 1 gene, resulting in podocyte dedifferentiation *in vitro* and manifesting as focal segmental glomerulosclerosis in experimental animal models. Stable knockdown of miR-193a in human parietal epithelial cells (PECs) promoted a podocyte phenotype. Furthermore, systemic knockdown of miR-193a in mice promoted podocyte-like features in PECs (expression of synaptopodin and Wilms tumor 1 protein). Conversely, transgenic overexpression of miR-193a in mice led to the suppression of a wide range of maturity markers in podocytes, including Wilms tumor 1 protein, nephrin, podocin, and synaptopodin. These data support the hypothesis that miR-193a might contribute to a loss of podocyte phenotype that is characteristic of collapsing glomerulopathy.

In a recent paper, Mishra et al¹⁰ extended these findings to describe a novel and quite interesting APOL1—miR-193 axis in podocytes in humans. Under high-glucose

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conditions, podocytes showed increased expression of miR-193a (a particular isoform of miR-193); inhibition of miR-193a reversed podocyte dedifferentiation. The authors showed evidence for an inverse relationship between miR-193a and APOL1. Thus miR-193a suppressed APOL1 translation; on the other hand, silencing of miR-193a enhanced the expression of APOL1 and preserved podocyte phenotype. In an observation with possible therapeutic implications, a vitamin D receptor antagonist down-regulated miR-193a, up-regulated APOL1 expression, and prevented dedifferentiation of cultured podocytes. [As an aside, with regard to another miR-193 family member and another apolipoprotein family member, a peptide derived from APOA1 (which shares minimal homology with APOL1) has been reported to induce miR-193-3p, which was associated with reduced expression of lipoxygenases and insulin-like growth factor-1 receptor, and thereby ameliorated pulmonary hypertension.¹¹]

In the current paper, Kumar et al¹ studied cell culture systems that model the transition in the parietal epithelium, as PECs migrate toward the glomerular vascular pole and acquire a podocyte phenotype. This model was developed by several groups, including those of Shankland et al,¹² who identified podocyte precursors from renin-expressing precursors and Romagnani and colleagues,¹³ who described renal progenitor cells along the Bowman capsule. In the current study,¹ using a culture system, as PECs differentiated into podocytes, APOL1 expression commenced on day 4, accompanied by a decrease in miR-193a expression. Down-regulation of APOL1 via siRNA increased miR-193a, which the authors interpreted as optimizing the PEC phenotype. Similarly, suppression of miR-193a enhanced APOL1 expression. The authors conclude that the absence of APOL1 promotes PEC phenotype and that the expression of APOL1 in PECs contributes to their differentiation into podocytes.

These findings are remarkable. As noted in the first paragraph, the *APOL1* gene is unique to certain primates; these primates include humans and gorillas (and in a modified form in baboons) but not chimpanzees, our nearest relative. Thus, as *APOL1* has arisen during the course of primate evolution, it appears that the APOL1–miR-193a axis has also arisen during the same time period. The *APOL1* gene appeared sometime after the divergence of Old World primates and New World primates, approximately 33 million years ago.² With this background, it is not at all clear, from an evolutionary perspective, why human podocytes are reliant on this axis to maintain a differentiated state. If this hypothesis is correct, we need to understand why one individual, null for *APOL1*, still has normal kidney function.¹⁴ Future work should address whether this APOL1–miR-193a axis functions in a similar way *in vivo* as it does *in vitro*, in relevant transgenic mouse models and in human kidneys. Vitamin D has been proposed to play a trophic role in podocyte physiology.¹⁵

It is quite interesting that a vitamin D receptor antagonist was found to suppress the APOL1–miR-193a expression, in light of its proposed inverse relationship with APOL1 and consequential effects on podocyte phenotype. This may be exploited for therapeutic purposes, with the limitation of possible toxicity from vitamin D deficiency.

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Supplemental Data

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