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Retinoic acid receptor-α in HIV-associated nephropathy

To the Editor: We have read the paper by Ratnam *et al.*[1] reporting that the expression of retinoic acid receptor-α (RARA) target genes were suppressed in the kidneys of HIV-1 transgenic mice (TG26), as well as those of patients with HIV-associated nephropathy (HIVAN). The overall enzymatic activity for retinoic acid synthesis was significantly reduced in the glomeruli of TG26 mice, suggesting that a defect in the synthesis of retinoic acid contributed to loss of protection by retinoic acid in HIVAN. They postulated that RARA agonists may be potential agents for treatment of HIVAN.

In this regard, we would like to share a similar finding with our recent work[2] in IgA nephropathy (IgAN). Using the GeneChip Human Genome U133 Plus 2.0 Arrays from Affymetrix (Santa Clara, CA), a total of 7761 gene expressions were identified that had an IgAN/normal gene expression ratio of 0.06- to 5.58-fold (312 were upregulated with a ratio $\geqslant$2.0-fold and 244 were downregulated with a ratio $\leqslant$0.2-fold). An analysis of the expression of the 30 most downregulated genes revealed that RARA was most downregulated in IgAN. Comparing the gene expression profile of patients with IgAN, non-IgAN (minimal change disease), and normal controls, the RARA gene expression profile was found to be downregulated to 0.41-fold (231 ± 77 vs 561 ± 227 units, $P<0.005$) in patients with IgAN compared with patients and normal controls. Our finding of downregulation of RARA in IgAN is similar to the finding of Ratnam *et al.*[1] of suppression of RARA target gene expression in TG26 mice and HIVAN patients.

The finding of downregulating of mRNA expression for RARA in IgAN may suggest a potential therapeutic approach for IgAN. Shaier's model of Thy-GN mice[3] is akin to the human disease of IgAN, as the Thy-GN mice have mesangial proliferative glomerulonephritis (GN) similar to human IgAN where there is also mesangial proliferative GN. In Shaier's report,[3] Thy-GN mice treated with RARA agonist had reduced proteinuria and normalization of blood pressure. We postulate that RARA-specific retinoids may provide a therapeutic approach to the therapy of IgAN. RARA belongs to the steroid hormone superfamily of nuclear receptor proteins, which exert their effects by binding specific DNA response elements, thus regulating gene expression I target cells.[4,5] Regulating or normalizing RARA mRNA expression in patients with IgAN may thus offer a novel therapeutic approach in terms of gene therapy. This is especially relevant to IgAN, which has hitherto no known specific therapy. In this respect, we are in complete agreement with Ratnam's postulate that RARA agonists may be potential agents for treatment of HIVAN.[1]

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The Authors Reply: Woo *et al*[1] performed a GeneChip microarray using total leukoctye ribonucleic acid isolated from patients with IgA nephropathy compared with those with minimal change disease and normal controls. Through this unbiased screening, they find that retinoic acid receptor-α (RARA) mRNA level is downregulated to 0.41-fold in patients with IgA nephropathy compared with patients with minimal change disease and normal controls. Their findings suggest an important role of RARA and retinoic acid signaling in patients with kidney disease. The role of retinoic acid has been demonstrated in many animal models of kidney disease.[2] However, the studies of retinoic acid and RARA in human disease are lacking. It would be interesting to determine RARA expression in kidneys of patients with IgA nephropathy and other kidney diseases. We were not able to determine the level of RARA mRNA in kidneys of patients with HIV-associated nephropathy. By immunostaining, we did not observe a difference in RARA in the kidney between patients with HIV-associated nephropathy and minimal change disease. Our data suggest that RARA-mediated target gene expression is suppressed in kidneys of HIV-1 transgenic mice because of impaired endogenous retinoic acid synthesis. Consistent with our findings,

Starkey JM *et al.*[3] also found a reduction of endogenous retinoic acid levels in diabetic kidneys of db/db mice. Future studies are required to determine the endogenous and local retinoic acid synthesis and the expression of RARA and RARA-mediated target gene expression in different human kidney diseases.

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