# Retinoids and Glomerular Regeneration

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**Summary:** Retinoids are essential in the development and function of several organs, exerting potent effects on stem cell systems. All-trans retinoic acid, through binding to the retinoic acid response elements, alters transcription of numerous genes in stem cells, leading to an exit from the self-renewing state and promoting differentiation. In the kidney, retinoids protect against injury and ameliorate function in multiple experimental models of disease. Recent evidence suggests that retinoids act on renal progenitors by promoting their differentiation into mature podocytes and retinoic acid–induced podocyte differentiation is impaired by proteinuria because of sequestration of retinoic acid by albumin. However, retinoic acid administration can revert renal progenitor differentiation and promote podocyte regeneration. A more complete understanding of retinoid-dependent renal progenitor differentiation into podocytes should reward us with new insights into the mechanisms of progression toward glomerulosclerosis.
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The incidence of chronic kidney disease is increasing worldwide, and this situation is emerging as a major public health problem. Progression to end-stage renal disease (ESRD) is common in chronic nephropathies, independent of the initial insult.[1] Glomerulosclerosis accounts for 90% of ESRD cases and presents common pathogenic mechanisms leading to glomerular scarring and progressive loss of renal function. Far from simply being a clinical measure, the onset of macroalbuminuria determines the beginning of the decrease of glomerular filtration rate and the development of an eventual ESRD.

In human beings, proteinuria has been proposed as a pivotal causative factor that predicts progression and renal outcomes in diabetic and nondiabetic renal disease.[1] Clinical trials in nondiabetic nephropathies (ramipril efficiency in nephropathy study) showed that decreasing proteinuria always retards renal disease progression.[1] Indeed, this study showed a glomerular filtration rate decrease that was 2- to 3-fold faster in patients with nephrotic-range proteinuria than in patients with less proteinuria after treatment with ramipril. Similar evidence was obtained from clinical trials in type 1 and in type 2 diabetic patients, and a meta-analysis performed on angiotensin-converting enzyme (ACE) inhibitor trials confirmed that proteinuria is a strong risk factor for the progression of chronic renal disease.[1] Preliminary observations in human beings showed regression of diabetic nephropathy after 10 years of normoglycemia induced by a pancreatic transplant.[1] Of note, in the latter, the regression of renal disease was observed, together with an unexpected glomerular architecture remodeling.[1]

The finding that ACE inhibition can reverse proteinuria and glomerulosclerosis already has been well established in animals. Indeed, when an ACE inhibitor and an angiotensin II (Ang II) receptor blocker were combined in a genetic model of progressive nephropathy, reduction of glomerular sclerosis was even more evident, particularly in those glomeruli that had less severe lesions. Performing three-dimensional analysis to estimate the volume of glomerular tuft, a reduction in extensiveness of sclerotic lesions and regeneration of new normal capillary tuft was shown, suggesting that remodeling of glomerular architecture is possible, and that some form of regeneration can occur. Moreover, the more relevant effects were detectable in glomeruli affected by sclerotic lesions in less than 25% of the tuft volume, supporting the hypothesis that only limited sclerotic areas could regress completely after ACE inhibition. Indeed, although in glomeruli affected more heavily by sclerosis only a significant reduction of the sclerosis volume was detectable, in glomeruli with more than 80% of the volume occupied by sclerosis, it was not possible to observe an advantage from the treatment.[2] These results were consistent with previous observations that showed that different degrees of podocyte loss correlated with the degree of extensiveness of sclerotic lesions and with the levels of proteinuria, defining different stages of glomerular damage ranging from transient proteinuria to progressive decrease of renal function.[3]

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Based on these findings, one possible mechanism that elucidates the effects observed after ACE inhibitor treatment could involve the restoration of podocyte number. Indeed, treatment with ACE inhibitors is beneficial on glomerular podocytes, not only by halting their loss, but also by increasing their number per capillary tuft.[4] Because podocytes have a limited capacity to divide, they cannot restore glomerular architecture through cell division upon injury and, thus, the mechanisms able to drive regression of glomerulosclerosis and neoformation of podocytes remain to be elucidated. In addition, although treatment of glomerular diseases with ACE inhibitors or Ang II–receptor blockers slows the progression of kidney disease, the mechanisms mediating their renoprotective effects only partially are known.[1] In addition to drugs acting on the renin-angiotensin system, several other compounds were proposed to target glomerulosclerosis. Such drugs include endothelin-receptor antagonists, statins, cytokines and chemokines or chemokine-receptor antagonists, anti–transforming growth factor-β antibodies, thiazolidinediones, vitamin D analogues, and growth-factor inhibitors.[5] In this complex scenario, retinoids can be added to the various molecules with renoprotective function that were widely investigated. The anti-inflammation, anticoagulation effects, as well as the proliferation- and immunity-modulating actions of retinoids, have been widely appreciated, but the potential role of these molecules in promoting kidney regeneration was unveiled only recently.

## RETINOIDS: CRITICAL REGULATORS OF STEM CELL FUNCTION

### Molecular mechanism of retinoids

Vitamin A (all-trans retinol) and its active metabolites, collectively called *retinoids*, regulate many events during vertebrate development. Pioneering studies of rodents fed a vitamin A–deficient diet described a complex neonatal syndrome affecting many organ systems.[6,7] Several experimental approaches have been used to investigate functions of retinoid signaling during early embryogenesis. These experiments were performed in various species, using both gain-of-function approaches (to study stage-specific or region-specific effects of excess retinoic acid [RA] signaling) and strategies to decrease retinoid signaling (eg, through pharmacologic inhibition of synthesizing enzymes).

The molecular basis of vitamin A action was elucidated when it was shown that its acidic metabolite, RA, acts as a ligand for transcription factors of the retinoic acid nuclear receptor (RAR) superfamily, switching them from potential repressors to transcriptional activators. RA is synthesized inside the cell starting from retinol with two enzymatic steps. The primary enzyme that metabolizes vitamin A to retinaldehyde is retinol dehydrogenase. Subsequently, RA is formed by oxidation of retinaldehyde, primarily via retinaldehyde dehydrogenase (ALDH)1a2 (aldehyde dehydrogenase 1 family, member A2),[8] and is transported to the nucleus bound to cellular retinoic acid binding protein-2 (CRABP2) where it can bind to RARα, β, and γ. All 3 RAR receptors can form a heterodimer complex with retinoid X receptor (RXR), which, bound to DNA, can activate transcription of RA primary response genes (Fig. 1). Activation of transcription is one of the first steps in the RA-associated differentiation process and occurs rapidly, within minutes to a few hours, after RA addition in cell culture experiments. The explanation of this process resides in the existence of numerous immediate early genes, direct targets of RA, containing a retinoic acid response element (RARE) to which the RXR/RAR heterodimer can bind. Many other genes that do not possess RARE are transcriptionally regulated indirectly from RA because direct target genes exist among different transcription factor genes that can generate secondary responses. Thus, retinoids provide an essential early signal that initiates a cascade of events that control many aspects of cell proliferation, differentiation, and apoptosis.[9,10]

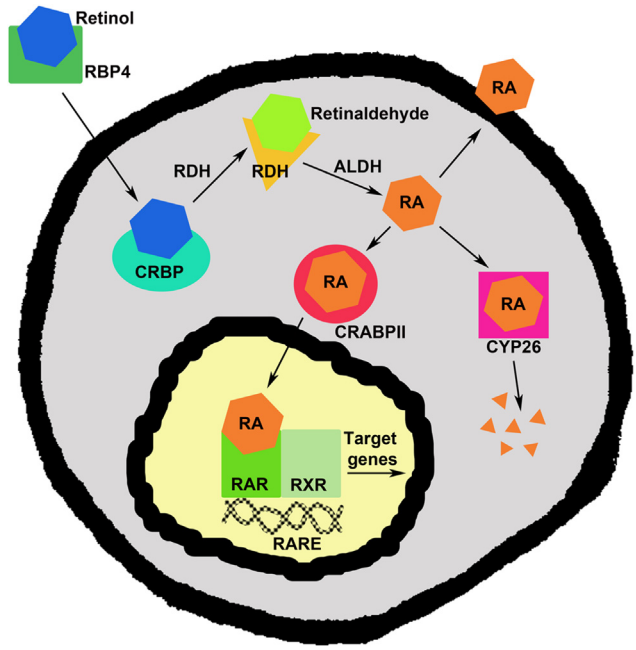


**Figure 1.** Regulation of retinoid signaling in stem cells. Retinol is taken up by retinol binding protein 4 (RBP4), transferred intracellularly by the receptor protein stimulated by retinoic acid 6, and transformed into retinaldehyde by retinol dehydrogenase (RDH). ALDHs generate RA, which acts within the nucleus as a ligand for nuclear receptors (heterodimers of RAR and RXR) to regulate transcriptional activity of target genes. Binding proteins for RA (CRABP) seem to be involved in this pathway. RA also can generate paracrine signaling on neighboring cells. RA is transformed into compounds subject to further metabolism and elimination by cytochrome P450 26 (CYP 26) enzymes.

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