VIDEO TRANSCRIPT

IgA Nephropathy and FSGS Injury Pathways Mediated by Endothelin-1 and Angiotensin II

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IgA nephropathy and focal segmental glomerulosclerosis, or FSGS, are chronic, progressive glomerular conditions.[1-3]

Both are characterized by proteinuria and are leading glomerular causes of kidney failure.[1-4]

While the pathogenesis of IgA nephropathy and FSGS are distinct, in both diseases, endothelin-1, ET-1, and angiotensin II, Ang II, work in tandem to exacerbate kidney injury that results in proteinuria and progression to kidney failure.[5-10]

Here we will explore the ways these two molecules drive disease progression.

We start by introducing ET-1 and Ang II; we'll then take a look at how they work in tandem to exacerbate injury and their specific roles in the progression of IgA nephropathy and FSGS.

ET-1 is a vasoactive peptide with hemodynamic and nonhemodynamic effects. ET-1 is ubiquitously produced throughout the body but particularly in the kidneys, including the glomerulus.[5,10]

It is produced by the podocytes, mesangial cells, and renal vasculature and tubules.[5,11,12]

Endothelin A receptors, which are highly responsive to ET-1, are found on the surface of podocytes, mesangial cells, and vascular endothelial cells.[13,14]

ET-1 can exacerbate several glomerular injuries that contribute to the progression of IgA nephropathy and FSGS.[5,7]

Ang II is a well-understood and therapeutically targeted vasoactive peptide that is part of the renin-angiotensin system, RAS. Ang II regulates fluid balance and blood pressure in addition to non-hemodynamic effects.[5,9]

Levels of both ET-1 and Ang II are increased in IgA nephropathy and FSGS.[7,9,10]

ET-1 and Ang II work in tandem to drive disease progression and have direct interactions that amplify their signaling.[5-8]

ET-1 and Ang II-mediated injuries, which are common to both IgA nephropathy and FSGS, include[5,13]

- vascular dysfunction[5,13]
- inflammation[5,13]
- tubulointerstitial injury[5,13]
- and, glomerular injury[5,13]

ET-1 and Ang II facilitate vasoconstriction leading to decreased glomerular filtration rate and endothelial dysfunction.[5,7,8]

ET-1 and Ang II promote tubular epithelial–mesenchymal transition, triggering matrix accumulation...and culminating in interstitial fibrosis and proteinuria.[15]

ET-1 and Ang II promote tissue infiltration of inflammatory cells and aggravate the initial glomerular injury that characterizes each disorder.[5,7]

More specifically, In IgA nephropathy, they exacerbate inflammation and increase mesangial cell proliferation,[3,5,10,16] and in FSGS, they damage podocytes.[2,5,7,13]

These injuries lead to deterioration of the glomerular filtration barrier, which can result in proteinuria.[5,7]

Let's take a closer look at the role of ET-1 in IgA nephropathy. ET-1 activates a number of pro-inflammatory and pro-fibrotic cells, signaling molecules, and mediators.[5,15]

ET-1 and Ang II signaling triggers mesangial hypercellularity and matrix accumulation, which in turn can cause sclerotic lesions that further inflame the environment.[5,15,16]

Now, in FSGS, the defining pathologic feature is targeted injury to podocytes.[5,17]

In FSGS, ET-1 binding to ET-A receptors on podocytes triggers cytoskeletal reorganization that may lead to podocyte injury, including podocyte effacement.[5,17] And, ET-1 and Ang II act together to exacerbate ongoing podocyte injury.[5,13]

In summary, ET-1 and Ang II play a fundamental role in the pathophysiology and progression of IgA nephropathy and FSGS.[7,15,16]

In IgA nephropathy, ET-1 and Ang II act together to amplify the inflammatory cytokine response and exacerbate glomerular, mesangial cell, and tubular damage—culminating in increased proteinuria and a progressive decline toward kidney failure.[5,7,8,15,16]

And, in FSGS, ET-1 and Ang II act in tandem to drive podocyte injury and loss—culminating in increased proteinuria and a progressive decline in kidney function.[5]

References:

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