The Role of Endothelin-1 and Angiotensin II in the Progression of IgA Nephropathy and Focal Segmental Glomerulosclerosis or FSGS

Endothelin-1 and angiotensin II are critical pathways that underlie the progression of kidney disease.[1-3]

IgA nephropathy and focal segmental glomerulosclerosis, or FSGS, are chronic, progressive glomerular conditions.[4-6]

Both are characterized by proteinuria and are leading glomerular causes of kidney failure.[4-7]

While the pathogenesis of IgA nephropathy and FSGS are distinct, there are similarities.

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.[1-3,8]

In this video, we will explore the ways these two molecules drive disease progression.

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.[1,9]

Endothelin A (ET_A) receptors, which are highly responsive to ET-1, are found on the surface of podocytes, mesangial cells, and vascular endothelial cells.[9,10]

ET-1 can exacerbate several glomerular injuries that contribute to the progression of IgA nephropathy and FSGS.[1,3,9]

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.[1,11]

In response to the initial insult in IgA nephropathy and FSGS, levels of ET-1 and Ang II increase substantially. Cross-talk between ET-1 and Ang II mutually upregulate one another.[2,3]

Acting via their receptors, both ET-1 and Ang II mediate injuries common to IgA nephropathy and FSGS.[1,9]

The compounding effect of ET-1 and Ang II result in damage to all components of the glomerular filtration barrier, causing proteinuria and glomerulosclerosis.[1,9]

Let's take a closer look at the role of ET-1 and Ang II in IgA nephropathy.

In IgA nephropathy, ET-1 and Ang II amplify mesangial cell proliferation, inflammation, vascular dysfunction, damage to glomerular filtration barrier, and tubulointerstitial injury, resulting in excess proteinuria.[1-3,6,12]

Increased proteinuria leads to tubulointerstitial inflammation and fibrosis, further increasing ET-1 and Ang II.[14] This will ultimately result in kidney failure.[15]

In fact, research shows that with every incremental increase of greater than 1 gram per day, kidney function can decline 10-25x faster.[16]

Unknown triggers initiate production of galactose-deficient IgA. Autoantibodies attach to these abnormal IgAs to form IgA immune complexes.[6,14]

Deposition of these immune complexes in the glomerular mesangium triggers an increase in ET-1 and Ang II production. Through cross-talk, Ang II upregulates ET-1 production while ET-1 increases the conversion of Ang I to Ang II.[1,2,6]

Activation of ET_A and AT_1 receptors results in damage to all components of the glomerular filtration barrier.[1]

Due to injury to podocytes, basement membrane, and endothelial cells, proteins increasingly leak across the glomerular barrier, and glomerulosclerosis occurs.[1,6]

Now, in FSGS, the defining pathologic feature is targeted injury to podocytes.[1,17]

In FSGS, ET-1 binding to ET_A receptors on podocytes triggers cytoskeletal reorganization that may lead to podocyte injury, including podocyte effacement. And, ET-1 and Ang II act together to exacerbate ongoing podocyte injury.[1,10]

In summary, the compounding effects of ET-1 and Ang II play a fundamental role in the pathophysiology and progression of IgA nephropathy and FSGS.[1,3,18,19]

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