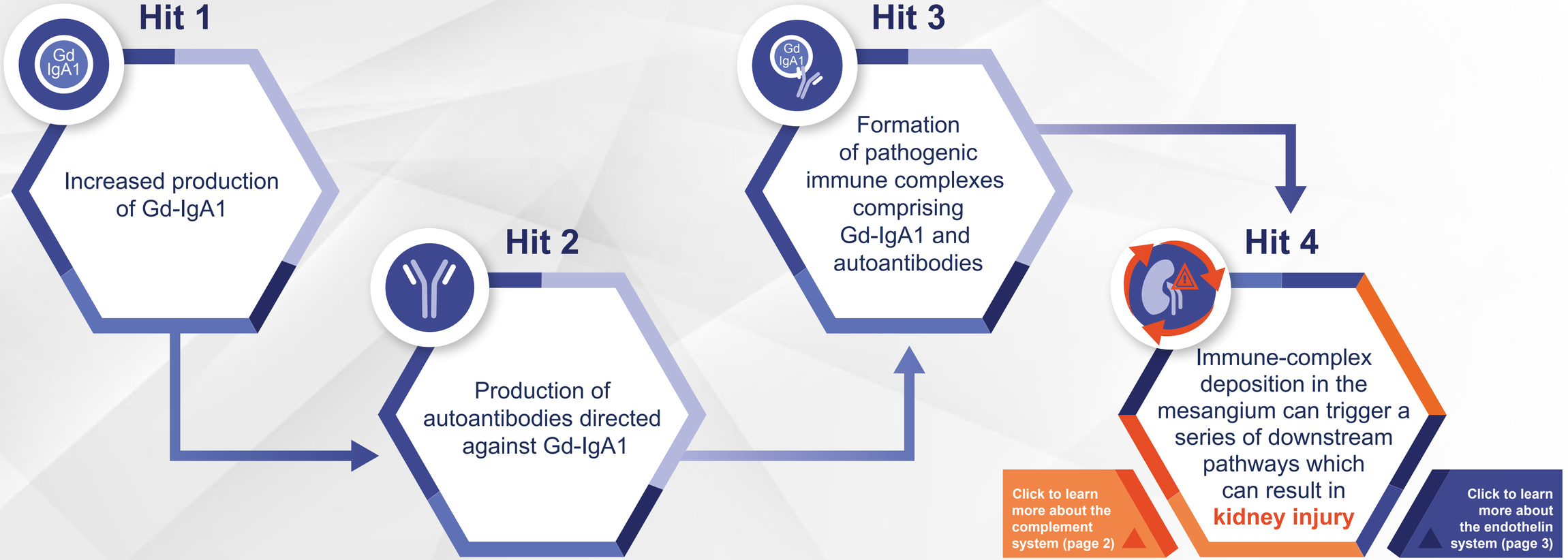
AT A GLANCE

IgA NEPHROPATHY DEVELOPS FOLLOWING MULTIPLE HITS[1-6]



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Gd, galactose-deficient; IgA, immunoglobulin A.

1. Rizk DV et al. *Front Immunol*. 2019;10:504. doi:10.3389/fimmu.2019.00504 2. Maillard N et al. *J Am Soc Nephrol*. 2015;26(7):1503-1512. doi:10.1681/ASN.2014101000 3. Medjeral-Thomas NR et al. *Semin Immunopathol*. 2021;43(5):679-690. doi:10.1007/s00281-021-00882-9 4. Kusano T et al. *Hum Pathol*. 2016;49:135-144. doi:10.1016/j.humpath.2015.10.013 5. Boyd JK et al. *Kidney Int*. 2012;81(9):833-843. doi:10.1038/ki.2011.501 6. Poppelaars F et al. *J Clin Med*. 2021;10(20):4715. doi:10.3390/jcm10204715.

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AT A GLANCE

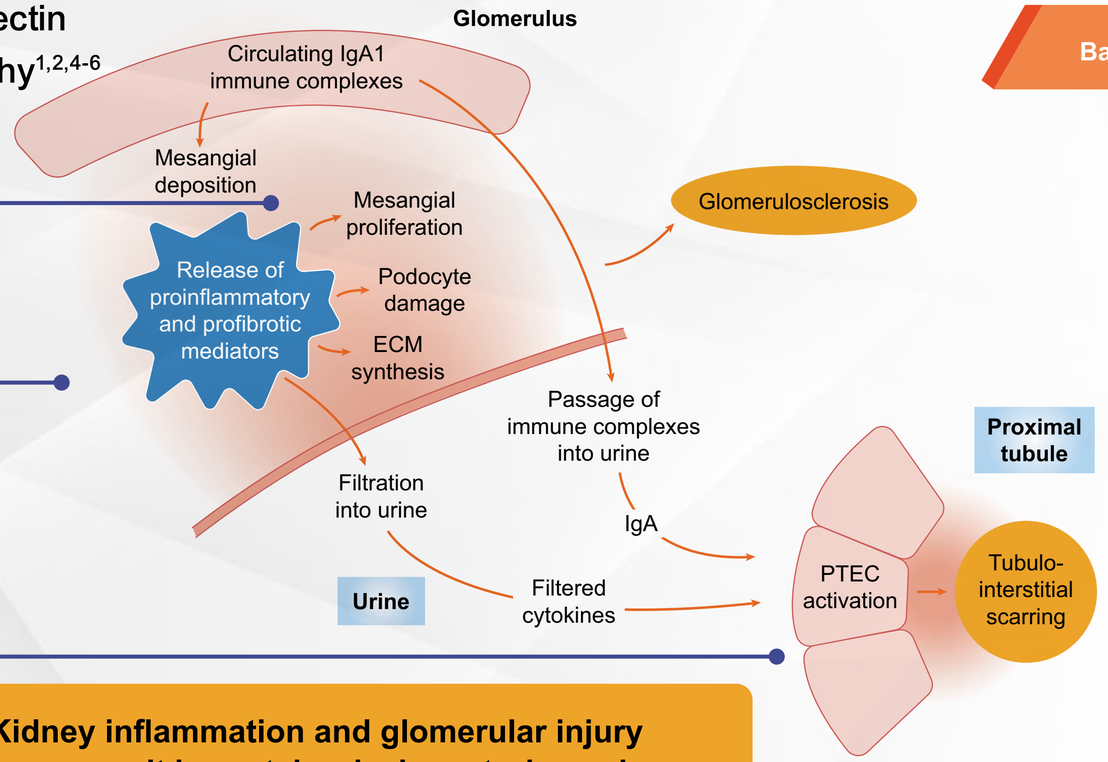
IMMUNE-COMPLEX DEPOSITION FOLLOWED BY COMPLEMENT ACTIVATION CAN CONTRIBUTE TO GLOMERULAR AND TUBULAR INJURY[1-3]

Overactivation of the alternative complement pathway, and less often, the lectin complement pathway, can be involved in the development of IgA nephropathy[1,2,4-6]

C3a and C5a stimulate proliferation of mesangial cells commonly observed in kidney biopsy specimens[2,7,8]

C5b-9 (MAC) increases the release of proteases, cytokines, and components of the ECM that disrupt the GBM, which can induce podocyte apoptosis and glomerular scarring[2]

C5b-9 formation on tubular epithelial cells and exposure to C5a can contribute to tubulointerstitial injury and fibrosis[6,9]



Kidney inflammation and glomerular injury may result in proteinuria, hematuria, and progressive kidney disease[1,3,10]

Adapted from Boyd JK et al.[3]

C, complement component; ECM, extracellular matrix; GBM, glomerular basement membrane; IgA, immunoglobulin A; MAC, membrane attack complex; PTEC, proximal tubular epithelial cell.

1. Rizk DV et al. *Front Immunol*. 2019;10:504. doi:10.3389/fimmu.2019.00504 2. Maillard N et al. *J Am Soc Nephrol*. 2015;26(7):1503-1512. doi:10.1681/ASN.2014101000 3. Boyd JK et al. *Kidney Int*. 2012;81(9):833-843. doi:10.1038/ki.2011.501 4. Medjeral-Thomas NR et al. *Semin Immunopathol*. 2021;43(5):679-690. doi:10.1007/s00281-021-00882-9 5. Poppelaars F et al. *J Clin Med*. 2021;10(20):4715. doi:10.3390/jcm10204715 6. Onda K et al. *BMC Nephrol*. 2011;12:64. doi:10.1186/1471-2369-12-64 7. Zhang Y et al. *Clin Exp Immunol*. 2017;189(1):60-70. doi:10.1111/cei.12961 8. Liu L et al. *J Clin Immunol*. 2014;34(2):224-232. doi:10.1007/s10875-013-9970-6 9. Boor P et al. *J Am Soc Nephrol*. 2007;18(5):1508-1515. doi:10.1681/ASN.2006121343 10. Lafayette RA, Kelebouris E. *Am J Nephrol*. 2018;47(suppl 1):43-52. doi:10.1159/000481636.

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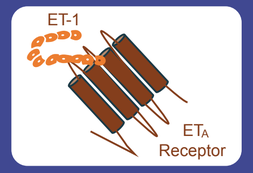
ENDOTHELIN SYSTEM ACTIVATION CAN CONTRIBUTE TO GLOMERULAR INJURY AND DISEASE PROGRESSION[1-5]

ET_A receptor signaling can activate key downstream pathways[4,6,7]

Back

Various kidney cell types make ET-1 and express ET_A receptors[5,8]

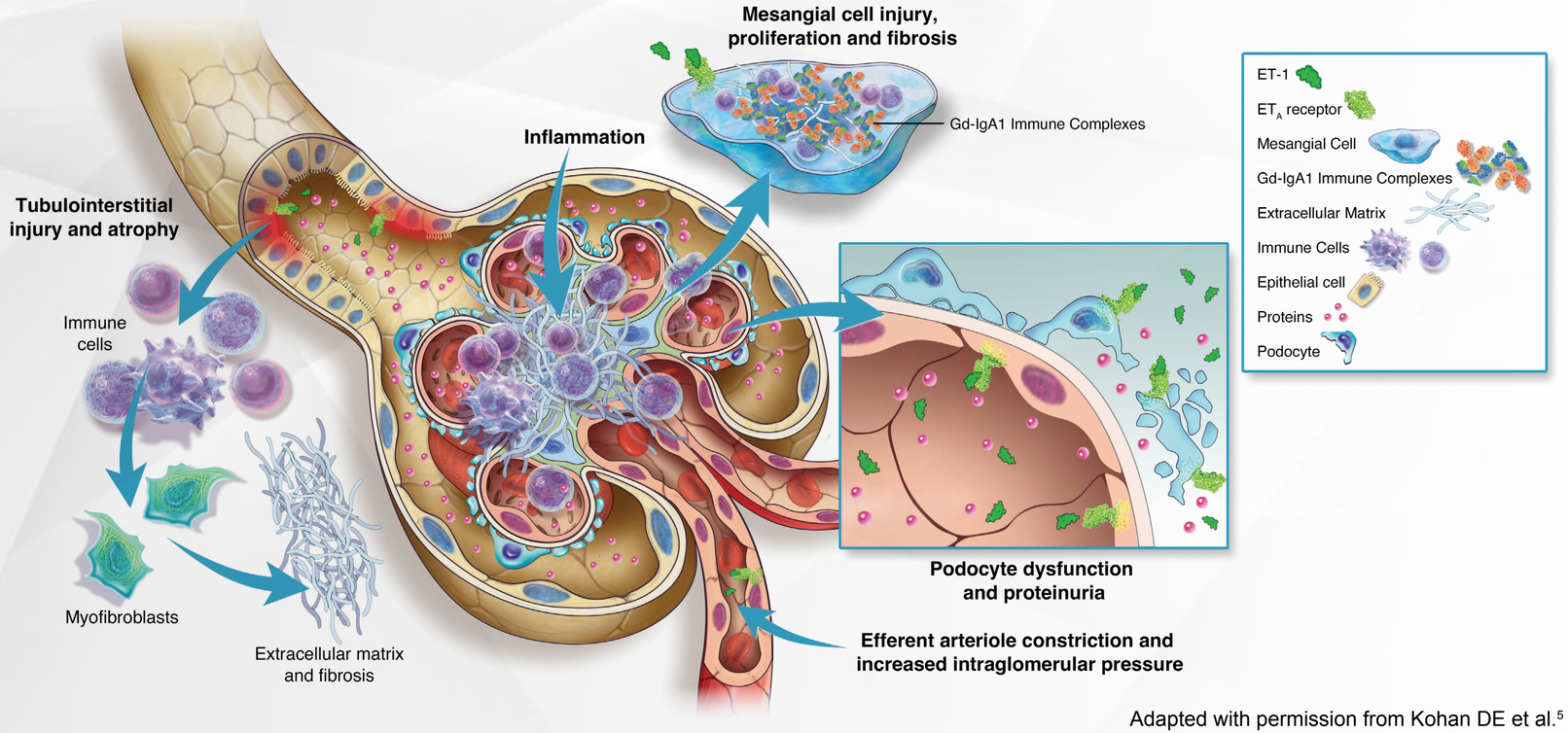


Kidney ET-1 may influence several physiological processes, including[5,8,9]:

- Glomerular arterial tone
- Fluid and sodium homeostasis

Increased kidney ET-1 production and ET_A receptor activation may cause glomerular injury through multiple mechanisms that may affect[4,5,8,9]:

- Vasculature
- Podocytes
- Kidney tubules
- Mesangial cells
- Inflammatory cells



Adapted with permission from Kohan DE et al.[5]

ET, endothelin; Gd, galactose-deficient; IgA1, immunoglobulin A1.

1. Lehrke I et al. *J Am Soc Nephrol*. 2001;12(11):2321-2329. doi:10.1681/ASN.V12112321 2. Zanatta CM et al. *Ren Fail*. 2012;34(3):308-315. doi:10.3109/0886022X.2011.647301 3. Tycová I et al. *Physiol Res*. 2018;67(1):93-105. doi:10.33549/physiolres.933670 4. Kohan DE, Barton M. *Kidney Int*. 2014;86(5):896-904. doi:10.1038/ki.2014.143 5. Kohan DE et al. *Kidney Int Rep*. 2023;8(11):2198-2210. doi:10.1016/j.ekir.2023.07.023 6. Komers R, Plotkin H. *Am J Physiol Regul Integr Comp Physiol*. 2016;310(10):R877-R884. doi:10.1152/ajpregu.00425.2015 7. Martínez-Díaz I et al. *Int J Mol Sci*. 2023;24(4):3427. doi:10.3390/ijms24043427 8. Kohan DE et al. *Compr Physiol*. 2011;1(2):883-919. doi:10.1002/cphy.c100039 9. Raina R et al. *Kidney Dis (Basel)*. 2020;6(1):22-34. doi:10.1159/000504623.

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