

Abstract Submission No.: A-0389

The Role of von Willebrand Factor in the Pathogenesis of C3 Glomerulopathy

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Objectives : C3 glomerulopathy (C3G) is a group of rare glomerular disease caused by dysregulation of alternative pathway of complement system activation. Endothelial cell injury plays an important role in the progression of C3G. von Willebrand factor (vWF) is a large adhesive glycoprotein mainly secreted by endothelial cells and platelets. However, the role of vWF in the pathogenesis of C3G is still unclear.

Methods : Patients: A total of 44 C3G patients diagnosed from 2012 to 2021 were included. Mouse: In C3G mouse model (FH^{m/m}P^{-/-}), plasma vWF level was detected and vWF level in kidney tissues and the colocalization with C3 and C5b-9 was assessed by immunofluorescence. A vWF-gene edited C3G mouse model (FH^{m/m}P^{-/-}vWF^{m/m}) was established using CRISPR/Cas9. Its clinical, pathological, prognosis features were collected.

Results : 59.09% of C3G patients showed obvious glomerular endothelial cell injury with higher Scr and UTP, lower plasma C3, worse prognosis and elevated plasma vWF level. In the kidney tissue, vWF was stained on the mesangial area and capillary walls, co-localized with C3 and C5b-9. Compared with WT mice, vWF level in plasma and kidney tissue of FH^{m/m}P^{-/-} mice were significantly increased, and was significantly positively correlated with the level of UTP. In kidney tissue, vWF was stained in mesangial area and capillary walls, and merged well with C3 and C5b-9. Compared with C3G mice, vWF gene edited mice showed significantly higher level of Scr and UTP, more severe kidney damage, more C3 and C5b-9 deposition in kidney tissue, and shorter survival time.

Conclusions : The level of vWF was increased in C3G patients and was related to the disease severity, glomerular endothelial cell injury and poor prognosis and gene editing of vWF led to the aggravation of kidney damage, indicating that vWF might play a regulatory role in the pathogenesis of C3G by inhibiting the excessive activation of complement.

FIG1.jpg

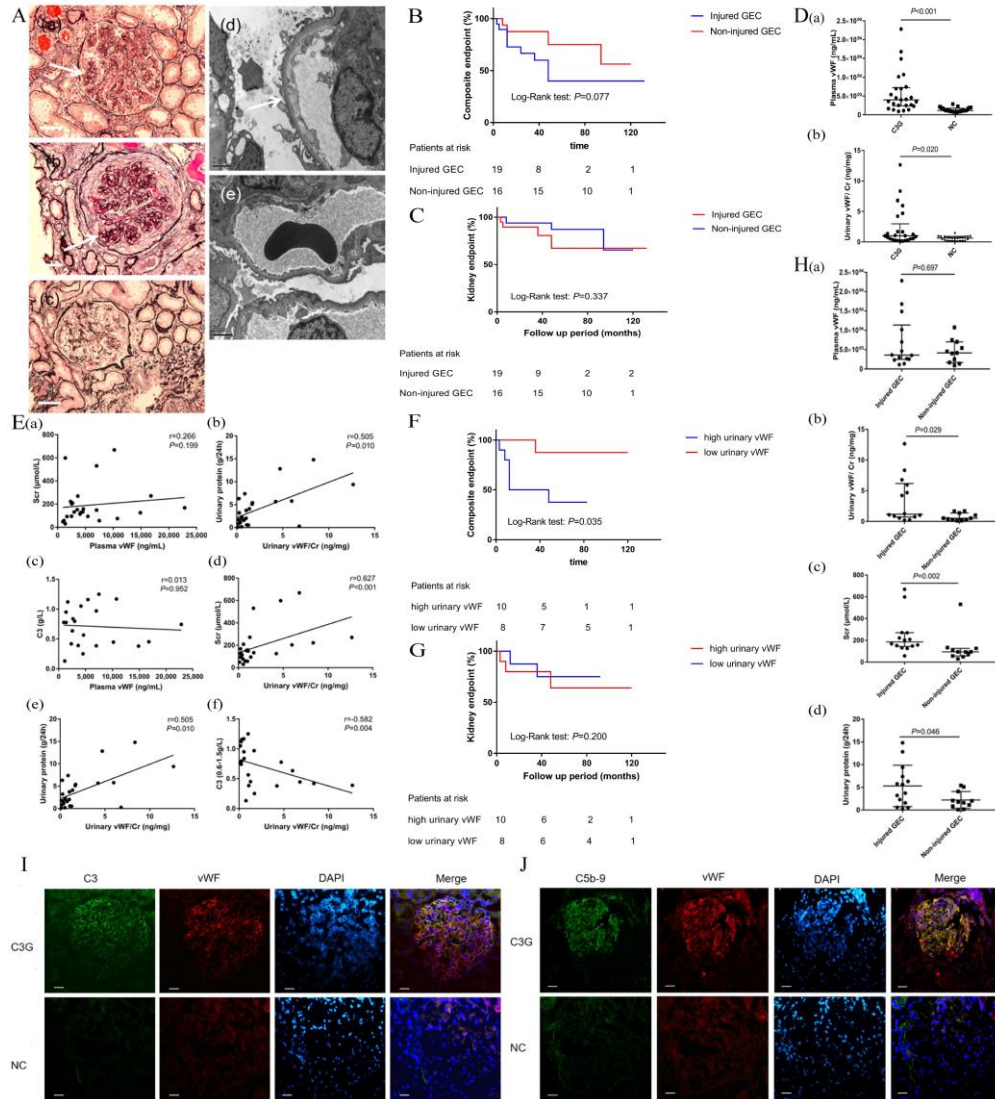


FIG1.jpg

