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Sublytic C5b-9 induces glomerular mesangial cell apoptosis through the cascade pathway of MEKK2-p38 MAPK-IRF-1-TRADD-caspase 8 in rat Thy-1 nephritis

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The apoptosis of glomerular mesangial cells (GMCs) in the early phase of rat Thy-1 nephritis (Thy-1N), a model of human mesangioproliferative glomerulonephritis (MsPGN), is primarily triggered by sublytic C5b-9. However, the mechanism of GMC apoptosis induced by sublytic C5b-9 remains unclear. In this study, we demonstrate that expressions of TNFR1-associated death domain-containing protein (*TRADD*) and IFN regulatory factor-1 (IRF-1) were simultaneously upregulated in the renal tissue of Thy-1N rats (*in vivo*) and in GMCs under sublytic C5b-9 stimulation (*in vitro*). *In vitro*, *TRADD* was confirmed to be a downstream gene of IRF-1, because IRF-1 could bind to *TRADD* gene promoter to promote its transcription, leading to caspase 8 activation and GMC apoptosis. Increased phosphorylation of p38 MAPK was verified to contribute to IRF-1 and *TRADD* production and caspase 8 activation, as well as to GMC apoptosis induced by sublytic C5b-9. Furthermore, phosphorylation of MEK kinase 2 (MEKK2) mediated p38 MAPK activation. More importantly, three sites (Ser153/164/239) of MEKK2 phosphorylation were identified and demonstrated to be necessary for p38 MAPK activation. In addition, silencing of renal MEKK2, IRF-1, and *TRADD* genes or inhibition of p38 MAPK activation *in vivo* had obvious inhibitory effects on GMC apoptosis, secondary proliferation, and urinary protein secretion in rats with Thy-1N. Collectively, these findings indicate that the cascade axis of MEKK2-p38 MAPK-IRF-1-*TRADD*-caspase 8 may play an important role in GMC apoptosis following exposure to sublytic C5b-9 in rat Thy-1N.

Biography

Wen Qiu is currently an Associate Professor at Department of Immunology of Nanjing Medical University. He is exploring the roles and mechanisms of complement especially C5b-9 in the induction of glomerular mesangial cell (GMC) apoptosis, inflammation and proliferation in rat Thy-1 nephritis as a widely used model of human mesangial proliferative glomerulonephritis (MsPGN) as well as the roles and mechanisms of IL-17 in astrocyte pathological changes in EAE mice. These include signal transduction, microRNA regulation, and transcriptional factor regulation. He is also exploring the effects of post-transcriptional regulation such as ubiquitination and acetylation on the activation of signaling molecules, transcription factors and histones.

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