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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 cell (GMC) in the early phase of rat Thy-1 nephritis (Thy-1N), a model of human mesangioproliferative glomerulonephritis (MsPGN), is mainly triggered by sublytic C5b-9. But the mechanism of GMC apoptosis induced by sublytic C5b-9 remains unclear. In current study, we demonstrated that the expression of TNFR1-associated death domain-containing protein (TRADD) and interferon regulatory factor-1 (IRF-1) was simultaneously up-regulated both in the renal tissue of Thy-1N rats (*in vivo*) and in the GMC under sublytic C5b-9 stimulation (*in vitro*). And in *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. Meanwhile, increased phosphorylation of p38 mitogen-activated protein kinase (p38 MAPK) was verified to contribute to IRF-1 and TRADD production and caspase 8 activation as well as GMC apoptosis treated by sublytic C5b-9. Furthermore, the phosphorylation of mitogen-activated protein kinase kinase 2 (MEKK2) was found to mediate p38 MAPK activation. More importantly, three sites (Ser-153/164/239) of MEKK2 phosphorylation were first identified and demonstrated to be necessary for p38 MAPK activation. Besides, silence of renal MEKK2, IRF-1 and TRADD gene or inhibition of p38 MAPK activation in *in vivo* displayed 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 the sublytic C5b-9 in rat Thy-1N

Biography

Yingwei Wang is currently working as a Professor at Department of Immunology of Nanjing Medical University. She is conducting research in exploring the mechanisms of Glomerular Mesangial Cell (GMC), apoptosis and proliferation in human mesangial proliferative glomerulonephritis (MsPGN). These include signal transduction, microRNA regulation and transcription factor regulation. She is also exploring the effects of ubiquitination and acetylation modification on the activation of signaling molecules, transcription factors and histones

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