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Sublytic C5b-9 triggers glomerular mesangial cell apoptosis in rat Thy-1 nephritis via Gadd45 activation mediated by Egr-1 and p300-dependent ATF3 acetylation

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The apoptosis of glomerular mesangial cells (GMCs) is considered to be an important contributor to the initiation and development of rat Thy-1 nephritis (Thy-1N) and is accompanied by sublytic C5b-9 deposition. However, the mechanism by which sublytic C5b-9 triggers GMC apoptosis has not been elucidated. In this study, functional and histological examinations were performed on GMCs treated with sublytic C5b-9 (*in vitro*) and renal tissues of Thy-1N rats (*in vivo*). The *in vitro* studies found that sublytic C5b-9 could trigger GMC apoptosis through upregulating Egr-1, ATF3, and Gadd45 expression. Egr-1-mediated post-transcriptional modulation of ATF3, Egr-1/ATF3-enhanced Gadd45 promoter activity, and p300-mediated ATF3 acetylation were all involved in GMC apoptosis. More importantly, the effective binding elements for Egr-1 and ATF3 to Gadd45β/γ promoters and the ATF3 acetylation site were identified. In vivo, silencing renal p300, Egr-1, ATF3, and Gadd45β/γ significantly decreased GMC apoptosis, secondary GMC proliferation, and urinary protein secretion in Thy-1N rats. Together, these findings implicate that sublytic C5b-9-induced activation of Egr-1/p300-ATF3/Gadd45 axis plays a critical role in GMC apoptosis in Thy-1N rats.

Biography

Yingwei Wang is currently a Professor at Department of Immunology of Nanjing Medical University. She is conducting research in exploring the mechanisms of sublytic C5b-9-induced glomerular mesangial cell (GMC) apoptosis, inflammation and proliferation in mesangial proliferative glomerulonephritis (MsPGN) by using rat Thy-1 nephritis model. These include signal transduction, microRNA regulation, and transcriptional factor regulation. She is also exploring the effects of ubiquitination, acetylation and phosphorylation modification on the activation of signaling molecules, transcription factors and histones.

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