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Sublytic C5b-9 induces IL-23 and IL-36a production by glomerular mesangial Cells via PCAF-Mediated KLF4 Acetylation in Rat Thy-1 nephritis

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Sublytic C5b-9 formation on glomerular mesangial cells in rat Thy-1 nephritis (Thy-1N), a model of human mesangioproliferative glomerulonephritis, is accompanied by the production of proinflammatory cytokines, but the relationship between sublytic C5b-9 and cytokine synthesis and the underlying mechanism remains unclear. To explore the problems mentioned above, in this study, we first examined the levels of proinflammatory ILs (e.g., IL-23 and IL-36a) as well as transcription factor (KLF4) and coactivator (PCAF) in the renal tissues of Thy-1N rats and in the glomerular mesangial cell line (HBZY-1) stimulated by sublytic C5b-9. Then, we further determined the role of KLF4 and PCAF in sublytic C5b-9-induced IL-23 and IL-36a production as well as the related mechanism. Our results showed that the levels of KLF4, PCAF, IL-23, and IL-36a were obviously elevated. Mechanistic investigation revealed that sublytic C5b-9 stimulation could increase IL-23 and IL-36a synthesis through KLF4 and PCAF upregulation, and KLF4 and PCAF could form a complex, binding to the IL-23 or IL-36a promoter in a KLF4-dependent manner, causing gene transcription. Importantly, KLF4 acetylation by PCAF contributed to sublytic C5b-9-induced IL-23 and IL-36a transcription. Besides, the KLF4 binding regions on IL-23 or IL-36a promoters and the KLF4 lysine site acetylated by PCAF were identified. Furthermore, silencing renal KLF4 or PCAF gene could significantly inhibit IL-23 or IL-36a secretion and tissue damage of Thy-1N rats. Collectively, these findings implicate that the KLF4/PCAF interaction and KLF4 acetylation by PCAF play a pivotal role in the sublytic C5b-9-mediated IL-23 and IL-36a production of 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) inflammation, apoptosis and proliferation in mesangial proliferative glomerulonephritis (MsPGN) by using rat Thy-1 nephritis model. These include signal transduction, microRNA regulation, transcriptional factor regulation as well as ubiquitination, acetylation and phosphorylation modification.

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