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자가면역 IgM 항체의 NFkB 억제를 통한 허혈성 신장 손상의 보호 효과

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Natural IgM Anti-Leucocyte Autoantibodies (IgM-ALA) Block Immune Mediated Proinflammatory Cytokine Release through Inhibition of NF-kB Activation

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Background: IgM-ALA reduce kidney ischemia-reperfusion injury (IRI) however, little is known about the mechanisms by which these antibodies attenuate IRI. IgM-ALA bind to receptors on leucocyte and endothelial cell membranes, tissues important in the pathogenesis of IRI. The purpose of the current studies was to examine the effect of IgM on cellular mechanisms that lead to attenuation of kidney IRI.

Methods: Wild type mice and IgM KO mice were subjected to kidney IRI with and without IgM pretreatment. At 24 hours we measured serum creatinine and evaluated kidney histology. In other studies, we cultured mouse glomerular endothelial cells (mGEC) and RAW264.7 macrophage cells using standard methods and tested the effect of IgM (25 μg/ml) on these cells activated with LPS (0.1 to 1 μg/ml) for 20 min to 24 hrs. We measured proinflammatory cytokine production by real time PCR and immunohistochemistry as well as phosphorylation and nuclear translocation of NF-kB by Western blot.

Results: LPS significantly increased CXCL1 production ($p<0.001$) by mGEC. IgM, but not IgM adsorbed with leukocytes to remove IgM-ALA, blocked CXCL1 production through inhibition of phosphorylation and nuclear translocation of NF-kB. IgM KO mice showed increased renal injury after IRI. IgM pretreatment, but not IgM depleted of IgM-ALA, significantly decreased sCr and tubular injury in wild type and IgM KO ($p<0.01$). Similar to in vitro data, IgM treated mice had significantly less labeling of MCP-1 and CXCL1 on kidney vascular endothelial cells co-expressing TLR4 and CD31 after IRI.

Conclusions: We show that IgM-ALA, in physiologic doses, inhibits proinflammatory cytokines production by preventing activation of NF-kB. These studies highlight the importance of naturally occurring IgM-ALA in regulating excess inflammation as occurs after ischemia reperfusion injury despite presence of competent regulatory T cells. IgM could pre-emptively be used to prevent renal IRI.

Key Words: 허혈 재관류 손상, 급성 신부전, IgM
Ischemia reperfusin, Acute kidney injury, NFkB