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실험적 당뇨 백서에서 proteasome inhibitor인 Bortezomib의 세포외 기질 축적에 대한 효과

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The Effect of Proteasome Inhibitor (Bortezomib) on ECM Accumulation in Experimental Diabetic Rat

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Background : Nuclear factor- kappa B (NF- κB) has been implicated in the transcriptional regulation of extracellular matrix (ECM) protein and recent studies have demonstrated that proteasome inhibitor blocks NF- κB activity and exerts an anti- fibrotic effect in human dermal fibroblasts and cardiac fibroblasts. However, the effect of proteasome inhibitor on ECM accumulation has never been explored in diabetic nephropathy. Purpose: This study was performed to investigate whether proteasome inhibition may ameliorate fibronectin expression in experimental diabetic glomeruli and in high glucose- stimulated mesangial cells.

Methods : In vivo, 32 Sprague- Dawley rats were injected either with diluent (n=16, C) or with STZ intraperitoneally (IP) (n=16, DM) and 8 rats from each group were treated with IP Bortezomib (Bo) (0.5 mg/kg/ week), a proteasome inhibitor, for 12 weeks. In vitro, rat mesangial cells (MCs) were cultured in media with 5.6 mM glucose (LG), LG+24.4 mM mannitol (LG+M), or 30 mM glucose (HG) with or without 10- 8 M Bo for 48 hours. Real time- PCR and Western blot for TGF- β and fibronectin (FN) were performed with sieved glomeruli and cell lysates. Glomerular TGF- β and FN protein expression were also assessed by immunohistochemistry (IHC). Translocation of NF- κB p65 subunit (NF- κB/p65) in cultured MCs was detected by laser scanning confocal microscope (LSCM).

Results : UAE was significantly higher in DM (1.99$\pm$0.35 mg/day) compared to C rats (0.45$\pm$0.04 mg/day) ($p<0.05$) and this increase in UAE in DM rats was inhibited by Bo treatment ($p<0.05$). Glomerular TGF- β and FN mRNA expression were significantly increased in DM by 115.9% and 176.8%, respectively, compared to C rats ($p<0.05$), and these increases were significantly ameliorated by the administration of Bo ($p<0.05$). Bo also inhibited the increases in TGF- β and FN protein expression in DM glomeruli ($p<0.05$). TGF- β and FN mRNA and protein expression were significantly increased in MCs exposed to HG ($p<0.05$), and these increases were abrogated in HG+Bo group ($p<0.05$). Compared to cytoplasmic distribution of NF- κB/p65 subunit in LG cells, a significant nuclear translocation of NF- κB/p65 subunit was observed in MCs at 30 minutes after HG stimulation, and this change was blocked by Bo treatment.

Conclusion : Proteasome inhibitor attenuates ECM accumulation under diabetic condition by inhibiting NF- κB/p65 subunit translocation and NF- κB may be a therapeutic target in diabetic nephropathy.

Key Words : 당뇨병성 신증, 세포외 기질, 프로테아좀 억제제
Diabetic nephropathy, ECM, Proteasome inhibitor