Selective Activation of Mitogen-Activated Protein (MAP) Kinase During the Progression of Renal Disease

*Sang-Joon Park, Kyu-Shik Jeong, Tae-Sook Jeong, Song-Hae Bok, *Cha-Soo Lee

*College of Veterinary Medicine, Kyungpook National University, Taegu City, Korea
Genetic Resources Center, Korea Research Institute of Bioscience and Biotechnology, Taejon City, Korea

Most renal diseases progress by consecutive cell responses such as hypertrophy, hyperplsia, proliferation, defferentiation, sclerosis, fibrosis and other cellular degenerative process. These cellular responses are mediated by the activation of various mitogens such as vasoconstrictors, growth factors, hormone, genotoxins and cytokines through mechanical, hemodynamic, immunological injury as well as metabolic abnormality. Consequently, multiple extracellular stimuli elicit specific cellular responses in the progression of various renal diseases through activation of mitogen-activated protein (MAP) kinase cascades. This study was conducted to examine the role of MAP kinase pathways as a convergence point of mitogenic stimuli in the progression of experimental nephrosis in rats. Uninephrectomized Sprague-Dawley rat repeatedly injected over four days with puromycin aminonucleoside (PAN) (1 mg/100g body wt) through 2 week intervals based on experimental scheme. Animals were sacrificed on days 10, 24, 38, 52, 66, 80. Maximal activation of c-Jun-NH2-terminal kinase (JNK) and extracellular signal regulated kinase (ERK) was detected on day 38. This activation gradually decreased until day 80 without activation of p38 MAP kinase. JNK and ERK activation was accompanied by an increase in the expression of SEK1/MKK4 and MEK1, known to immediate upstream protein kinase of JNK and ERK, respectively. These activations were concommittently demonstrated by immunohistochemistry analysis using specific phospho-JNK and ERK antibody. Immunoreactivity of phospho-ERK was markedly increased in glomerular region, possibly due to localization of mesangial cells and infiltrating macrophage on day 38. Phospho-JNK kinase activation was localized to activated T-cell, fibroblast and some tubular cell. Phospho-JNK kinase was associated with apoptosis in renal glomerular and tubular cells as well as infiltrating inflammatory cells during the process of renal sclerosis even if apoptotic positive cells were not significantly detected in their numbers as immunoreactivity positive cells for JNK or ERK kinase *in vivo*. These results indicate that JNK and ERK MAP kinase paly a critical role as putative mediators in the progression of PAN-induced nephrosis and suggest that upregulation of specific JNK, ERK kinase *in vivo* is mainly associated with long-term regulation of renal disease.