Role of p38 MAPK in Kidney Disease Progression

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Properties of the p38 MAPK signaling pathway

The mitogen- activated protein kinase (MAPK), including p38 MAPK, extracellular signal- regulated kinase (ERK) and c- Jun N- terminal kinase (JNK) are the major intracellular signal transduction molecules that control cellular responses to cytokines and stress[1]. Of these MAP kinases, this lecture focuses on p38 MAPK which has been implicated in the pathogenesis of kidney disease by many recent investigations. p38 MAPK was first isolated as a 38 kDa protein which was rapidly tyrosine phosphorylated in response to lipopolysaccharides (LPS) simulation[2]. So far, four isoforms of p38 MAP kinase, alpha, beta, gamma and delta, have been cloned in mammals[3, 4]. All the p38 MAPKs have the Thr- Gly- Tyr (TGY) dual phosphorylation motif and, like the other MAP kinases, MAPK kinases (MAPKK) such as MKK3 and MKK6 activate p38 MAPK through phosphorylation at Thr180 and Tyr182[5]. The MAPKKs are activated by MKK kinases (MAPKKK, MAP3K) and several MAPKKKs such as MTK1, MLK3, DLK, ASK1 and TAK1 have been reported[6]. Different MAPKKKs may mediate different upstream signals, and such diversity may explain why the p38 pathway can be activated by various stimuli including osmotic shock, inflammatory cytokines, LPS, UV light and growth factors[7]. MTK1, one of the MAPKKKs, is bound to and activated by the stress- inducible Growth Arrest and DNA Damage 45 family of proteins (GADD 45- alpha/beta/gamma)[8]. The binding of GADD45 family of proteins to the N- terminal domain of MTK1 induces MTK1 N- C dissociation, dimerization, and autophosphorylation at Thr- 1493, which leads to the activation of the kinase catalytic domain[9]. MTK1 activation may lead to activation of JNK and p38 MAPK depending on the cell types or stimulation conditions[9- 15]. Specifically in renal tubular cells, GADD45- gamma appears to activate p38 MAPK but not JNK or ERK[16]. Activated p38 MAPK has various biological functions which include activation of transcriptions factors such as MAPK- activated protein kinase 2 (MAPKAPK2), activating transcription factor- 2 (ATF- 2), and myocyte enhance factor 2 (MEF2) as well as production of proinflammatory cytokines, and induction of apoptosis[7, 17].

Implication of the p38 MAPK pathway in the pathogenesis of kidney disease

There is growing evidence that p38 MAPK may contribute to the damage of kidney cells in vitro. In cultured renal tubular cells, exposure to glucose activates p38 MAPK, and inhibition of this activation abrogates both glucose induced TGF- beta1 transcriptional activation and TGF- beta1 synthesis[18]. Other investigators observed that p38 MAPK mediates TNF- alpha production in cultured renal tubular cells after ischemic stress[19], and that p38 MAPK mediates IL- 6 production by TNF- alpha in cultured mesangial and proximal tubular cells[20]. In addition, pharmacological inhibition of p38 in cultured renal tubular cells significantly reduces TGF- beta1- induced gene expression for procollagen- Ialpha1[21]. In cultured mesangial cells, it has been found that p38 MAPK mediates thrombospondin- 1 production and subsequent latent TGF- beta1 activation by angiotensin II[22], as well as osteopontin production and mesangial cell proliferation by hypoxia[23]. Comparatively less number of investigations is available in animal models and far fewer in human renal diseases. Enhanced phosphop38 MAPK was found at podocytes of rodent kidneys with nephrotic syndrome[24]. Inhibition of P38 phosphorylation reduces renal chemokine expression, crescentic formation, and glomerular sclerosis and/or interstitial fibrosis, resulting in preserved renal function in a rat model of crescentic glomerulonephritis[25]. It has been found that p38 MAPK inhibitor effectively downregulates monocyte chemoattractant protein- 1, intercellular adhesion molecule- 1 and glomerular macrophage infiltration in nephrotoxic nephritis rats[26]. Accordingly, pharmacological inhibition of p38 in mice with autoimmune injury reduces macrophage and T cell infiltration into the kidneys[27]. For humans, enhanced phosphorylation of

p38 MAPK was detected at podocytes and parietal epithelial cells in the biopsy specimens from the patients with glomerulonephritis[24]. Moreover, it has been demonstrated that p38 activation correlates with the renal injury in various human glomerular diseases[28, 29].

Summary

p38 MAPK is activated by various stresses and stimuli and then it targets various proteins for transcription and translation. p38 signaling pathway is not a simple chain reaction: it responds to various stimuli and each component of the pathway transmits signals while interacting with other cellular components at the same time. Since p38 signaling pathway functions in a cell specific and in a stimulus specific manner, the consequences of signaling become even more complex. We have increasing number of in vitro and in vivo data on the p38 MAPK pathway but our knowledge in its specific function especially in the renal system is far from satisfactory. Progress is expected in understanding the structure and function of the p38 MAPK to target this signaling pathway in human kidney diseases.

References

1) Kyriakis JM, Avruch J: Mammalian mitogen-activated protein kinase signal transduction pathways activated by stress and inflammation. *Physiol Rev* 81:807-869, 2001
2) Han J, Lee JD, Bibbs L, Ulevitch RJ: A MAP kinase targeted by endotoxin and hyperosmolarity in mammalian cells. *Science* 265:808-811, 1994
3) Lechner C, Zahalka MA, Giot JF, Moller NP, Ullrich A: ERK6, a mitogen-activated protein kinase involved in C2C12 myoblast differentiation. *Proc Natl Acad Sci USA* 93:4355-4359, 1996
4) Jiang Y, Gram H, Zhao M, New L, Gu J, Feng L, Di Padova F, Ulevitch RJ, Han J: Characterization of the structure and function of the fourth member of p38 group mitogen-activated protein kinases, p38delta. *J Biol Chem* 272:30122-30128, 1997
5) Raingeaud J, Whitmarsh AJ, Barrett T, Derijard B, Davis RJ: MKK3- and MKK6-regulated gene expression is mediated by the p38 mitogen-activated protein kinase signal transduction pathway. Mol Cell Biol 16:1247-55, 1996
6) Ono K, Han J: The p38 signal transduction pathway: activation and function. *Cell Signal* 12:1-13, 2000
7) Raingeaud J, Gupta S, Rogers JS, Dickens M, Han J, Ulevitch RJ, Davis RJ: Pro-inflammatory cytokines and environmental stress cause p38 mitogen-activated protein kinase activation by dual phosphorylation on tyrosine and threonine. *J Biol Chem* 270:7420-7426, 1995
8) Takekawa M, Saito H: A family of stress-inducible GADD45-like proteins mediate activation of the stress-responsive MTK1/MEKK4 MAPKKK. *Cell* 95:521-530, 1998
9) Miyake Z, Takekawa M, Ge Q, Saito H: Activation of MTK1/MEKK4 by GADD45 through induced N-C dissociation and dimerization-mediated trans autophosphorylation of the MTK1 kinase domain. *Mol Cell Biol* 27:2765-2776, 2007
10) Chi H, Lu B, Takekawa M, Davis RJ, Flavell RA: GADD45beta/GADD45gamma and MEKK4 comprise a genetic pathway mediating STAT4-independent IFNgamma production in T cells. *EMBO J* 23:1576-1586, 2004
11) Lu B, Yu H, Chow C, Li B, Zheng W, Davis RJ, Flavell RA: GADD45gamma mediates the activation of the p38 and JNK MAP kinase pathways and cytokine production in effector TH1 cells. *Immunity* 14:583-590, 2001
12) Yang J, Zhu H, Murphy TL, Ouyang W, Murphy KM: IL-18-stimulated GADD45 beta required in cytokine-induced, but not TCR-induced, IFN-gamma production. *Nat Immunol* 2:157-164, 2001
13) Shaulian E and Karin M: Stress-induced JNK Activation is Independent of Gadd45 induction. *J Biol Chem* 274:29595-29598, 1999
14) Wang X, Gorospe M, Holbrook NJ: Gadd45 is not required for activation of c-Jun N-terminal kinase or p38 during acute stress. *J Biol Chem* 274:29599-29602, 1999
15) Papa S, Zazzeroni F, Bubici C, Jayawardena S, Alvarez K, Matsuda S, Nguyen DU, Pham CG, Nelsbach AH, Melis T, De Smaele E, Tang WJ, D'Adamio L, Franzoso G: Gadd45 beta mediates the NF-kappa B suppression of JNK signalling by targeting MKK7/JNKK2. *Nat Cell Biol* 6:146-153, 2004
16) Shin GT, Kim DR, Lim JE, Yim H, Kim H: Upregulation and function of GADD45gamma in unilateral ureteral obstruction. *Kidney Int*: 2008 [Epub ahead of print]
17) Stokoe D, Campbell DG, Nakielny S, Hidaka H, Leevers SJ, Marshall C, Cohen P: MAPKAP kinase-2; a novel protein

kinase activated by mitogen-activated protein kinase. *EMBO J* 11:3985-3994, 1992
18) Fraser D, Brunskill N, Ito T, Phillips A: Long-term exposure of proximal tubular epithelial cells to glucose induces transforming growth factor-beta 1 synthesis via an autocrine PDGF loop. *Am J Pathol* 163:2565-2574, 2003
19) Meldrum KK, Meldrum DR, Hile KL, Yerkes EB, Ayala A, Cain MP, Rink RC, Casale AJ, Kaefer MA: p38 MAPK mediates renal tubular cell TNF-alpha production and TNF-alpha-dependent apoptosis during simulated ischemia. *Am J Physiol Cell Physiol* 281:563-570, 2001
20) Leonard M, Ryan MP, Watson AJ, Schramek H, Healy E: Role of MAP kinase pathways in mediating IL-6 production in human primary mesangial and proximal tubular cells. *Kidney Int* 56:1366-1377, 1999
21) Prakash J, Sandovici M, Saluja V, Lacombe M, Schaapveld RQ, de Borst MH, van Goor H, Henning RH, Proost JH, Moolenaar F: Intracellular delivery of the p38 mitogen-activated protein kinase inhibitor SB202190[4-(4-fluorophenyl)-2-(4-hydroxyphenyl)-5-(4-pyridyl)1H-imidazole] in renal tubular cells: a novel strategy to treat renal fibrosis. *J Pharmacol Exp Ther* 319:8-19, 2006
22) Naito T, Masaki T, Nikolic-Paterson DJ, Tanji C, Yorioka N, Kohno N: Angiotensin II induces thrombospondin-1 production in human mesangial cells via p38 MAPK and JNK: a mechanism for activation of latent TGF-beta1. *Am J Physiol Renal Physiol* 286:F278-287, 2004
23) Sodhi CP, Batlle D, Sahai A: Osteopontin mediates hypoxia-induced proliferation of cultured mesangial cells: role of PKC and p38 MAPK. *Kidney Int* 58:691-700, 2000
24) Koshikawa M, Mukoyama M, Mori K, Suganami T, Sawai K, Yoshioka T, Nagae T, Yokoi H, Kawachi H, Shimizu F, Sugawara A, Nakao K: Role of p38 mitogen-activated protein kinase activation in podocyte injury and proteinuria in experimental nephrotic syndrome. *J Am Soc Nephrol* 16:2690-2701, 2005
25) Wada T, Furuichi K, Sakai N, Hisada Y, Kobayashi K, Mukaida N, Tomosugi N, Matsushima K, Yokoyama H: Involvement of p38 mitogen-activated protein kinase followed by chemokine expression in crescentic glomerulonephritis. *Am J Kidney Dis* 38:1169-1177, 2001
26) Sheryanna A, Bhangal G, McDaid J, Smith J, Manning A, Foxwell BM, Feldmann M, Cook HT, Pusey CD, Tam FW: Inhibition of p38 mitogen-activated protein kinase is effective in the treatment of experimental crescentic glomerulonephritis and suppresses monocyte chemoattractant protein-1 but not IL-1beta or IL-6. *J Am Soc Nephrol* 18:1167-1179, 2007
27) Iwata Y, Wada T, Furuichi K, Sakai N, Matsushima K, Yokoyama H, Kobayashi K: p38 Mitogen-activated protein kinase contributes to autoimmune renal injury in MRL-Fas lpr mice. *J Am Soc Nephrol* 14:57-67, 2003
28) Stambe C, Nikolic-Paterson DJ, Hill PA, Dowling J, Atkins RC: p38 Mitogen-activated protein kinase activation and cell localization in human glomerulonephritis: correlation with renal injury. *J Am Soc Nephrol* 15:326-336, 2004
29) Sakai N, Wada T, Furuichi K, Iwata Y, Yoshimoto K, Kitagawa K, Kokubo S, Kobayashi M, Hara A, Yamahana J: Involvement of extracellular signal-regulated kinase and p38 in human diabetic nephropathy. *Am J Kidney Dis* 45:54-65, 2005