

허혈/재관류 급성신손상에서 HSP70의 면역조절기능에 관한 연구

고려대학교 의과대학 내과학교실

윤기철, 조은정, 최혜민, 조상경, 조원용, 김형규

Heat Shock Protein-70 (HSP70) Induced Renoprotective Effect is Mediated by CD4+ CD25+ Foxp3+ Regulatory T Cells in Ischemia/reperfusion (I/R) Induced AKI

Ki Chul Yoon, Eun Jung Cho, Hye Min Choi
Sang-Kyung Jo, Won Yong Cho, Hyoung Kyu Kim

Department of Internal Medicine, Korea University Medical College

Several recent reports demonstrated immune modulatory effect of HSPs in addition to their well known function as molecular chaperones. HSP70 induced by heat preconditioning (HP) has been demonstrated to decrease inflammation and injury in I/R induced AKI. CD4+ CD25+ Foxp3+ regulatory T cells (Tregs) has recently been recognized as an important player in decreasing kidney injury after I/R injury. The aim of this study was to test whether HP induced HSP 70 exert renoprotective effect through Tregs. Thirty min bilateral I/R injury was done with or without heat preconditioning in mice (42°C for 15min). Quercetin, for inhibition of HSP70 or PC61 for depleting Tregs were administered and various molecular and flow cytometric analyses were performed. Induction of HSP70 was observed not only in kidney, liver, lung but also in immune cells in spleen. Heat preconditioned splenocytes demonstrated reduced proliferative response upon mitogenic stimuli suggesting that HP has immune modulatory function. In addition, adoptive transfer of splenocytes from heat preconditioned mice into T cell deficient nu/nu mice failed to reconstitute postischemic injury that is in contrast with adoptive transfer of splenocytes from normal mice where postischemic injury was reconstituted. HSP 70 induction in splenocytes was accompanied by expansion of splenic Tregs and it was associated with markedly reduced kidney injury and inflammation upon subsequent I/R injury. While depleting Tregs before HP abolish the renoprotective effect (Tregdep+HP+I/R), adoptive transfer of these cells back into Treg-depleted mice partially restored the beneficial effect of HP (Tregdep+Tregadop tranf+HP+I/R). Significantly increased Foxp3 gene expression as well as increased infiltration of these cells into kidney were also observed in heat preconditioned ischemic kidneys. To gain better insight about the direct causal relationship between HSP70 and Tregs in I/R injury, quercetin was administered before HP. Inhibition of HSP 70 by quercetin suppressed the expansion of Tregs and this was associated with partial loss of beneficial effect of HP in I/R injury (Q+HS+I/R). These results can suggest that renoprotective effect of HSP 70 might be partially mediated by their immune modulatory effect through Tregs. Further understanding of cytoprotective or immune modulatory mechanisms of various stress proteins might facilitate discovery of new targets or drug development in the prevention or treatment of AKI.

Key Words: 허혈/재관류, HSP70, 조절 T 임파구
Ischemia/reperfusion, HSP70, Tregs