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Metformin improves dysfunction of mesenchymal stem cells associated with chronic kidney disease via senescence inhibition

Hyun jin Noh[1], Mi Ra Yu[2], Hyoungnae Kim[1], Soon Hyo Kwon[1], Jin Seok Jeon[1], Dong Cheol Han[1]
[1]Department of Nephrology, Soon Chun Hyang University Seoul Hospital, Korea, Republic of
[2]Department of Hyonam Kidney Laboratory, Soon Chun Hyang University Seoul Hospital, Korea, Republic of

Objectives: Mesenchymal stem cells (MSC) are promising source of cell-based regenerative therapy. In patients with chronic kidney disease (CKD) who may need kidney transplantation in the future, autologous cell transplantation is preferred over allogenic transplantation since the latter may increase the risk of allosensitization. Therefore, adequate cell functionality of endogenous MSC is a critical factor for the success of cell therapies in CKD patients.

Methods: We investigated the effects of metformin on CKD-associated cellular senescence using MSC isolated from sham operated and subtotal nephrectomized mice and further explored the protective role of metformin-treated CKD MSC in renal progression. The clinical significance was examined using adipose-tissue derived MSC (ADMSC) from healthy subjects and CKD patients.

Results: When compared to normal MSC, CKD MSC displayed reduced proliferation and early senescence as determined by cell morphology, increased oxidative stress, accumulation of DNA damage response marker p53 binding protein 1 (53BP1), phospho p53, $p16^{INK4a}$, and β-gal expression, and decreased cyclin-dependent kinase 4 (CDK4) and cyclin D. CKD MSC exhibited activation of NFκB resulting in expression of senescence-associated secretory phenotype (SASP) factors compared to normal MSC. All of these changes were significantly prevented by metformin treatment. In vivo, metformin-treated CKD MSC attenuated inflammation and fibrosis in UUO kidney and adenine diet-induced CKD model as compared to CKD MSC. Co-culture of LPS or TGF-β1-treated HK2 cells with metformin-treated CKD MSC markedly decreased LPS or TGF-β1-induced tubular expression of proinflammatory markers and fibrogenesis when compared to CKD MSC suggesting paracrine action of CKD MSC enhanced by metformin. Finally, we confirmed CKD-associated cellular senescence in patient-derived ADMSC compared to control subjects which was partially rescued by metformin treatment. A significant correlation was found between NF-κB activity and creatinine or cystatin C-based eGFR in human ADMSC.

Conclusions: Our data suggest that metformin inhibits cellular senescence of CKD MSC and improves their renoprotective effects.