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Resveratrol effectively suppress CD4+ T cell related allo-immune responses by modulation of AMPK/mTOR pathway

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Background: The aim of this study is to investigate the effect of resveratrol on effector T cell under tacrolimus (Tac)-based immune suppression.

Methods: First, we investigated the suppressive effect of resveratrol on T cell proliferation or T-cell associated cytokine level upon T-cell specific stimulation. Second, we determined the protective effect of resveratrol on the inflammation of human primary tubular epithelial cells (HPRTEpiC) induced by inflammatory cytokine or activated T cells and also investigated the suppressive effect on the proliferation of T cells after co-culture with HPRTEpiC. Third, we investigated the pathway of the protective action of resveratrol on T cell or HPRTEpiC. Lastly, we investigated whether addition of resveratrol to tacrolimus can protect allograft tissue by suppression of effector $CD4^+$ T cell in mice skin allograft model.

Results: In T cell experiment using PBMCs isolated from healthy volunteers, addition of resveratrol to Tac suppressed all effector T cell subset and also significantly decrease T cell associated inflammatory cytokine level and also mRNA expression. Next, treatment with inflammatory cytokine or co-culture with activated T cells significantly induced secretion of IL-6 and IL-8 from HPRTEpiC and, addition of resveratrol considerably reduces those cytokines. Third, T cell showed significantly proliferation after co-culture with HPRTEpiC, but addition of resveratrol significantly suppressed it. Those protective effects of resveratrol were mediated by the augmentation of AMPK and reciprocal suppression of mTOR both in T cells and HPRTEpiC. In vivo experiment, addition of resveratrol combined with Tacrolimus significantly prolonged the skin graft survival with the suppression of Th1 and Th17 cells.

Conclusion: The results of this study suggests that addition of resveratrol to Tac is beneficial in terms of the regulation of effector T cells; hence it could be proposed as strategy to compensate immune suppressive effect of tacrolimus.

Keywords: AMPK, Kidney Transplantation, mTOR, Resveratrol, Th17