TARP-induced Protease Activated Receptor 1 Expression and Rab11 with its Effector Rip11 in Hypoxic Cardiomyocytes

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May 5, 2020

Abstract

Background: PAR1 activation plays an important role in acute myocardial infarction, but the mechanism underlying the PAR1 expression under hypoxia is not clear. Method and Result: Cardiomyocytes from neonatal rats, cultured in hypoxic conditions, showed decreased PAR1 expression. The introduction of TRAP rescued the loss of PAR1 expression within 1 h of treatment. However, PAR1 expression was not affected by PAR1 activation, under normoxic condition. We detected mRNA expressions of Rab11A, Rab11B, FIP2, FIP3,and Rip11 but no Rab25, FIP1 and FIP4 in cardiomyocytes. Rab11A protein levels increased and reached the peak during the first 4h of hypoxia (4h: 179.93% ± 9.82% of control, control = normoxic group, n=5, $P<0.05$) and thereafter decreased; however, Rab11B protein decreased. Addition of TRAP caused 15,87 folds decrease in hypoxia-induced Rab11A expression, but 8.96 folds increase in hypoxia-decreased Rab11B expression after 4 h of hypoxia. Knockdown (with siRNA) of Rab11B, but not Rab11A, caused decreased PAR1 expression. Knockdown of Rip11 significantly inhibited the TRAP-rescued-PAR1 expression in cardiomyocytes during hypoxia. Rip11 levels decreased during hypoxia. The ratio of phosphorylated vs. non-phosphorylated Rip11 in TRAP-treated group and pervanadate-treated group showed 2 folds and 7 folds of that in vehicle group, respectively ($P<0.05$,n = 5). HIF-1α knockdown (with siRNA) inhibited TRAP-rescued-PAR1 expression and Rip11 expression in hopxia cardiomyocytes. Conclusion: PAR1 activation reverses hypoxia-inhibited PAR1 expression through inhibiting Rab11A,enhancing Rab11B expression and phosphorylated HIF-1α-induced-Rip11 in cardiomyocytes during hypoxia.

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