Epac-1/Rap-1 signaling pathway orchestrates the reno-therapeutic effect of ticagrelor against renal ischemia/reperfusion model

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Abstract

Despite the renal expression of P2Y12, the purinergic receptor for adenosine diphosphate, few data are available to discuss the renotherapeutic potential of ticagrelor, one of its reversible blockers. Indeed, the tonic inhibitory effect of this receptor has been linked to the activation of exchange protein activated by cyclic adenosine monophosphate-1 (Epac-1) protein through the cyclic adenosine monophosphate cascade. Epac-1 is considered a crossroad protein, where its activation has been documented to manage renal injury models. Hence, the current study aimed to investigate the possible therapeutic effectiveness of ticagrelor, against renal ischemia/reperfusion (I/R) model with emphasis on the involvement of Epac-1 signaling pathway using R-CE3F4, a selective Epac-1 blocker. Accordingly, rats were randomized into four groups; viz., sham-operated, renal I/R, I/R post-treated with ticagrelor for 3 days, and ticagrelor + R-CE3F4. Treatment with ticagrelor ameliorated the I/R-mediated structural alterations and improved renal function manifested by the reduction in serum BUN and creatinine. On the molecular level, ticagrelor enhanced renal Epac-1 mRNA expression, Rap-1 activation (Rap-1-GTP) and SOCS-3 level. On the contrary, it inhibited the protein expression of JAK-2/STAT-3 hub, TNF-Ŭ and MDA contents, as well as caspase-3 activity. Additionally, ticagrelor enhanced the protein expression/content of AKT/Nrf-2/HO-1 axis. All these beneficial effects were obviously antagonized upon using R-CE3F4. In conclusion, ticagrelor reno-therapeutic effect is partly mediated through modulating the Epac-1/Rap-1-GTP, AKT/Nrf-2/HO-1 and JAK-2/STAT-3/SOCS-3 trajectories, pathways that integrate to afford novel explanations to its anti-inflammatory, anti-oxidant, and anti-apoptotic potentials.

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