

# Activated ROCK/Akt/eNOS and ET-1/ERK pathways in 5-fluorouracil-induced cardiotoxicity: modulation by simvastatin

Hanan Salah ,Radwa Nasser Muhammad, Nada Sallam

## Abstract

5-Fluorouracil (5-FU) is used in the treatment of different solid tumors; however, its use is associated with rare, but serious cardiotoxicity. Nevertheless, the involvement of ROCK/NF- $\kappa$ B, Akt/eNOS and ET-1/ERK1/2 trajectories in the cardiotoxic effect and in the potential cardioprotective upshot of simvastatin has been elusive. Male Wistar rats were allocated into 5-FU (50 mg/kg/week; i.p, 6 weeks), simvastatin (15 mg/kg/day; p.o, 8 weeks) treated groups and simvastatin + 5-FU, besides the normal control group. 5-FU-induced cardiotoxicity boosted the serum level of N-terminal pro-brain (B-type) natriuretic peptide (NT-proBNP), aortic contents of endothelin (ET)-1 and thromboxane (TX) A<sub>2</sub>, as well as cardiac contents of NADPH oxidases (Nox), cyclooxygenase (COX)-2, malondialdehyde (MDA), phosphorylated Akt (p-Akt), phosphorylated extracellular signal-regulated kinase (p-ERK)1/2 and the protein expressions of rho-kinase (ROCK) and caspase-3. On the other hand, it suppressed cardiac reduced glutathione (GSH) and phosphorylated endothelial nitric oxide synthase (p-eNOS). Contrariwise, co-administration with simvastatin overcame these disturbed events and modulated the ROCK/NF- $\kappa$ B, Akt/eNOS and ET-1/ERK1/2 signaling pathways. This study highlights other mechanisms than coronary artery spasm in the 5-FU cardiotoxicity and reveals that NT-proBNP is a potential early marker in this case. Moreover, the cross-talk between ROCK/NF- $\kappa$ B, ROS/COX-2/TXA<sub>2</sub>, Akt/eNOS and ET-1/ERK1/2 pathways contributes via different means to upsetting the vasoconstriction/vasodilatation equilibrium as well as endothelial cell function and finally leads to cardiomyocyte stress and death-the modulation of these trajectories offers simvastatin its potential cardio-protection against 5-FU.

*Scientific Reports* 2020, September