The interrupted cross-talk of inflammatory and oxidative stress trajectories signifies the effect of artesunate against hepatic ischemia/reperfusion-induced inflammasomopathy

Hanan Salah ,Mai El-Sayed Ghoneim, Dalaal M Abdallah, Abdelhadi Mohamed Shebl

Abstract

The antimalarial drug artesunate (Art) has proven its beneficial effects against ischemia/reperfusion (I/R) injury in diverse organs, but its potential role against hepatic I/R is still obscure. This study, hence, examined whether treatment with Art alone or in combination with rapamycin (Rapa), an mTOR inhibitor, can ameliorate hepatic I/R injury via targeting the NLRP3 inflammasome signaling pathway. Rats were divided into hepatic sham- and I/R-operated rats. The latter were either left untreated (I/R group) or treated with Art, Rapa, or their combination. On the molecular level, all treatment regimens succeeded to hinder inflammasome assembly and activation, assessed as NLRP3, ASC, cleaved caspase-1, caspase-11, N-terminal cleaved gasdermin-D (GSDMD-N), IL-1ϐ, and IL-18. This effect was associated by the inhibition in the harmful signaling pathways HMGB1/RAGE and TLR4/MyD88/TRAF6 to inactivate the transcription factor NF-əB and the production of its pro-inflammatory cytokines IL-1ϐ, IL-18, IL-6, and TNF-Ŭ. Additionally, this effect entailed the inhibition of ICAM-1/MPO/ROS cascade, which in turn hampered cell demise induced by apoptosis, manifested as correction of the imbalanced Bcl2/Bax, as well as pyroptosis (LDH, cleaved caspase-1, caspase-11, GSDMD-N, IL-1ϐ, and IL-18), and necrosis. The corrected pathways were reflected on the improved liver function (serum ALT, AST, and LDH) and microscopical hepatic architecture. Noteworthy, the effect of Art on all parameters exceeded significantly that of Rapa and even improved the effect of the latter in the combination group. In conclusion, our results suggest novel roles for Art in abating functional and structural I/R-induced hepatic abnormalities via several traversing cross-talking pathways that succeeded to abate NLRP3 inflammasome and cell death.

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