Artesunate activates mitochondrial apoptosis in breast cancer cells via iron-catalyzed lysosomal reactive oxygen species production

In this study, the semisynthetic artemisinin-derivative artesunate (ART) was shown to induce ROS production and cell death in MCF-7 breast cancer cells. ART impacted the endo-lysosomal compartment, causing perinuclear clustering of endosomes and lysosomes. ART induced cytochrome $c$ release from mitochondria, a parameter that indicates mitochondrial outer membrane permeabilization (MOMP) and is a key event of mitochondrial apoptosis. Lysosomal iron chelation blocked all measured parameters of ART-induced PCD, whereas lysosomal iron loading enhanced cell death, thus identifying lysosomal iron as the lethal source of ROS upstream of MOMP. To assess a potential role of LMP in ART signaling, the impact of ART on the BH3-only protein Bid and the contribution of cathepsins to ART-induced cell death were determined. ART did not activate Bid and cathepsin inhibitors did not inhibit ART-induced cell death. Thus, LMP was not a component of ART signaling in MCF-7 cells. Yet, ART enhanced tumor necrosis factor alpha (TNF)-mediated Bid cleavage. Combined treatment of MCF-7 cells with ART and TNF resulted in potent enhancement of cell death. This may contribute to ART in vivo toxicity towards breast cancer cells, as TNF is expressed at higher levels in breast cancer than in benign breast tissue.

The results suggest that ART triggers mitochondrial apoptosis with hierarchical signaling from lysosomes to mitochondria. As LMP was not involved, ART-induced lysosomal cell death is mechanistically distinct from previous reports of lysosome-to-mitochondria apoptotic signaling.

Artemisinins are selectively toxic towards cancer cells in vitro and in vivo. Selective toxicity of artemisinins could be enabled by higher expression of transferrin receptors and higher iron content in cancerous tissue and increased susceptibility of cancer cells towards ROS. The results of this study suggest a potential clinical use of artemisinins for targeting cancer-specifically altered highly acidic iron-rich lysosomes.

Artemisinins have an excellent safety record in malaria treatment. Yet, safety of artemisinins in cancer treatment needs to be carefully re-evaluated. This work discusses implications of the presented insights into ART-induced PCD in cancer cells for the rational design of in vivo studies. Off-label use of artemisinin...
antimalarials for the treatment of cancer should not be considered outside of clinical trials.