Cellular Physiology and Biochemistry

Cell Physiol Biochem 2014;34:2232-2244
DOI: 10.1159/000369666
Published online: December 08, 2014
Accepted: November 06, 2014

1421-9778/14/0346-2232$39.50/0

Original Paper

Stimulation of Suicidal Erythrocyte Death by Artesunate

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Key Words
Phosphatidylserine • Artesunate • Calcium • Ceramide • ROS • Eryptosis

Abstract
Background: The artemisinin derivative artesunate is effective in the treatment of severe malaria and is considered for the treatment of malignancy. Artesunate triggers tumor cell apoptosis, an effect at least in part mediated by mitochondria. Even though lacking mitochondria, erythrocytes may similarly enter suicidal death or eryptosis, which is characterized by cell shrinkage and breakdown of the phospholipid asymmetry of the cell membrane with phosphatidylserine translocation to the erythrocyte surface. Triggers of eryptosis include increase of cytosolic Ca^{2+}-activity ($[Ca^{2+}]_i$), ceramide formation, and oxidative stress. The present study explored whether artesunate stimulates eryptosis. ***Methods:*** Phosphatidylserine exposure at the cell surface was estimated from annexin V binding, cell volume from forward scatter, $[Ca^{2+}]_i$ from Fluo3-fluorescence, ceramide abundance from binding of specific antibodies, and oxidative stress from 2′,7′-dichlorodihydrofluorescein-diacetate fluorescence. ***Results:*** A 48 h exposure of human erythrocytes to artesunate significantly increased the percentage of annexin-V-binding cells (≥ 9 µg/ml) without significantly influencing forward scatter. Artesunate significantly increased $[Ca^{2+}]_i$. The stimulation of annexin-V-binding by artesunate (15 µg/ml) was significantly blunted but not abolished by removal of extracellular Ca^{2+}. Artesunate increased the ceramide abundance at the cell surface and the 2′,7′-dichlorodihydrofluorescein-diacetate fluorescence. ***Conclusions:*** Artesunate stimulates phosphatidylserine translocation at the erythrocyte cell membrane, an effect at least partially due to increase of $[Ca^{2+}]_i$, stimulation of ceramide formation and generation of oxidative stress.

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Introduction

Artesunate is a first line treatment for severe malaria [1-10]. Artesunate may be effective against further pathogens including viruses [11]. Beyond that, artesunate is considered for the treatment of malignancy [12-27]. Its efficacy in malignancy may at least in part result from its ability to induce tumor cell apoptosis [13, 14, 23, 25, 26, 28-31]. The proapoptotic effect has been attributed in part to mitochondria [23, 25, 29]. Artemisinin, an antimalarial drug related to artesunate, has previously been reported to inhibit erythrocyte cation channels [32].

Even though lacking nuclei and mitochondria, key organelles in the execution of apoptosis, erythrocytes may enter eryptosis, a suicidal cell death characterized by cell shrinkage [33] and cell membrane scrambling with exposure of phosphatidylserine at the cell surface [34]. Triggers of eryptosis may include increase of cytosolic Ca^{2+} activity ($[Ca^{2+}]_i$) [34], formation of ceramide [35], energy depletion [34], activated caspases [36-40], activation of casein kinase 1α [41, 42], Janus-activated kinase JAK3 [43], protein kinase C [44], or p38 kinase [45], as well as impaired activity of AMP activated kinase AMPK [46], cGMP-dependent protein kinase [37], PAK2 kinase [47], sorafenib sensitive kinases [48], and sunitinib sensitive kinases [49]. Moreover, eryptosis is stimulated by a wide variety of xenobiotics [35, 49-79] including several natural substances [34] including gambogic acid [80], tannic acid [81], ipratropium [82], withaferin [83], tanshinone [58], thymoquinone [84], ursolic acid [85], honokiol [86], saponin [87], apigenin [88], oridonin [89], and alpha-lipoic acid [36].

The present study explored, whether artesunate stimulates eryptosis. To this end, human erythrocytes from healthy individuals were treated with artesunate and phosphatidylserine surface abundance, cell volume, $[Ca^{2+}]_i$, ceramide abundance and reactive oxygen species (ROS) determined by flow cytometry.

Materials and Methods

Erythrocytes, solutions and chemicals

Fresh Lithium-Heparin-anticoagulated blood samples were kindly provided by the blood bank of the University of Tübingen. The study is approved by the ethics committee of the University of Tübingen (184/2003 V). The blood was centrifuged at 120 rcf for 20 min at 23°C and the platelets and leukocytes-containing supernatant was disposed. Erythrocytes were incubated *in vitro* at a hematocrit of 0.4% in Ringer solution containing (in mM) 125 NaCl, 5 KCl, 1 $MgSO_4$, 32 N-2-hydroxyethylpiperazine-N-2-ethanesulfonic acid (HEPES), 5 glucose, 1 $CaCl_2$; pH 7.4 at 37°C for 48 h. Where indicated, erythrocytes were exposed to artesunate (Sigma Aldrich, Schnelldorf, Germany) at the indicated concentrations. Stock solutions of 100 mg/ml artesunate dissolved in DMSO were used. For comparison, the effect of DMSO similar to the highest quantity added from the stock solution was tested (0.35 µl DMSO /ml Ringer in fig.1, 2 and 0.15 µl DMSO/ml Ringer in Fig. 3).

Analysis of annexin-V-binding and forward scatter

After incubation under the respective experimental condition, 50 µl cell suspension was washed in Ringer solution containing 5 mM $CaCl_2$ and then stained with Annexin-V-FITC (1:200 dilution; ImmunoTools, Friesoythe, Germany) in this solution at 37°C for 20 min under protection from light. In the following, the forward scatter (FSC) of the cells was determined, and annexin-V-FITC fluorescence intensity was measured with an excitation wavelength of 488 nm and an emission wavelength of 530 nm on a FACS Calibur (BD, Heidelberg, Germany).

Measurement of intracellular Ca^{2+}

After incubation, erythrocytes were washed in Ringer solution and then loaded with Fluo-3/AM (Biotium, Hayward, USA) in Ringer solution containing 5 mM $CaCl_2$ and 5 µM Fluo-3/AM. The cells were incubated at 37°C for 30 min and washed twice in Ringer solution containing 5 mM $CaCl_2$. The Fluo-3/AM-loaded erythrocytes were resuspended in 200 µl Ringer. Then, Ca^{2+}-dependent fluorescence intensity

was measured with an excitation wavelength of 488 nm and an emission wavelength of 530 nm on a FACS Calibur.

Determination of ceramide formation

To determine ceramide abundance, a monoclonal antibody-based assay was used. After incubation, cells were stained for 1 h at 37°C with 1µg/ml anti-ceramide antibody (clone MID 15B4; Alexis, Grünberg, Germany) in phosphate-buffered saline (PBS) containing 0.1 % bovine serum albumin (BSA) at a dilution of 1:10. After two washing steps with PBS-BSA, cells were stained for 30 min with polyclonal fluorescein-isothiocyanate (FITC)-conjugated goat anti-mouse IgG and IgM specific antibody (Pharmingen, Hamburg, Germany) diluted 1:50 in PBS-BSA. Unbound secondary antibody was removed by repeated washing with PBS-BSA. Samples were then analyzed by flow cytometric analysis at an excitation wavelength of 488 nm and an emission wavelength of 530 nm.

Determination of reactive oxygen species (ROS)

ROS production was determined utilizing 2′,7′-dichlorodihydrofluorescein diacetate (DCFDA) [90]. Briefly, the cells were suspended in FACS buffer and the fluorescence was analysed with flow cytometry (FACS-calibur from Becton Dickinson; Heidelberg, Germany). DCFDA fluorescence intensity was measured in FL-1 with an excitation wavelength of 488 nm and an emission wavelength of 530 nm.

Statistics

Data are expressed as arithmetic means ± SEM. As indicated in the figure legends, statistical analysis was made using ANOVA with Tukey's test as post-test and *t* test as appropriate; n denotes the number of different erythrocyte specimens studied. Since different erythrocyte specimens used in distinct experiments are differently susceptible to triggers of eryptosis, the same erythrocyte specimens have been used for control and experimental conditions.

Results

The present study was designed to possibly disclose an effect of artesunate on eryptosis, the suicidal erythrocyte death. A hallmark of eryptosis is cell membrane scrambling with phosphatidylserine translocation to the cell surface.

Binding of labeled Annexin-V was determined utilizing flow cytometry in order to identify phosphatidylserine exposing erythrocytes. The erythrocytes were incubated for 48 hours in Ringer solution without or with artesunate (3 – 35 µg/ml) prior to the

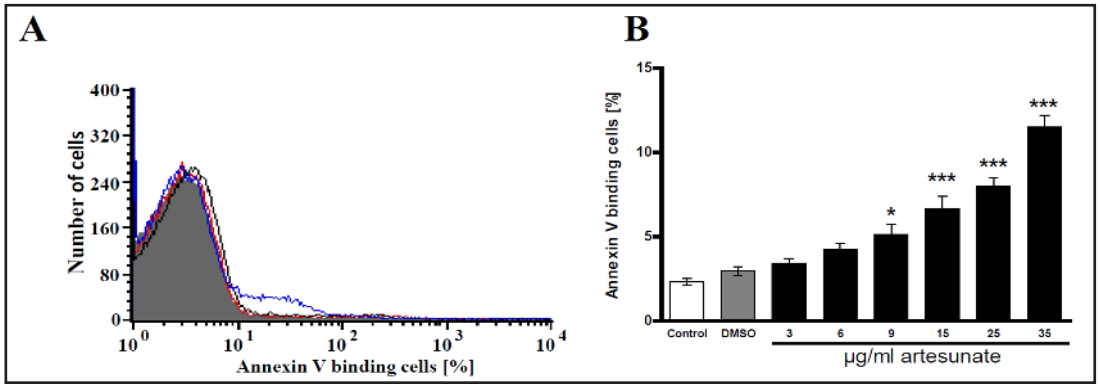

Fig. 1. Effect of artesunate on phosphatidylserine exposure. A. Original histogram of annexin-V-binding of erythrocytes following exposure for 48 h to Ringer solution without (grey area) and with (red, black, blue line) presence of 6, 15, 35 µg/ml artesunate respectively. B. Arithmetic means ± SEM of erythrocyte annexin-V-binding (n = 16) following incubation for 48 h to Ringer solution without (white bar) or with (black bars) presence of artesunate (3 - 35 µg/ml). For comparison, the effect of 0.35 µl DMSO/ml Ringer is shown (grey bar). *($p<0.05$), ***($p<0.001$) indicate significant difference from DMSO alone (ANOVA).

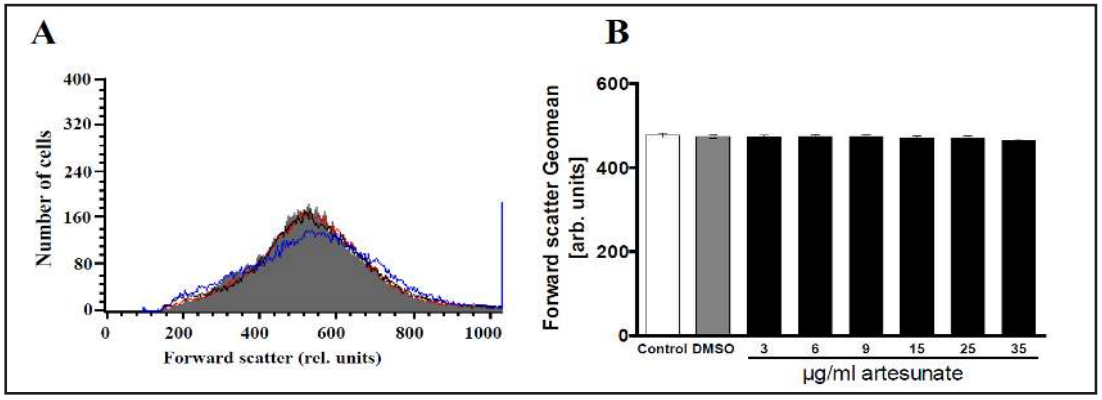

Fig. 2. Effect of artesunate on erythrocyte forward scatter. A. Original histogram of forward scatter of erythrocytes following exposure for 48 h to Ringer solution without (grey area) and with (red, black, blue line) presence of 6, 15, 35 µg/ml artesunate respectively. B. Arithmetic means ± SEM (n = 16) of the normalized erythrocyte forward scatter (FSC) following incubation for 48 h to Ringer solution without (white bar) or with (black bars) presence of artesunate (3 - 35 µg/ml). For comparison, the effect of 0.35 µl DMSO/ml Ringer is shown (grey bar).

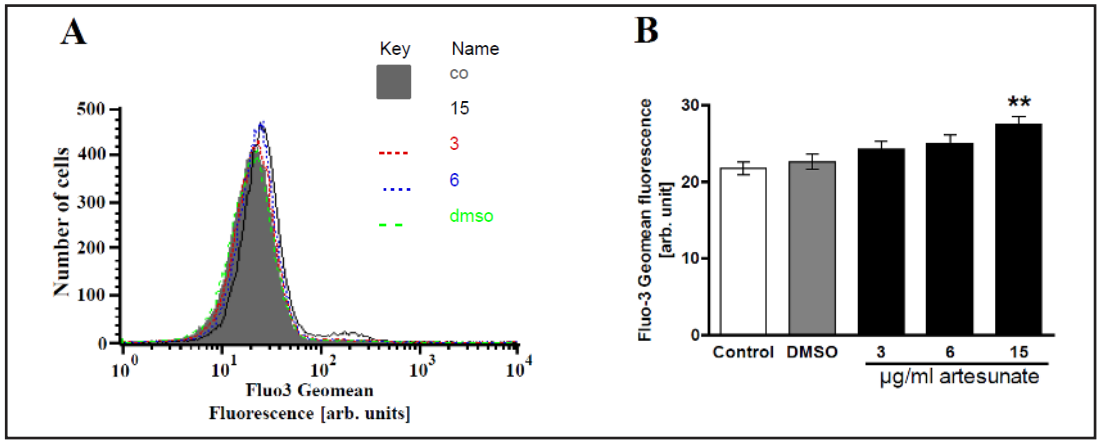

Fig. 3. Effect of artesunate on erythrocyte Ca^{2+} activity. A. Original histogram of Fluo3 fluorescence in erythrocytes following exposure for 48 h to Ringer solution without DMSO and artesunate (grey area), with DMSO (green line) and with presence of 3, 6, 15 µg/ml artesunate (red, blue, black line). B. Arithmetic means ± SEM (n = 16) of the Fluo3 fluorescence (arbitrary units) in erythrocytes exposed for 48 h to Ringer solution without (white bar) or with (black bars) presence of artesunate (3 - 15 µg/ml). For comparison, the effect of 0.15 µl DMSO/ml Ringer is shown (grey bar). ** ($p<0.01$) indicate significant difference from DMSO alone.

measurements. As illustrated in Fig. 1, a 48 h exposure to artesunate enhanced the percentage of annexin-V-binding erythrocytes, an effect reaching statistical significance at 9 µg/ml artesunate concentration. Accordingly, artesunate treatment was followed by erythrocyte cell membrane scrambling with translocation of phosphatidylserine to the cell surface.

Alterations of cell volume were estimated from forward scatter in flow cytometry. Forward scatter was determined following a 48 hours incubation of human erythrocytes in Ringer solution without or with artesunate (3 – 35 µg/ml). As shown in Fig. 2, forward scatter tended to decrease following incubation of human erythrocytes in Ringer solution with artesunate, an effect, however, not reaching statistical significance.

In order to test whether artesunate affected cytosolic Ca^{2+} activity ($[Ca^{2+}]_i$), Fluo3 fluorescence was determined in flow cytometry. As illustrated in Fig. 3, a 48 h exposure to artesunate (3 – 15 µg/ml) increased Fluo3 fluorescence, an effect reaching statistical significance at 15 µg/ml artesunate concentration. Thus, artesunate increased $[Ca^{2+}]_i$.

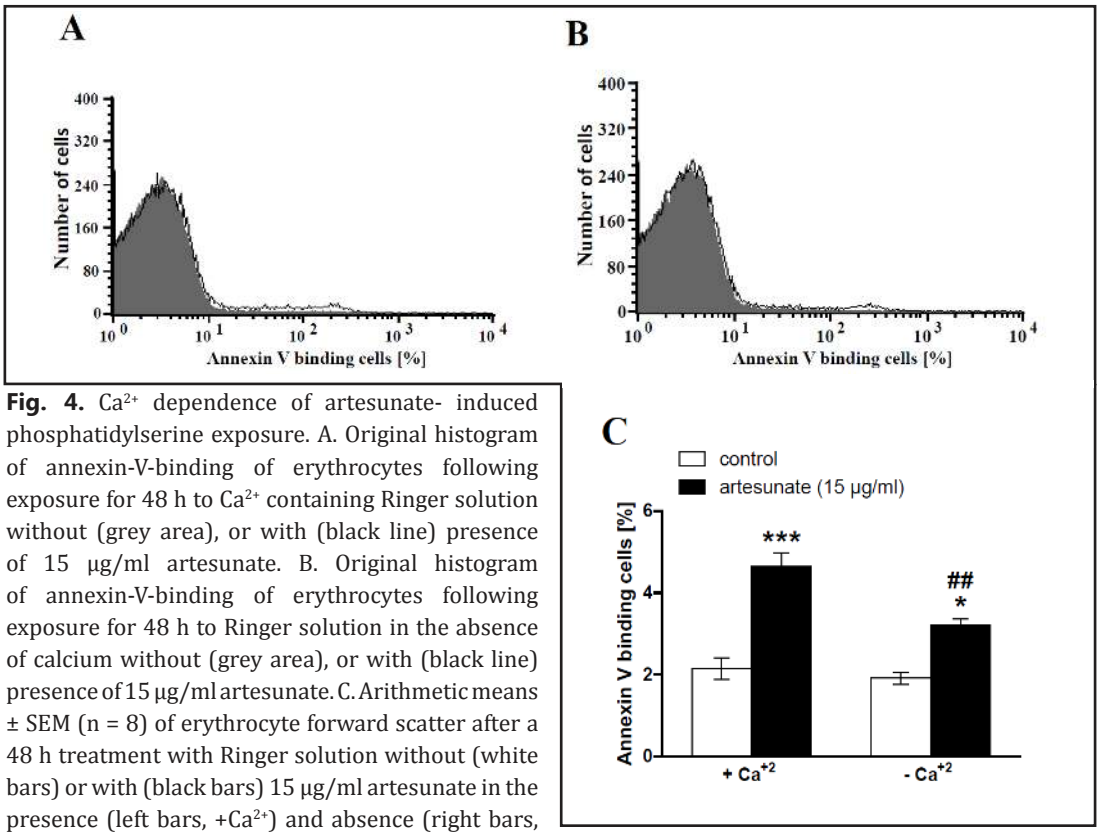

Fig. 4. Ca^{2+} dependence of artesunate- induced phosphatidylserine exposure. A. Original histogram of annexin-V-binding of erythrocytes following exposure for 48 h to Ca^{2+} containing Ringer solution without (grey area), or with (black line) presence of 15 µg/ml artesunate. B. Original histogram of annexin-V-binding of erythrocytes following exposure for 48 h to Ringer solution in the absence of calcium without (grey area), or with (black line) presence of 15 µg/ml artesunate. C. Arithmetic means ± SEM (n = 8) of erythrocyte forward scatter after a 48 h treatment with Ringer solution without (white bars) or with (black bars) 15 µg/ml artesunate in the presence (left bars, $+Ca^{2+}$) and absence (right bars, $-Ca^{2+}$) of calcium. *($p<0.05$), *** ($p<0.001$) indicates significant difference from the absence of artesunate, ## ($p<0.01$) indicates significant difference from the respective value in the presence of Ca^{2+}.

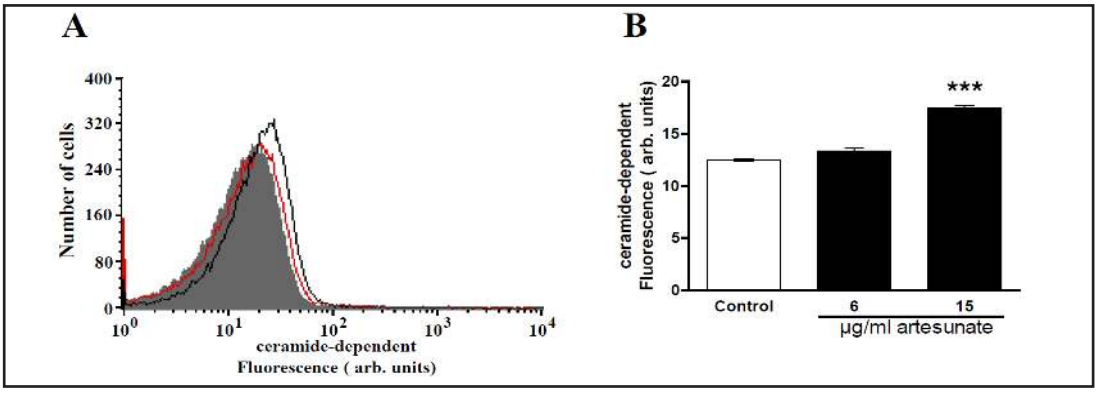

Fig. 5. Effect of artesunate on ceramide formation. A. Original histogram of ceramide surface abundance of erythrocytes following exposure for 48 h to Ringer solution without (grey shadow) and with (red, black line) presence of 6 or 15 µg/ml artesunate, respectively. B. Arithmetic means ± SEM (n= 6) of ceramide abundance after a 48 h incubation in Ringer solution without (white bar) or with 15 µg/ml artesunate (black bar). *($p<0.05$) indicates significant difference from the absence of artesunate (*t* test).

Additional experiments tested whether the artesunate-induced cell membrane scrambling required entry of extracellular Ca^{2+}. To this end, erythrocytes were exposed for 48 h to 15 µg/ml artesunate in the presence or nominal absence of extracellular Ca^{2+}. As illustrated in Fig. 4, removal of extracellular Ca^{2+} significantly blunted the increase of annexin-V-binding following artesunate treatment. However, even in the absence of extracellular

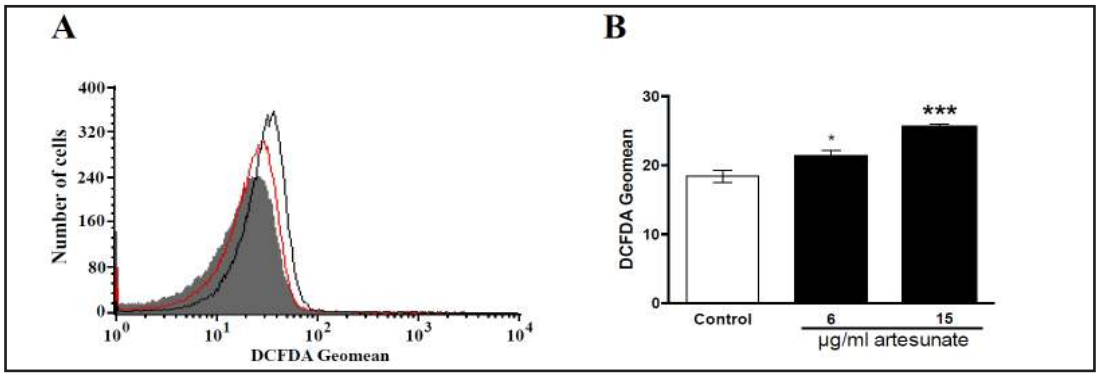

Fig. 6. Effect of artesunate on reactive oxygen species. A. Original histogram of 2′,7′-dichlorodihydrofluorescein diacetate (DCFDA) fluorescence in erythrocytes following exposure for 48 hours to Ringer solution without (grey shadow) and with (red, black line) presence of 6 or 15 µg/ml artesunate respectively. B. Arithmetic means ± SEM (n =6) of erythrocyte DCFDA fluorescence following incubation for 48 hours to Ringer solution without (white bar) or with (black bar) presence of artesunate (6 or 15 µg/ml). *** ($p<0.001$) indicates significant difference from the absence of artesunate (paired *t*-test).

Ca^{2+} artesunate significantly increased the percentage of annexin-V-binding erythrocytes. Thus, the effect of artesunate on phosphatidylserine translocation was partially but not fully dependent on entry of extracellular Ca^{2+}.

In order to test, whether artesunate-induced cell membrane scrambling was paralleled by formation of ceramide, which could trigger eryptosis without requirement of increased $[Ca^{2+}]_i$, the ceramide abundance at the erythrocyte surface was determined utilizing a specific anti-ceramide antibody. As illustrated in Fig. 5, a 48 h exposure of erythrocytes to 15 µg/ml artesunate significantly increased the abundance of ceramide at the erythrocyte surface.

Additional experiments were performed to explore whether artesunate modified the formation of reactive oxygen species (ROS). To this end, ROS was determined utilizing 2′,7′-dichlorodihydrofluorescein diacetate (DCFDA). As shown in Fig. 6, a 48 hours exposure to artesunate (≥ 6 µg/ml) significantly increased the DCFDA fluorescence, indicating that artesunate triggered oxidative stress.

Discussion

The present study discloses a novel effect of artesunate. The observations reveal that treatment of erythrocytes with artesunate leads to cell membrane scrambling with phosphatidylserine translocation to the erythrocyte surface. Phosphatidylserine exposure at the cell surface is the most important hallmark of eryptosis, the suicidal death of erythrocytes. The artesunate concentration (9 µg/ml) required for the stimulation of erythrocyte cell membrane scrambling was in the range of those approached *in vivo* [91].

The cell membrane scrambling following artesunate treatment is paralleled and partially caused by increase of $[Ca^{2+}]_i$. However, the increase of $[Ca^{2+}]_i$ does not fully account for the stimulation of eryptosis by artesunate, but artesunate triggered phosphatidylserine exposure even in the absence of extracellular Ca^{2+}. Besides its effect on $[Ca^{2+}]_i$, artesunate stimulated the formation of ceramide and induced oxidative stress. Ceramide and oxidative stress are both powerful stimulators of eryptosis [34]. Artesunate has previously been shown to induce oxidative stress [92, 93] and the proapoptotic effect of artesunate is inhibited by the antioxidant N-acetyl-cysteine [94]. To the best of our knowledge, a stimulating effect of artesunate on ceramide formation has never been shown before.

Artesunate tended to decrease cell volume, an effect, however, not reaching statistical significance. Eryptotic cell shrinkage may result from increase of $[Ca^{2+}]_i$ with subsequent

activation of Ca^{2+} sensitive K^+ channels, K^+ exit, cell membrane hyperpolarization, Cl^- exit and thus cellular loss of KCl with osmotically obliged water [33].

The physiological function of phosphatidylserine exposure at the erythrocyte surface is to trigger the elimination of defective erythrocytes and thus to protect against hemolysis [34]. Hemolysis of defective erythrocytes results in release of hemoglobin, which may be subsequently filtered at the renal glomeruli, precipitate in the acidic lumen of renal tubules and thus occlude the nephrons [95].

Eryptosis may further foster the removal of infected erythrocytes in malaria [96]. The malaria pathogen *Plasmodium* enters erythrocytes and induces oxidative stress on the host cell leading to activation of several ion channels of the host cell membrane including Ca^{2+}-permeable erythrocyte cation channels [97, 98]. Ca^{2+} entry through the unselective cation channels triggers eryptosis leading to clearance of the infected erythrocytes from circulating blood [96]. Thus, eryptosis of infected erythrocytes counteracts parasitemia and may thus favourably influence the clinical course of malaria [96]. Along those lines, several genetic erythrocyte disorders including sickle-cell trait, beta-thalassemia-trait, homozygous Hb-C and homozygous G6PD-deficiency foster eryptosis and thus protect against a severe course of malaria [34, 99-101]. The same holds for clinical conditions with accelerated eryptosis, such as iron deficiency [102]. Moreover, several xenobiotics triggering eryptosis including lead [103], chlorpromazine [104] or NO synthase inhibitors [105] have previously been shown to favourably influence the clinical course of murine malaria. At least in theory, the favourable effect of artesunate on the clinical course of malaria [1-10] may thus in part result from stimulation of eryptosis.

Excessive eryptosis may, however, lead to anemia due to phagocytosis and subsequent removal of phosphatidylserine exposing erythrocytes. Anemia may be prevented as long as accelerated clearance of erythrocytes during stimulated eryptosis is outweighed by similarly increased formation of new erythrocytes [34]. Phosphatidylserine exposing erythrocytes may further bind to CXCL16/SR-PSO expressed by endothelial cells in the vascular wall [106] and may further stimulate blood clotting and thrombosis [107-109]. Accordingly, phosphatidylserine exposing erythrocytes may impair microcirculation [35, 107, 110-113]. The proeryptotic effect of artesunate may be particularly strong in clinical disorders with accelerated eryptosis, such as sepsis [114], fever [115], malaria [103, 104, 116], sickle cell disease [117], thalassemia [118, 119], Wilson's disease [120], iron deficiency [121] hepatic failure [122], malignancy [123], metabolic syndrome [124], diabetes [40, 125], dehydration [70], renal insufficiency [126], hemolytic uremic syndrome [127], hyperphosphatemia [79] and phosphate depletion [128]. Under those conditions the use of artesunate may be contraindicated.

Conclusion

Artesunate stimulates erythrocyte cell membrane scrambling, an effect at least partially due to increase of cytosolic Ca^{2+} activity, ceramide formation and oxidative stress.

Disclosure Statement

The authors of this manuscript state that they do not have any conflict of interests and nothing to disclose.

Acknowledgements

The authors acknowledge the meticulous preparation of the manuscript by Tanja Loch. The study was supported by the Deutsche Forschungsgemeinschaft and the Open Access Publishing Fund of Tuebingen University.

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