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Original Paper

Taurolidine Sensitivity of Eryptosis, the Suicidal Erythrocyte Death

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Key Words
Phosphatidylserine • Cell volume • Eryptosis • Calcium

Abstract
Background/Aims: The taurine derivative Taurolidine is effective against diverse bacteria and tumor growth. In the treatment of cancer, the substance is effective in part by triggering suicidal death or apoptosis of tumor cells. The Taurolidine-induced apoptosis involves mitochondria. Erythrocytes lack mitochondria but are nevertheless able to enter suicidal erythrocyte death or eryptosis, which is characterized by cell shrinkage and cell membrane scrambling with phosphatidylserine translocation to the erythrocyte surface. Signaling of eryptosis includes increase of cytosolic Ca^{2+} activity ($[Ca^{2+}]_i$), oxidative stress and ceramide. The present study explores, whether Taurolidine induces eryptosis and, if so, which cellular mechanisms are involved. ***Methods:*** Phosphatidylserine exposure at the cell surface was estimated using annexin-V-binding, cell volume using forward scatter, $[Ca^{2+}]_i$ using Fluo3-fluorescence, reactive oxygen species (ROS) formation using 2',7'-dichlorodihydrofluorescein (DCF)-dependent fluorescence, and ceramide abundance using specific antibodies. ***Results:*** A 48 hours exposure of human erythrocytes to Taurolidine (60 µg/ml) significantly enhanced the percentage of annexin-V-binding cells, significantly decreased forward scatter and significantly increased Fluo3-fluorescence and ceramide abundance, but not DCF-fluorescence. The effect of Taurolidine on annexin-V-binding was virtually abrogated by removal of extracellular Ca^{2+}. ***Conclusion:*** Taurolidine triggers cell shrinkage and phospholipid scrambling of the erythrocyte cell membrane, an effect at least in part due to Ca^{2+} entry and paralleled by increase of ceramide abundance.

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Introduction

Taurolidine is an effective antibacterial substance [1-8] utilized to counteract catheter-related infections [9-24]. The substance is further effective against malignancy both, *in vivo* and *in vitro* [25-29]. Taurolidine curtails tumor blood supply by suppressing angiogenesis [29, 30]. Most importantly Taurolidine triggers suicidal tumor cell death or apoptosis [28-30], an effect involving mitochondria [29, 30]. Moreover, it generates oxidative stress specifically in tumor cells [28]. Side effects of taurolidine include liver injury [31] and stimulation of nociception [32].

Erythrocytes lack mitochondria, but may, in analogy to apoptosis, enter suicidal death of erythrocytes or eryptosis [33-35], which is characterized by cell shrinkage [36] and cell membrane scrambling with phosphatidylserine translocation to the cell surface [33]. Cellular mechanisms orchestrating eryptosis include increase of cytosolic Ca^{2+} activity ($[Ca^{2+}]_i$) [33], ceramide [33], caspases [33, 37, 38], G-protein Galphai2 [39], casein kinase 1α [33], Janus-activated kinase JAK3 [33], protein kinase C [33], and p38 kinase [33]. Eryptosis is suppressed by AMP activated kinase AMPK [33], cGMP-dependent protein kinase [33], mitogen and stress activated kinase MSK1/2 [40], and PAK2 kinase [33]. Eryptosis may be triggered by hyperosmotic shock [33], oxidative stress [33], energy depletion [33], radiation [41, 42], and a wide variety of small molecules [33, 40, 43-87]. Several inbitors of eryptosis have been identified [88-91]. Eryptosis is enhanced in several clinical conditions including iron deficiency [33], dehydration [33], hyperphosphatemia [33], vitamin D excess [33], chronic kidney disease (CKD) [92-97], hemolytic-uremic syndrome [98], autoimmune hemolytic anemia [99], diabetes [33], hypertension and dyslipidemia [100], hepatic failure [101], malignancy [102-104], arteritis [105], systemic lupus erythematosus [106], sepsis [107, 108], malaria [33, 109, 110], sickle-cell disease [33], beta-thalassemia [33], Hb-C and G6PD-deficiency [33], Wilsons disease [107], as well as advanced age [33]. Eryptosis is fostered by storage for transfusion [41, 42, 58, 111]. Erythrocytes from newborns rapidly undergo eryptosis following exposure to oxidative stress [33, 112].

The present study explored, whether Taurolidine stimulates eryptosis. To this end human erythrocytes from healthy volunteers were exposed to Taurolidine and phosphatidylserine surface abundance, cell volume, $[Ca^{2+}]_i$, ROS formation, and ceramide abundance determined by flow cytometry.

Materials and Methods

Erythrocytes, solutions and chemicals

Fresh Li-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 g for 20 min at 21 °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; pH 7.4), 5 glucose, 1 $CaCl_2$, at 37°C for 48 hours. Where indicated, erythrocytes were exposed for 48 hours to Taurolidine (Sigma Aldrich, Hamburg, Germany).

Annexin-V-binding and forward scatter

After incubation under the respective experimental condition, a 150 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. The annexin-V-abundance at the erythrocyte surface was subsequently determined on a FACS Calibur (BD, Heidelberg, Germany). Annexin-V-binding was measured with an excitation wavelength of 488 nm and an emission wavelength of 530 nm. A marker (M1) was placed to set an arbitrary threshold between annexin-V-binding

cells and control cells. The same threshold was used for untreated and Taurolidine treated erythrocytes. A dot plot of forward scatter (FSC) vs. side scatter (SSC) was set to linear scale for both parameters. The threshold of forward scatter was set at the default value of "52" [113].

Intracellular Ca^{2+}

After incubation, erythrocytes were washed in Ringer solution and loaded with Fluo-3/AM (Biotium, Hayward, USA) in Ringer solution containing 5 µM Fluo-3/AM. The cells were incubated at 37°C for 30 min. 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.

Reactive oxidant species (ROS)

Oxidative stress was determined utilizing 2',7'-dichlorodihydrofluorescein (DCF) diacetate. After incubation, a 150 µl suspension of erythrocytes was washed in Ringer solution and stained with DCF diacetate (Sigma, Schnelldorf, Germany) in Ringer solution containing DCF diacetate at a final concentration of 10 µM. Erythrocytes were incubated at 37°C for 30 min in the dark and washed two times in Ringer solution. The DCF-loaded erythrocytes were resuspended in 200 µl Ringer solution and ROS-dependent fluorescence intensity was measured at an excitation wavelength of 488 nm and an emission wavelength of 530 nm on a FACS Calibur (BD).

Ceramide abundance

For the determination of ceramide, a monoclonal antibody-based assay was used. To this end, cells were stained for 1 hour at 37°C with 1 µg anti ceramide antibody (clone MID 15B4, Alexis, Grünberg, Germany) in PBS containing 0.1% bovine serum albumin (BSA) at a dilution of 1:10. The samples were washed twice with PBS-BSA. The cells were stained for 30 minutes 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. The samples were analyzed by flow cytometric analysis with an excitation wavelength of 488 nm and an emission wavelength of 530 nm. As a control, secondary antibody alone was used.

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 elucidated whether Taurolidine is capable to stimulate eryptosis, the suicidal erythrocyte death. In a first step, the effect of Taurolidine on cell membrane scrambling with phosphatidylserine translocation to the cell surface was determined. Phosphatidylserine exposing erythrocytes were identified from annexin-V-binding which was quantified by flow cytometry. Prior to measurements, the erythrocytes were incubated for 48 hours in Ringer solution without or with Taurolidine (15 – 60 µg/ml). As shown in Fig. 1, a 48 hours exposure to Taurolidine significantly increased the percentage of phosphatidylserine exposing erythrocytes at all Taurolidine concentrations tested.

A second hallmark of eryptosis is cell shrinkage. Erythrocyte volume was thus estimated from forward scatter which was quantified with flow cytometry. Prior to measurements, the erythrocytes were again incubated for 48 hours in Ringer solution without or with Taurolidine (15 – 60 µg/ml). As illustrated in Fig. 2, Taurolidine (60 µg/ml) significantly decreased the average erythrocytes forward scatter at all Taurolidine concentrations tested.

Fluo3-fluorescence was determined as a measure of cytosolic Ca^{2+} activity ($[Ca^{2+}]_i$). As shown in Fig, 3, a 48 hours incubation with 15 - 60 µg/ml Taurolidine significantly increased

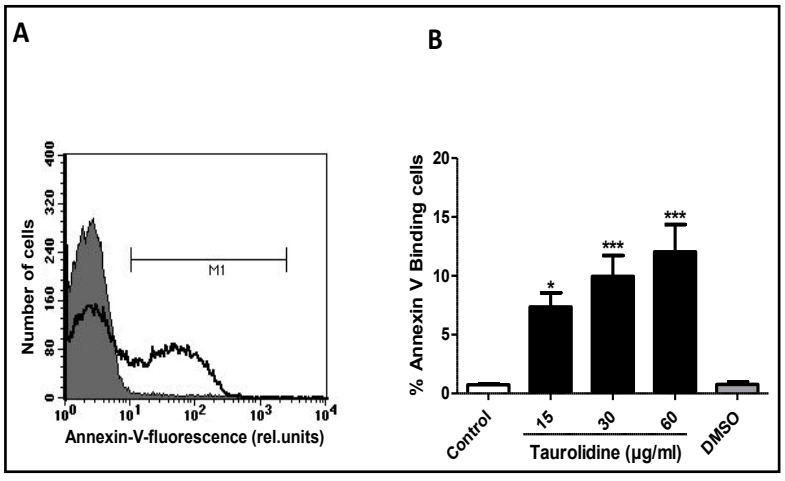

Fig. 1. Effect of Taurolidine on phosphatidylserine exposure. A. Original histogram of annexin-V-binding of erythrocytes following exposure for 48 hours to Ringer solution without (grey area) and with (black line) presence of 60 µg/ml Taurolidine. B. Arithmetic means ± SEM (n = 15) of erythrocyte annexin-V-binding following incubation for 48 hours to Ringer solution without (white bar) or with (black bars) Taurolidine (15, 30, 60 µg/ml). For comparison, the effect of the solvent DMSO (grey bar). *(p<0.05) ***(p<0.001) indicates significant difference from the absence of Taurolidine (ANOVA).

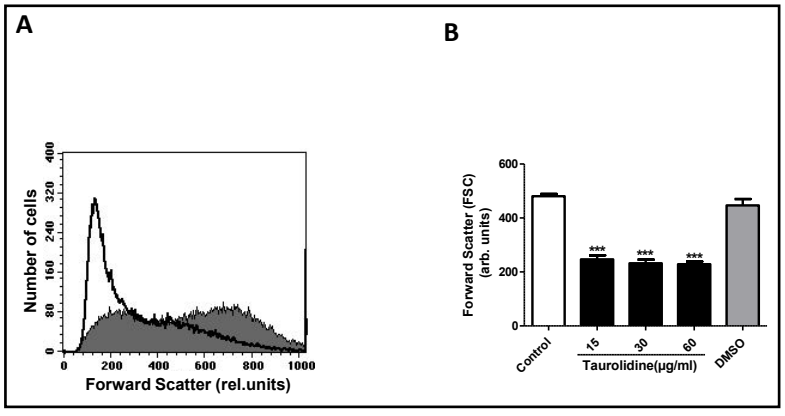

Fig. 2. Effect of Taurolidine on erythrocyte forward scatter. A. Original histogram of forward scatter of erythrocytes following exposure for 48 hours to Ringer solution without (grey area) and with (black line) presence of 60 µg/ml Taurolidine. B. Arithmetic means ± SEM (n = 15) of the erythrocyte forward scatter (FSC) following incubation for 48 hours to Ringer solution without (white bar) or with (black bars) Taurolidine (15, 30, 60 µg/ml). **(p<0.01) ***(p<0.001) indicates significant difference from the absence of Taurolidine (ANOVA).

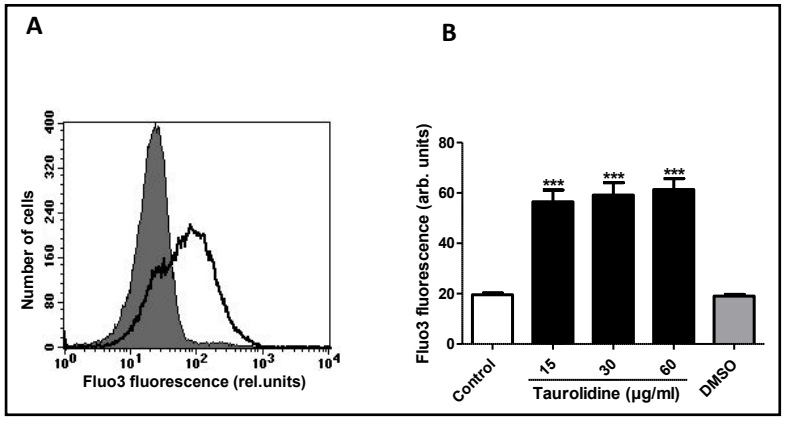

Fig. 3. Effect of Taurolidine on cytosolic Ca^{2+}. A. Original histogram of Fluo3-fluorescence reflecting cytosolic Ca^{2+} activity of erythrocytes following exposure for 48 hours to Ringer solution without (grey area) and with (black line) presence of 60 µg/ml Taurolidine. B. Arithmetic means ± SEM (n = 15) of Fluo3-fluorescence reflecting cytosolic Ca^{2+} activity of erythrocytes following incubation for 48 hours to Ringer solution without (white bar) or with (black bars) Taurolidine (15, 30, 60 µg/ml). For comparison, the effect of the solvent DMSO (grey bar). ***(p<0.001) indicates significant difference from the absence of Taurolidine (ANOVA).

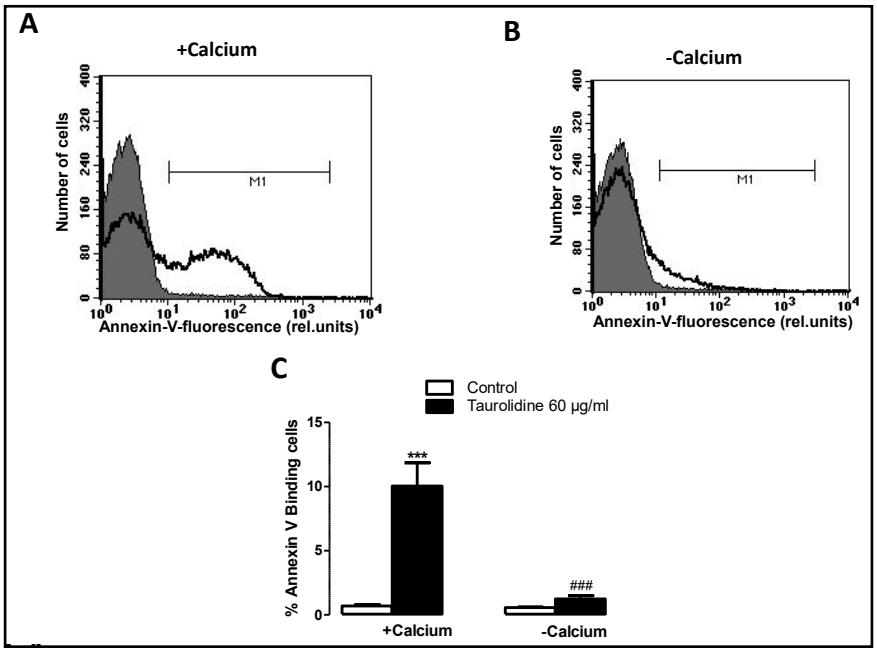

Fig. 4. Ca^{2+} sensitivity of Taurolidine-induced phosphatidylserine exposure. A,B. Original histogram of annexin-V-binding of erythrocytes following exposure for 48 hours to Ringer solution without (grey areas) and with (black lines) Taurolidine (60 µg/ml) in the presence (A) and absence (B) of extracellular Ca^{2+}. C. Arithmetic means ± SEM (n = 11) of annexin-V-binding of erythrocytes after a 48 hours treatment with Ringer solution without (white bars) or with Taurolidine (60 µg/ml) in the presence (left bars, + Ca^{2+}) and absence (right bars, - Ca^{2+}) of Ca^{2+}. ***(p<0.001) indicates significant difference from the absence of Taurolidine, ###(p<0.001) indicates significant difference from the presence of Ca^{2+} (ANOVA).

the Fluo3-fluorescence at all Taurolidine concentrations tested.

A next series of experiments explored whether the Taurolidine-induced translocation of phosphatidylserine required entry of extracellular Ca^{2+}. To this end, erythrocytes were incubated for 48 hours in the absence or presence of 60 µg/ml Taurolidine in the presence or nominal absence of extracellular Ca^{2+}. As illustrated in Fig. 4, removal of extracellular Ca^{2+} significantly blunted the effect of taurolidine on annexin-V-binding. In the absence of extracellular Ca^{2+}, Taurolidine tended to increase the percentage of annexin-V-binding erythrocytes, an effect, however, not reaching statistical significance (Fig. 4). Thus, Taurolidine-induced cell membrane scrambling was in large part triggered by entry of extracellular Ca^{2+}.

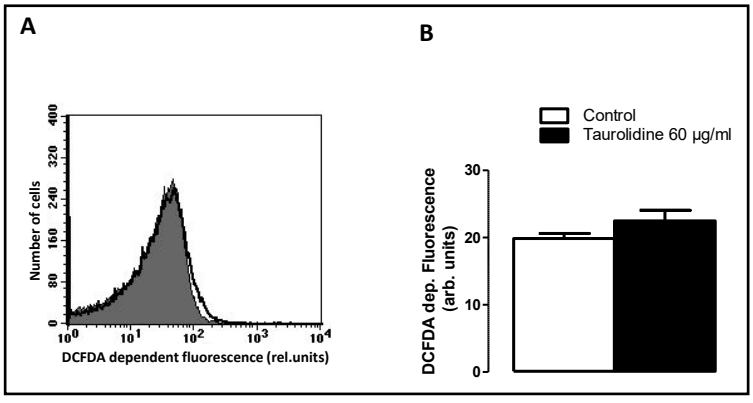

Fig. 5. Effect of Taurolidine on reactive oxygen species (ROS). A. Original histogram of 2′,7′-dichlorodihydrofluorescein (DCF) fluorescence reflecting ROS of erythrocytes following exposure for 48 hours to Ringer solution without (grey area) and with (black line) presence of 60 µg/ml Taurolidine. B. Arithmetic means ± SEM (n = 15) of DCF fluorescence in erythrocytes following incubation for 48 hours to Ringer solution without (white bar) or with (black bars) Taurolidine (60 µg/ml). For comparison, the effect of the solvent DMSO (grey bar).

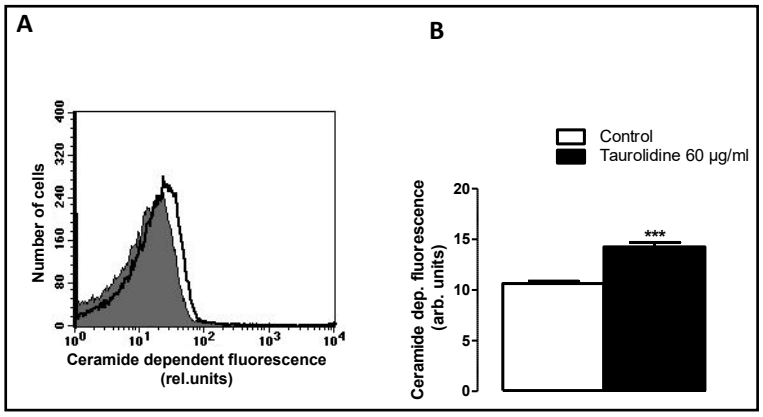

Fig. 6. Effect of Taurolidine on ceramide abundance. A. Original histogram of ceramide abundance in erythrocytes following exposure for 48 hours to Ringer solution with solvent DMSO (grey area) and with presence of Taurolidine (60 µg/ml) (black line). B. Arithmetic means ± SEM (n = 5) of ceramide abundance in erythrocytes following incubation for 24 hours to Ringer solution without (white bar) or with (black bars) presence of Taurolidine (60 µg/ml). ***($p<0.001$) indicates significant difference from the absence of Taurolidine (ANOVA).

Ca^{2+} entry and eryptosis are known to be stimulated by oxidative stress. Reactive oxygen species (ROS) was thus quantified utilizing 2′,7′-dichlorodihydrofluorescein (DCF) diacetate. As a result, DCF fluorescence was similar after 48 hours incubation without and with 60 µg/ml Taurolidine (Fig. 5).

A further known stimulator of eryptosis is ceramide. Ceramide abundance at the erythrocyte surface was thus quantified utilizing specific antibodies. As shown in Fig. 6, a 48 hours exposure to 60 µg/ml Taurolidine significantly increased the ceramide abundance.

Discussion

The present observations uncover a novel effect of Taurolidine, i.e. the stimulation of eryptosis, the suicidal erythrocyte death. Treatment of erythrocytes with Taurolidine was followed by cell membrane scrambling with phosphatidylserine translocation to the erythrocyte surface. Taurolidine further triggered cell shrinkage, another hallmark of eryptosis [58]. The concentration required for stimulation of eryptosis was similar to those required to trigger apoptosis of tumor cells [114-117] and to those achieved in patients [118].

The effect of Taurolidine on cell membrane scrambling and cell shrinkage was paralleled by a significant increase of Fluo3-fluorescence reflecting cytosolic Ca^{2+} activity. The effect of Taurolidine on cell membrane scrambling was in large part dependent on Ca^{2+} entry from the extracellular space. Accordingly, removal of extracellular Ca^{2+} virtually abrogated the Taurolidine induced eryptosis. Taurolidine-induced cell shrinkage could result from Ca^{2+} entry, activation of Ca^{2+} sensitive K^+ channels, K^+ exit, cell membrane hyperpolarization, Cl^- exit and thus cellular loss of KCl with water [58].

Taurolidine-induced cell membrane scrambling and cell shrinkage were paralleled by increased abundance of ceramide which is known to sensitize erythrocytes for the scrambling effect of Ca^{2+} [58]. Apparently, Taurolidine has only little effect on oxidative stress.

Eryptotic erythrocytes are rapidly cleared from circulating blood [33] and the physiological function of eryptosis is the removal of defective erythrocytes prior to hemolysis with release of hemoglobin, which passes the renal glomerular filter and precipitates in the acidic lumen of renal tubules thus occluding the affected nephrons with subsequent renal failure [119]. Hemoglobin could further affect microcirculation [120].

The loss of erythrocytes following clearance of phosphatidylserine exposing erythrocytes from circulating blood may, however, surpass the formation of new erythrocytes by erythropoiesis and thus lead to anaemia [33]. Phosphatidylserine exposing erythrocytes may further adhere to endothelial cells of the vascular wall [121], stimulate blood clotting and trigger thrombosis [122-124], thus impairing microcirculation [122, 125-129].

Conclusion

In conclusion, Taurolidine stimulates eryptosis with cell membrane scrambling and cell shrinkage, an effect paralleled by and in large part due to Ca^{2+} entry and ceramide.

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Disclosure Statement

The authors have no competing interests.

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