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*Review Article*

# Triggers, Inhibitors, Mechanisms, and Significance of Eryptosis: The Suicidal Erythrocyte Death

**Elisabeth Lang and Florian Lang**

*Department of Physiology, University of Tübingen, Gmelinstrasse 5, 72076 Tübingen, Germany*

Correspondence should be addressed to Florian Lang; florian.lang@uni-tuebingen.de

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Suicidal erythrocyte death or eryptosis is characterized by erythrocyte shrinkage, cell membrane blebbing, and cell membrane scrambling with phosphatidylserine translocation to the erythrocyte surface. Triggers of eryptosis include $Ca^{2+}$ entry, ceramide formation, stimulation of caspases, calpain activation, energy depletion, oxidative stress, and dysregulation of several kinases. Eryptosis is triggered by a wide variety of xenobiotics. It is inhibited by several xenobiotics and endogenous molecules including NO and erythropoietin. The susceptibility of erythrocytes to eryptosis increases with erythrocyte age. Phosphatidylserine exposing erythrocytes adhere to the vascular wall by binding to endothelial CXC-Motiv-Chemokin-16/Scavenger-receptor for phosphatidylserine and oxidized low density lipoprotein (CXCL16). Phosphatidylserine exposing erythrocytes are further engulfed by phagocytosing cells and are thus rapidly cleared from circulating blood. Eryptosis eliminates infected or defective erythrocytes thus counteracting parasitemia in malaria and preventing detrimental hemolysis of defective cells. Excessive eryptosis, however, may lead to anemia and may interfere with microcirculation. Enhanced eryptosis contributes to the pathophysiology of several clinical disorders including metabolic syndrome and diabetes, malignancy, cardiac and renal insufficiency, hemolytic uremic syndrome, sepsis, mycoplasma infection, malaria, iron deficiency, sickle cell anemia, thalassemia, glucose 6-phosphate dehydrogenase deficiency, and Wilson's disease. Facilitating or inhibiting eryptosis may be a therapeutic option in those disorders.

## 1. Introduction

The lifespan of circulating erythrocytes is limited by senescence to 100–120 days [1–3]. In senescent erythrocytes hemichromes bind to and cluster the anion exchanger protein band 3 (AE1), leading to attachment of complement C3 fragments and antiband 3 immunoglobulins [4]. Prior to senescence, erythrocytes may enter suicidal death or eryptosis, characterized by erythrocyte shrinkage and cell membrane scrambling with translocation of phosphatidylserine from the inner leaflet of the cell membrane to the erythrocyte surface [5, 6]. Phosphatidylserine avidly binds annexin V, which is thus employed to identify eryptotic cells [5, 6].

The present paper lists triggers and inhibitors or eryptosis, the mechanisms involved in the regulation of eryptosis, and the (patho-) physiological significance of eryptosis. The reader is encouraged to study earlier reviews on further aspects of eryptosis [6–12].

## 2. Triggers and Inhibitors of Eryptosis

As listed in Table 1, a wide variety of xenobiotics and endogenous small molecules may trigger eryptosis. Moreover, eryptosis is triggered by several other stressors, such as osmotic shock [13], energy depletion [14], oxidative stress [11, 15], or increase of temperature [16]. Eryptosis is inhibited by a variety of xenobiotics (Table 2), by nitric oxide [17], and by erythropoietin [18, 19].

The susceptibility to stimulation of eryptosis increases with erythrocyte age [20]. The enhanced spontaneous eryptosis of aged erythrocytes is abrogated by the antioxidant N-acetyl-L-cysteine [20]. The mechanism rendering aged erythrocytes particularly vulnerable to eryptosis remained ill-defined [20]. Young erythrocytes are particularly sensitive to suicidal death following decline of erythropoietin, a phenomenon termed neocytolysis [21].

Erythrocytes from newborns are relatively resistant to several triggers of eryptosis but are highly susceptible to

Table 1: Stimulators of eryptosis.

| Stimulators | References |
|---|---|
| A23187 | [9] |
| Acrolein | [49] |
| $\alpha$-lipoic acid | [50] |
| Aluminium | [18, 51] |
| Amantadine | [52] |
| Amiodarone | [53] |
| Amphotericin B | [54] |
| Amyloid | [55] |
| Anandamide | [56] |
| Anti-A IgG | [57] |
| Apigenin | [58] |
| Aristolochic acid | [59] |
| Arsenic | [60, 61] |
| Artesunate | [62] |
| Azathioprine | [63, 64] |
| Bay 11-7082 | [65, 66] |
| Bay-Y5884 | [67] |
| Beauvericin | [68] |
| Benzethonium | [69] |
| betulinic acid | [70] |
| Bismuth chloride | [71] |
| Cadmium | [72] |
| Carbon monoxide | [73] |
| Carmustine | [74] |
| Celecoxib | [75] |
| Ceramide (acylsphingosine) | [76] |
| Chlorpromazine | [77] |
| Chromium | [78] |
| Ciglitazone | [79] |
| Cisplatin | [80] |
| Copper | [81] |
| Cordycepin | [82] |
| Cryptotanshinone | [83] |
| Curcurmin | [84] |
| Cyclosporine | [85, 86] |
| CD95/Fas/ligand | [87] |
| Dermaseptin | [88] |
| Dicoumarol | [89] |
| Dimethylfumarate | [90] |
| Enniatin A | [91] |
| Estramustine | [92] |
| Ferutinin | [93] |
| Fluoxetine | [94] |
| FTY720 | [95] |
| Fumagillin | [96] |
| Gambogic acid | [97] |
| Gedunin | [98] |
| Geldanamycin | [99] |
| Glycation | [100] |

Table 1: Continued.

| Stimulators | References |
|---|---|
| Glycophorin-C | [101] |
| Gold chloride | [102] |
| Gold nanorods | [103] |
| Gossypol | [104] |
| Granzyme B | [105] |
| Hemin | [106] |
| Hexavalent chromium | [107] |
| Hemolysin | [108] |
| Honokiol | [109] |
| Indoxyl sulfate | [110] |
| IPA3 | [111] |
| Ipratropium bromide | [112] |
| Lead | [113] |
| Leukotriene C(4) | [16] |
| Lipopeptides | [114] |
| Listeriolysin | [115] |
| Lithium | [116] |
| Lumefantrine | [117] |
| Lysophosphatidic acid | [9] |
| Mercury | [118] |
| Methyldopa | [119] |
| Methylglyoxal | [120] |
| Miltefosine | [121] |
| Mitotane | [122] |
| Mitoxantrone | [123] |
| Monensin | [124] |
| Nitazoxanide | [125] |
| Novobiocin | [126] |
| Nystatin | [127] |
| Ochratoxin A | [128] |
| Oridonin | [129] |
| Oxysterol | [130] |
| Paclitaxel | [131, 132] |
| PAF | [133] |
| Parthenolide | [65, 66] |
| Patulin | [134] |
| Penta-O-galloyl-$\beta$-D-glucose | [135] |
| Peptidoglycan | [136, 137] |
| Phloretin | [138] |
| Phorbol-12 myristate-13 acetate | [9] |
| Phosphate | [139] |
| Phytic acid | [140] |
| Plumbagin | [128] |
| Polyphyllin D | [141] |
| Probucol | [142] |
| Prostaglandin $E_2$ | [29] |
| Pyrvinium pamoate | [143, 144] |
| Radiocontrast agents | [145] |
| Retinoic acid | [146] |
| Ribavirin | [147] |

Table 1: Continued.

| Stimulators | References |
|---|---|
| Rifampicin | [148] |
| Rotenone | [149] |
| Salinomycin | [150] |
| Selenium (sodium selenite) | [151] |
| Shikonin | [126] |
| Silver ions | [152] |
| Sorafenib | [153] |
| Sphingomyelinase | [154] |
| Sphingosine | [155] |
| Sulindac sulfide | [156] |
| Sunitinib | [157] |
| Tannic acid | [94] |
| Tanshinone IIA | [158] |
| Thioridazine | [159] |
| Thrombospondin-1-receptor CD47 | [160] |
| Thymoquinone | [161] |
| Tin | [162] |
| Trans-cinnamaldehyde | [163] |
| Tyrosinase | [164] |
| Ursolic acid | [165] |
| Valinomycin | [166] |
| Sodium vanadate | [167] |
| Vitamin K(3) | [168] |
| Withaferin A | [169] |
| Zearalenone | [170] |
| Zinc | [171] |

eryptosis following oxidative stress [22–24]. The exquisite sensibility of fetal erythrocytes to oxidative stress is presumably instrumental for their removal following birth. The high oxygen affinity of fetal hemoglobin is favourable in the oxygen-depleted intrauterine environment but not after birth [25]. Thus, replacement of fetal erythrocytes by adult erythrocytes is mandatory for adequate oxygen transport after birth.

## 3. Signaling Regulating Eryptosis

A major trigger of eryptosis is the increase of cytosolic $Ca^{2+}$ activity ($[Ca^{2+}]_i$) [6]. The increase of $[Ca^{2+}]_i$ mainly results from $Ca^{2+}$ entry through $Ca^{2+}$-permeable unselective cation channels [26, 27], which are permeable to both $Na^+$ and $Ca^{2+}$ [28]. The channels are activated by prostaglandin $E_2$ ($PGE_2$) [29, 30]. Pharmacological inhibition of cyclooxygenase or phospholipase-$A_2$ disrupts the activation of the channels following osmotic shock [29]. The $Ca^{2+}$ permeable unselective cation channels are further activated by isosmotic replacement of NaCl with sorbitol [28] and by substitution of extracellular $Cl^-$ with gluconate, $Br^-$, $I^-$, or $SCN^-$ [28]. They are further activated by oxidative stress or defects of antioxidative defence [31–34], which thus trigger $Ca^{2+}$ entry and eryptosis [5, 28]. Activation of the channels by oxidative stress is

Table 2: Inhibitors of eryptosis.

| Inhibitors | References |
|---|---|
| Adenosine | [172] |
| Amitriptyline | [173] |
| Caffeine | [174] |
| Catecholamines (isoproterenol) | [175] |
| Chloride | [176] |
| D4476 | [143] |
| Dibutyryl-cGMP | [17] |
| Dithiothreitol | [5] |
| EIPA | [177] |
| EPO | [19] |
| Erythropoietin | [19, 178] |
| Flufenamic acid | [179] |
| Furosemide | [180] |
| Glutathione | [38] |
| 7-monohydroxyethylrutoside | [40] |
| N-acetylcysteine | [18, 20] |
| Naringin | [181] |
| NBQX/CNQX | [182] |
| Niflumic acid | [44] |
| Nitroprusside (NO-donor) | [17] |
| NPPB | [44] |
| Papanonoate (NO-donor) | [17] |
| P38 Inh III | [183] |
| Resveratrol | [184] |
| (R)-DRF053 | [143] |
| Salidroside | [39] |
| SB203580 | [183] |
| Staurosporine | [14] |
| Trolox | [31] |
| Urea | [185] |
| Vitamin E | [35–37] |
| Xanthohumol | [186] |
| Zidovudine | [187] |

reversed by the reducing agent dithiothreitol [5]. Accordingly, erythrocytes are protected against oxidative stress by several antioxidants including vitamin E [35–37] glutathione [38], salidroside [39], 7-monohydroxyethylrutoside [40], trolox [31], or N-acetylcysteine [18, 20]. The channels involve the transient receptor potential channel TRPC6 [26]. The increase in $[Ca^{2+}]_i$ and eryptosis following $Cl^-$ removal were thus blunted in erythrocytes from gene-targeted mice lacking TRPC6 [26].

The increase of $[Ca^{2+}]_i$ following activation of the cation channels is followed by cell shrinkage due to activation of $Ca^{2+}$-sensitive $K^+$ channels [41, 42], cell membrane hyperpolarization, increase in the electrical driving force for $Cl^-$ exit, and the cellular loss of KCl with osmotically obliged water [43]. The $Cl^-$ exit requires erythrocyte $Cl^-$ channels [44], which are activated by oxidative stress [45, 46]. Cell shrinkage occurs as long as cellular $K^+$ loss through the $Ca^{2+}$-sensitive $K^+$ channels outcasts the $Na^+$ entry through the

unselective cation channels. Sustained exit of $K^+$ and entry of $Na^+$ may lead to dissipation of respective ion gradients across the cell membrane, to cell membrane depolarization, and thus to entry of $Cl^-$ and cell swelling [47]. Excessive cell swelling jeopardises the integrity of the cell membrane and may trigger hemolysis [28, 47].

An increase of $[Ca^{2+}]_i$ further stimulates cell membrane scrambling with breakdown of phosphatidylserine asymmetry of the erythrocyte cell membrane and translocation of phosphatidylserine to the erythrocyte surface [48]. $Ca^{2+}$ sensitivity of the machinery leading to cell membrane scrambling is increased by ceramide [6]. Osmotic shock and a variety of further stimulators of eryptosis activate a phospholipase $A_2$ with following formation platelet-activating factor, which in turn activates a ceramide producing sphingomyelinase [6].

Triggering cell membrane scrambling may involve but does not necessarily require activation of caspases [6, 103, 224], which are expressed in erythrocytes [225, 226], cleave the anion exchanger AE1 [225], and stimulate phosphatidylserine exposure of erythrocytes [227]. Caspase activation participates, for instance, in the triggering of eryptosis by leukotrienes [16] and $\alpha$-lipoic acid [50]. The caspases are further activated by oxidative stress [228]. $Ca^{2+}$ entry and $Ca^{2+}$-dependent cell membrane scrambling do, however, not require activation of caspases [48, 76, 229].

Signaling influencing eryptosis further involves Janus-activated kinase JAK3 [222]. The kinase is phosphorylated at Tyr 980 and thus activated by energy depletion [222]. JAK3 activation contributes to the stimulation of cell membrane scrambling following energy depletion and the effect of energy depletion on eryptosis is blunted by pharmacological or genetic knockout of JAK3 [222].

Eryptosis following energy depletion is inhibited by the energy sensing AMP-activated kinase (AMPK) [27]. Even without induction of energy depletion, eryptosis is increased in AMPK$\alpha$1-deficient mice [27]. The excessive eryptosis in AMPK$\alpha$1-deficient mice leads to profound anemia and splenomegaly due to trapping of eryptotic erythrocytes in the spleen [27]. AMPK deficiency is paralleled by downregulation of p21-activated kinase 2 (PAK2) which presumably participates in the inhibition of eryptosis [111].

Pharmacological evidence points to a role of casein kinase 1$\alpha$ (CK1$\alpha$) in the increase in $[Ca^{2+}]_i$ and subsequent stimulation of eryptosis upon exposure of erythrocytes to oxidative stress or following energy depletion [143]. Pharmacological activation of CK1$\alpha$ opens cation channels and thus triggers $Ca^{2+}$ influx into erythrocytes [144]. Osmotic shock activates p38 kinase in human erythrocytes [183] and pharmacological inhibition of p38 kinase blunts the eryptosis following osmotic shock [183]. Eryptosis is apparently inhibited by sorafenib- [153] and sunitinib- [157] sensitive kinases.

Eryptosis is further inhibited by cGMP-dependent protein kinase (cGKI) [217]. cGKI deficient mice suffer from severe anemia and splenomegaly due to excessive eryptosis [217]. cGKI deficiency is at least partially effective by increasing $[Ca^{2+}]_i$ [217]. The kinase is stimulated by nitric oxide (NO) [230–233], a powerful inhibitor of eryptosis [17]. NO is stored in erythrocytes and may be released upon deoxygenation of hemoglobin [234–236]. Eryptosis is inhibited by NO-donors such as nitroprusside [17] at concentrations within or even below the range of those effective in nucleated cells [237, 238]. NO is at least partially effective downstream of $Ca^{2+}$ as it protects against eryptosis induced by the $Ca^{2+}$ ionophore ionomycin without appreciably affecting the ionomycin-induced increase of $[Ca^{2+}]_i$. NO blunts apoptosis of nucleated cells in part by caspase inhibition [239, 240]. However, caspases are not required for the stimulation of eryptosis following increase of $[Ca^{2+}]_i$ [6]. Similar to its effect in nucleated cells [241–245] NO increases nitrosylation of enzymes, which are necessary for induction of cell membrane scrambling [17]. Conversely, protein S-nitrosylation is decreased by treatment of erythrocytes with ionomycin. Enzymes affected include the antiapoptotic enzyme thioredoxin, which is activated by S-nitrosylation [17, 242]. As shown in nucleated cells compromised thioredoxin activity enhances oxidative stress [242, 243]. The effect of NO is partially mimicked by dibutyryl-cGMP [17]. In contrast to low concentrations [17], excessive concentrations of the nitroprusside stimulate eryptosis presumably through oxidative stress [246–248]. NO release is particularly fast from HbF, which has thus a particular potency to counteract eryptosis and inducing vasodilation [249, 250]. In sickle cell disease increased levels of antisickling HbF counteract oxidative stress [251] and presumably eryptosis.

Collectively erythrocyte survival and eryptosis are regulated by an amazingly complex cellular machinery involving $[Ca^{2+}]_i$, ceramide, oxidative stress, caspases, nitroxide, and a variety of kinases. Most triggers of eryptosis are mainly effective by increasing $[Ca^{2+}]_i$ and/or enhancing ceramide abundance in the cell membrane. Unlike in apoptosis of nucleated cells, caspases do not play a dominant role in the triggering of eryptosis. Survival of erythrocytes does require the activity of several kinases including AMPK and cGKI. Activation of other kinases, such as CK1$\alpha$ and JAK3, triggers eryptosis. The phosphorylation targets of the kinases required for the stimulation or inhibition of eryptosis are still ill-defined. Clearly, tremendous additional experimental effort is required for full understanding of the eryptotic machinery.

## 4. Significance of Eryptosis

Phosphatidylserine exposing erythrocytes are rapidly cleared from circulating blood [190] as phosphatidylserine binds to respective receptors of phagocytosing cells leading to engulfment and degradation of the affected erythrocytes [6]. As long as accelerated loss of eryptotic erythrocytes is matched by an equivalent increase of erythropoiesis, the number of circulating erythrocytes remains unaffected [6]. The enhanced turnover of erythrocytes is then reflected by an increased percentage of reticulocytes [6]. As soon as the loss of erythrocytes by eryptosis outcasts the formation of new erythrocytes, anemia develops [6].

Phosphatidylserine-exposing erythrocytes further adhere to the vascular wall by binding of phosphatidylserine to endothelial CXC-Motiv-Chemokin-16/Scavenger receptor

for phosphatidylserine and oxidized low density lipoprotein (CXCL16/SR-PSOX) [252]. Further structures binding phosphatidylserine-exposing erythrocytes include the heparin-binding domain [253] of endothelial or subendothelial thrombospondin-1 (TSP) [254] or endothelial phosphatidylserine receptors [255]. As adherence of eryptotic erythrocytes to endothelial cells is virtually abrogated by silencing of endothelial CXCL16/SRPSO or by coating phosphatidylserine at the erythrocyte surface with annexin V, the erythrocytes bind apparently in large part by interaction of phosphatidylserine with endothelial CXCL16/SRPSO [252]. Phosphatidylserine exposing erythrocytes further adhere to blood platelets [252, 256]. The adherence of phosphatidylserine-exposing erythrocytes to vascular wall and to blood platelets compromises microcirculation [252, 257]. Phosphatidylserine-exposing erythrocytes may further trigger blood clotting and thus foster thrombosis [257].

## 5. Diseases Associated with Enhanced Eryptosis

Increased eryptosis contributes to the pathophysiology of diverse clinical disorders (Table 3) and is observed in a variety of knockout mice (Table 4). Eryptosis is augmented following dehydration, an effect paralleled by increase of $1,25(OH)_2D_3$ plasma levels [188]. Along those lines, enhanced eryptosis is observed in Klotho deficient mice which suffer from excessive $1,25(OH)_2D_3$ formation [218, 219]. The eryptosis in those mice is blunted by vitamin D deficient diet [218, 219]. Eryptosis is further triggered by severe phosphate depletion [193], an effect presumably due to compromised ATP generation.

The percentage of phosphatidylserine-exposing erythrocytes is enhanced in iron deficiency which leads to decrease of cell volume and increase of cytosolic $Ca^{2+}$ concentration [190]. The enhanced $[Ca^{2+}]_i$ results from activation of the $Ca^{2+}$ permeable unselective cation channels [190] and possibly from increased oxidative stress [258]. The enhanced eryptosis is paralleled by accelerated clearance of iron-deficient erythrocytes, which thus compounds the anemia [190].

Eryptosis is enhanced in malignancy [259]. Little is known about underlying mechanisms. The effect is compounded by cytostatic treatment, as a wide variety of cytostatic drugs do not only trigger apoptosis of tumor cells but as well suicidal death of erythrocytes (Table 1).

The percentage of phosphatidylserine-exposing erythrocytes in circulating blood is increased in diabetic patients [120, 224, 260]. Eryptosis is stimulated by methylglyoxal [120], which accumulates in hyperglycemia [261]. Methylglyoxal is at least partially effective by interference with glycolysis and by decrease of ATP and GSH concentrations [120]. Hyperglycemia imposes oxidative stress [262] with GSH depletion [262], increase of malondialdehyde concentrations [262], increased SOD activity [263], and erythrocyte lipid peroxidation [260]. Eryptosis has further been postulated to be enhanced in metabolic syndrome [191].

Eryptosis is further enhanced in chronic kidney disease (CKD) [19, 196], a condition invariably associated with anemia [264, 265]. The anemia of CKD is commonly attributed to lack of renal erythropoietin release and subsequent impairment of erythropoiesis [266, 267]. CKD is further commonly paralleled by iron deficiency [266, 268–271]. However, CKD leads to enhanced percentage

Table 3: Diseases associated with enhanced eryptosis.

| Diseases associated with accelerated eryptosis | References |
|---|---|
| Dehydration | [188] |
| Hypoxia | [189] |
| Iron deficiency | [190] |
| Metabolic syndrome | [191] |
| Diabetes mellitus | [192] |
| Phosphate depletion | [193] |
| Neocytolysis | [21] |
| Hemolytic anemia | [194] |
| Heart failure | [195] |
| Renal insufficiency | [19, 196, 197] |
| Hemolytic uremic syndrome | [198] |
| Sepsis | [199] |
| Mycoplasma infection | [200] |
| Malaria | [8, 85, 105, 201, 202] |
| Sickle cell disease | [189, 203–209] |
| Thalassemia | [203, 204, 206, 210, 211] |
| Glucose-6-phosphate dehydrogenase (G6PD) deficiency | [203, 212, 213] |
| Wilson's disease | [81] |
| AE1 mutation | [214] |
| GLUT1 mutation | [215] |

Table 4: Altered eryptosis in gene-targeted mice.

| Targeted gene | References |
|---|---|
| *Enhanced eryptosis* | |
| GCLM-deficiency | [31] |
| Annexin 7 deficiency | [216] |
| Defective hemoglobin (sickle cell, thalassemia) | [205, 206] |
| cGMP-dependent protein kinase type I (cGKI) deficiency | [217] |
| AMP-activated protein kinase deficiency | [27] |
| Klotho deficiency | [218, 219] |
| EPO excess | [220] |
| AE1 deficiency | [221] |
| *Reduced eryptosis* | |
| PAF receptor deficiency | [133] |
| Jak3 deficiency | [222] |
| PDK1 deficiency | [223] |
| TRPC6 deficiency | [26] |

of phosphatidylserine exposing erythrocytes [19, 196, 197] and accelerated clearance of circulating erythrocytes [272]. Accordingly, profound anemia occurs even in patients who are adequately treated with erythropoietin and thus have normal reticulocyte numbers in circulating blood [197]. Erythrocytes from CKD patients are exposed to oxidative stress [273]. The enhanced eryptosis in CKD patients is further partially due to hyperphosphatemia [139] and in part due to accumulation of uremic toxins, such as vanadate [167], acrolein [49], indoxyl sulfate [110], and methylglyoxal [120]. Acrolein and methylglyoxal may be partially effective by depleting the cells from glutathione [274].

Eryptosis is triggered by hemolytic uremic syndrome (HUS), characterized by hemolytic anemia with fragmented erythrocytes, thrombocytopenia, and acute renal failure [198]. The disorder may result from intoxication with bacterial shiga toxin or from complement activation due to lack of complement-inactivating factor H [198]. Plasma from HUS patients triggers in erythrocytes from healthy volunteers phosphatidylserine exposure, cell shrinkage, increase in cytosolic $Ca^{2+}$ activity, and ceramide formation [198]. The effect of patient plasma on eryptosis is abolished by plasmapheresis or filtration at 30 kDa. Eryptosis is similarly triggered by activated complement [198]. Mechanisms involved include oxidative stress and lipid peroxidation [275]. Both are imposed by neutrophils [276].

Severe eryptosis is observed in sepsis [199]. Again, plasma from septic patients stimulates phosphatidylserine exposure, cell shrinkage, increase in cytosolic $Ca^{2+}$ activity, and ceramide formation in erythrocytes from healthy individuals [199]. The effect is mimicked by exposure of erythrocytes to supernatant of pathogens and paralleled by enhanced sphingomyelinase activity [199]. Again, sepsis imposes oxidative stress [277], which may participate in the triggering of eryptosis.

Enhanced eryptosis is observed in Wilson's disease [81], a genetic disorder caused by $Cu^{2+}$ accumulation due to inactivating mutations of $Cu^{2+}$-secreting ATP7B [278]. The eryptosis is paralleled by mild anemia [278]. Eryptosis in Wilson's disease is in large part secondary to activation of acid sphingomyelinase with ceramide formation [81]. Moreover, erythrocytes from patients with Wilson's disease are exposed to oxidative stress [279] presumably due to copper-related oxidants [280].

A mutation of the anion exchanger AE1 in humans [214] or genetic knockout of the carrier in mice [221] is followed by opening of the $Ca^{2+}$ permeable unselective cation channels in erythrocytes and thus by accelerated eryptosis. An extremely rare mutation of GLUT1 turns the carrier into a $Ca^{2+}$ permeable unselective cation channel similarly enhancing eryptosis [215].

The susceptibility to eryptosis is increased in sickle cell anemia, thalassemia, and glucose 6-phosphate dehydrogenase deficiency [203, 281, 282]. Enhanced phosphatidylserine exposure fosters adhesion of the erythrocytes to endothelial cells [283–286]. Adhesion of sickle cells to the pulmonary vascular wall is fostered by activated neutrophils [283]. The binding of sickle cells to endothelial cells is decreased by annexin V indicating that it is largely due to endothelial adhesion of erythrocytic phosphatidylserine [287] but may, in addition, involve very late-activating antigen-4 (VLA-4) and CD36 [288]. HbF counteracts eryptosis and endothelial adhesion of sickle cells to endothelial cells [24, 251, 287, 289, 290]. Expression of HbF could be enhanced by hydroxyurea, which thus decreases sickling and thus vasoocclusive complications [251, 291]. HbF may, however, sensitize erythrocytes to oxidative stress-induced eryptosis (see Section 2), which may, at least in theory, limit the therapeutic benefit of hydroxyurea. Heterozygous carriers of the genetic disorders, such as heterozygous sickle cell carriers (HbA/S), do not spontaneously become suicidal and the respective individuals are virtually healthy [281]. Nevertheless, the erythrocytes are more sensitive to the eryptotic effects of oxidative stress [281].

The malaria pathogen *Plasmodium falciparum* imposes oxidative stress on the host erythrocytes and thus activates several ion channels in the erythrocyte cell membrane [292], including the oxidant-sensitive $Ca^{2+}$-permeable erythrocyte cation channels [45, 46, 293]. The channels accomplish uptake of nutrients, $Na^+$ and $Ca^{2+}$ as well as disposal of waste products, and are thus required for intraerythrocytic survival of *Plasmodium falciparum* [8, 281, 292–294]. The $Ca^{2+}$ entry following activation of the $Ca^{2+}$-permeable cation channels leads, however, to stimulation of eryptosis [32–34] and subsequent clearance of the affected erythrocytes from circulating blood [295]. The pathogen sequesters $Ca^{2+}$ thus slowing the increase of $[Ca^{2+}]_i$ [296]. The pathogen further digests hemoglobin and exports the respective amino acids [297]. *Plasmodium falciparum* infection eventually leads to cell membrane scrambling with exposure of phosphatidylserine [105, 294, 298, 299] and subsequent phagocytotic clearance of pathogen-containing erythrocytes [300, 301]. The pathogen may further foster erythrocyte senescence contributing to the clearance of infected cells [301, 302]. Adherence of phosphatidylserine-exposing erythrocytes to endothelial cells further leads to tissue sequestration of *Plasmodium*-infected cells allowing partial immune evasion of pathogen-containing erythrocytes [303].

Upon infection, eryptosis is accelerated in erythrocytes from heterozygous carriers of the sickle-cell trait (HbA/S), beta-thalassemia-trait, homozygous Hb-C, and G6PD-deficiency thus leading to early clearance of infected erythrocytes, decreased parasitemia, and a relatively mild course of the disease [1, 203–206, 210, 212, 281, 300]. As shown for HbA/S erythrocytes [281], spontaneous eryptosis is in those individuals usually not clinically relevant. Following infection with *P. falciparum*, however, the formation of $PGE_2$, $Ca^{2+}$ permeability, phosphatidylserine exposure at the cell surface, and removal by macrophages are all augmented in HbA/S carriers [281]. The accelerated eryptosis in iron deficiency similarly confers some protection against a severe course of malaria [304]. Moreover, parasitemia and clinical course of malaria can be favourably influenced by pharmacological stimulation of eryptosis, for example, by lead [305], chlorpromazine [85], and inhibition of NO synthase by L-NAME [201]. Importantly, the pathogen should be unable to become resistant to therapeutic acceleration of eryptosis,

which depends on host cell mechanisms and is thus not at the genetic disposal of the pathogen. Along those lines, the pathogen remained unable to overcome the relative resistance of sickle cell trait carriers to malaria.

## 6. Conclusions

Similar to apoptosis of nucleated cells, eryptosis is a physiological mechanism eliminating defective erythrocytes in order to prevent hemolysis and subsequent release of hemoglobin into circulating blood. Excessive eryptosis may, however, cause anemia and impede microcirculation. Orchestration of eryptosis involves $Ca^{2+}$-permeable unselective cation channels, ceramide, caspases, and a variety of kinases including Janus-activated kinase 3, AMP-activated kinase, cGMP-dependent protein kinase, casein kinase 1$\alpha$, p38 kinase, protein kinase C, and p21-activated kinase 2. The sensitivity to eryptosis is enhanced in aged erythrocytes. Fetal erythrocytes are particularly sensitive to oxidative stress. Eryptosis is triggered by a wide variety of xenobiotics and enhanced eryptosis is observed in several clinical conditions including dehydration, diabetes, cardiac and renal insufficiency, hemolytic uremic syndrome, sepsis, malaria, iron deficiency, sickle cell anemia, thalassemia, glucose 6-phosphate dehydrogenase deficiency, and Wilson's disease. Drugs and nutrients inhibiting eryptosis may open novel therapeutic options in the treatment of anemia and deranged microcirculation. Eryptosis stimulating xenobiotics may at least in theory accelerate removal of *Plasmodium* infected erythrocytes and thus favourably influence the clinical course of malaria.

## Abbreviations

AE1: Band 3 or anion exchanger 1
AMPK: AMP-activated kinase (AMPK)
$[Ca^{2+}]_i$: Cytosolic $Ca^{2+}$ concentration
CD36: Cluster of differentiation 36
cGK: cGMP-dependent protein kinase
CK1$\alpha$: Casein kinase 1$\alpha$
CXCL16/SR-PSOX: CXC-Motiv-Chemokin-16/Scavenger receptor for phosphatidylserine and oxidized low density lipoprotein (SR-PSOX)
GSH: Reduced glutathione
GCLM: Glutamate cysteine ligase modulator
G6PDH: Glucose-6-phosphate dehydrogenase
Hb: Hemoglobin
HUS: Hemolytic uremic syndrome
JAK3: Janus-activated kinase JAK3
L-NAME: L-NG-Nitroarginine Methyl Ester
NADPH: Nicotinamide adenine dinucleotide phosphate
NO: Nitric oxide
PAK2: p21-activated kinase PAK2
$PGE_2$: Prostaglandin $E_2$
ROS: Reactive oxygen species
SOD: Cu, Zn-superoxide dismutase
TRPC6: Transient receptor potential channel 6
TSP: Thrombospondin-1
VLA-4: Very late-activating antigen-4.

## Conflict of Interests

The authors declare that no competing financial interests exist. The sponsor(s) had no role in study design, collection, writing, analysis and interpretation of data, or in the decision to submit the paper for publication.

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