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Ceramide in the regulation of eryptosis, the suicidal erythrocyte death

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Abstract Similar to apoptosis of nucleated cells, erythrocytes may undergo eryptosis, a suicidal death characterized by cell shrinkage and phospholipid scrambling of the cell membrane leading to phosphatidylserine exposure at the cell surface. As eryptotic erythrocytes are rapidly cleared from circulating blood, excessive eryptosis may lead to anemia. Moreover, eryptotic erythrocytes may adhere to the vascular wall and thus impede microcirculation. Stimulators of eryptosis include osmotic shock, oxidative stress and energy depletion. Mechanisms involved in the stimulation eryptosis include ceramide formation which may result from phospholipase A2 dependent formation of platelet activating factor (PAF) with PAF dependent stimulation of sphingomyelinases. Enhanced erythrocytic ceramide formation is observed in fever, sepsis, HUS, uremia, hepatic failure, and Wilson's disease. Enhanced eryptosis is further observed in iron deficiency, phosphate depletion, dehydration, malignancy, malaria, sickle-cell anemia, beta-thalassemia and glucose-6-phosphate dehydrogenase-deficiency. Moreover, eryptosis is triggered by osmotic shock and a wide variety of xenobiotics, which are again partially effective by enhancing ceramide abundance. Ceramide formation is inhibited by high concentrations of urea. As shown in Wilson's disease, pharmacological interference with ceramide formation may be a therapeutic option in the treatment of eryptosis inducing clinical disorders.

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Abbreviation

AE1	Anion exchanger 1
AMP	Adenosinmonophosphate
AMPK	AMP activated kinase
GMP	Cyclic guanosinmonophosphate
CXCL16	CXC-Motiv-Chemokin 16
HUS	Hemolytic uremic syndrome
G6PD	Glucose-6-phosphate dehydrogenase
GLUT1	Glucose transporter 1
PAF	Platelet activating factor
PAK2	p21-activated kinase 2
PDK1	Phosphoinositide dependent kinase 1
TRPC6	Transient receptor potential channel C6

Introduction

Mature erythrocytes eventually undergo senescence leading to their removal from circulation within 100–120 days [1–3]. Erythrocyte senescence involves binding of hemichromes to band 3 with subsequent band 3 clustering, deposition of complement C3 fragments and binding of anti-band 3 immunoglobulins [4].

Erythrocytes may face injury prior to senescence. Defective erythrocytes may eventually undergo hemolysis and release hemoglobin, which may be filtered in renal glomeruli and subsequently precipitate in the acidic lumen of renal tubules [5]. To avoid hemolysis, erythrocytes may enter suicidal death or eryptosis, which is characterized by cell shrinkage and cell membrane scrambling [6–9].

The cell shrinkage serves to counteract cell swelling, the phosphatidylserine exposure fosters phagocytosis [10, 11] and thus clearance of affected erythrocytes from circulating blood [12].

Excessive stimulation of eryptosis, however, causes anemia as soon as the clearance of eryptotic erythrocytes from circulating blood surpasses the formation of new erythrocytes [6–9]. Phosphatidylserine exposing erythrocytes further adhere to the vascular wall [9] and blood platelets [13], trigger blood clotting and thrombosis and interfere with microcirculation [9]. Thus, enhanced eryptosis may become pathophysiologically relevant. Eryptosis is distinct from programmed erythrocyte necrosis [14].

Mechanisms involved in the triggering of eryptosis include ceramide formation. The present review briefly discusses the cellular mechanisms involved in the triggering of eryptosis with particular emphasis on ceramide. It further discusses the contribution of ceramide to the triggering of eryptosis in disease and by xenobiotics. The reader is encouraged to consult earlier, more extensive reviews providing the description of further aspects of eryptosis [6–8, 15–18].

Triggers and clinical conditions associated with enhanced eryptosis

A wide variety of chemicals triggers eryptosis [18–31]. Moreover, enhanced eryptosis is observed in several disorders including iron deficiency [12], phosphate depletion [32], dehydration [33], Parkinson's disease [34], fever [35], sepsis [36], hemolytic anemia [37], hemolytic uremic syndrome (HUS) [38], end stage renal disease [39–41], metabolic syndrome [42], diabetes [43–45], hepatic failure [46], malignancy [47], malaria [7, 48–52], sickle-cell disease [15, 50, 51, 53–56], thalassemia [51, 53, 55, 57–59], glucose-6-phosphate dehydrogenase (G6PD)-deficiency [55, 60], Wilson's disease [17], mutation or lack of the anion exchanger [61] and an extremely rare mutation of GLUT1 turning the carrier into a Ca^{2+} permeable cation channel [62]. Enhanced suicidal erythrocyte death is further observed following return from high altitude, a phenomenon affecting mainly newly formed erythrocytes (neocytolysis) [63].

Role of calcium in eryptosis

Eryptosis is stimulated by increase in cytosolic Ca^{2+} activity [64–66], which is known to trigger vesiculation of the cell membrane [67] and cell membrane scrambling [45, 68, 69]. Increased cytosolic Ca^{2+} activity further activates the cysteine endopeptidase calpain, an enzyme degrading the cytoskeleton and thus leading to cell membrane blebbing [70]. Beyond that, an increase of cytosolic Ca^{2+} activity is followed by stimulation of Ca^{2+}-sensitive K^+ channels [71–73] with subsequent K^+ efflux, hyperpolarization of the cell membrane, Cl^- exit [74] and thus cell shrinkage due to loss of cellular KCl with osmotically obliged water [74]. Mechanisms increasing cytosolic Ca^{2+} activity include Ca^{2+} entry through non-selective cation channels [75–79]. The molecular identity of the cation channels is still ill defined but apparently involves TRPC6 [80]. The Ca^{2+} permeable cation channels are stimulated by osmotic shock [81, 82], oxidative stress [82, 83] and Cl^- removal [79, 81, 83].

Oxidative stress and further signaling triggering eryptosis

Oxidative stress [55, 84, 85] or impaired antioxidative defence [86–88] triggers eryptosis. Oxidative stress is not only effective by activating the Ca^{2+}-permeable cation channels [83] but, in addition activates erythrocyte Cl^- channels [89, 90], which contribute to eryptotic cell shrinkage [91]. Oxidative stress further stimulates eryptosis by activation of caspases [65, 92, 93].

The signalling governing eryptosis involves several kinases [18]. Eryptosis is fostered by activation of casein kinase 1α, Janus-activated kinase JAK3, protein kinase C, and p38 kinase [18]. Eryptosis is inhibited by AMP activated kinase AMPK, cGMP-dependent protein kinase, PAK2 kinase, sorafenib sensitive kinases and sunifinib sensitive kinases [18].

Gene targeted mice with enhanced eryptosis include mice lacking AMP-activated protein kinase [94], cGMP-dependent protein kinase [95], Klotho [96], or AE1 [97]. Moreover, enhanced eryptosis is observed in mice expressing excessive erythropoietin levels [98]. Decreased eryptosis is observed in mice deficient in PAF receptor [99], PDK1 [100] or TRPC6 [80]. The susceptibility to eryptosis increases with erythrocyte age [101, 102].

Sphingomyelin breakdown and ceramide formation

A major stimulator of eryptosis is ceramide [103, 104], which has previously been shown to participate in the triggering of apoptosis of a wide variety of cell types [105–111]. Sphingolipids consist of an sphingoid base, i.e. a 1,3-dihydroxy-2-aminoalken backbone with Sphingosine, i.e. (2*S*, 3*R*, 4*E*)-2-amino-4-octadecene-1,3-diol, being the most prevalent backbone of mammalian sphingolipids. The attachment of sphingosine to a fatty acid via an amide ester bond results in the formation of ceramide [112, 113].

Ceramides contain fatty acids with very different chain lengths from 2 to 36 carbon atoms in the acyl chain and also differ in their saturation. Modification of ceramide by attachments of various headgroups results—for instance—in sphingomyelin, gangliosides, sulfatides, globosides or cerebrosides [112, 113]. Sphingomyelin, an ester of a ceramide moiety and a hydrophilic phosphorylcholine headgroup, is the most prevalent sphingolipid in the cell membrane [112, 113]. Ceramide is mainly generated via a de novo synthesis pathway or by hydrolysis of sphingomyelin, a step catalyzed by sphingomyelinases [for review see [114]]. Under certain circumstances ceramide is also generated by a retrograde activity of ceramidases converting sphingosine into ceramide or by hydrolysis of complex glycosylated lipids or ceramide 1-phosphate [for review see [114]]. Sphingomyelinases cleave phosphodiester bonds and belong to the family of hydrolases. The pH value, but also the composition of the membrane, determines the activity of sphingomyelinases [115, 116] and, therefore, sphingomyelinases are classified into an acid and several neutral and alkaline sphingomyelinases. The acid sphingomyelinase functions best at a pH of 4.5–5.0, but the lipid composition of the membrane alters the Km of the enzyme and thereby acid sphingomyelinase also functions at higher pH for instance at plasma membranes [116]. Acid and neutral sphingomyelinases are the enzymes, which are mainly involved in eryptosis as evidenced by genetic and pharmacological studies using functional inhibitors of the acid sphingomyelinase such as amitriptyline or imipramine [104, 117–119].

Besides the hydrolysis of sphingomyelin, ceramide is generated de novo by the activity of several enzymes including serine palmitoyl-transferase and ceramide synthases. The serine palmitoyl-transferase catalyzes the condensation of L-serine and palmitoyl CoA to 3-ketosphinganine, which is the rate-limiting enzyme in sphingolipid biosynthesis. 3-ketosphinganine is reduced to sphinganine by a reductase. The N-acylation of sphinganine to dihydro-ceramide is catalyzed by ceramide synthases. Finally, dihydro-ceramide is desaturated by desaturase to ceramide [120]. At present six ceramide synthases, i.e. ceramide synthase 1–6, are cloned. The ceramide synthases employ acyl-CoA of distinct length to generate (dihydro) ceramide in the de novo biosynthesis pathway and the specificity of each ceramide synthase is limited to a certain chain length, for instance CerS1 uses mostly C18-fatty acyl CoA [121], CerS2 can utilize a wider range of very long chain (VLC) fatty acyl CoAs (C20 to C26) [122]. CerS3 incorporates ultra-long chain fatty acyl CoAs (C26 to C32) [123, 124], CerS4 uses C18- and C20-fatty acyl CoAs [125]. CerS5 has specificity only for C16-fatty acyl CoA [123], and CerS6 can use both C14- and C16-fatty acyl CoAs [126].

Role of ceramide in eryptosis and adhesion to the vascular wall

In erythrocytes ceramide is generated following osmotic shock by sphingomyelin breakdown [103]. Ceramide sensitizes erythrocytes to the eryptotic effect of enhanced Ca^{2+} concentration [103]. Along those lines erythrocyte cell membrane scrambling following osmotic shock is mimicked by addition of C_6-ceramide, C_{16}-ceramide or addition of bacterial sphingomyelinase [103].

The mechanisms involved in ceramide induced eryptosis remained incompletely understood. In nucleated cells ceramide fosters receptor clustering in lipid rafts and formation of a death-inducing signalling complex (DISC) [127–130], modifies the membrane curvature and thus compromises cell membrane integrity [131, 132]. In erythrocytes ceramide is similarly localized in clusters [133]. Ceramide modifies the interaction of the membrane with the cytoskeleton and increases membrane fragility [133]. Eventually, ceramide-induced changes in the membrane lead to vesiculation, rigidity and enhanced membrane permeability [133].

Enhanced ceramide abundance is involved in the triggering of eryptosis by fever [35], sepsis [36], hemolytic anemia [37], HUS [38], end stage renal disease [40], hepatic failure [46], and Wilson's disease [17]. Table 1 lists various xenobiotics triggering eryptosis at least in part by increasing the ceramide abundance. Ceramide formation is inhibited by amitriptyline [117, 134] and urea [135]. The enzyme accomplishing the formation of ceramide has, however, remained ill defined. In sepsis [36], HUS [38] and end stage renal disease [40], the eryptosis could be triggered by exposure of erythrocytes from healthy individuals to patient plasma. In theory, the plasma could harbour a ceramide-producing enzyme such as sphingomyelinase in those diseases. Sphingomyelinase activity has indeed been detected in the serum of patients suffering from Wilson's disease [17]. In erythrocytes, ceramide formation could be triggered by platelet-activating factor PAF [99]. Osmotic erythrocyte shrinkage triggers PAF formation by a phospholipase A2 [99]. Erythrocytes express PAF receptors at the erythrocyte surface and exposure of erythrocytes to PAF stimulates sphingomyelin breakdown and ceramide formation, effects disrupted by genetic knockout of the PAF receptor [99]. Exposure of erythrocytes to bacterial sphingomyelinase triggers eryptosis and subsequent adhesion of the erythrocytes to endothelial cells [136]. Adhesion is blunted by phosphatidylserine-coating annexin-V, by addition of neutralizing antibodies against endothelial CXCL16 and by silencing of the CXCL16 gene with small interfering RNA. Pretreatment of the endothelial cells with bacterial sphingomyelinase upregulates CXCL16 protein abundance thus fostering adhesion not only by triggering of

Table 1 Chemicals stimulating eryptosis at least in part by increasing ceramide abundance

Stimulators	References
Acrolein	[139]
Amyloid	[140]
Apigenin	[141]
Aristolochic acid	[142]
Arsenic	[143, 144]
Bacterial pore-forming toxins	[14]
Bacterial sphingomyelinase	[136]
Baicalein	[145]
Benzethonium	[146]
Bilirubin	[46]
Bismuth chloride	[147]
Copper	[17]
Curcumin	[148]
Cyclosporine	[69, 149]
Dermaseptin	[150]
Ellipticine	[151]
Estramustine	[152]
Fluoxetine	[153]
FTY720	[154]
Fumagillin	[155]
Gambogic acid	[156]
Geldanamycin	[157]
Hemin	[158]
Hexavalent chromium	[159]
Honokiol	[160]
Indoxyl sulfate	[161]
Juglone	[162]
α-Lipoic acid	[163]
Lumefantrine	[164]
Mercury	[165]
Methyldopa	[166]
Methylglyoxal	[45]
Mitoxantrone	[167]
Nitazoxanide	[168]
Ochratoxin A	[169]
Oridonin	[170]
Paclitaxel	[171, 172]
PAF	[99]
Penta-*O*-galloyl-β-*D*-glucose	[173]
Peptidoglycan	[174]
Piperlongumine	[175]
Plumbagin	[176]
Rifampicin	[177]
Rotenone	[178]
Saponin	[179]
Selenium (sodium selenite)	[180]
Shikonin	[181]
Sorafenib	[182]
Sphingosine	[183]
Sulforaphane	[184]
Sulindac sulfide	[185]
Sunitinib	[186]
Tannic acid	[187]
Tanshinone IIA	[188]
Tin	[189]
Tyrosinase	[190]
Ursolic acid	[191]
Vitamin K(3)	[192]
Withaferin A	[193]
Zinc	[194]

eryptosis but as well by enhancing docking molecules at the endothelial surface [136]. Transmembrane CXCL16 serves as an endothelial adhesion molecule not only for eryptotic cells but as well for lymphocytes [137]. CXCL16 expression is enhanced in atherosclerotic lesions [137, 138]. It is tempting to speculate that the preferred CXCL16 expression in atherosclerotic plaques could foster recruitment of eryptotic erythrocytes to those sites, which could contribute to the development of thrombosis.

Conclusions

Ceramide formation participates in the stimulation of eryptosis, the suicidal erythrocyte death. Several diseases and a wide variety of xenobiotics stimulate eryptosis at least in part by increasing ceramide abundance. Ceramide formation is stimulated by PAF, which is generated by a phospholipase A2. Additional experiments are required to define the ceramide-generating enzyme(s) and the molecular mechanisms involved in ceramide-dependent cell membrane scrambling.

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