Mechanisms and Significance of Eryptosis, the Suicidal Death of Erythrocytes

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Key Words

Apoptosis • Red blood cells • Anemia • Sepsis • Diabetes • Renal insufficiency • Erythropoietin • Malaria

Abstract

Eryptosis, the suicidal death of erythrocytes, is characterized by erythrocyte shrinkage, blebbing, and phospholipid scrambling of the cell membrane. Eryptosis is triggered by increased cytosolic Ca^{2+} activity, which may result from Ca^{2+} entry through PGE_2 -activated Ca^{2+} -permeable cation channels. The Ca^{2+} sensitivity of the scrambling machinery is enhanced by ceramide, which is formed by an acid sphingomyelinase, an enzyme stimulated by platelet-activating factor. Eryptosis is enhanced in a variety of clinical conditions such as sickle-cell anemia, β -thalassemia, glucose-6-phosphate dehydrogenase deficiency, hereditary spherocytosis, paroxysmal nocturnal hemoglobinuria, myelodysplastic syndrome, phosphate depletion, iron deficiency, sepsis, hemolytic uremic syndrome, renal insufficiency, diabetes, malaria, mycoplasma infection, and Wilson's disease. Eryptosis is enhanced in mouse models of sickle cell anemia and thalassemia, as well as in mice lacking functional annexin 7, cGMP-dependent protein kinase type I, AMP-activated protein kinase, Janus kinase 3, anion exchanger 1, adenomatous polyposis coli, or Klotho. Eryptosis is triggered by osmotic shock, oxidative stress, energy depletion, hyperthermia, and

a myriad of small molecules. Eryptosis is inhibited by a variety of substances including nitric oxide and catecholamines. Erythropoietin counteracts eryptosis in part by inhibiting the Ca^{2+} -permeable cation channels. Excessive erythropoietin concentrations lead, however, to formation of erythrocytes, which are particularly sensitive to eryptotic stimuli. Accelerated eryptosis may be compensated by enhanced erythropoiesis, which is apparent from reticulocytosis. If the compensation is not sufficient, clinically relevant anemia develops. Beyond that, adhesion of eryptotic erythrocytes to the vascular wall may lead to impairment of microcirculation.

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Introduction

Mature, circulating erythrocytes undergo senescence with subsequent clearance of the aged erythrocytes, which limits the life span to approximately 100–120 days (for references see [1]). Erythrocyte senescence involves binding of hemichromes to band 3, clustering of band 3, and deposition of complement C3 fragments and anti-band 3 immunoglobulins.

Prior to senescence, erythrocytes may, however, experience injury which compromises their integrity and thus triggers suicidal erythrocyte death or eryptosis [1]. Ery-

ptosis is similar to apoptosis. However, erythrocytes lack nuclei and mitochondria, important organelles in the machinery executing apoptosis. Accordingly, erythrocytes lack several features of apoptosis including mitochondrial depolarization and condensation of nuclei. However, eryptosis shares several other features of apoptosis, such as cell shrinkage, membrane blebbing, and cell membrane scrambling, leading to phosphatidylserine exposure at the cell surface [1].

In this review, mechanisms regulating, triggering, and inhibiting the suicidal erythrocyte death or eryptosis are briefly described. As only 30 references are allowed for this review, only the most recent papers on eryptosis are cited. Earlier references are available in a previous review [1].

Mechanisms Triggering Eryptosis

Ca²⁺

Eryptosis is elicited by an increase in cytosolic Ca²⁺ activity [1]. Ca²⁺ stimulates cell membrane scrambling and activates the cysteine endopeptidase calpain, an enzyme that degrades cytoskeletal proteins thus causing cell membrane blebbing [1]. Ca²⁺ further activates Ca²⁺-sensitive K⁺ channels with subsequent efflux of K⁺, hyperpolarization of the cell membrane, and Cl⁻ exit due to enhanced electrical gradient. The cellular loss of KCl is followed by the exit of osmotically obliged water, thus leading to cell shrinkage [1].

The increase in cytosolic Ca²⁺ activity may result from activation of nonselective cation channels mediating Ca²⁺ entry [1]. The molecular identity of the cation channels is incompletely understood, but presumably involves transient receptor potential channel 6 [1]. The cation channels are activated by a wide variety of challenges including osmotic shock, oxidative stress, and Cl⁻ removal [1]. Hyperosmotic shock is affected at least in part by stimulation of cyclooxygenase with generation of prostaglandin E₂, which in turn activates the cation channel [1].

Ceramide

The Ca²⁺ sensitivity of erythrocyte cell membrane scrambling and cell shrinkage is enhanced by ceramide, which similarly stimulates eryptosis [1]. Ceramide may be produced from cell membrane sphingomyelin by sphingomyelinase, which may either be expressed in erythrocytes or released into plasma and act from outside [1]. Ceramide formation may be stimulated by platelet-activating factor (PAF), which is in turn formed from cell membrane lipids by a phospholipase [1]. The phospholipase is activated and thus PAF released following osmotic erythrocyte shrinkage. Erythrocytes do express PAF receptors, and exposure of erythrocytes to PAF stimulates ceramide formation [1]. Gene-targeted mice lacking PAF receptors are insensitive to the effects of PAF on ceramide formation and eryptosis [1].

Additional Mechanisms

A wide variety of further mechanisms and challenges participate in the triggering or regulation of eryptosis. Eryptosis is stim-

ulated by energy depletion, which is at least partially affected by activation of protein kinase C [1].

Eryptosis is further activated following oxidative stress or following impairment of antioxidative defense [1]. Oxidative stress activates the Ca²⁺-permeable cation channels, thus stimulating Ca²⁺ entry. Oxidative stress further activates erythrocyte Cl⁻ channels, which contributes to eryptotic cell shrinkage. In addition, oxidative stress activates caspases, which could stimulate eryptosis, but are not required for eryptosis following Ca²⁺ entry [1].

Eryptosis is regulated by a variety of kinases, such as cGMP-dependent protein kinase type I, AMP-activated kinase, and Janus kinase 3 (table 1). A powerful inhibitor of eryptosis is nitric oxide, which renders erythrocytes partially resistant against the eryptotic effects of increased cytosolic Ca²⁺ activity (table 2).

Diseases Associated with Enhanced Eryptosis

Excessive eryptosis is observed in a variety of diseases (table 1). Several genetic defects of hemoglobin synthesis, such as sickle cell anemia and thalassemia; erythrocyte enzymes, such as glucose-6-phosphate dehydrogenase deficiency; or carriers, such as the anion exchanger 1, are associated with enhanced vulnerability of the erythrocytes against stimulators of eryptosis [1]. In one family with excessive eryptosis, a mutation of GLUT1 was observed, turning the glucose carrier into a Ca²⁺-permeable cation channel. More importantly, enhanced eryptosis is observed in common diseases, such as iron deficiency, diabetes, and renal insufficiency. As eryptosis is highly sensitive to temperature and triggered by hyperthermia (table 2), eryptosis is expected to occur in fever. Excessive eryptosis is observed in sepsis and in hemolytic uremic syndrome. Hemolytic disorders analyzed thus far have been shown to be paralleled by excessive eryptosis. It appears that hemolysis is only the tip of the iceberg and that in most affected erythrocytes parallel eryptosis prevents lysis with subsequent release of hemoglobin into the plasma [1].

Eryptosis is triggered following invasion of the malaria pathogen *Plasmodium*. Following entry into the erythrocyte, the pathogen induces oxidative stress, which activates the Ca²⁺-permeable cation channels and thus triggers eryptosis. The suicidal death is followed by the clearance of the infected erythrocyte together with the pathogen, thus counteracting parasitemia. At least in mice, several substances triggering eryptosis have been found to favorably influence the clinical course of the disease [1].

Enhanced eryptosis is observed in newly formed erythrocytes of healthy individuals returning from high

altitudes or space flight, a phenomenon called 'neocytolysis'. The enhanced eryptosis in patients with paroxysmal nocturnal hemoglobinuria and myelodysplastic syndrome preferably affects lighter and, thus, presumably younger erythrocytes, pointing to neocytolysis in those diseases [2]. At this stage, the mechanisms underlying neocytolysis have remained elusive [1]. Notably, a similarly enhanced susceptibility to eryptosis is observed in erythrocytes drawn from erythropoietin-overexpressing transgenic mice [1]. Possibly, erythropoietin stimulates in progenitor cells the expression of genes sensitizing the erythrocytes to eryptotic challenges. As a result, erythrocytes undergo, in part, suicidal death as soon as the erythropoietin concentrations decline. The premature clearance of erythrocytes may serve to normalize blood erythrocyte concentration as soon as it is no longer needed and the plasma erythropoietin concentrations fall. Accordingly, neocytolysis may accelerate the negative feedback regulation of erythrocyte abundance, which otherwise would take 120 days. Additional experimental efforts are needed to prove or disprove this speculation.

Excessive eryptosis has also been observed in several gene-targeted mice, thus pointing to molecules involved in the regulation of erythrocyte survival (table 1). Similar to human disease, mice with defective hemoglobin (sickle cell, thalassemia) suffer from accelerated suicidal erythrocyte death. A mouse model resembling sickle cell anemia is the A7 mouse. Similar to sickle cell trait erythrocytes, A7-deficient erythrocytes generate excessive PGE₂, which in turn activates the cation channels with subsequent eryptosis [3]. Eryptosis is inhibited by cGMP-dependent protein kinase type I, AMP-activated protein kinase. Accordingly, gene-targeted mice lacking one of those kinases suffer from accelerated eryptosis. Similarly, endothelin inhibits eryptosis, and mice lacking the endothelin B receptor suffer from accelerated eryptosis. Knockout of the anion exchanger 1 is followed by severely enhanced eryptosis and anemia despite excessive formation of new erythrocytes. As pointed out above, mice overexpressing erythropoietin harbor erythrocytes particularly sensitive to eryptosis. In Klotho deficiency, the excessive formation of 1,25(OH)₂D₃ leads to moderately enhanced eryptosis. In adenomatous polyposis coli-deficient mice, the appearance of intestinal tumors is paralleled by increased eryptosis. In some mice, the erythrocytes may be resistant to specific stimulators of eryptosis, such as mice expressing decreased levels of phosphoinositide-dependent kinase 1 or mice lacking the PAF receptor or transient receptor potential channel 6 (table 1).

Table 1. Diseases associated with enhanced eryptosis and mouse models associated with enhanced or decreased eryptosis

	Effective through			Ref.
	Ca ²⁺	Cer.	other	
<i>Diseases associated with accelerated eryptosis</i>				
Iron deficiency	+			1
Phosphate depletion			+	1
Neocytolysis			+	1
Sepsis		+		1
Hemolytic anemia	+	+	+	1
Hemolytic uremic syndrome	+	+		1
Renal insufficiency	+			1
Diabetes			+	4, 5
Malaria	+			1, 6, 7
Sickle-cell disease			+	1
Thalassemia			+	1, 8
G6PD deficiency			+	1
Wilson's disease		+		1
AE1 mutation	+			1
GLUT1 mutation	+			1
Paroxysmal nocturnal hemoglobinuria			+	2
Myelodysplastic syndrome			+	2
Hereditary spherocytosis			+	8
Mycoplasma infection				9
Hyperthermia	+	+	+	10
<i>Mouse models with enhanced eryptosis</i>				
Defective hemoglobin (sickle cell, thalassemia)	+			1
Annexin A7 deficiency	+			3
cGKI deficiency	+			1
AMPK deficiency	+			1
Endothelin B receptor deficiency	+			12
AE1 deficiency	+			1
APC deficiency			+	13
Klotho deficiency	+			1
EPO excess	+			1
<i>Mouse models with reduced eryptosis</i>				
PDK1 deficiency	+			1
TRPC6 deficiency	+			1
PAF receptor deficiency		+		1
JAK3 deficiency			+	11

G6PD = Glucose-6-phosphate dehydrogenase; AE1 = anion exchanger 1; cGKI = cGMP-dependent protein kinase type I; AMPK = AMP-activated protein kinase; JAK3 = Janus kinase 3; APC = adenomatous polyposis coli; EPO = erythropoietin; PDK1 = phosphoinositide-dependent kinase 1; TRPC6 = transient receptor potential channel 6. Mechanisms: Ca²⁺ = stimulation of Ca²⁺ entry; Cer. = stimulation of ceramide formation; other = inhibition of ATP depletion, etc. To limit the number of references, preference is given to reviews.

Table 2. Stimulators and inhibitors of eryptosis

	Concen- tration	Effective through			Ref.		Concen- tration	Effective through			Ref.
		Ca ²⁺	Cer.	other				Ca ²⁺	Cer.	other	
<i>Stimulators</i>											
Parthenolide, μM	30			+	15	α-lipoic acid, μM	10	+	+	+	14
Peptidoglycan, μg/ml	50	+	+		1	Aluminium, μM	10–30	+			1
Phytic acid, mM	1			+	26	Amantadine, μg/ml	0.2	+			1
Prostaglandin E ₂ , pM	100				1	Amiodarone, μM	0.1	+			1
Radiocontrast agent, mM	5	+		+	1	Amphotericin B, μg/ml	0.5	+		+	1
Retinoic acid, μM	3	+			1	Amyloid, μM	0.5–1		+		1
Selenium (sodium selenite), ng/ml	200	+	+		1	Anandamide, μM	2.5	+			1
Silver ions nM	100			+	1	Anti-A IgG, μg/ml	0.5	+			1
Thrombospondin-1 receptor CD47				+	1	Arsenic, μM	7–10	+	+	+	1
Thymoquinone, μM	3			+	1	Azathioprine, μg/ml	2	+			1
Tin, μM	30	+	+	+	1	Bay 11-7082, μM	10	+		+	15
Valinomycin, nM	1			+	1	Bay-Y5884, μM	20	+			1
Sodium vanadate, μg/ml	10	+			1	Beauvericin, μM	1	+			16
Sphingosine, μM	0.1	+			27	Benzethonium, μM	2.5	+			17
Vitamin K(3), μM	1		+		1	Bismuth chloride, μg/ml	500	+	+		1
Zinc, μM	25	+	+		1	Cadmium, μM	5.5	+		+	1
<i>Inhibitors</i>											
Adenosine, μM	10–30	+		+	1	Ceramide (acylsphingosine), μM	50			+	1
Amitriptyline, μM	50		+	+	1	Chlorpromazine, μM	10	+			1
Blebbistatin, μM	10	+			28	Ciglitazone, μM	5–10	+			1
Caffeine, μM	50–500	+		+	1	Cisplatin, μM	1	+			1
Catecholamines (isoproterenol), μM	IC50: 1	+			1	Copper, μM	3		+		1
Chloride, mM	110	+			1	Cordycepin, μM	60	+			1
EIPA, μM	IC50: 0.2	+			1	Curcumin, μM	1	+	+		1
Endothelin 1, nM	100	+			12	Cyclosporine, μM	10		+	+	1
EPO, U/ml	1	+			1	CD95/Fas/ligand				+	1
Flufenamic acid, μM	10	+			1	Dimethylfumarate, μM	70	+		+	18
NBQX/CNQX, μM	10–50	+			1	Enniatin A, μM	2.5	+		+	19
Niflumic acid, μM	100			+	1	FTY720, μM	10	+			20
NO (nitroprusside), μM	1			+	1	Glycation		+			21
NPPB, μM	100			+	1	Glycophorin-C				+	1
Phlorhizin, μM	10	+			29	Gold chloride, μg/ml	0.75	+			1
Resveratrol, μM	5	+		+	1	Hemin, μM	1–10	+	+		1
Sarafotoxin 6c, nM	10	+			12	Hemolysin, U/ml	1	+			1
Staurosporine, nM	500			+	1	IPA3, μM	5			+	22
Thymol, μg/ml	2.5	+		+	30	Lead, μM	0.1	+			1
Urea, μM	650		+	+	1	Leukotriene C(4), nM	10	+			1
WHI-P131/JANEX-1, μM	156				11	Lipopeptides, μM	1			+	1
WHI-P154, μM	11.2				11	Listeriolysin, ng/ml	10	+		+	1
Xanthohumol, μM	1	+		+	1	Lithium, mM	1	+			23
Zidovudine, μg/ml	2	+			1	Mercury, μM	1		+	+	1
Cer. = Stimulation of ceramide formation; other = ATP depletion, etc.											

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Eryptosis is triggered by a wide variety of small molecules (table 2). The substances are effective by increased cytosolic Ca^{2+} activity, stimulation of ceramide formation, and/or further mechanisms such as ATP depletion, oxidative stress, and/or caspase 3 activation (table 2). A variety of substances inhibit eryptosis. Most of those substances directly or indirectly inhibit Ca^{2+} entry. On the other hand, some substances decrease the Ca^{2+} sensitivity of cell membrane scrambling.

Consequences of Eryptosis

Phosphatidylserine-exposing erythrocytes are rapidly cleared from circulating blood. They bind to respective receptors of macrophages and are then engulfed and degraded [1]. As a result, excessive eryptosis leads to anemia unless the enhanced loss of erythrocytes is compensated by similarly enhanced formation of new erythrocytes. The formation of new erythrocytes is apparent from the percentage of reticulocytes. Thus, accelerated eryptosis may be apparent from reticulocytosis rather than anemia.

Phosphatidylserine-exposing erythrocytes further adhere to the vascular wall and may therefore impede

microcirculation [1]. It is particularly intriguing to speculate that PGE_2 -stimulated excessive eryptosis leads to the breakdown of microcirculation in kidney medulla following acute renal failure.

Conclusions

Similar to apoptosis of nucleated cells, eryptosis is the suicidal death of mature erythrocytes. Eryptosis is accomplished by a complex machinery involving activation of ion channels, stimulation or inhibition of kinases, and formation of ceramide. Accelerated eryptosis is encountered in a wide variety of diseases and is stimulated by a large number of small molecules. Future experiments are expected to uncover additional triggers and inhibitors of eryptosis, as well as further signaling molecules contributing to the orchestration of the tightly regulated suicidal erythrocyte death.

Disclosure Statement

The authors state that they have no conflict of interest to disclose.

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