Review

Eryptosis - the Neglected Cause of Anemia in End Stage Renal Disease

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Key Words

Eryptosis • Cell shrinkage • Cell membrane scrambling • End-stage renal disease (ESRD) • Uremic toxins • Microcirculation

Abstract

End stage renal disease (ESRD) invariably leads to anemia which has been mainly attributed to compromised release of erythropoietin from the defective kidneys with subsequent impairment of erythropoiesis. However, erythropoietin replacement only partially reverses anemia pointing to the involvement of additional mechanisms. As shown more recently, anemia of ESRD is indeed in large part a result of accelerated erythrocyte loss due to suicidal erythrocyte death or eryptosis, characterized by cell shrinkage and cell membrane scrambling with phosphatidylserine translocation to the cell surface. Phosphatidylserine exposing erythrocytes are bound to and engulfed by macrophages and are thus rapidly cleared from circulating blood. If the loss of erythrocytes cannot be fully compensated by enhanced erythropoiesis, stimulation of eryptosis leads to anemia. Eryptotic erythrocytes may further adhere to the vascular wall and thus impair microcirculation. Stimulators of eryptosis include complement, hyperosmotic shock, energy depletion, oxidative stress, and a wide variety of xenobiotics. Signaling involved in the stimulation of eryptosis includes increase of cytosolic Ca^{2+} activity, ceramide, caspases, calpain, p38 kinase, protein kinase C, Janus-activated kinase 3, casein kinase 1 α , and cyclin-dependent kinase 4. Eryptosis is inhibited by AMP-activated kinase, p21-activated kinase 2, cGMP-dependent protein kinase, mitogen- and stress-activated kinase MSK1/2, and some illdefined tyrosine kinases. In ESRD eryptosis is stimulated at least in part by a plasma component, as it is triggered by exposure of erythrocytes from healthy

individuals to plasma from ESRD patients. Several eryptosis-stimulating uremic toxins have been identified, such as vanadate, acrolein, methylglyoxal, indoxyl sulfate, indole-3-acetic acid and phosphate. Attempts to fully reverse anemia in ESRD with excessive stimulation of erythropoiesis enhances the number of circulating suicidal erythrocytes and bears the risk of interference with microcirculation. At least in theory, anemia in ESRD could preferably be treated with replacement of erythropoietin and additional inhibition of eryptosis thus avoiding eryptosis-induced impairment of microcirculation. A variety of eryptosis inhibitors have been identified, their efficacy in ESRD remains, however, to be shown.

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Introduction

Mature circulating erythrocytes enjoy an average life span of more than 100 days, which is eventually limited by senescence [1]. Prior to that, erythrocytes may be removed by suicidal death or eryptosis, which is characterized by erythrocyte shrinkage and breakdown of the cell membrane asymmetry with translocation of phosphatidylserine from the cell inside to the cell membrane surface [1-8].

Eryptotic erythrocytes are rapidly cleared from circulating blood [1, 9], as phosphatidylserine exposing erythrocytes bind to respective receptors of phagocytes, are engulfed and are subsequently degraded [1]. As soon as the loss of erythrocytes by stimulated eryptosis surpasses parallel stimulation of erythropoiesis, anemia develops [1].

Phosphatidylserine at the surface of eryptotic erythrocytes further binds to endothelial cells in large part by interaction of phosphatidylserine with the CXC-Motiv-Chemokin 16/ Scavenger receptor (CXCL16/SRPSO) [1]. The adherence of erythrocytes to the vascular wall compromises microcirculation [1]. Moreover, phosphatidylserine exposing eryptotic erythrocytes bind to blood platelets and may thus trigger blood clotting and thrombosis [1]. Enhanced eryptosis is observed in diverse clinical conditions (see Table 1).

Susceptibility to eryptosis increases with erythrocyte age [39] and the percentage of eryptotic erythrocytes increases following storage of blood [40-71]. Erythrocytes from newborns are highly sensitive to oxidative stress leading to rapid eryptosis and subsequent clearance of those erythrocytes following birth [1].

Eryptosis is triggered by complement, hyperosmotic shock, energy depletion, oxidative stress, cellular K⁺ loss, increase of temperature and a wide variety of xenobiotics [32, 43, 54, 64, 72-111].

Cellular mechanisms contributing to orchestration of eryptosis

Eryptosis is triggered by diverse signaling mechanisms [1]. Most importantly, eryptosis is stimulated by a sustained increase of cytosolic Ca²⁺ activity ([Ca²⁺]_i) [1]. Ca²⁺ may enter via Ca²⁺-permeable unselective cation channels. The channels are activated by

Table 1. Clinical conditions with enhanced eryptosis

Clinical conditions with enhanced eryptosis
chronic kidney disease [10-13]
diabetes [14, 15]
hepatic injury [16]
cardiac failure [17]
hemolytic uremic syndrome [1, 18]
dehydration [19]
phosphate depletion [1]
calcitriol excess [20]
inflammation [21]
arteritis [22]
fever [23]
sepsis [24]
systemic lupus erythematosus [25]
mycoplasma infection [1]
malaria [26-28]
iron deficiency [29]
sickle cell anemia [30]
thalassemia [30]
glucose 6-phosphate dehydrogenase deficiency [31, 32]
hereditary spherocytosis [2, 23]
paroxysmal nocturnal haemoglobinuria [1]
Wilson's disease [1]
Parkinson's disease [33]
malignancy [2, 34, 35]
advanced age [36-38]
Newborns [1]

prostaglandin E₂ (PGE₂) [112]. An increase of [Ca²⁺]_i is followed by activation of Ca²⁺-sensitive K⁺ channels leading to cell membrane hyperpolarization, Cl⁻ exit, cellular loss of KCl with osmotically obliged water and thus cell shrinkage [1]. An increase of [Ca²⁺]_i further activates a scramblase leading to cell membrane scrambling with translocation of phosphatidylserine from the inner leaflet of the cell membrane to the erythrocyte surface [1]. The cell membrane scrambling is sensitized for the stimulating effect of Ca²⁺ by ceramide [6]. Ceramide is generated by a sphingomyelinase which is activated by platelet-activating factor (PAF), a product of phospholipase A₂ [112].

Stimulation of eryptosis may further involve the heterotrimeric G-protein subunit Gαi2 [113]. Several stimulators of eryptosis including oxidative stress, leukotrienes and α-lipoic acid are effective through activation of caspases [1, 114]. Eryptosis may be triggered by genetic knockout of adenosine 5'-monophosphate deaminase (AMPD3) [115]. Somewhat surprisingly, regulatory small noncoding RNAs (ncRNAs) contribute to the orchestration of eryptosis [116].

Eryptosis is sensitive to a number of kinases. Eryptosis is stimulated by protein kinase C [1], cyclin-dependent kinase 4 (CDK4) [1, 117], p38 mitogen activated kinase [1], casein kinase 1α (CK1α) [1], and Janus-activated kinase JAK3 [118]. Eryptosis is suppressed by the energy sensing AMP-activated kinase (AMPK) [1], p21-activated kinase 2 (PAK2) [1], mitogen- and stress-activated kinase MSK1/2 [119], sorafenib and sunitinib sensitive tyrosine kinases [1], and the cGMP-dependent protein kinase (cGKI). The cGKI is stimulated by nitric oxide (NO), which is accumulated in erythrocytes and is a powerful inhibitor of eryptosis [1].

Enhanced eryptosis in chronic kidney disease

In end-stage renal disease (ESRD), the reduced renal production and release of erythropoietin (EPO) [120-128] as well as iron deficiency [120, 125, 129-132] compromise erythropoiesis, an effect contributing to but not accounting for the development of anemia [133, 134].

Compelling evidence suggests that anemia in ESRD results in large part from accelerated clearance of circulating erythrocytes due to stimulation of eryptosis [10-13, 135-140]. In erythropoietin treated patients on dialysis anemia prevails despite enhanced numbers of reticulocytes [10, 136]. Thus, the anemia is not normalized despite overcompensation of erythropoietin deficiency. The persistence of anemia is due to enhanced eryptosis [10, 136]. In ESRD, the percentage of phosphatidylserine-exposing erythrocytes is positively correlated with erythropoietin dosage and the percentage of reticulocytes. The percentage of phosphatidylserine-exposing erythrocytes is significantly higher in patients under hemodialysis than in healthy volunteers [10, 136] and even significantly higher in patients on peritoneal dialysis than in healthy volunteers and in patients on hemodialysis [10].

Eryptosis in ESRD is in large part due to a plasma component, as exposure of erythrocytes drawn from healthy individuals to plasma from ESRD patients significantly increases the percentage of phosphatidylserine exposing erythrocytes [10, 136]. In patients on hemodialysis, plasma drawn from patients immediately before a dialysis session, but not plasma drawn from patients immediately after a dialysis session stimulates eryptosis [136]. Thus, eryptosis is in large part due to a dialysable plasma component. Despite the removal of eryptosis-inducing plasma components, the percentage of eryptotic erythrocytes is significantly increased immediately after a hemodialysis session, indicating that hemodialysis, in addition to removing eryptosis-stimulating plasma components, per se stimulates eryptosis [136]. In patients on peritoneal dialysis, the percentage of phosphatidylserine-exposing erythrocytes was positively correlated with dialysis volume [10].

The plasma components accounting for the stimulation of eryptosis presumably include several uremic toxins (see Table 2).

Table 2. Eryptosis-inducing Uremic toxins

Eryptosis-inducing Uremic toxins
vanadate [141]
acrolein [13]
methylglyoxal [142]
indoxyl sulfate [12, 143]
indole-3-acetic acid [12]
phosphate [144]

Fig. 1. Anemia in ESRD is the result of enhanced eryptosis on the one hand and impaired formation of erythropoietin on the other. Treatment of anemia in ESRD with replacement of erythropoietin alone does not normalize blood count. Erythropoietin inhibits the unspecific erythrocyte cation channels but cannot prevent accelerated eryptosis in ESRD. Attempts to normalize blood count by administration of excessive erythropoietin jeopardizes microcirculation due to enhanced formation of erythrocytes eventually entering eryptosis and thus adhering to the vascular wall.

The stimulation of eryptosis in ESRD is in part due to increase of $[Ca^{2+}]_i$, oxidative stress and ceramide [10, 136].

The impact of stimulated eryptosis on anemia in ESRD is similar or even higher than that of erythropoietin deficiency. For instance, the percentage of phosphatidylserine-exposing erythrocytes was twice as high in freshly drawn blood from ESRD patients on peritoneal dialysis as in blood from healthy volunteers [10]. In view of the rapid clearance of phosphatidylserine-exposing erythrocytes from circulating blood [1], a doubling of phosphatidylserine-exposing erythrocytes in circulating blood is expected to decrease erythrocyte life span to half. If erythropoiesis would remain constant, the decrease of erythrocyte life span should reduce the number of circulating erythrocytes to half. Thus, severe anemia in ESRD patients can only be prevented by overcompensating erythropoietin deficiency leading to rates of erythropoiesis higher than those in healthy individuals (Figure 1).

In addition to its impact on anemia, eryptosis may interfere with microcirculation, as phosphatidylserine-exposing erythrocytes adhere to the vascular wall [145]. Phosphatidylserine-exposing erythrocytes further stimulate blood clotting [1]. Excessive eryptosis could thus contribute to the known increase of cardiovascular risk in uremic patients [146, 147].

In view of the above considerations, attempts to normalize blood count in ESRD patients by stimulation of erythropoiesis increase erythrocyte turnover and thus the number of phosphatidylserine-exposing erythrocytes in circulating blood. Moreover, even though erythropoietin inhibits the Ca^{2+} permeable cation channel and thus Ca^{2+} entry [137], the chronic application of erythropoietin leads to the formation of erythrocytes with enhanced susceptibility to eryptosis [148]. Accordingly, the untoward side effects of inadequately high treatment with erythropoietin or other erythropoiesis-stimulating agents [133, 147, 149, 150] may at least partially be due to enhanced eryptosis.

Inhibitors of eryptosis

In view of the above considerations, treatment of anemia in ESRD should not be restricted to replacement of erythropoietin, but should in addition counteract accelerated eryptosis. As a matter of fact, the stimulation of eryptosis by plasma from uremic patients could be reversed *in vitro* by addition of L-carnitine [135]. A large number of further substances have previously been shown to inhibit eryptosis (Table 3).

Given the complexity of the machinery triggering eryptosis and given the diversity of uremic toxins, many of the above substances may fail to prevent excessive eryptosis in ESRD. In any case, substantial additional experimental effort is needed to uncover the adequate substance or combination of substances for the prevention of premature erythrocyte death in ESRD.

Conclusions

Similar to apoptosis of nucleated cells, erythrocytes may enter eryptosis, the suicidal erythrocyte death characterized by erythrocyte shrinkage and cell membrane scrambling. Cellular mechanisms orchestrating eryptosis include Ca^{2+} -permeable, PGE_2 -activated cation channels, ceramide, oxidative stress, caspases, calpain, and several kinases. Enhanced eryptosis is observed in a wide variety of clinical conditions and triggered by a myriad of xenobiotics. Eryptotic cells adhere to endothelial cells, thus interfering with microcirculation, and are rapidly cleared from circulating blood thus causing anemia. Similar to erythropoietin deficiency, excessive eryptosis is a major cause of anemia in ESRD. As treatment of anemia in ESRD by overcompensation of erythropoietin deficiency necessarily leads to increased numbers of circulating suicidal erythrocytes with the respective impairment of microcirculation, a therapeutic approach is needed combining replacement of erythropoietin with inhibition of eryptosis.

Table 3. Inhibitors of eryptosis

Inhibitors of eryptosis
L-carnitine [135]
including Adenosine [5]
Amitriptyline [5]
Caffeine [5]
Catecholamines (isoproterenol) [5]
D4476 [5]
Dibutyryl-cGMP [5]
Dithiothreitol [5]
EIPA [5]
Erythropoietin [5]
Flufenamic acid [5]
Furosemide [5]
Glutathione [5]
7-monohydroxyethylrutoside [5]
N-acetylcysteine [5]
Naringin [5]
NBQX/CNQX [5]
Niflumic acid [5]
Nitroprusside (NO-donor) [5]
Papanonoate (NO-donor) [5]
NPPB [5]
p38 Inh III [5]
Resveratrol [5, 78]
(R)-DRF053 [5]
Salidroside [5]
SB203580 [5]
Staurosporine [5]
Trolox [5]
Urea [5]
Vitamin E [5]
Xanthohumol [5]
Zidovudine [5]
Vitamin C [31]
Cinnamaldehyde [78]
Hydroxytyrosol [85]
Indicaxanthin [151]
Teriflunomide [152]

Author Disclosure Statement

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