Suicide for Survival - Death of Infected Erythrocytes as a Host Mechanism to Survive Malaria

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Key Words

Apoptosis • Red blood cells • Malaria • Oxidative stress • Anemia

Abstract

The pathogen of malaria, *Plasmodium*, enters erythrocytes and thus escapes recognition by the immune system. The pathogen induces oxidative stress to the host erythrocyte, which triggers eryptosis, the suicidal death of erythrocytes. Eryptosis is characterized by cell shrinkage, membrane blebbing and cell membrane phospholipid scrambling with phosphatidylserine exposure at the cell surface. Phosphatidylserine-exposing erythrocytes are identified by macrophages which engulf and degrade the eryptotic cells. To the extent that infected erythrocytes undergo eryptosis prior to exit of *Plasmodia* and subsequent infection of other erythrocytes, the premature eryptosis may protect against malaria. Accordingly, any therapeutical intervention accelerating suicidal death of infected erythrocytes has the potential to foster elimination of infected erythrocytes, delay the development of parasitemia and favorably influence the course of malaria. Eryptosis is stimulated by a wide variety of triggers including osmotic shock, oxidative stress, energy depletion and a wide variety of xenobiotics. Diseases associated with accelerated eryptosis include sepsis, haemolytic uremic

syndrome, malaria, sickle-cell anemia, beta-thalassemia, glucose-6-phosphate dehydrogenase (G6PD)-deficiency, phosphate depletion, iron deficiency and Wilson's disease. Among the known stimulators of eryptosis, paclitaxel, chlorpromazine, cyclosporine, curcumin, PGE₂ and lead have indeed been shown to favourably influence the course of malaria. Moreover, sickle-cell trait, beta-thalassemia trait, glucose-6-phosphate dehydrogenase (G6PD)-deficiency and iron deficiency confer some protection against a severe course of malaria. Importantly, counteracting *Plasmodia* by inducing eryptosis is not expected to generate resistance of the pathogen, as the proteins involved in suicidal death of the host cell are not encoded by the pathogen and thus cannot be modified by mutations of its genes.

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Introduction

Pathogens may enter host cells and thus escape the immune system. Within the host cell the pathogens may replicate until they exit in order to infect other cells. Host cells may be forced to support the pathogen by increased nutrient supply and waste disposal across the cell membrane [1]. Altered transport across the cell membrane is particularly important during infection of

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erythrocytes with the malaria pathogen *Plasmodium* [2], a disease causing 300-500 million clinical cases and 1-3 million deaths per year [3]. Substrate turnover of noninfected erythrocytes is low but very high in erythrocytes harbouring replicating *Plasmodium* with its extensive nutrient requirements [2]. For instance, an infected erythrocyte consumes 40-100 times more glucose than a non-infected cell [2]. In order to establish the required transmembrane transport, *Plasmodium* induces the so-called new permeability pathways (NPP) [4]. NPP accomplish the transport of nutrients and waste products, the maintenance of osmotic equilibrium and cell volume regulation as well as the entry of Na^+ and Ca^{2+} into the host cell thus adjusting the electrolyte composition of the host cytosol to the requirements of the parasite [2]. Inhibition of NPP [5-9] eventually disrupts the intraerythrocyte survival of the pathogen. Moreover, the percentage of infected erythrocytes is decreased by removal of extracellular Ca^{2+} [10-12].

NPP include inwardly rectifying [13-16] and outwardly rectifying [15, 16] anion channels as well as non-selective cation channels [17-20]. The *Plasmodium* imposes oxidative stress on host cells [21-25], and this has been proposed to be required for the activation of the channels [15].

One consequence of the cation channel activation is the triggering of suicidal erythrocyte death or eryptosis [26]. While the channels are required for intraerythrocytic survival, replication and maturation of the pathogen, they limit the life span of the infected erythrocyte and thus of the intracellular pathogen. The case is made that manipulating the suicide of infected erythrocytes may be a strategy to fight the pathogen, to decrease parasitemia and thus to favorably influence the clinical course of malaria. Most importantly, the proteins involved in suicidal erythrocyte death are encoded by the host and do not mutate under selective pressure on the pathogen. Thus, fighting the pathogen with this strategy is not expected to generate resistance.

In the following, a description of the mechanisms and signaling involved in suicidal erythrocyte death will be followed by a discussion of stimulators, respective diseases and inhibitors of eryptosis as well as of the putative role of eryptosis in malaria.

Suicidal erythrocyte death

Usually, erythrocytes within 100-120 days undergo senescence, which eventually results in the clearance

of the aged erythrocytes [27-29]. Senescence comprises binding of hemichromes to band 3, clustering of band 3, and deposition of complement C3 fragments and anti-band 3 immunoglobulins [30]. Hemichromes are ferric Hb derivatives with characteristic absorption and electron spin resonance spectra in which the sixth heme ligand is either the distal histidine, in which case the process is reversible (“reversible hemichromes”) or another aminoacid residue from the globin (“irreversible hemichromes”). Hemichrome formation depends on the amount of met-Hb formed and is accelerated by oxidants such as superoxide or H_2O_2 that enhance the formation of met-Hb [27]. Prior to senescence-dependent removal, erythrocytes may, similar to nucleated cells, undergo a suicidal death program which accomplishes the disposal of abundant, defective or potentially harmful cells [31, 32]. Suicidal death of nucleated cells or apoptosis [31, 32] is paralleled by cell shrinkage, nuclear condensation, DNA fragmentation, mitochondrial depolarization, cell membrane blebbing and breakdown of phosphatidylserine asymmetry of the plasma membrane [33-39]. Stimulators of apoptosis include activation of death receptors such as CD95 [40-42] or $\text{TNF}\alpha$ [43], cell injury due to oxidative stress [44, 45], cytostatic drugs [46], radiation [47], osmotic shock [48], alkaline stress [49], Na^+/H^+ exchanger inhibitors [50] or bile salts [51]. Apoptotic cells are identified by macrophages recognizing [52], engulfing and subsequently degrading [53] phosphatidylserine-exposing cells.

Mature erythrocytes have lost their nuclei and mitochondria, important organelles in apoptosis. Nevertheless, erythrocytes may undergo suicidal death characterized by cell shrinkage, membrane blebbing and phosphatidylserine exposure, all features typical of apoptotic nucleated cells [54-56].

A major stimulator of eryptosis is an increase in cytosolic Ca^{2+} activity [54-56], which leads to cell membrane vesiculation [57], stimulates cell membrane scrambling [58-60] and activates the cysteine endopeptidase calpain, an enzyme degrading the cytoskeleton and thus causing cell membrane blebbing [61]. Ca^{2+} may enter through nonselective cation channels [62-66]. The molecular identity of those channels is incompletely understood but may include TRPC6 [67]. The cation channels are activated by osmotic shock [68, 69], oxidative stress [70, 71] and Cl^- removal [64, 68, 71].

Ca^{2+} , in addition, stimulates Ca^{2+} -sensitive K^+ channels [72-74] with subsequent efflux of K^+ , hyperpolarization of the cell membrane and Cl^- exit [75]. The cellular loss of KCl with osmotically obliged water

causes cell shrinkage [75].

A second major stimulator of cell membrane scrambling is ceramide [76]. Eryptosis is further stimulated by energy depletion [77], oxidative stress [78-80] or impaired antioxidative defence [81-83]. Oxidative stress involves activation of the Ca^{2+} -permeable cation channels [71]. Moreover, oxidative stress activates erythrocyte Cl^- channels [15, 84] which contribute to eryptotic cell shrinkage [85]. Oxidative stress further activates caspases [55, 86, 87].

Suicidal erythrocyte death may be triggered by a wide variety of stimulators [88] including ligation of specific surface antigens, such as glycophorin-C [89], the thrombospondin-1 receptor CD47 [90] and the death receptor CD95/Fas [91]. Eryptosis may further be stimulated by ceramide (acylsphingosine) [76], prostaglandin E_2 [64], platelet activating factor [92], anti-A IgG antibodies [93], hemolysin from *Vibrio parahaemolyticus* [94], listeriolysin [95], paclitaxel [96], amantadine [97], azathioprine [98], amiodarone [99], retinoic acid [100], ciglitazone [101], chlorpromazine [58], peptidoglycan [102], cyclosporine [60], methylglyoxal [59], amyloid peptides [103], anandamide [104], Bay-Y5884 [105], curcumin [106], arsenic [107], methyl dopa [108], valinomycin [109], aluminium [110], mercury [111], lead [112], gold [113], selenium [114], vanadium [115], cadmium [116], tin [117], and copper [118].

Eryptosis participates in the pathophysiology of several clinical conditions, including sepsis [119], hemolytic uremic syndrome [120], renal insufficiency [121], malaria [10], sickle-cell anemia [122, 123], beta-thalassemia [80], glucose-6-phosphate dehydrogenase (G6PD)-deficiency [80], phosphate depletion [124], and Wilson's disease [118]. Enhanced eryptosis in sepsis [119] and hemolytic uremic syndrome [120] is secondary to the capability of serum from respective patients to trigger eryptosis.

The Ca^{2+} -permeable cation channels and thus eryptosis are inhibited by erythropoietin [121], which similarly inhibits apoptosis of erythrocytic progenitor cells [125, 126]. The inhibitory effect of erythropoietin on eryptosis increases the life span of circulating cells [126]. Interestingly, however, *in vitro* eryptosis of erythrocytes from erythropoietin-overexpressing mice is enhanced [127]. Possibly, these erythrocytes are adapted to high erythropoietin signaling and are, therefore, more sensitive to *in vitro* removal of erythropoietin [128]. Dopamine, isoproterenol and epinephrine inhibit eryptosis by decreasing the activity of the Ca^{2+} -permeable cation channels [129]. The cation channels [68, 69] and thus eryptosis [130] are further inhibited by amiloride [69] and

ethylisopropylamiloride (EIPA) [130]. Additional inhibitors of eryptosis include flufenamic acid [131], adenosine [132], zidovudine [133] and caffeine [134]. The most powerful known inhibitor of eryptosis is nitric oxide [135], which could be released from erythrocytes [136-138], whereby oxygenated hemoglobin binds and desoxygenated hemoglobin releases NO [137, 139-143]. Nitric oxide is partially effective through activation of cGMP-dependent protein kinases [135, 144, 145]. Accordingly, deficiency in cGMP-dependent protein kinase type I (cGKI) leads to excessive eryptosis, severe anemia and splenomegaly [146].

Eryptosis in malaria

As indicated above, *Plasmodium falciparum* depends on the activation of ion channels in the erythrocyte cell membrane, as they allow the uptake of nutrients, Na^+ and Ca^{2+} and the disposal of waste products [2]. *Plasmodium falciparum* activates the ion channels by inducing oxidative stress [15, 18, 84]. The opening of the Ca^{2+} -permeable cation channels is followed by Ca^{2+} entry and stimulation of eryptosis [81-83]. The clearance by macrophages limits the life span of the infected eryptotic cells [147]. Thus, the pathogen faces a dilemma. On the one hand, it requires the channels in the erythrocyte membrane for the uptake of nutrients and the replacement of K^+ by Na^+ in the erythrocyte cytosol. On the other hand, the associated Ca^{2+} uptake eventually triggers eryptosis of the parasitized erythrocyte [10] and the opening of those channels thus limits the period of safe dwelling in the host cells.

The intraerythrocytic pathogen deals with this dilemma by delaying the execution of eryptosis. It sequesters Ca^{2+} and thus keeps the intra-erythrocytic free Ca^{2+} concentration together with the activity of the erythrocyte Ca^{2+} pump low [148]. In addition it prevents premature hemolysis of its host erythrocyte by decreasing the colloid osmotic pressure of the erythrocyte cytosol. This is accomplished by excess haemoglobin digestion and by export of the haemoglobin-derived amino acids through the NPP [149]. Eventually, *Plasmodium* infection results in breakdown of the phospholipids asymmetry across the erythrocyte membrane and exposure of phosphatidylserine [10, 150-154].

Phosphatidylserine exposure, in turn, has been demonstrated for trophozoite-infected erythrocytes to stimulate their phagocytotic clearance [155, 156]. On the other hand, phosphatidylserine exposure report-

edly facilitates tissue sequestration of trophozoite-infected cells and, thus, contributes to the partial immune evasion of the late stages [150, 157]. In addition to triggering phosphatidylserine exposure, the intraerythrocytic pathogen ages its host cell, i.e., it induces a dramatic, time-compressed acceleration of normal erythrocyte senescence which contributes to the clearance of infected cells [156, 158]. In particular, this occurs in infected erythrocytes with sickle-cell trait, beta-thalassemia-trait, homozygous Hb-C and G6PD-deficiency which fosters the clearance of these erythrocytes already in the ring stage of infection and which underlies the partial resistance to malaria of the carriers of these erythrocytes [27, 155, 159, 160].

Erythrocytes with haemoglobinopathies or G6PD-deficiency are highly prone to enter eryptosis [80, 159-163] and pharmacological induction of phosphatidylserine exposure of ring stage-infected erythrocytes reportedly accelerates their clearance [155]. Thus, manoeuvres accelerating eryptosis may result in premature clearance of the intraerythrocytic parasite.

As a matter of fact, iron deficiency [164], lead [165], chlorpromazine [166] and inhibition of NO synthase by L-NAME [167] decrease parasitemia and partially enhance the survival of *Plasmodium berghei*-infected mice eventually by accelerating erythrocyte death. Thus, several conditions are known, which are associated with enhanced susceptibility to eryptosis and at the same time with a milder course of malaria. Among those, sickle cell trait is an example of a condition which is not associated with the problem of developing resistance of the pathogen since the physiology of the host cell is not at the genetic disposition of the pathogen.

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