REVIEW ARTICLE

Understanding the relation between red cell morphology and its membrane composition

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ABSTRACT

Red blood cell morphological alterations are the most common, arising from mutations in genes encoding numerous red blood cell membrane proteins. A healthy red cell membrane has a unique composition in which the lipid bilayer is connected to spectrin, a built-in membrane skeleton responsible for the cell's exceptional mechanical stability and pliability, thereby enabling the cell to traverse narrow capillaries and optimize gas exchange. Alterations in various proteins of the red blood cell membrane cytoskeleton and their interactions with the lipid bilayer disrupt membrane interconnections, leading to loss of surface area, reduced mechanical stability, membrane fragmentation, and various hereditary morphological disorders, such as spherocytosis, stomatocytosis, and elliptocytosis. Numerous studies in the literature examine morphological alterations of red blood cells in health and disease, but no comprehensive review has examined the relationship between morphological anomalies and membrane composition. In this review, we highlight the probable aspects of membrane composition changes that lead to morphological alterations in red blood cells and elucidate the molecular basis of these changes.

Keywords: Red cell, Spectrin, Stomatin, Spherocytosis, Stomatocytosis.

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INTRODUCTION

The flexible membrane of the biconcave red cell, with a high surface-to-volume ratio, allows the red cell to suffer significant reversible elastic distortion as it constantly passes through tiny blood vessels during microcirculation. The ability of red cells to deform is crucial for their circulation, which is necessary for the transportation of oxygen and carbon dioxide. Pathological conditions and exposure to environmental toxicants, such as chemicals or heavy metals1 can cause significant changes in discocyte morphology. One of the unique characteristics of red blood cells is their capacity to change shape; variations in their membrane properties can impair this ability, thereby interrupting and sometimes blocking circulation.[2] Clinical signs that may be fatal or benign are frequently observed as a result of altered circulation (ranging from capillary blockage and reduced blood supply to tissues to organ damage and necrosis). Red blood cell flexibility is compromised in inherited red blood cell diseases, but the mechanisms underlying this are incompletely understood.[2] According to the literature, numerous review papers address red blood cell morphology and its relationship with various red blood cell diseases; however, no study has examined in depth the mechanisms underlying morphological alterations resulting from modifications in membrane composition.

METHODOLOGY

Use of scientific databases for literature search: During the preparation of this review article, we extensively used databases such as Web of Science, ScienceDirect, and the National Library of Medicine (PubMed).

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Healthy Red Cell Morphology

The human red cell is among the simplest of all cells. Mature red cells have lost their nucleus, mitochondria, and internal membranes and are essentially sacks of hemoglobin. Human red blood cells are biconcave discoid, with diameters ranging from 7.5 to 8.7 µm and thicknesses of approximately 1.7 to 2.2 µm. The membrane skeleton, along with integral proteins and the lipid bilayer, constitutes the red blood cell membrane. The structural proteins, such as ankyrin, spectrin, actin, protein 4.1, and many others, form the multi-protein complex that constitutes the cytoskeleton of the red cell membrane. The red blood cell membrane is generally highly flexible yet stable, primarily due to interactions among integral membrane proteins, transmembrane proteins, and the lipid bilayer. α and β spectrin interact side by side to form a flexible rod, resembling the structure of heterodimers that assemble into tetramers. Ankyrin connects spectrin tetramers to band 3, thereby providing the necessary structural balance. Band 3, regarded as the most abundant integral protein, acts as an anion carrier, facilitating exchange of HCO_3^- for Cl^-

across the cell membrane. On the other hand, Band 3 is also responsible for the formation of the meshwork formed with ankyrin and may be further synchronized by protein 4.2 upon binding to the same site as Band 3. Production of junctional complexes occurs when several spectrin tetramers from the network bind to actin protofilaments, with tropomodulin, tropomyosin, and adducin acting as regulating proteins. The spectrin binding affinity with actin is raised when Protein 4.1 and β-spectrin interact with each other at the actin binding site. Protein 4.1 also binds to glycophorin C to stabilize the membrane cytoskeleton [3-5] Table 1. Because of its exceptional capacity for intermittent massive distortion, the red cell can circulate through blood vessels with a periphery of just 2- to 3 µm. It has been demonstrated that the spectrin network's dynamic cytoskeletal remodeling promotes fluidity[6] (Figure 1). Heritable blood diseases are each a crucial factor in disrupting the structural and mechanical stability of the spectrin meshwork and the overall discoid shape of the red cell [4]. In addition to the proper functioning of all major cytoskeletal proteins, the cholesterol-to-phospholipid ratio of the red cell membrane is an essential factor that regulates membrane pliability and is responsible for the maintenance of normal red cell morphology.[7-9]

Stomatocytosis

This uncommon red cell morphological alteration can be categorized into dehydrated hereditary stomatocytosis (DHSt) and overhydrated hereditary stomatocytosis (OHS).[10-14] Among hereditary stomatocytosis (HST), DHSt has the

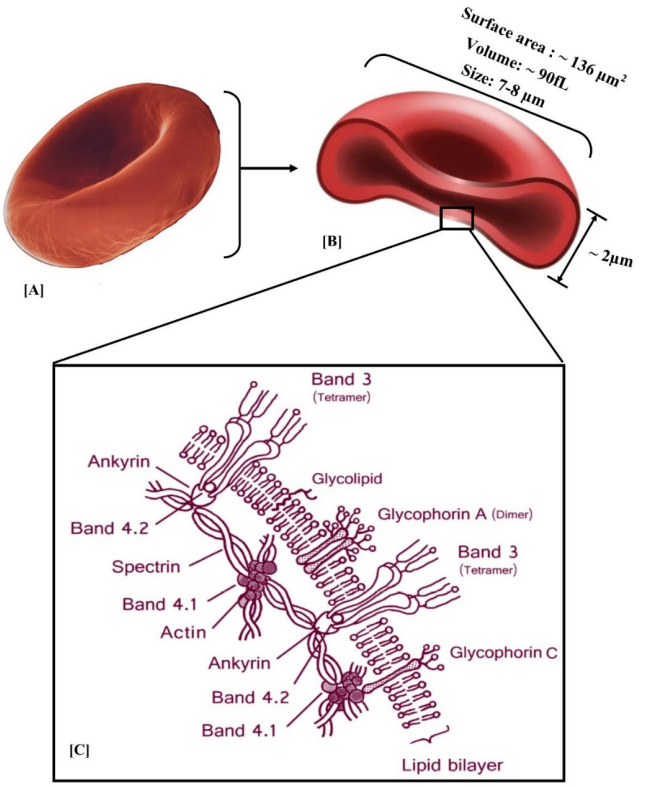


Figure 1: Illustration showing the location of different proteins in a red cell. (A) Mature normal red cell (B)The shape of a human red cell with average geometric parameters, and (C) Schematic organization of the red cell membrane. This illustration is based on review article.[6]

Table 1: The major proteins of the human red cell

Category	*Type*	*Component*	*Molecular Weight (Da)*	*Role*
Protein	Integral	Glucose Transporter (GLUT1)	55,000	• Facilitates transport of glucose molecules across the membrane
	Integral	Glycophorin A, B, C	31,000 23,000 29,000	• Mainly contribute a negative charge and blood group antigens
	Integral	Band 3 (AE1)	100,000	• Facilitates exchange of Cl^- and HCO_3^- ions. • Helping to maintain the biconcave shape of RBC
	Peripheral	Ankyrin	215,000	• Key cytoskeletal protein, maintaining the structure and stability of the cell. • Helps to link Spectrin to Band 3.
	Peripheral	Spectrin	485,000	• Helps to maintain the shape and flexibility of the cell. • Form a mesh-like cytoskeleton.
	Peripheral	Actin	43,000	• Provide support for the membrane structure. • Links with spectrin filament.
	Peripheral	Protein 4.1 & 4.2	{74,000 72,000}	• Helps to stabilize spectrin and actin filament interaction.
	Peripheral	Tropomyosin	{29,000 27,000}	• Mainly regulate the cytoskeleton and its stability.
	Peripheral	Adducin	{105,000 100,000}	• Plays a crucial role in the regulation of the structure and function of the cell membrane. • Particularly regulates the actin filament

Source: Mathews CK, Van Holde KE, Ahern KG. Lipid, Membrane and Cellular Transport. Biochemistry, 3rd ed. 2000.[3]

highest incidence, occurring in approximately 1 in 50000 births.[15] Both morphological disorders alter intracellular cation content and cell volume due to leakage of the univalent cations Na^+ and K^+.[16]

Membrane Structural Changes

Stomatocytosis is autosomal-dominant. From asymptomatic to severely hemolytic, the phenotype can vary. The primary hallmark of the DHSt is red cell dehydration resulting from cation efflux, particularly K^+, and water loss.[17] As a result, the Mean Corpuscular Hemoglobin Concentration (MCHC) increases, but surprisingly, red cell viability is not markedly affected. The phenotype can range from moderate anemia with normal or marginally elevated Mean Corpuscular Volume (MCV), and such patients exhibit stomatocytes with characteristic mouth features on peripheral blood smears (Table 2).

Functional Impairments in Red Blood Cells and the Responsible Molecular Factors

Studies of DHSt patients from North American families using copy number and linkage analyses, as well as exome sequencing, have revealed that all affected patients have PIEZO1 protein mutations, which are encoded by the FAM38A gene.[18] The channel components that create pores and control mechanotransduction, as well as the activation of stretch-activated cation channels in mammalian cells, are referred to as PIEZO proteins, which are also present in red cells. The PIEZO proteins may be crucial for maintaining the volume and cation balance of red blood cells [19, 20] (Figure 2). In contrast to DHSt, the red blood cells in overhydrated hereditary stomatocytosis (OHS) exhibit a 20 to 40-fold cation leak, leading to overhydration.[21] Although this type of stomatocytosis is uncommon (20 cases have been reported worldwide), it produces the most severe morphological abnormalities of red blood cells. OHS is also associated with hemolytic anemia, characterized by a significant rise in MCV and a decline in MCHC in red blood cells, as well as reticulocytosis. All of these red blood cell characteristics result from their extreme hydration. Because there are typically many more stomatocytes on the blood smear in this form than in the DHSt, the diagnosis is relatively straightforward. Recent studies suggest that the OHS has the RhAg (Rh-associated glycoprotein) mutations p.Ile61Arg and p.Phe65Ser. RhAg is a member of the band three complex and is thought to function as a gas channel or ammonium transporter.[22,23] Studies also indicate that another membrane protein, Stomatin, has not been found mutated in OHS but is expressed at low levels or absent in OHS [24]. In cholesterol-rich membrane regions, stomatin and stomatin-like proteins interact with a variety of ion channels and control channel activity in a cholesterol-dependent way.[25-28] Human stomatin, in particular, interacts with the glucose transporter GLUT1, controlling the influx of glucose and dehydroascorbate into red blood cells, and also plays a vital role in scaffolding.[29,16] Therefore, its low level or absence is responsible for overhydrated hereditary stomatocytosis (OHS).

Familial pseudohyperkalemia and cryocytosis are two additional types of stomatocytosis that have been documented. Since stomatocytes are infrequent and hemolytic anemia is absent, familial pseudohyperkalemia is unique in that red blood cells leak K^+ at normal room temperature but not at physiological temperature. Patients who have the cryocytosis (CHC) type show moderate hemolytic anemia. Numerous Band 3 mutations also convert the anion exchanger into a cation transporter.[30-32]

Hereditary Spherocytosis (HS)

HS is one of the most common hereditary membrane disorders found. The occurrence of HS is predominantly higher among individuals of northern European ancestry, with a diagnosis rate of 1:2000 individuals.[15] Hereditary spherocytosis (HS) can be identified in early infancy, sometimes even during the neonatal phase or, in more severe cases, before birth. HS leads to hemolytic anemia and jaundice. The clinical manifestations include pallor due to anemia, jaundice due to elevated bilirubin levels, and splenomegaly, as the spleen is the site where nondeformable HS red blood cells are sequestered and phagocytized.

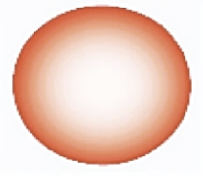
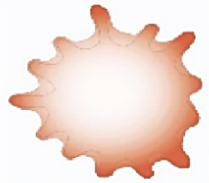
Membrane Structural Changes

A congenital red cell membrane disorder characterized by spherical red cells having a smaller diameter with no visible pallor under the microscope, and carrying more hemoglobin than normal.[33,34] Due to mutations in genes, spectrin density and spectrin network connectivity are lost in patients with HS, reducing the overall flexibility of red cells and making them more osmotically fragile[35] (Table 2).

Functional Impairments in Red Blood Cells and the Responsible Molecular Factors

The lipid bilayer is anchored to the membrane skeleton via various proteins, and alterations in these proteins cause HS. Protein interactions mediated by vertical connections are thought to contribute to red blood cell membrane stability. The accountable factors for HS include mutations in α-spectrin (SPTA1) and β-spectrin (SPTB) genes, ankyrin (ANK1), band 3 (SLC4A1), band 4.2 (EPB42), and β–adducin.[36] Decreased spectrin density and abnormalities in other cytoskeletal proteins increase the severity of HS. The cytoskeleton in healthy red blood cells is formed when spectrin molecules bind to actin via two-dimensional linkages. In normal red cells, each actin filament is roughly bound to 5 to 5.5 spectrin molecules. However, spectrin network connectivity, which depends on spectrin density, is reduced in patients with HS. Furthermore, patients with HS can have a spectrin network connectivity as low as 3.3 spectrin per actin. The severity of HS is directly linked to the extent of spectrin network connectivity loss; i.e., the fewer spectrin molecules per actin, the greater the severity. This loss of spectrin and other cytoskeletal proteins, along with vesicle formation from the

Table 2: Relationship between membrane composition and morphological alterations

Morphology	Membrane Composition	Outcomes of Morphology
 **Discocyte**	Normal levels of lipids (phospholipids, glycolipids and cholesterol) and proteins (peripheral and integral).	Biconcave discoid shape, flexible, ideal for gas exchange and circulation.
 **Stomatocyte**	Inner leaflet phospholipids are increased (e.g., phosphatidylethanolamine), alteration in membrane proteins like band 3 & stomatin.	Mouth feature erythrocyte on blood smears, decreased deformability, seen in some hemolytic anemias.
 **Spherocyte**	Reduced spectrin or ankyrin levels, causing membrane loss, decreased pliability and increased membrane rigidity.	Spherical in shape with the absence of biconcave nature, reduced surface area-to-volume ratio, flexibility is markedly reduced, susceptible to hemolysis.
 **Elliptocyte**	Mutations primarily involve red cell membrane proteins like spectrin, ankyrin, Band 3 or Protein 4.1 which form the cytoskeleton of the red cell.	Elliptical, oval, or elongated erythrocytes, more rigid, associated with hereditary elliptocytosis.
 **Acanthocyte**	Altered lipid composition, predominantly increased cholesterol-to-phospholipid ratio.	Spiked with uneven projections, reduced flexibility, seen in liver disease or abetalipoproteinemia.
 **Echinocyte**	Increase in outer leaflet phospholipids, often linked with changes in pH or ATP reduction.	Spiculated erythrocytes, with numerous short projections throughout the membrane, seen in uremia or after storage.

Source of pictures: http://clinical-laboratory.blogspot.com/2013/03/clinical-laboratory-blood-cell_9.html

lipid bilayer, promotes progressive membrane loss in red blood cells. Spherical red blood cells (spherocytes) have reduced deformability because the cell progressively releases vesicles with a greater lipid-to-protein concentration, thereby reducing the overall membrane surface area.[37]

Hereditary Elliptocytosis

Hereditary elliptocytosis (HE) is an uncommon condition that varies both clinically and genetically, affecting the red blood cell membrane and presenting with a spectrum of clinical manifestations. The worldwide incidence of HE is 1:2000–4000; however, in particular African regions where malaria is common, the incidence can reach as high as 1:100 due to increased resistance of erythrocytes to malaria.[38]

Membrane Structural Changes

The red cells are elliptical-shaped and are present in a peripheral blood smear. The carrier status can range from asymptomatic to severe hemolytic anemia that requires blood transfusions. Abnormalities of several membrane proteins cause the mechanical faults of the red cell membrane skeleton. Usually, red blood cells are discoid and flexible. Still, in HE, they become elliptical (oval or elongated) due to mutations in genes that maintain the assembly and pliability of the red blood cell membrane. These mutations primarily involve membrane proteins such as ankyrin, spectrin, Band 3, and Band 4.1, which form the red cell cytoskeleton.[39] (Table 2)

Functional Impairments in Red Blood Cells and the Responsible Molecular Factors

Protein 4.1 (EPB41 gene) and Spectrin α, β (SPTA1 and SPTB genes) are hotspots of mutation in HE.[40] The disturbance of α-β heterodimer formation is the consequence of the α-spectrin mutation—mutations in β-spectrin result in an α-β heterodimer that cannot generate spectrin tetramers. Mutations in protein 4.1 prevent spectrin tetramers from binding to actin, thereby leading to an erroneously assembled cytoskeletal scaffold and ultimately to red blood cell membrane disintegration and decreased surface area. The spleen filters out and eliminates the Heinz bodies from the bloodstream. Whereas healthy red blood cells remain viable for 120 days before clearance by the spleen, HE red blood cells have a reduced lifespan due to reduced membrane flexibility and mechanical instability. Most people with HE don't show any symptoms; the condition is inadvertently found on a blood smear. However, a minor percentage of patients have hemolytic anemia, which manifests as anemia, jaundice, and splenomegaly. There are also reports of hemolytic anemia, hydrops fetalis, and neonatal jaundice associated with HE patients.[41-43]

Acanthocytes

Acanthocytes, often termed spur cells, result from membrane lipid abnormalities and are present in patients with end-stage renal disease, liver disease, anemia, pyruvate kinase deficiency,[44] and other conditions.

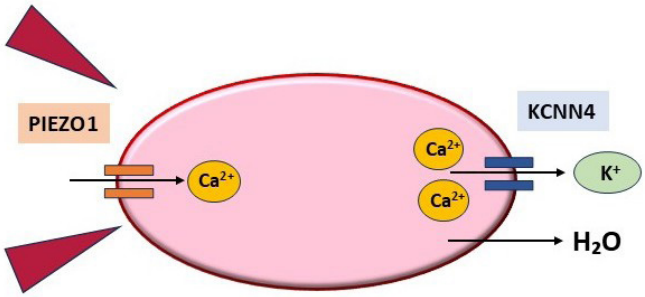


Figure 2: Schematic diagram portraying the interaction between PIEZO1 and KCNN4 as a red cell travels through the blood vessels. In narrow capillaries and sinusoids, the red cell encounters mechanical stress (represented by arrowheads), which results in activation of PIEZO1 and Ca^{2+} entry. Increased intracellular Ca^{2+} leads to activation of KCNN4 (an intermediate conductance calcium-activated potassium channel that plays a role in regulating membrane potential and maintaining calcium homeostasis), and K^+ efflux ensues. Subsequent water loss results in a temporary decrease in red cell volume and facilitates passage through narrow capillaries. This illustration is based on a review article.[20]

Membrane Structural Changes

Acanthocytes are red blood cells with irregular, pointed projections on their cell surface, resulting from changes in the lipid composition of the red blood cell membrane. This unusual morphology is strongly related to modifications in both the lipid and protein configurations of the red cell membrane (Table 2).

Functional Impairments in Red Blood Cells and the Responsible Molecular Factors

Acanthocytes are associated with an elevated cholesterol-to-phospholipid ratio in the outer leaflet of the red blood cell membrane, disrupting standard membrane structure and triggering the formation of spicules or projections. The microsomal triglyceride transfer protein (MTTP) gene mutation is observed in such cases. It leads to disorders such as abetalipoproteinemia (an ailment that affects lipid absorption) and certain liver diseases, in which cholesterol metabolism is disturbed.[45,46] It is well known that membrane proteins, in addition to lipids, play a role in maintaining the structure and stability of red blood cells. Communication between lipids and proteins (spectrin and ankyrin) is disrupted, thereby perturbing membrane assembly and contributing to the irregular shape observed in acanthocytosis. The red cell cytoskeleton maintains the discoid shape of a normal red cell, and alterations to these proteins result in deformation of the cell membrane. Neuroacanthocytosis syndromes (a group of neurodegenerative disorders) are a condition seen in.[47] Moreover, abetalipoproteinemia and liver disease are also observed in acanthocytosis, where lipid metabolism is altered. In such cases, misshapen red cell morphology contributes to increased hemolysis, and a reduced red cell lifespan is observed.[48,49]

Echinocytes

Echinocytes (from the Greek word echinos, meaning "sea urchin"), also termed burr cells, are very much prevalent in individuals with liver and kidney disease.[48]

Membrane Structural Changes

Echinocytes are red cells with small, frequent projections that are evenly spaced on their cell surface. These morphological alterations are usually reversible and often arise from changes in the cell membrane's environment or composition. Echinocytes usually display a surface that is homogenously spiculated with short, sharp projections that are more evenly distributed than those observed in acanthocytes. The shape change is more often a reaction to environmental factors than to inherent genetic mutations[48] Table 2.

Functional Impairments in Red Blood Cells and the Responsible Molecular Factors

The transformation into echinocytes is primarily driven by external factors, such as alterations in pH, ion imbalances in the extracellular fluid, or ATP depletion, which distort the lipid bilayer of the cell membrane. These changes may lead to augmented phosphatidylserine exposure and alterations in the outer and inner leaflets of the red cell membrane. Modifications in the cholesterol-to-phospholipid ratio also play a significant role in echinocyte formation [48]. Factors such as a hypertonic environment or dehydration may also contribute to their appearance. One of the most common causes is uremia, where toxic waste products build up in the blood due to kidney failure, leading to the formation of echinocytes.[48] Echinocytes can also appear as an artifact in blood samples, often due to prolonged exposure to anticoagulants such as EDTA. Echinocytes are also observed in conditions such as liver disease, viral infections after severe burns, or certain anemias, but the changes may be limited if the underlying cause is corrected [49].

CONCLUSION

In summary, understanding the shape of red blood cells and their relationship to membrane composition is crucial for appreciating their versatility and activity. Red blood cell shape, flexibility, and microcirculatory function are directly influenced by the membrane structure, which is composed primarily of proteins and lipids. Modifications in the membrane lipid ratio, mutations of genes such as SPTA1, SPTB, ANK1, SLC4A1, FAM38A, leading to alteration of proteins like spectrin, ankyrin, Band 3, and PIEZO, or the protein-lipid connections may lead to morphological alterations, such as spherocytosis, stomatocytosis, elliptocytosis, etc., which are often indicative of underlying red cell membrane skeleton disorders. Moreover, the membrane configuration plays a pivotal role in maintaining osmotic equilibrium and providing pliability, both of which are crucial for the cell's survival under mechanical stress in the circulation.

Clinical Implications and Future Directions

Understanding the relationship between red blood cell morphology and membrane structure is key to diagnosing and treating conditions such as HS, HE, and Stomatocytosis, in which abnormal red blood cell morphology, due to membrane defects, leads to various clinical complications. Furthermore, advances in research and diagnostics employ proteomic and lipidomic profiling for in-depth membrane analysis, and the use of Gene-editing tools to study or correct membrane protein mutations can be successfully carried out if the underlying relationship between membrane structure and morphology is understood correctly. Therefore, this article will elucidate the structural basis for a more rational approach to future research and advanced clinical diagnosis.

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PEER-REVIEWED CERTIFICATION

During the review of this manuscript, a double-blind peer-review policy has been followed. The author(s) of this manuscript received review comments from a minimum of two peer-reviewers. Author(s) submitted revised manuscript as per the comments of the assigned reviewers. On the basis of revision(s) done by the author(s) and compliance to the Reviewers' comments on the manuscript, Editor(s) has approved the revised manuscript for final publication.