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Review Article

The Red Blood Cell Not Only for Colour Identity but with Complex Material Properties

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Abstract

The red blood cells are biconcave disc in shape, flattened and depressed in the center. The shape with its high surface area to volume (SAPV) ratio helps to accelerate diffusion of gases. The red cell membrane consists of bilayers of proteins and lipids which are rich in the glycosphingolipids that reside on the red blood cells and serve as the major determinants for the discovery of blood groups that are of major importance in blood group serology, paternity dispute and in transfusion medicine. Not only that, the membrane proteins carry the various blood group antigens, transporting ions, endothelial cells as signaling receptors and adhesive properties. This makes the red blood cells possible not to experience protein synthesis and for that no viral attack on them. The red blood cell abnormalities are being regulated by three constitutive characteristics namely, the geometry of the cell that is the cell surface to volume ratio, cytoplasm viscosity powered by intracellular haemoglobin concentration and membrane deformability. This review highlights on the importance of the red blood cell in our diagnosis and also its importance in study of red blood cell morphology to assist in the classification of numerous disease condition which can be treated with mere blood film microscopy.

Keywords: Red blood Cells; Haemoglobins; Membrane Proteins; Oxygen; Erythropoiesis

Introduction

The red blood cells are biconcave disc in shape, flattened and depressed in the center. The shape of the red blood cells with its high surface area to volume (SAPV) ratio helps to accelerate diffusion of gases [1]. The mature red blood cell is anucleated and the cytoplasm is enriched with haemoglobin full of iron - containing molecules that carries oxygen and gives red colour of the blood [2]. The red cell membrane consists of bilayers of proteins and lipids. Glycolipids, phosphatidylcholine, and sphingomyelin are related in the outer half of the bilayer; phosphatidylinositols, phosphatidyl ethanolamine, and phosphatidyl serine occur in the interior layer facing the cytoplasm. These properties in the red cell membrane provide physiological function for the cell stability and deformability when passing the circulatory system. The approximate number of 2-4 million new erythrocytes is produced per second in human adult [3].

The production of red blood cell starts from the bone marrow and circulate for about 100 - 120 days before death and each circulates for 60 seconds [4]. All the vertebrates have red blood cells except ice fish that lives in oxygen rich cold water that makes distribution of oxygen freely in the blood [5]. The human red blood cell has a disc diameter of approximately 6.2 - 8.2 mm and minimum thickness in the center of 0.8 - 1 mm [6,7]. Among other blood particles like platelet 150,000 - 400,000 per

microlitre and leucocytes 4,000 - 11,000 per microlite red blood cell is much more common 5 - 6 million per microlitre. The colour of the red blood cell is made possible following the hemic iron ion in the haemoglobin. The anucleate nature of the red blood cell in the vertebrate explained the high density of non - coding deoxyribonucleic acid(DNA) in the genome [8]. But at the final stage of maturity without nucleic acid is called reticulocyte and losses the cellular organelles. There are two forms of nucleated red blood cells that exist in mammals - normoblast and megaloblast where the normoblast undergoes the normal erythropoiesis to mature red blood cells and megaloblast occurs in a disease condition called megaloblastic anaemia. Although the mature red blood cells in mammals do not contain DNA and cannot synthesize RNA because of no nucleic acid and organelle [9]. This makes the red blood cells possible not to experience protein synthesis and for that no viral attack on them [10]. The erythropioesis leads to the production of red blood cells that is triggered by hormone called erythropoietin from the kidney. The red blood cell programmed death is called eryptosis [11] and increased in varieties of diseases. This destruction of red blood cell can be seen in varieties of disease conditions such as sepsis, haemolytic uraemic syndrome, malaria, sickle cell anaemia, beta - thalasemia, glucose - 6 - phosphate dehydrogenase deficiency, phosphate depletion, iron deficiency anaemia, Wilson's disease. This programmed red cell death is also induced by a lot of factors such as osmotic shock, oxidative stress, energy stress, energy depletion, endogenous mediators and xenobiotics. The xenobiotics are inform of exogenous or foreign substances be it chemical, environmental pollutants or drugs that affect the shape of red blood cell and human life in general.

Brief history

The discovery of red blood cell in 1658 was of its first time by Jan Swammerdan [12]. He was a Dutch biologist (1637-1650). In 1674, Anton Von Leewenhoek described the microscopic nature of the red cell as being 25,000 times smaller than a fine grain of sand. Followed by Karl Landsteiner in 1901 and Alfred Von Decastello and Adriano Sturli in 1902 discovered A, B, O and AB blood group respectively. All these reside on the red blood cell membrane where the genes or antigens are located. Dr Max Perutz 1959 [13], by the use of X -ray crystallography, discovered the structure of haemoglobin being the red blood cell protein that carries the oxygen. The cell membrane of the red blood cell has specific membrane proteins fullwa, stomastins (band-7), G-proteins, and B-adrenergic receptors. The biologic and structural membrane of it was described by Gorter and Grendel [14] in 1925 which was the first approach in the description of red cell membrane as bimolecular layers of lipids on the chromocytes of blood. The mosaic model structure and isolation of spectrin of red cell membrane were made possible through the works of Singer and Marchesi [15,16] respectively. Also Steck and his colleagues [17] worked out the topology of the red cell membrane proteins.

The glycosphingolipids reside on the red blood cells and serve as major determiner for the discovery of blood groups that is of major importance in blood groups serology, paternity dispute and in transfusion medicine. This consists of protein, polysaccharides and less frequently lipids. While the lipids and nucleic acid are antigenic only when combined with proteins and polysaccharides. The discovery of ABO blood groups were made possible by the work of Karl Landsteiner in 1900 through the sugar terminal on its outer surface. The A and B specificities were able to come to realities because of N-acetylgalactosamine and D - galactose respectively to give A and B blood group while the O group has no sugar terminal. The uniqueness of the red blood cells makes it so special that at maturity there is no nucleus and create space for much haemaglobin and enough oxygen accommodation. In erythroids cells B-adrenergic receptor signaling increases C-AMP levels and regulate the entrance of malarial parasites into the normal red cells [18,19].

The red cell membrane proteins posses various blood group antigens, transporting ions, endothelial cells (signaling receptors) and adhesive properties. The membrane which has materials transport functions has the ability to mobilize items such as ions, water, urea, gas and also in the discovery of assorted types of blood group systems. The Band 3- anion transporter has the transport function and this describes the Diego blood group that is located on the structural part of membrane [20]. Aquaporin 1 is a water transporter, this defines the Colton blood group and the urea -transporter describes the Kidd antigens protein that is the Kidd blood group antigen. Interestingly, another aspect is that, the red blood cell functions as a gas transporter which depicts the Rhesus blood group (RhAG) and the associated unusual blood group phenotype Rh null. Basal cell adhesion molecule(BCAM) is a plasma membrane glycoprotein that defines the Lutheran blood group known as LU or laminin - binding protein and also known

as cluster of differentiation 239 (CD239). The Protein 4.1 R shows weak expression of Gerbich blood group but the glycophorin C and D glycoprotein, finally defines Gerbich blood group. The GPC and GPD are minor sialoglycoproteins of human red blood cell and play important roles in the maintenance of shape and stability of red cell membrane. The GPC and GPD also serve as the red blood cell receptors for plasmodium merozoites. However, this encompassed the Kell Blood group and the Mcleod unusual phenotype (lack of Kx antigen and greatly reduced expression of kell antigens). The clearance of chemokine has been associated with Duffy protein which makes the Duffy blood group [21]. In gas transport function; it serves as presumptive CO_2 transporter and carbonic anhydrate which turns into a macromolecular complex termed "metabolon", that plays the function of regulating ion and gas in the red blood cell. The ion transport function:- this has the function of ion exchange which occurs in the cell membrane. The Na^+-K^+-ATPase, Ca^{++}ATPase, Na^+-K^+-Cl^- cotransporter, and Gardos channel and also zeta potential and the shear stress occur on the cell membrane. The surface electrostatic potential on the red blood cell is achieved by the scalic acid residues. The zeta potential is an electro-chemical property that determines the net electrical charge of molecules on the cell surfaces. The normal zeta potential of the red blood cell is-15.7 millivolts (mv) [22]. The sialic acid is also called N-acetylneuraminic acid that is an amino-sugar component that assists in cellular communication. It is a naturally occurring building block for glycoproteins and gangliosides present in cell membranes. The shear stress promotes the passage of red blood cell in constructed vessels by the release of adenosine triphosphate (ATP) which helps the wall to relax and leads to normal blood flow [23]. This has the cardio protective effect which is possible following the production of hydrogen sulfide a signaling gas that acts to relax vessel walls which converts the sulfur compound into hydrogen sulfide. This happens when garlic is taken as a cardio protective agent [24]. The red blood cells as body's immune response occur when they are being lysed by bacteria pathogens and led to the release of free radical from the haemoglobin breakdown, the cell wall and membrane of the pathogen lead to death [25,26]. The red blood cells contain no nucleus and protein biosynthesis is currently assumed to be absent in them.

The phosphatidy choline resides at the outer half of the red cell membrane that forms the highly fluids lipid regions while sphingomyelin induces rigidity [27]. Some binding groups are determined by the structure of those external carbohydrates [28]. Moreover, cytoskeleton of the red blood cell has several proteins under the lipid bilayer that forms the filamentous network. Furthermore, this maintains the membrane integrity, shape, flexibility and lipid organization [29]. This red blood cell membrane shows complex material properties. It is highly elastic and flexible (100-fold softer than latex membrane of comparable thickness), this helps to withstand any pressure and when this undergoes tensile stress without disintegration at uniform cell membrane surface area. The lipid bilayer is composed of equivalent amount of cholesterol and phospholipids. There is a significant feature of lipid bilayer levels that are asymmetrically distributed. The phosphatidyl- cholin and sphingomylin are predominantly localized in the outer monolayer of the lipid bilayer while most of phosphatidyl serine (ps) and phosphoinositides are localized in the inner monolayer [30]. Transmembrane protein exhibits diverse functional heterogeneity serving as cation, water and urea transporter, as adhesive proteins involved in interactions of red cells with other blood cells and endothelial cells, in cell signaling events and in some yet-to-be defined functions [31]. The structural integrity of the red blood cell membrane proteins, band-3, glycophorin C and RhAG that link the bilayer to the membrane skeleton through the interaction of their cytoplasm domains with ankyrin [32,33] while glycophorin C links through its interaction with proteins 4.1R [34,35]. The red cell membrane deformities for the past thirty years from the studies carried out from the healthy and patients have showed that the red cell disorders occur following changes in molecular processes and membrane functions [36-40]. The red blood cell of normal shape has the ability to extend linearly up to 250%, but a little increase of 3% to 4% in the surface area leads to cell lyses. This shows that any induced red cell deformation whether *in vitro* or *in vivo* has no significant effect in the membrane surface area. The work of Salzer and Murphy., *et al*. 2001 and 2004 [41,42] respectively showed that the movement of phospholipid from the outer to the inner layer of the red cell is by the enzyme "Flippases" and "floppases" do the opposite against a concentration gradient that requires enough energy. The "Scramblases" do the work by moving the phospholipids bi-directionally down their concentration gradients in energy-independent manner (Salzer U 2001, Murphy Sc., *et al*. 2004). Red blood cell not only as you see the colour but with complex material properties it has. Membrane protein as a linking function, band 3 also assembles various glycolytic enzymes, the presumptive Co_2 transporter, and carbonic anhydrate into a macromolecular complex termed a metabolon,

which may play a key role in regulating red cell membrane and ion and gas transport function. The red blood cell abnormalities are being regulated by three constitutive characteristics namely, the geometry of the cell that is the cell surface to volume ratio, cytoplasmic viscosity powered by intracellular haemoglobin concentration and membrane deformability [37-39].

Cytoplasm viscosity

The defect in red cell haemoglobin concentration in form of hypochromic or hypochromasia is due to impaired haemoglobin synthesis, failure of haem synthesis. The cell also looks hypochromic in appearance due to iron deficient and the damage to the red cells after formation is observed in the cell membrane structural appearance of poikilocyte. Poikilocytosis results from both intrinsic and extrinsic factors. The intrinsic factors occur as membrane defects, enzyme defects and haemoglobinopathy that render the red cell prone to shape alterations. The extrinsic factors arise from drugs, chemical and toxins. In some disease conditions such as anaemia, hereditary spherocytosis, hereditary elliptocytosis (red cell oval in shape or egg shape), thalassemia, folate and vitamin B-12 deficiency, kidney and liver diseases result from changes in red cell morphology. In these types of diseases there is tendency to see poikilocytes. which may be oval, tear-drop, and sickle or irregularly contracted.

Membrane deformability

Spherocyte is when the red cell is fewer disc-like than normal red cells. This results from genetic defects by the interaction between immunoglobulin and action of bacterial toxins. Acanthocytes is when the red cells appear in spine shape shown over the surface of the cells. This is associated with abnormal phosopholipid metabolism [43-45] or with inherited membrane protein abnormities as in Mcleod phenotype induced by Kell precursor deficiency (Kx) [46] also in spur cell anaemia seen in severe liver disease [47]. Leptocytes is a situation when the shape of the red cell appearing unusually thin as in case of severe iron deficiency or thalassemia. The cells may stain as rings of membrane with a large unstained central area.

Conclusion

The knowledge of red blood cell morphology is of utmost importance in the field of medicine. This is because of the vital roles it plays in transfusion science, blood group serology, paternity dispute, and in the diagnosis of blood disorders such as hypochromasia, spherocytosis, acanthocytosis, that are seen in iron deficiency anaemia, liver and kidney diseases. Moreover, the red cell membrane proteins posses various blood group antigens, transporting ions, endothelial cells (signaling receptors) and adhesive properties. Also, the mature red blood cell is anucleated and the cytoplasm is enriched with haemoglobin full of iron-containing molecules that carries oxygen and gives red colour of the blood. The red blood cell not only as you see the colour but with numerous complex material properties.

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