Red blood cell membrane – Is it a mirror for systemic non-hematological genetic disorders?

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Red blood cell membrane is an elegant system. Our knowledge of the red blood cell membrane skeleton continues to increase. As a result much knowledge has been acquired about shape change of red cells in inherited and acquired disease states related to hematological disorders like hereditary spherocytosis, hereditary elliptocytosis, etc. The osmotic gradient created by separating hemoglobin from the plasma drives water into the cell, and the electrical gradient established by the “fixed anions” of hemoglobin creates Donnan forces that also lead to an increase in cell water. The red blood cell has to compensate for these hemoglobin – induced gains in cell water otherwise hemolysis will occur. This is done by creating a disequilibrium of the permanent cation Na and K. A large number of studies have defined on transport process importance in establishing and maintaining the cation disequilibrium in red cells. Numerous reports of altered in transport in many pathologic erythrocytes are also available.

The Na, K-adenosine triphosphatase (Na, K-ATPase), also known as the Sodium –potassium pump, is a membrane associated enzyme responsible for maintaining the high internal K concentration and low internal Na concentration characteristic of most animal cells. It couples the hydrolysis of ATP to the transport of Na and K across the plasma membrane against their respective electrochemical gradients. The Na, K-ATPase consists of two noncovalently linked polypeptides, a catalytic a subunit, with a molecular weight of ~100,000 and a smaller glycosylated b subunit with a molecular weight of ~55,000. A small peptide with a molecular weight of ~10,000 termed g subunit has also been identified in purified preparations of the enzyme. Most functions of the Na, K ATPase have been localized to the a subunit. The a subunit contains the binding sites for ATP and ouabain, it is phosphorylated by ATP and undergoes ligand dependant conformational changes accompanying the binding, occlusion, and translocation of ions. b subunit is essential for Na, K-ATPase structure and function. It is unclear how cation translocating enzymes couple the hydrolysis of ATP to the transport of cations across the membrane. Enhanced Na⁺-Li⁺ exchange activity has been reported in red blood cells of white patients with essential hypertension compared to RBC of normotensive individuals. The transport pathways for Li⁺ ions across RBC have been identified. They include Na⁺⁻Li⁺ exchange or countertransport, Na⁺⁻Li⁺ cotransport anion exchange, the Na⁺,K⁺-ATPase.

The human red blood cell membrane is reinforced along its entire cytoplasm by a two-dimensional network of peripheral proteins that closely adhere to the membrane proper through specific protein-protein interactions. This network functions to stabilize the membrane bilayer without compromising its deformability, thus enabling the RBC to withstand the shearstress during its turbulent passage through the vasculature. Perturbations of the skeleton have been shown to cause irreversible alterations in the permeability, integrity, deformation and shape change of the cells leading to red blood cell pathology. The proteins essential to the integrity of the skeleton are band 1 plus band 2 (a and b subunits of spectrin
respectively), band 4.1 and actin. Spectrin exists in situ as heterodimers, tetramers and higher oligomers, with tetramers as the predominant form.

The actin is thought to be associated into protofilaments. Band 2.1, ankyrin is located at the cytoplasmic surface of the red blood cell membrane ghost and is responsible for the high affinity, saturable binding of spectrin to the membrane bilayer. Another important aspect of the organization of the skeleton is the structure and dynamics of band 3, the anion transporter. This integral membrane protein not only regulates the anionic potential of erythrocytes, but also together with ankyrin and perhaps band 4.1 forms the major crossbridge between the membrane bilayer and the skeleton.

Our knowledge of the red blood cell membrane skeleton is far from complete because there are many unanswered questions and unexplored areas of importance. The interesting article appearing in this issue “Family based analysis of quantitative changes of erythrocyte membrane proteins in essential hypertension” again brings forth the fact that red cell membrane reflects the genetic as well as the environmental effects in apparently unrelated disorder like Essential Hypertension (EH). In the present article the authors have made an attempt to quantify genetic and environmental contributions to quantitate variability of erythrocyte membrane proteins in EH. The study is well designed and adequate control have been taken. The substantial influence of genetic dominance on the variation of cytoskeletal protein 4.1 and glucose transporter seems to reflect the major gene effect. They found that genetic contribution to anion exchanger variation was stronger in hypertensive (88%) than in normotensives (36%). The levels of glucose transporters were controlled by common underlying genes with strong pleiotropic effect.

These data therefore provide evidence to support the genetic component of quantitative changes in membrane proteins of RBC in EH. The pleiotropic effects of common underlying genes seem to be responsible for variations in the transport proteins likely associated with genetic susceptibility to EH.

The contribution from the field of molecular genetics may offer great promise in understanding the pathophysiology of this disorders. Essential hypertension is a polygenic disorder that results from the inheritance of a number of susceptibility genes. Recent preliminary findings suggest that no single region within the human genome contains genes with a major contribution to essential hypertension. The region on chromosome 11 is the first to point to a new candidate gene for hypertension that has arisen out of a genome search, but replication of these results at a higher significance is necessary before positional cloning can be justified.

References