Metabolic pathways of the red blood cell

Red blood cells are highly specialised cells that are adopted to perform their main function of transporting oxygen from the lungs to the rest of the body tissues. Red blood cells are formed in the bone marrow and developed from the pluripotent hematopoietic stem cells (HSCs). The red blood cell contains haemoglobin that authorizes the transport of oxygen and carbon dioxide. Haemoglobin is a pigment that gives the red blood cell their red colour, red blood cells are also known as erythrocytes. Red cells are approximately 7. 8 micrometres in diameter and have a biconcave disk shape; this shape gives the cell a larger surface-to-volume ratio. (Klinken, P S. 2001)

The biochemistry of the red blood cell is complex; the red blood cell is covered in a thin membrane made of chemically complex lipids, proteins and carbohydrates in a highly organized structure. This membrane is extremely flexible, when the red cell has to pass through small minute blood vessels; the shape of the red cell gets distorted. Once the deforming stress is removed the red cell springs back to shape. This flexibility is of course within reason; if the membrane is stretched to a limit the cell can be damaged or destroyed. The membrane is freely permeable to water, oxygen, carbon dioxide, glucose, urea and certain other substances; the membrane however is impermeable to haemoglobin and does not allow the pigment to leave the cell. (Ranney, 1995)

The red cell membrane has a group of molecules on its surface that confer blood group specificity. The ABO blood group can be typed for all humans and many other primates. The system of ABO consists of four allelic genes A, B, AB and O. These genes code for sugar- residue transferase enzymes. There are two antigens and two antibodies that are mainly responsible for

the ABO type. A specific combination of these four components determines an individual's blood type in the majority of cases. The surfaces of red cells are all covered with antigenic molecules; antigens are proteins that induce a specific immune response. The ABO antigen, which is known as the H antigen is a glycoprotein or glycolipid with a terminal L-fructose. The O-gene is an amorph a hidden gene and has no effect on antigenic structure and leaves H-antigen unchanged. The group A gene product adds N-acetyl galactosamine to the H antigen, whereas the group B gene product adds the sugar D-galactose. (Kitchen, blood transfusion 2007)

These blood groups have substance that are mainly made of carbohydrates linked to protein, and it is the usually the chemical structure of the carbohydrate that determines the specific blood type. These substances are antigens that induce the production of antibodies when injected into a patient lacking the antigen. Detection and recognition of the blood group antigen can be achieved by the use of blood serum containing the antibodies. The wide variety of different red cell antigens makes it highly unlikely that two people can have the same array of blood group substance, unless they are identical twins. (Kitchen, blood transfusion 2007)

The red blood cell is mainly composed of haemoglobin the molecule necessary for oxygen transport, approximately 95% of the dry weight. In more detail haemoglobin is a protein molecule that contains four polypeptide chains (a tetramer), each chain consists of more than 140 amino acids. Each chain has a chemical structure attached known as a Haeme-group. Haeme is made of a ring like organic compound known as porphyrin, which has an iron atom attached. It is this iron atom that reversibly binds the oxygen atom as

the blood travels between the lungs and the tissues. There are a total of four iron atoms in each molecule of haemoglobin, which can in accordance to their number attach four oxygen atoms. The complexity of the porphyrin and protein structure provides the correct settings for the iron atom so that it binds and releases oxygen under certain appropriate physiological conditions.

Another important term is affinity; the affinity of haemoglobin for oxygen is so great that the oxygen pressure in the lungs causes about 95 percent of the haemoglobin to be saturated with oxygen. As the oxygen tension decreases the red blood cells pass through the tissues in the body, and the oxygen molecules dissociates from the haemoglobin and is readily available for diffusion across the red cell membrane and the plasma to sites where it is used. The proportion of haemoglobin saturated with oxygen is not directly in proportion to the oxygen pressure. Red blood cells have this affinity due to 2, 3-DPG a molecule produced in a bypass of the Leubering-Rapoport shunt metabolic pathway which will be mentioned in more detail.

The principal source for energy for red blood cells is glucose, which is taken up by facilitated diffusion in an insulin independent fashion. Red cells do not contain mitochondria and can therefore not readily metabolize glucose aerobically and produce the ATP that way. The metabolism of the human red blood cell consists of the Glycolytic pathway (Embden-Meyerhof pathway) and the Hexose Monophosphate shunt. For the red blood cells the pathways protect the haemoglobin molecule, the membrane lipids and structural proteins from oxidative stress. They also assist in the structural integrity of the red cell, and regulate the volume of the cell. These metabolic networks

are also different to others in the respect that the red cell does not generate biomass: its main task is to produce the necessary cofactors (ATP, NADPH, and NADH) for maintaining its osmotic balance and electro-neutrality and fighting oxidative stresses. (Wiback 2002)

The Glycolytic pathway (Embden-Meyerhof pathway) is a common metabolic pathway for the cells in the human body. The pathway is a sequence of 10 chemical reactions taking place in the cell that metabolises glucose into lactate, releasing energy that is then captured and stored in ATP. These reactions in red blood cells give a net yield of two ATP molecules and two molecules of pyruvate (pyruvic acid) for one molecule of glucose including coenzymes and inorganic phosphate; however there is no net production of NADH. (Kitchen, haematology 2007)

Many systems are linked to the Glycolytic pathway and cannot function without the metabolisation of glucose and the subsequent energy required, driving the mechanism of these systems. However the most significant one is the sodium-pottasium pump. The most important cation within the red blood cell is potassium; plasma and extracellular fluids have sodium as their major cation. It is important to maintain the sodium and potassium concentration which is carried out by a pumping mechanism controlled by the enzymes within the red cell. Red cells like majority of cells undergo osmotic effects, when left in a very dilute solution of sodium chloride, the red cells absorb water, which means the increase in volume and gain a more spheroid shape; in concentrated salt solutions the red cells lose water and shrink. (Lacelle 1966)

The glycolysis pathway also reduces NAD+ to NADH which is an important contributer to the enzyme methemoglobin reductase. This enzyme assists in the pathway to reduce methemoglobin to haemoglobin. The ferrous iron group in the haem- molecule is oxidised to its ferric state ($Fe2+$) by oxidative stress on the molecule, the enzyme methemoglobin reductase reconverts it back to its normal ferrous state. NADH acts as the electron donor, highlighting its importance in the metabolic pathway.

Any defects of the glycolytic enzymes will result in insufficient ATP production which is necessary for the maintenance of the structural integrity of the red blood cell. The sodium is retained in the cytoplasm of the cell resulting in extracellular water entering the red cell by way of osmosis. This osmotic effect causes the red cell to swell; leading to damage of the red cell membrane, this then causes the haemoglobin pigment and other contents too escape from the cells, leaving a ghost structure. This is known as haemolysis, and can also occur by physical damage, when blood is heated or undergoes great pressure, or is subjected to very low temperatures. When the damage of the red cells is extensive and for a prolonged period of time, haemolytic anaemia occurs. Subsequently the red cells will be unable to diffuse through the capillaries during the circulation and will build to a red pulp to be deposited in the spleen.

Defects of glycolytic enzymes are uncommon however and 95% of those cases are associated with Pyruvate kinase and are restricted to red blood cells. Pyruvate kinase is a rare autosomal recessive condition that causes a mutation or alteration in a gene known as PKLR located on chromosome 1. Consequently the pyruvate kinase enzyme is not expressed. (Meza, N et al.

2009) Without the pyruvate kinase enzyme, red blood cells break down causing low levels of red cells in the body (haemolytic anaemia). An individual would have to receive two altered copies of the PKLR gene, one from each parent; this is known as autosomal recessive inheritance. Symptoms in a newborn include prolonged jaundice and anaemia. Older children would appear pale due to the anaemia and may suffer from irregular incidents of jaundice. (MuÃ±oz, 2003)

The Leubering-Rapoport shunt is a branch of the normal glycolytic pathway, this pathway produces 2, 3-diphosphoglycerate (2, 3-DPG). Most cells contain trace amounts of 2, 3-DPG, however red blood cells have a high concentration of 2, 3-DPG because of its importance in regulating the affinity of haemoglobin for oxygen. An estimated 15-20% of glucose undergoing the Glycolytic pathway passes through this shunt. This results in the reaction catalysed by phosphoglycerate kinase being bypassed, and no net ATP is produced. (Hess, 2007) a defect in the glycolytic enzyme can result in a reduction in the concentration of 2, 3-diphosphoglycerate. This can cause the haemoglobin-oxygen affinity curve to shift further left thereby preventing the necessary amount o oxygen to reach the lung tissues.

Another major metabolic pathway is the Hexose monophosphate shunt also known as the pentose phosphate pathway. Normally 5% of the glucose metabolized by the red cell passes through an oxidative pathway, the Hexose monophosphate shunt. It does not give a net ATP yield, but the process produces two NADPH molecules per molecule of glucose-6-phosphate entering the shunt. NADPH is significant as it reduces oxidized gluthathione in the erythrocyte. Reduced gluthathione is required to

maintain sulphydryl groups in their reduced state which maintains the structural integrity of the haemoglobin and the cytoskeleton.

A defect of the Hexose monophosphate shunt is the glucose-6-phosphate dehydrogenase deficiency, cause by an X-linked disorder which is characterized by a lack of the enzyme or by a dysfunctional enzyme. Individuals that suffer from this defect are usually asymptomatic; however oxidant stress can cause acute episodes of haemolysis. The oxidant stress can be caused by drugs especially antimalarials an infection or Fava beans.

In conclusion the importance of the biochemistry of red blood cells has been highlighted in this account. The metabolic pathways of the red blood cell are very complex however their main function seems to be to ensure that red blood cell maintains its structure and cytoskeleton. This is important for the red cells to transport oxygen across the human body. If the cell structure is compromised then the oxygen will not reach the lung tissues accordingly, which can cause asphyxia or even death. The loss of red cells is also significant as it can result in haemolytic anaemia which can be controlled but can leave the individual short breathed and pale. This account also touches a little bit on ABO blood grouping, which is also linked to the structure and biochemistry of the red cell. Even though it's mainly genetically linked, any phenotypic outcome would present a specific disorder, this information is important as it can be used late in blood transfusion. Also in the case of pyruvate kinase deficiency which is a commone enzymatic deficiency, it occurs worldwide however most cases have been reported in northern Europe, Japan and the United States. Its prevalence ranges from an estimated 51 cases per million by gene frequency studies. A cure is not

required as it can be controlled, if it was not for the affect it has on an individual's life quality. Subsequently suffered might suffer from irregular bouts during their lifespan.