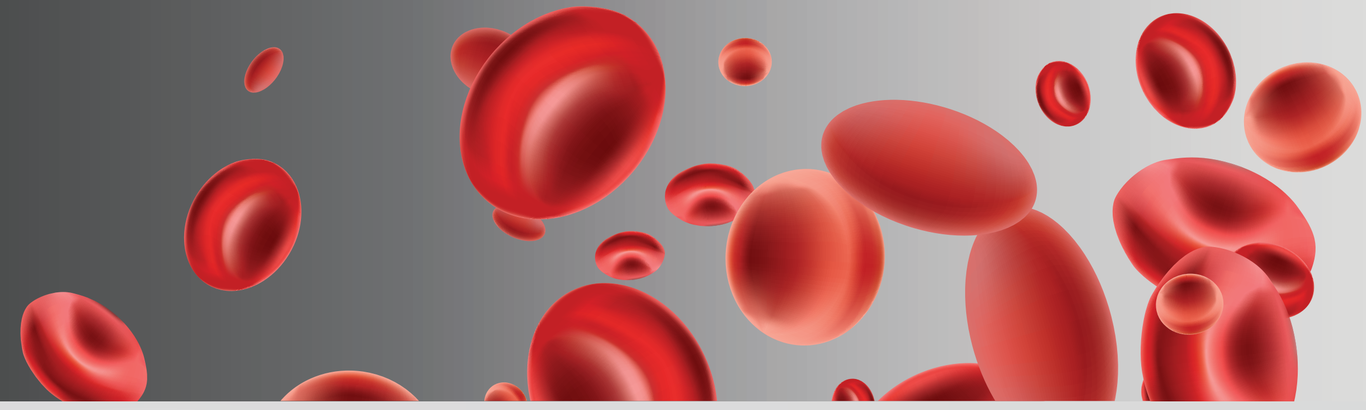
Red Blood Cell Metabolic Profiling and Functions



Metabolic Functions

RBCs are also known as red blood corpuscles, red cells, erythroid cells, haematids, or erythrocytes. They are the most common type of blood cell, and their primary functions are to carry oxygen to organs and tissues using the circulatory system as a means of transport and to carry carbon dioxide, a waste product of metabolism, to the lungs. RBCs are well equipped with redundant antioxidant systems, which are vital to their function and integrity. Damage of red blood cell function, defined as hemolysis, has been shown to significantly contribute to many severe clinical pathologies.

A single red blood cell traverses the adult circulatory system in ~1 min; therefore, during its average lifetime of 120 days, one RBC undergoes on the order of 105 cycles of high flow conditions in the aorta, followed by multiple trips through tight capillary spaces.

The development of new advanced metabolomic technologies, such as OMEGA scan, are producing large-scale data sets for the analysis and study of metabolic RBC biochemical networks. These RBC metabolomic networks can be divided into several focused biochemical pathways. Seven primary functions of the red blood cell are shown labeled in the central pathway figure:

(1) Anaerobic conversion of glucose to pyruvate to produce ATP and the export of lactate is a primary function; In RBCs, pyruvate is reduced to lactic acid, a three-carbon hydroxyacid, the product of anaerobic glycolysis. Each mole of glucose yields 2 moles of lactate, which are then excreted into blood. Two molecules of lactic acid contain exactly the same number of carbons, hydrogens, and oxygens as one molecule of glucose; however, there is sufficient free energy available from the cleavage and rearrangement of the glucose molecule to produce 2 moles of ATP per mole of glucose converted into lactate. The RBC uses most of this ATP to maintain electrochemical and ion gradients across its plasma membrane.

(2) The Interchange between pyruvate and lactate to produce NAD+ is also used to maintain the ferric-ferrous charge balance between methemoglobin (metHb) and hemoglobin (Hb) by NAD+ control of cytochrome b5 reductase, another prime biochemical pathway in the RBC. If the ferrous heme (Fe2+) iron contained in the prosthetic group of Hb is oxidized to ferric (Fe 3+) heme to form methemoglobin (metHb), the affinity of Hb toward oxygen is dramatically decreased. To preserve its functionality, Hb has to be maintained in the reduced state. Only 1% of Hb in the RBC is present in this metHb (Fe 3+) state. Any Hb-Fe 3+ is reduced back to Hb-Fe2+ in a reaction catalyzed by the cytochrome b5 reductase using NADH as an electron donor.

(3) The production of 2,3-diphosphoglycerate through the Rapoport-Leubering Shunt binds to oxyhemoglobin to maintain the balance of free oxygen by effecting the higher order structure of hemoglobin; During standard glycolysis, 3-phospho-D-glyceroyl phosphate (1,3-BPG) is converted to 3-phospho-D-glycerate (3-PG) in a single step catalyzed by phosphoglycerate kinase, generating ATP. By directing 1,3-BPG to the Rapoport-Luebering shunt, the cell gives up the production of ATP and instead produces 2,3-BPG, a key regulator in erythrocytes, which acts to regulates oxygen release from hemoglobin and delivery to tissues. 2,3-bisphosphoglycerate, the most concentrated organophosphate in the erythrocyte, forms 3-PG by the action of bisphosphoglycerate phosphatase.

(4) Human red blood cells are not able to synthesize ATP de novo. However, they do have active nucleic acid salvage pathways, that is, routes by which nucleosides or bases can be recycled to give nucleotide triphosphates. The exact structure of the salvage pathways (e.g., starting from adenine or adenosine) has not yet been studied in sufficient detail. The nucleic acid salvage pathway introduces nucleotide diphosphates to the cell which allows the glycolytic pathway to produce ATP.

(5A) The oxidative arm of the pentose phosphate pathway produces NADH that coordinates with glutathione levels to provide reactive oxygen species (ROS) protection and anti-oxidative detoxification. In contrast to other cells, the oxidative pentose phosphate pathway is the main source of reducing equivalents in the RBCs due to a lack of mitochondria. Glucose-6-phosphate dehydrogenase (G6PDH) diverts away a portion of glucose-6-phosphate from glycolytic ATP production and starts NADP+ reduction. The oxidative pentose phosphate pathway is linked to the nucleic acid salvage pathway through the non-oxidative arm (5B).

(6) In healthy human RBCs, a significant percentage of glutathione is present in the reduced form (GSH) which can be utilized for the reduction of ascorbate, oxidized proteins, and oxidized lipids. Enzymes using GSH as reducing equivalents are called glutaredoxins (GRx). The enzyme responsible for GSH recycling is glutathione reductase (GR), which reduces glutathione disulfide (GSSG) back to the reduced GSH via consumption of NADPH. The exact ratio between GSH and GSSG is determined by health status, activity status, environmental conditions and genealogy.

(7) Sustaining arginine production and the use of the urea cycle to promote nitric oxide (NO) control and polyamine synthesis is a less studied, but an essential biochemical pathway in RBCs. There is accumulating evidence that RBCs play an important role in the control of systemic NO metabolism, transport, and release of vasoactive substances, participating in systemic control of cardiovascular function and cardioprotection.

(8) Because red blood cells lack mitochondria they has no functional TCA cycle. By varying flux through the pentose phosphate pathway, cells can balance the use of glucose for ATP (energy) or NADPH (antioxidant). Citrate uptake and metabolism can contribute up to approximately 20% to 30% lactate.

(c) Conversion PEP to pyruvate via pyruvate kinase (PYK) is another major step in the glycolytic pathway where ATP is formed from phosphoenol pyruvate (PEP). ATP inhibits pyruvate kinase, similar to the inhibition of PFK. Pyruvate kinase is also inhibited by acetyl-coenzyme A, traditionally generated from pyruvate in cells with intact mitochondria.

(d) The rate limiting step of G6P to 6GP lactone is controlled by levels of NADPH. Glucose-6-phosphate dehydrogenase (G6PDH) is the rate-controlling enzyme of this pathway. It is allosterically stimulated by NADP+ and strongly inhibited by NADPH and acetyl CoA.

Metabolic Control Points

Interpretation of quantitative changes in the metabolome of RBCs must include knowledge of both major biochemical pathways, but also their control points - those critical steps influence pathway changes and enzymatic regulation. Numerous metabolite feedback mechanisms influence changes in RBC metabolomic profiles, including control points labeled in the central figure:

(a) Glucose phosphorylation is controlled and regulated by excess levels of G6P. glucose-6-phosphate. If G6P accumulates in the RBC cell, there is feedback inhibition of hexokinase (HK) to slow down glucose consumption until G6P is transformed into the glycolytic pathway.

(b) The conversion of F6P to FBP is controlled by ATP concentration. The phosphorylation of fructose 6-phosphate is highly exergonic and irreversible, and phosphofructokinase (PFK), the enzyme that catalyzes it, is the key enzyme in glycolysis. Low ATP will accelerate commitment of the conversion of F6P to FBP to generate additional ATP.

Non -Quantitative Analysis

While a selected quantitative analysis provides a deep understanding of the absolute changes in metabolite concentrations in the RBC, there are hundreds of other metabolites that provide an even deeper understanding of the changes and compensation to stress that occur within the red blood cell during disease including oxidative stress, nutrient deprivation, RBC storage or environmental change. The HMT library of over 950 metabolites observed in the RBCs by OMEGA scan include many metabolic classes: biological amines, amino acids, organic acids, polyols, amino sugars, polyamines, vitamins, nucleic acids and many others, including many small peptides of growing biological importance.

Relative expression of these metabolites can be compared within these major pathways. Within the glycolytic pathway over 30 metabolites are measured, with AMP and 2,3-DPG among the most abundant representing major outcomes of anaerobic metabolism. Within the pentose phosphate pathway and nucleic acid salvage pathway over 80 metabolites are observed and measured with hypoxanthine and inosine as two of the most abundant. These most abundant are labeled red in the central pathway figure, lesser abundant in yellow, lower abundant in green and not measured in gray.

OMEGA scan measures over 80 short and medium chain fatty acids and over 35 gamma -glu dipeptides. These short and medium chain fatty acids and their derivatives, act on osmotic pressure within the red blood cell. Since shape shifting of the red blood cell requires membrane mobility and osmotic pressure stability, the role of short and medium chain fatty acids and their derivatives in this process have yet to be fully elucidated. These smaller fatty acids have been linked to osmotic fragility of the red blood cell. The osmotic fragility of red blood cells is a composite index of their shape, hydration, and, within certain limitations, proneness to in vivo destruction. Since RBCs do not contain mitochondria and rely upon glucose for energy production, the role of these fatty acids are still under investigation.

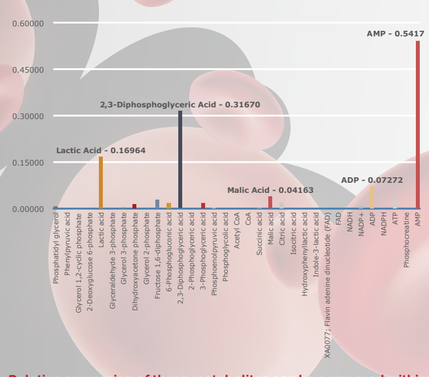
The role of gamma-glu dipeptides in red blood cells has yet to be fully investigated as well however, OMEGA scan is allowing for a more in-depth discovery of RBC metabolic pathways. Gamma-Glu Glu, gamma-Glu-Gln and gamma-Glu-Cys are among the most abundant of these peptides. Likely, these provide essential amino acids (Glu, Gln and Cys) to support high levels of glutathione required in the red blood cell as anti-oxidant response nutrients. The high level of gamma-Glu-ethanolamine is likely linked to the mobility and composition of the lipid membrane required for shape shifting. Lipids comprise nearly 50% of the mass of the RBC membrane with phosphatidyl ethanolamine being one of the most abundant.

Pentose Phosphate Pathway Nucleic Acid Salvage Pathway

in order of abundance (greatest to least)

- Hypoxanthine
- Nicotinamide
- Inosine
- IMP
- Adenosine
- Guanine
- Uric acid
- GMP
- Guanosine
- Ribulose 5-phosphate;
- GDP
- Sedoheptulose 7-phosphate
- CMP
- UMP
- CDP-choline
- Ribose 5-phosphate
- Theobromine
- Deoxy-5-methylcytidylate
- ADP-ribose 1 -2 cyclic phosphate
- 3'-AMP
- Uridine;
- GTP
- Cytidine
- dAMP
- 2'-CMP
- Ribulose 1,5-diphosphate
- Pseudouridine
- Orotic acid
- Orotidine
- 3'-CMP
- UDP
- dADP
- N1-Methylguanosine
- Xanthine
- 1-Methyladenosine
- NAD+
- Paraxanthine
- UTP
- IDP
- 5'-Deoxy-5'-methylthioadenosine
- 7-Methylxanthine
- Uracil
- Adenine
- Adenine
- P1, P4-Di(adenosine-5') tetraphosphate
- 2'-Deoxyinosine
- 2'-Deoxyinosine
- 2-Deoxyribose 1-phosphate
- 2',3'-cCMP
- 3-N-Propylxanthine
- 2'-Deoxyguanosine
- 2'-Deoxyadenosine;5'-Deoxyadenosine
- dCMP
- 3-Methylguanine;7-Methylguanine
- PRPP
- dATP
- 2'-Deoxycytidine
- Xanthosine
- CDP
- 1,7-Dimethylguanosine
- 1-Methylnicotinamide
- cAMP
- 3-Methylxanthine
- dTMP
- NMN
- XMP
- dTDP
- dCDP
- 1-Methyluric acid
- CTP
- Dihydroorotic acid
- Hydrouracil
- 3'-AMP
- dGMP
- Adenosine
- Nicotinamide riboside
- Caffeine
- 2'-Deoxyinosine
- Cytosine
- 3-Methyluridine
- cCMP;2',3'-cCMP
- Adenylosuccinic acid
- Nicotinamide riboside

Relative Abundance Glycolytic Pathway



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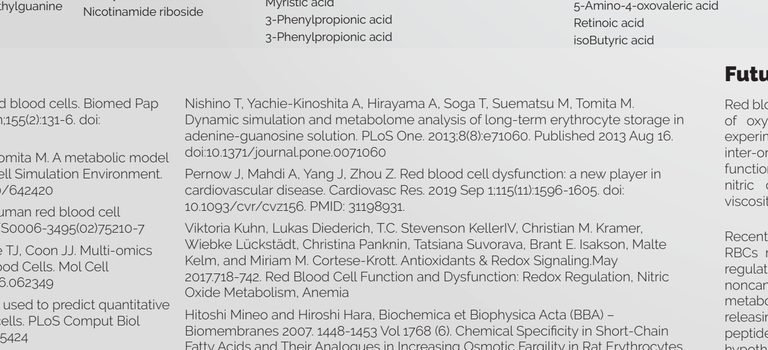


Within the pentose phosphate pathway and nucleic acid salvage pathway over 80 metabolites are observed and measured with hypoxanthine and inosine as two of the most abundant.

Short and Medium Chain Fatty Acids

in order of abundance (greatest to least)

- 1,6-Hexanedioic acid
- 11-amino-undecanoic acid
- Crotonic acid
- 4-Oxovaleric acid
- 3-methyl-2-oxobutanoic acid
- 3-methylbut-3-enoic acid
- Lauric acid
- 12(S)-HETE
- 6-Aminohexanoic acid
- 3-hydroxy-dodecanedioic acid
- Pelargonic acid
- 6-Aminohexanoic acid;Leu
- 5-Aminovaleric acid;Val;2-Amino-2-methylbutyric acid
- 3-aminopropanoic acid
- 3-methylbut-2-enoic acid
- 10-Amino-10-oxodecanoic acid
- 3-amino-octanoic acid
- 3-Aminoisobutyric acid
- Glyceric acid
- 2-Aminoisobutyric acid
- 12-hydroxy-5,8,10-heptadecatrienoic acid
- 5-Aminovaleric acid;Val;2-Amino-2-methylbutyric acid
- pent-4-enoic acid
- 9-HODE
- 3-Amino-2-hydroxyhexanoic acid
- 3-Hydroxy-3-methylglutaric acid
- Decanoic acid
- Myristic acid
- 3-Phenylpropionic acid
- 3-Phenylpropionic acid
- Hexanoic acid
- Hexanoic acid
- Azelaic acid
- Octanoic acid
- Glutaric acid
- GABA;3-Aminobutyric acid
- 2-Hydroxyglutaric acid
- 2-Oxohexanoic acid
- 3-Hydroxybutyric acid;2-Hydroxybutyric acid
- Heptanoic acid
- Isovaleric acid;Valeric acid;DL-2-Methylbutyric acid
- 2-Amino-2-(hydroxymethyl)-1,3-propanediol
- 3-Hydroxybutyric acid;2-Hydroxybutyric acid;2-Hydroxyisobutyric acid
- 2-Amino-2-methylbutyric acid
- 2-Aminoadipic acid
- Octanoic acid
- Butyric acid;Isobutyric acid
- DiHODE
- Myristoleic acid
- DiHODE
- Undecanoic acid
- 2-Amino-5-hydroxypentanoic acid
- 2-Aminoadipic acid
- 14:2(6,9)
- 3-Hydroxybutyric acid
- 2-Hydroxyvaleric acid;2-Hydroxyisovaleric acid
- 1H-Imidazole-4-propionic acid
- 7-Oxo-11-dodecenoic acid
- 5-Amino-4-oxovaleric acid
- Retinoic acid
- isoButyric acid
- 2-Hydroxybutyric acid
- 2-Hydroxyvaleric acid
- Mucic acid
- 2-Hydroxyoctanoic acid;8-Hydroxyoctanoic acid
- Suberic acid
- 2-(Creatinine-3-yl)propionic acid
- 2-(4-Hydroxyphenyl)propionic acid
- 3-Hydroxyphenylacetic acid
- Sebacic acid
- 2-Oxoglutaric acid
- Dodecanedioic acid
- 10-Hydroxydecanoic acid
- Hydantoin-5-propionic acid
- 2,6-Diaminopimelic acid
- 2-Keto-glutaramic acid
- 2-Hydroxyoctanoic acid;8-Hydroxyoctanoic acid
- 6-Hydroxyhexanoic acid;2-Hydroxy-4-methylvaleric acid
- 6-Hydroxyhexanoic acid;2-Hydroxy-4-methylvaleric acid
- 3-Guanidinopropionic acid
- 2-Hydroxy-4-methylvaleric acid
- Diaminoheptanedioic acid

Gamma-Glu Peptides

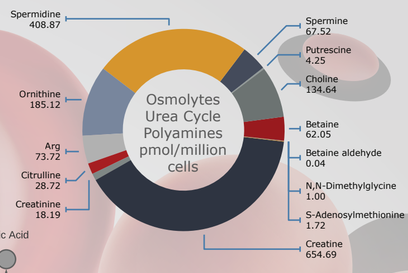
in order of abundance (greatest to least)

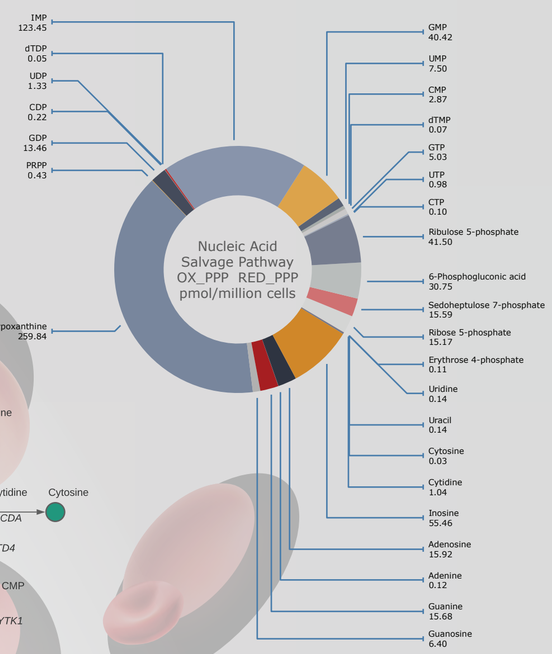
- gamma-Glu-ethanolamine
- gamma-Glu-Gln
- Gamma-Glu-Glu
- gamma-Glu-Gly-Ala
- gamma-Glu-Asn
- gamma-Glu-Cys
- Gamma-Glu-Ornithine
- gamma Glu-Asn
- gamma-Glu-Asp
- Gamma-Glu-Val
- gamma-Glu-Ser
- gamma-Glu-Ser
- gamma-glu-val
- gamma-Glu-Val-Gly
- gamma-Glu-Gly
- gamma-Glu-Gly
- gamma-Glu-Lys
- gamma-Glu-Phe
- gamma-Glu-Ala
- gamma-Glu-Arg
- gamma-Glu-Gly
- gamma-Glu-Cys
- gamma-Glu-Val
- gamma-Glu-Met
- gamma-Glu-Thr
- gamma-Glu-Ornitine
- gamma-Glu-Val-Gly
- gamma-Glu-Val
- gamma-Glu-Asn
- gamma-Glu-Val-Gly
- gamma-Glu-Asn
- gamma-Glu-His
- gamma-Glu-Asp
- gamma-Glu-Leu
- gamma-Glu-Ala

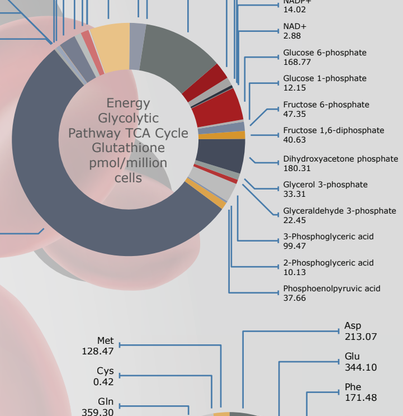
Quantitative Analysis Using OMEGA Scan

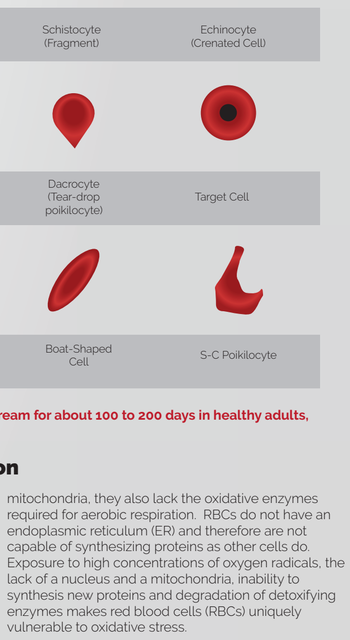
Deep-coverage metabolomic profiling by OMEGA scan has revealed a well-defined collection of metabolic pathways in human red blood cells. A set of intracellular metabolite concentrations can identify the qualitative state of metabolic networks during different environmental and biological states. OMEGA scan is able to accurately measure the concentration profile of over 93 metabolites essential in RBC metabolism. The dynamic range of concentrations (pmol/million cells) spans over 4 orders of magnitude. The ability to measure numerous metabolite concentrations from less than a few million RBCs presents a powerful tool that could be used to evaluate the metabolic state of a RBC biological systems using a minimal set of cells.

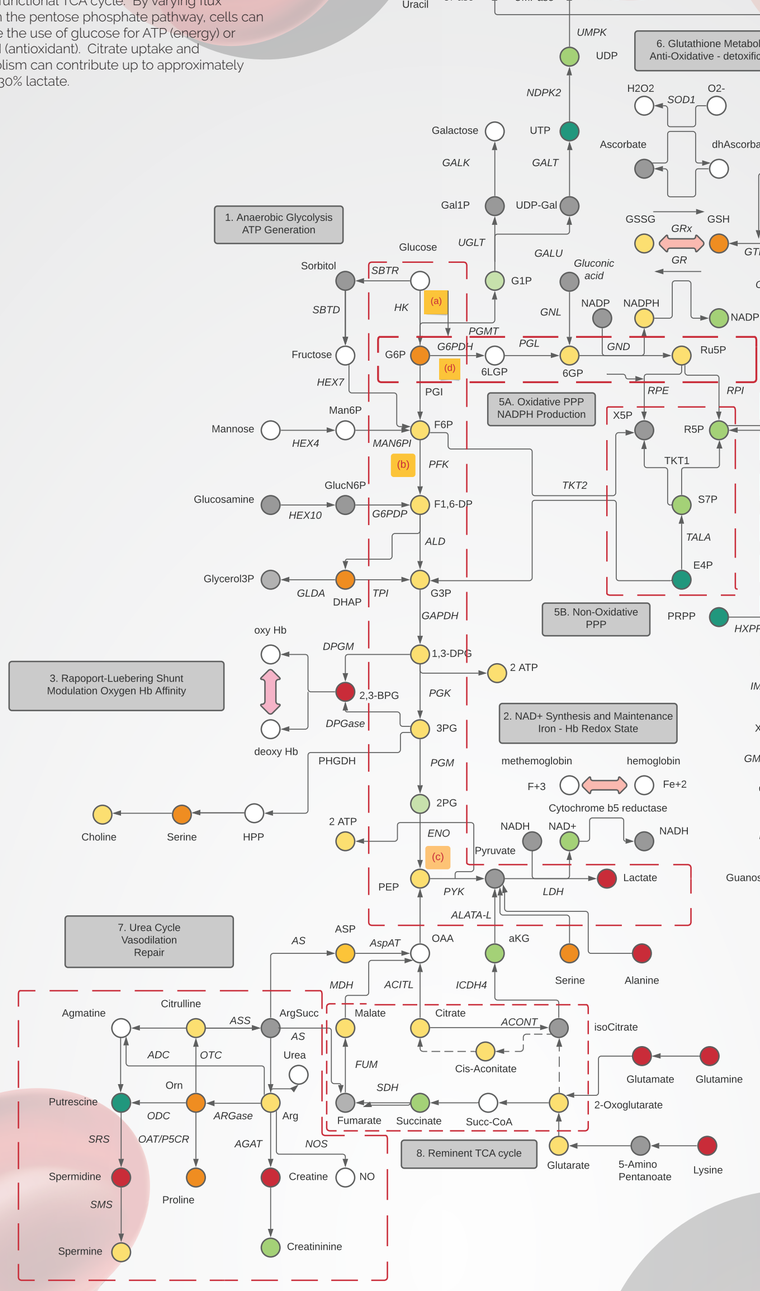
Omega Scan provides over 93 quantitative metabolites covering all major pathways and over 4-orders of magnitude between highest (lactate) and lowest (cytosine).











Introduction

The essential biochemical pathways in red blood cells (RBC) to maintain cellular and biological function are established and kinetic information corresponding to many enzymatic reactions in these pathways are available, however, the quantitative and physiological role of this metabolism is still an open question and how these cells adapt to change and disease remain strong areas of research. Deep-coverage metabolomics data sets by OMEGA Scan are now allowing for more complete characterization of biological systems operating within the red blood cell. Using concentration and relative expression metabolomic profiles we can now examine closely metabolic changes in RBC networks. OMEGA Scan, HMT's premier profiling platform, provides a wide coverage of over 900 polar metabolites and their changes allowing researchers to gain new insights into the metabolic state of the red blood cell.

Shape and Function

Human red blood cells are very flexible. Their dumbbell shape allows them to squeeze through tight capillaries. Their lack of a nucleus and other organelles enables them to have the maximum space in which it can accommodate oxygen carrying hemoglobin. The familiar discoid donut-like shape of RBCs is fundamental for their physiological function as it increases overall cell flexibility and creates a high cellular surface area-to-volume ratio allowing for efficient gas exchange. The ability of RBCs to alter their shape and deform is supported by an ATP dependent mobile cytoskeleton.

Shape can also be an indication of a specific cellular phenotype or metabolic disease.

Matured red blood cells live in circulation in the bloodstream for about 100 to 200 days in healthy adults, while in infants, they live for 80 to 90 days.

Cellular Structure linked to Function

Erythrocytes do not possess a nucleus. This permits these cells to contain more hemoglobin. Since the red blood cells do not have a nucleus, they do not participate in cell division.

Red blood cells also do not possess mitochondria. As such, they rely on anaerobic respiration, without oxygen, for the production of energy in the form of ATP. It has been found that under normal conditions about 90% of total imported glucose is used to generate ATP through glycolysis and the remaining 10% of glucose is directed down the hexose monophosphate shunt. Cells use this alternative pathway to generate reducing equivalents (NADPH) which are used by RBCs primarily to reduce glutathione. See the central pathway figure.

Erythrocytes utilize the energy produced by anaerobic respiration as they circulate all the oxygen they carry to other cells that need it. This ensures that oxygen is solely used for other cells and is not wasted in the process of aerobic respiration which requires oxygen to produce ATP. In addition, because red blood cells lack mitochondria, they also lack the oxidative enzymes required for aerobic respiration. RBCs do not have an endoplasmic reticulum (ER) and therefore are not capable of synthesizing proteins as other cells do. Exposure to high concentrations of oxygen radicals, the lack of a nucleus and a mitochondria, inability to synthesis new proteins and degradation of detoxifying enzymes makes red blood cells (RBCs) uniquely vulnerable to oxidative stress.

Oxidative stress is now known to be a major factor in the development of most pathological events associated with neurological disorders, CHD, diabetes, cancer, and human aging. RBCs are prone to oxidative stress being the first cells in the body to be exposed to stressful stimuli. Metabolic profiling using OMEGA scan measures over 900 metabolites enabling researchers to more fully understand and track changes in RBCs due to stress and disease.

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Metabolite coverage obtained using OMEGA Scan from Human Metabolome Technologies for Axcella Health (Cambridge, MA).

Future Studies

Red blood cells were considered exclusively as transporters of oxygen and nutrients to the tissues. More recent experimental evidence indicates that RBCs are important inter-organ communication systems with additional functions, including participation in the control of systemic nitric oxide metabolism, redox regulation and blood viscosity.

Recent clinical and experimental evidence indicates that RBCs may be directly involved in tissue protection and regulation of cardiovascular homeostasis by exerting further noncanonical functions, including nitric oxide (NO) metabolism, as well as erythrocrine function (i.e., by releasing bioactive molecules (including bioactive peptides), including NO, NO metabolites, and ATP. Many hypotheses on the role of noncanonical functions of RBCs in cardiovascular homeostasis have been put forward, and evidence of a central role played by RBCs in cardiovascular protection is accumulating. However, many aspects of RBC-mediated control of NO metabolism and ATP release are still speculative.

Several diseases and maladies are known to directly affect red blood cell function including, diabetes, CVD, Sickle cell anemia, Hemolytic uremic syndrome , Beta-thalassemia, Iron deficiency, Aplastic Anemia, Leukemia, Lymphoma, Iron Deficiency Anemia and Pernicious Anemia.

Taken together, there is accumulating evidence that RBCs, in addition to their conventional role of transporting oxygen and carbon dioxide, play an important role in control of systemic NO metabolism, transport of vasoactive substances, participate in systemic control of cardiovascular function and cardioprotection and are linked to several diseases and clinical phenotypes.

Summary

A fundamental understanding of the full potential of RBC function starts with the understanding of their metabolic profile. Using advanced metabolomic technologies, such as HMT's OMEGA Scan, over 900 cellular metabolites in RBC lysates can be measured. These metabolites cover a large range of pathways including those basic to their function – glycolysis, generation of NAD+, NADH, ATP, establishing GSH concentration, control of oxy and deoxyHB, control over iron oxidation, glucose and sugar metabolism, urea cycle metabolism, amino acid metabolism, osmotic pressure and much more as shown in the central pathway figure. A deep dive into the metabolomic profile of RBCs is contributing to the advancement of the understanding of RBC function and reaction to stress and disease. In addition, adding the quantitative assessments of over 90 metabolites now allow accurate measurements and absolute comparisons of metabolic pathways under different cellular and biological conditions. RBCs are versatile and critical components connected to overall health and survival. OMEGA scan represents a significant advancement for these studies.

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