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Mini Review

A review of the mitochondrial and glycolytic metabolism in human platelets and leukocytes: Implications for their use as bioenergetic biomarkers ☆

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ABSTRACT

The assessment of metabolic function in cells isolated from human blood for treatment and diagnosis of disease is a new and important area of translational research. It is now becoming clear that a broad range of pathologies which present clinically with symptoms predominantly in one organ, such as the brain or kidney, also modulate mitochondrial energetics in platelets and leukocytes allowing these cells to serve as "the canary in the coal mine" for bioenergetic dysfunction. This opens up the possibility that circulating platelets and leukocytes can sense metabolic stress in patients and serve as biomarkers of mitochondrial dysfunction in human pathologies such as diabetes, neurodegeneration and cardiovascular disease. In this overview we will describe how the utilization of glycolysis and oxidative phosphorylation differs in platelets and leukocytes and discuss how they can be used in patient populations. Since it is clear that the metabolic programs between leukocytes and platelets are fundamentally distinct the measurement of mitochondrial function in distinct cell populations is necessary for translational research.

Contents

Abbreviations: ROS/RNS, reactive oxygen species/reactive nitrogen species; OCR, oxygen consumption rate; ECAR, extracellular acidification rate; XF, extracellular flux analyzer

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Introduction

Circulating leukocytes and platelets are programmed for distinct roles in normal physiology which include mediating the inflammatory process, thrombosis, clearance of foreign bodies and sensing and responding to systemic biological signals in the circulation. The dynamic functions of peripheral blood leukocytes and platelets require an integrated metabolic machinery to meet energetic demand during normal physiology which is likely to involve both glycolysis and mitochondrial oxidative phosphorylation. The role of both these important ATP generating pathways in supporting the biological function of platelets and leukocytes has been recognized but these findings have not been integrated into an overall understanding of these cell types in human subjects. This review analyzes the similarities and differences in the glycolytic and oxidative metabolic profiles in leukocytes and platelets from human subjects and discusses the implications of these findings for the utilization of these cell types for translational research.

Biological functions and metabolic programs of platelets and leukocytes

The myeloid lineage supports the greatest variety of differentiated circulating cells which include erythrocytes, platelets, neutrophils, and monocytes. Monocytes are phagocytic cells with a uni-lobular nucleus that have an important role in the innate immune system [1–3]. Once secreted from the bone marrow into the blood, these cells survey the body for sites of inflammation. On encountering inflammatory stress signals the monocytes must rapidly activate and migrate to areas of injury where they can differentiate into the pro-inflammatory (M1) or anti-inflammatory (M2) phenotype [3]. In the M1 state the activated monocyte–macrophage cell undergoes a metabolic switch from oxidative phosphorylation to glycolysis [4]. This change is important to provide substrates for biosynthetic programs, maintain mitochondrial membrane potential and also provide ATP to the cell [5]. Inhibition of oxidative phosphorylation also increases reactive oxygen species (ROS) production which exerts bactericidal activities [5]. During the resolution of inflammation, the macrophages transform into the alternatively activated M2 phenotype and a more oxidative phosphorylation phenotype [6]. Thus the metabolic programs of monocyte/macrophage populations are highly plastic and adapt to facilitate the changing function of these cells in the inflammatory process. Whether early changes in metabolic phenotype associated with exposure to pro-inflammatory conditions can be detected in the pre-differentiated monocyte in the circulation is not clear. Typically, differentiation of the M1/M2 macrophages occurs at the site of inflammation not in the circulation. From the translational perspective the pre-differentiated monocyte is the dominant form in the circulation. Monocytes are then a potentially good sensor of metabolic stressors such as hyperlipidemia or hyperglycemia in the circulation of patients.

Lymphocytes are derived from the lymphoid lineage and are uni-nucleated cells that play an important role in adaptive immunity [7]. This heterogeneous population of cells is normally in a quiescent state and primarily uses mitochondria to meet their energetic demands [8]. Activation of lymphocytes is associated with a switch to a metabolic phenotype with an increase in both glycolytic function and mitochondrial oxygen consumption [9]. This is essential for their diverse immunological functions, which includes clonal expansion and the production of cytokines and antibodies [10–13]. From a translational perspective, the abundance, heterogeneity, and reactivity of these cells make them ideal for investigating the relationship of bioenergetics with the disease processes associated with inflammation.

Neutrophils serve an essential function in the innate immune system and are the first line of defense during bacterial infection. Neutrophils eliminate and destroy microorganisms by phagocytosis, generation of ROS, the extrusion of genomic DNA as Neutrophil Extracellular Traps (NETs), and by the release of cytotoxic granules [14,15]. Neutrophils have very few mitochondria which do not play a role in energy metabolism, but maintain their mitochondrial membrane potential for apoptotic signaling [16–18]. The energy required for neutrophil chemotaxis and activity is derived from glycolysis [19]. The translational applications of the oxidative burst in neutrophils have been well studied, but less is known regarding the regulatory role of glycolysis under normal and pathological conditions in these cells [20].

Platelets are cytoplasmic fragments that are released by megakaryocytes in the bone marrow and stored in the spleen. These anuclear cells play an important role in hemostasis and are essential for thrombus formation at sites of injury. With a lifetime of 5–7 days in the circulation and no nucleus their metabolic program must be stable over this time period and be available for the energy requiring processes engaged when they are activated. At a basal state both oxidative phosphorylation and glycolysis play a role in energy production in platelets [21,22]. Platelet aggregation results in an increase in glycolytic metabolism but it has been shown that a robust oxidative phosphorylation system is required to enable optimal levels of platelet functionality [23]. Platelets have been used widely in translational research in a broad range of pathological conditions including neurological disorders and diabetes [24]. In the next section we will demonstrate how the basal cellular bioenergetics are different between these cell types and the implications these findings have for translational research which use these cells as sensors of pathological changes in mitochondrial dysfunction.

Leukocytes and platelets as systemic biomarkers of metabolic stress

Many chronic pathological conditions such as metabolic syndrome, cancer and atherosclerosis are associated with an inflammatory response with the release of proinflammatory mediators particularly the cytokines. Leukocytes and platelets respond to these pro-inflammatory mediators in the systemic circulation through an activation process which changes the cellular phenotype as discussed in the previous section. Several investigators have tested the concept that leukocytes and platelets can act as biomarkers of mitochondrial dysfunction associated with several diseases including diabetes, neurodegenerative diseases, atherosclerosis and cancer [24–28]. For example, patients with septic shock demonstrated a strong association between decreased mitochondrial function, specifically loss of ATP synthase activity, in peripheral blood mononuclear cells and increased mortality [25]. It has also been shown that platelets from patients with type 2 diabetes have lower mitochondrial membrane potential and higher ATP content compared to controls [29]. A study of mononuclear cells in type 2 diabetes showed that the mitochondrial mass was decreased and that the mitochondria were hyperpolarized [30]. Mitochondrial complex I activity was found to be decreased in aged platelets [31] and those obtained from patients with Alzheimer's disease had higher mitochondrial membrane potential than controls [32]. Furthermore, platelets derived from normal individuals with a maternal history of Alzheimer's had lower cytochrome c oxidase activity [33]. It has been reported that leukocytes from patients with leukemia have higher numbers of circular dimer mitochondrial DNA compared to healthy controls, suggesting that leukocyte mitochondrial function is also important in cancer [34]. Mitochondria isolated from mononuclear cells in patients with fibromyalgia exhibited lower membrane potential and levels of coenzyme Q10 but increased superoxide production [35].