Scientific Research Publishing

Journal of Biosciences and Medicines, 2023, 11, 37-47
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Platelets Play an Integral Role in Body Heat Production and Maintenance: A Newly Proposed Function

Thirugnana Subramanian*

Department of Pediatric Hematology and Oncology, Washington University School of Medicine, Saint Louis, MO, USA
Email: thirusubraman@gmail.com

How to cite this paper: Subramanian, T. (2023) Platelets Play an Integral Role in Body Heat Production and Maintenance: A Newly Proposed Function. *Journal of Biosciences and Medicines*, **11**, 37-47.
https://doi.org/10.4236/jbm.2023.113005

Received: February 9, 2023
Accepted: March 7, 2023
Published: March 10, 2023

Abstract

In platelets, most of the ADP is stored in dense granules and released into extracellular space through exocytosis as a signaling molecule upon platelet activation. Glycolysis and the TCA cycle consume considerable amounts of ADP; however, limiting quantities of available ADP to make ATP through OXPHOS result in failure of ATP production and release of energy as heat into the surroundings. Thus, body heat may be a potential product of circulating platelets. Furthermore, the incomplete OXPHOS process causes the production of ROS that leads to earlier platelet death resulting in shorter life span. In the future, this new function may have a wide variety of clinical applications.

Keywords

ADP, ATP, Oxidative Phosphorylation, Platelets, Reactive Oxygen Species

1. Introduction

Platelets are the smallest (2 - 4 μm in diameter) blood cells that are integral in clot formation to prevent blood loss upon injury and serve to maintain the integrity of the vasculature. Their life span is between 7 - 10 days, whereas other cells in our body live much longer. They are anucleate and possess functional mitochondria numbering between 5 - 8 per platelet [1]. Apart from mitochondria, platelets have other organelles like ribosomes, Golgi bodies and endoplasmic reticulum for RNA and protein synthesis. In addition, platelets have three types of vesicles namely α-granules, dense granules, also known as δ-granules, and lysosomes [2]. These granules play important roles in hemostasis and thrombosis.

*Retired Staff Scientist.

α-granules are the most abundant granules ranging from 50 to 80 per platelet, measuring 0.2 to 0.5 μm in diameter, and occupying 10% of the platelet volume. They contain membrane associated receptors (αIIbβ3, P-selectin) and soluble proteins involved in hemostasis (fibrinogen, VWF), inflammation (cytokines, interleukins-8) and wound healing (VEGF, FGF). The dense granules are the second most abundant granules ranging from 3 to 8 per platelet, measuring 0.15 μm in diameter, and occupying approximately 1% of the platelet volume. They contain bioactive molecules such as serotonin and histamine, adenine nucleotides (ADP/ATP), polyphosphates, pyrophosphates, calcium and magnesium. The lysosomes are the least abundant granules ranging from 1 to 3 per platelet and measuring 0.1 to 0.5 μm in diameter. They contain enzymes that degrade all biological macromolecules such as proteins, nucleic acids, carbohydrates, and lipids.

Platelets are produced by the megakaryocytes of the bone marrow and released into the blood stream through the process of thrombopoiesis. In humans, the megakaryocytes release 1×10^{11} platelets into the blood circulation every day. There are $1.5 - 4.5 \times 10^{8}$ platelets/mL of blood in a normal healthy adult [1]. Thrombopoiesis is controlled by the cytokine, thrombopoietin [3], which is produced in the liver by the parenchymal and sinusoidal endothelial cells as well as in the kidney by proximal convoluted tubule cells to maintain a constant number of platelets [4]. Abnormal thrombopoiesis can lead to clinically significant disorders such as thrombocytopenia, defined as a platelet counts less than 1.5×10^{8} platelets/mL, and thrombocythemia, a platelet counts greater than 6×10^{8} platelets/mL. Thrombocytopenia can lead to inadequate clot formation and increased risk of bleeding, and thrombocythemia can increase the risk of thrombotic events, including stroke, peripheral ischemia and myocardial infarction [5]. Platelets were first identified by Bizzozero in 1882 and recognized to play a role in hemostasis and thrombosis [6] [7] From that time onwards, physicians, clinicians, and scientists are still working to study the biogenesis, morphology, physiology and functions of platelets. So far it has been proposed that platelets have several functions in hemostasis, thrombosis, inflammation, angiogenesis, wound healing, anti-microbial activities, and apoptosis [1].

A portion of the chemical energy that we consume is converted into heat for maintaining our body temperature. In most animals, body heat is simply lost to the environment, and they normally have a well-developed insulation system to retain the body heat. Still, it is not clearly understood which organ of our body facilitates the process of heat production and how body temperature is maintained. It is well known that the hypothalamus region of the brain is responsible for thermoregulation [8], but it is not reported to produce heat. Following the analysis of available literature, it is being proposed, for the first time, that platelets are the cells most responsible for heat production and contribute to temperature maintenance in healthy individuals.

2. Material & Methods

Available literature regarding mitochondria, glucose metabolism, electron trans-

port chain, oxidative phosphorylation, uncouplers, reactive oxygen species, apoptosis, life span of cells, adenine nucleotides, body heat production, thermoregulation, platelet biogenesis, morphology, physiology, and function were collected through PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Google (https://www.google.com). Out of several abstracts collected, only 70 related full articles (including reviews) with a coverage of years1958 to 2022 were first selected in a preliminary search. The selected articles were further analyzed twice for exclusion and inclusion criteria, and only 34 articles which are more potentially relevant for our hypothesis were finally used and the remaining less relevant 36 articles were excluded in this study to support the newly proposed function of heat production and body temperature maintenance by platelets. Our search was limited to the papers published in English.

3. Results

Defective ATP synthesis in platelets: I have collected and analyzed information from the literature to support my proposed hypothesis that platelets maintain body temperature. The results of the analyses are presented in Table 1. In all cells, ADP is the only molecule that functions to acquire energy and forms the high energy molecule ATP during glycolysis, tricarboxylic acid (TCA) cycle, electron transport chain (ETC) reaction, and oxidative phosphorylation (OXPHOS).

Table 1. Analysis of parameters to support the hypothesis that platelets produce heat and maintain the body temperature.

	Parameters	Effect	Observation	Conclusion
1	ATP synthesis from OXPHOS [9] [10] [11]	No ATP synthesis	Low ADP due to compartmentalization in dense granule	Energy released as heat
2	ROS formation [1] [12] [13] [14]	Platelet death by apoptosis	ROS formation due to incomplete OXPHOS	Lower life span of platelet
3	Solid organs and tissues	Not too hot	Normal temperature	Cannot serve as heat generators
4	RBC and WBC	No TCA cycle, ETC, and OXPHOS in RBC	No mitochondria in RBC and WBC are low in number	Cannot serve as heat generators
5	Stored ATP	Not available for heat generation	Used for vital functions	May not serve as heat generators
6	Exercise [15] [16] [17] [18]	More epinephrine production	More platelets near muscles	Temperature increased near muscle
7	Sex [19] [20] [21] [22]	Platelets number difference	Females have more platelets than males	Females' body temperature is more than males'
8	Pathological conditions [23] [24] [25] [26]	Platelets abnormal levels	Thrombocytopenia or thrombocythemia	Alternate mechanism

ATP: adenosine triphosphate; OXPHOS: oxidative phosphorylation; ADP: adenosine diphosphate; ROS: reactive oxygen species, RBC: red blood cells; WBC: white blood cells.

In addition to serving as an energy capturing molecule in ATP production, only a small portion of ADP serves as a signaling molecule. In platelets, most of the ADP molecules (653 mM) are compartmentalized into dense granules along with ATP that serve as signaling molecules [9]. Since little free ADP is available, it can be used for making ATP in glycolysis and TCA cycle through substrate level phosphorylation reaction but will not be available for making ATP through OXPHOS. So, the energy must be released as heat into the surroundings and can serve as a source of heat in maintaining the body temperature. It has been shown that the uncoupler of OXPHOS, carbonyl cyanide 3-chlorophenylhydrazone (CCCP), did not affect the concentration of ATP in control and thrombin treated platelets [10] indicating that there is no ATP generation through OXPHOS. In those platelets the mitochondrial respiration was normal with maximal oxidation of fuels.

Glucose enters platelets using glucose transporters (GLUT1 and GLUT3) through insulin signalings [11]. In addition, platelets have glycogen storage vesicles that serve as a reservoir for energy production during shortage of glucose in conditions such as diabetes and heavy exercise. The glucose metabolism of platelets along with other cells is presented in **Figure 1**. In all cells except platelets and RBCs, glucose is completely oxidized to CO_2 and water along with the production of ATP through glycolysis, TCA cycle, ETC, and finally OXPHOS. The

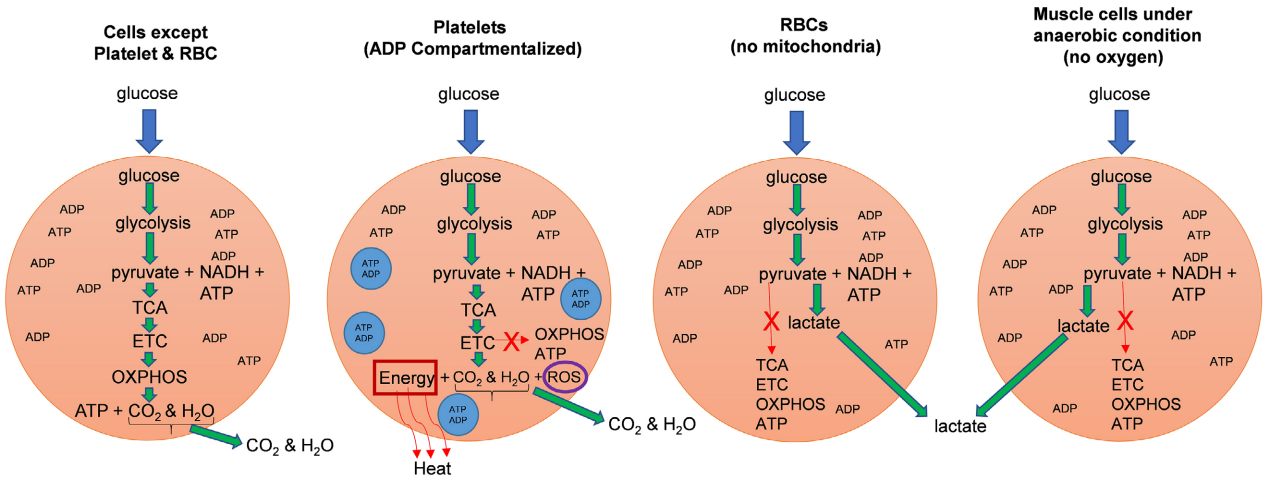

Figure 1. Illustration of heat and ROS production from glucose metabolism in platelets. For comparison RBC and other cells at aerobic and anaerobic conditions are shown. In all cells except platelet and RBC under normal condition glucose is completely oxidized to CO_2 and water with the production of ATP. All TCA cycle, ETC, and OXPHOS are active. RBC does not have mitochondria and the pyruvate at the end of glycolysis is converted to lactate and there is no TCA cycle, ETC, and OXPHOS. Muscle cells under anaerobic condition cannot carryout TCA cycle, ETC, and OXPHOS because of the insufficient oxygen and there will not be any ATP production through OXPHOS. In platelet, most of the ADP is compartmentalized along with ATP in dense granules as shown in blue circles. Due to the unavailability of free ADP, platelet cannot synthesis ATP through OXPHOS. TCA cycle and ETC are active and oxidize glucose to CO_2 and water. The energy (dark red square) from the oxidation of glucose at the end of ETC is liberated as heat into the surroundings (red arrows). Since OXPHOS is incomplete, mitochondria produce ROS (purple oval). In all 4 cell models, glycolytic ATP synthesis is active. The thick arrows indicate direction of glucose catabolism. The thin red arrows with × marks denote further catabolism is blocked. RBC: red blood cell; ATP: adenosine triphosphate; ADP: adenosine diphosphate; NADH+: reduced nicotinamide adenine dinucleotide; TCA: tricarboxylic acid; ETC: electron transport chain; OXPHOS: oxidative phosphorylation; ROS: reactive oxygen species.

RBCs do not have mitochondria and hence there is no TCA cycle, ETC, or OXPHOS. The pyruvate produced at the end of glycolysis is converted to lactate by the lactate dehydrogenase (LDH) enzyme and released into the circulation. It should be noted that restriction of any one of the substrates of TCA, ETC, and OXPHOS will inhibit ATP synthesis. During anaerobic conditions such as exercise, oxygen is not available to muscle cells and further oxidation of pyruvate is shut down without proceeding to TCA cycle, ETC, and OXPHOS, resulting in the conversion of all pyruvates into lactate which is released into the circulation. In platelets all substrates are available except ADP. As mentioned earlier, most of the ADP is compartmentalized into dense granules as a signaling molecule. Only a limited amount of ADP is available as free form and can be used for ATP synthesis in glycolysis. Since ADP is not available for ATP synthesis in the last step of oxidation, other reactions such as TCA cycle and ETC may be completed except OXPHOS. The protons from NADH+ and electrons from ETC consume oxygen and generate H_2O without making ATP. The energy from the ETC is liberated as heat and diffused into the neighboring cells. Thus, it can be inferred that the body heat is produced by the platelets. Since this process is not complete like in other cells where the whole energy is captured as ATP, it is possible that the platelets may produce more reactive oxygen species (ROS) that induce platelet death (apoptosis) at a much faster rate than other cells in the body.

Increased ROS formation in platelets: Oxidative stress is the imbalance arising from intracellular overproduction of ROS and the intracellular antioxidant response. It is the mechanism through which many of the human diseases including aging are caused. ATP production relies on the coupling between the proton gradient on both sides of the inner mitochondrial membrane (ETC) and this proton motive force to feed the ATP synthase complex (OXPHOS) [12]. If this coupling is not complete, it leads to the production of ROS, a process called electron leak [13]. The important source of ROS in cells has been reported to be the mitochondria with active ETC [14]. According to the hypothesis, if OXPHOS is incomplete, then there is no ATP production in platelets leading to the production of ROS. It has been shown that the mitochondrial uncouplers that block the synthesis of ATP production also produce ROS in normal cells [15] [16]. In those cells, ETC is normal without ATP production. Generation of ROS can lead to cell death by apoptosis, and this happens to platelets [1]. This leads to a shorter life span of 7 - 10 days compared to other cells. In addition, dinitrophenol (DNP) is an uncoupler of OXPHOS used by human for weight loss and discontinued due to its associated fatality [15]. Since DNP is an uncoupler, it can induce toxic effect through the production of ROS supporting the hypothesis.

Solid organs and tissues may not produce heat: If we assume solid organs and tissue produce body heat, the core temperature of the organ must be remarkably high, but this does not happen in the body. In addition, if the solid organs and tissue produce heat through ETC, they may die much faster and have a shorter life span due to ROS production. So, solid organs and tissues are not likely the source of heat under normal conditions.

RBC and WBC cannot produce heat: RBCs do not have mitochondria and cannot serve as a heat generator. WBCs numbers are low when compared to RBCs and platelets and cannot produce sufficient amount of heat to solely maintain the body temperature. In addition, both have longer life span confirming that they cannot serve as heat generators.

Stored ATP may not be used for heat generation: ATP is an energy currency and has many vital functions in our bodies such as synthesis of macromolecules, muscle contraction, purinergic signaling, and active ion transport. So, stored ATP may not be available for heat production.

Effect of exercise on platelet count and body temperature: Several studies [17] [18] [19] have shown that acute exercise increases the platelet count transiently and the increase is caused by the liberation of platelets from the spleen storage. During exercise, the plasma concentration of epinephrine is increased more than 5 times (>3500 pM) [20] and that causes the release of platelets from spleen. Since there are more platelets, they can increase the body temperature. In addition, exercise can produce an anaerobic condition in muscles due to the requirement of more oxygen. Anaerobic respiration may be exothermic like fermentation and can generate heat near muscles. Moreover, platelets can accumulate near muscles due to anaerobic condition that may mislead platelets to an inflammation-like condition. So, platelet accumulation near muscles can produce increased temperature.

Sex alters platelet count and body temperature: Platelet count varies from person to person, but females have higher average platelet count than males. It has been reported that 15% to 20% more platelets are seen in females than males [21] [22]. Albeit minor, females have higher body temperature than males [23] [24]. Males have higher metabolic rate than females and females have better body insulation system than males. Given these two conditions, males and females should have comparable body temperatures, but this is not the case. The reason may be explained by the higher number of platelets seen in females.

Pathological conditions and body temperature: Under pathological conditions, the platelet levels can increase or decrease causing thrombocythemia or thrombocytopenia respectively depending on the severity of the conditions. For example, during early viral infections, platelet levels often increase due to inflammation [25] and decrease at advanced stages of infection due to decreased production or increased destruction [26] [27] [28]. Typically, viral infections raise body temperature, resulting in fever. During such a condition (thrombocytopenia), the body may switch to an alternate mechanism to produce heat for maintaining the body temperature that will be discussed in discussion section.

4. Discussion

Platelets are tiny, anucleate cells with several active mitochondria in each cell. They have a short life span of 7 - 10 days [1]. ADP is an important molecule that serves as an energy transferring molecule from glucose to various functions of the biological system. Without ADP, the energy cannot be captured during gly-

colysis, TCA cycle, ETC, and OXPHOS. If this is the case, why are most of the platelets' ADP compartmentalized in dense granules as signaling molecules and thus limiting their availability to accept the energy to form ATP through OXPHOS? With this question in mind, I started analyzing the data from the literature and proposed that platelets produce heat during ETC which serves to maintain the body temperature at a constant level. The hypothalamus can regulate body temperature but cannot produce heat. There are several suggestions in the literature regarding the organs that produce heat such as the heart and the liver. If these organs produce heat, how can they be sufficient to maintain the whole-body temperature? For instance, assume a heating unit in a house that maintains the temperature around 22˚C - 25˚C. To maintain this temperature, the core temperature of the heating unit must be remarkably high. In the same sense, if we assume that the heat is produced by an organ of our body, the organ must reach remarkably elevated temperature. Even though blood circulation can transfer the heat to the whole body, the organ responsible for heat production would not be able to tolerate that high of temperatures resulting in organ failure. Our body temperature is almost uniform with a very minor fluctuation. Platelets are circulating throughout the body and can transfer the heat to the whole body uniformly. Thus, the liver and heart are less likely responsible for the production of body heat.

Another important aspect to rule out that organs such as the liver and the heart are not producing heat is the ROS effect. Mitochondria are the major site of intracellular ROS formation [14]. ROS can cause damage to the cells and the damaged cells will die due to apoptosis. In our body, ROS is controlled by the presence natural antioxidants like glutathione and there may not be any harmful effect of ROS under normal conditions [15] [16]. If the level of ROS outcompetes the antioxidant effect, this will cause deleterious effects on the cells that can lead to cell death by apoptosis. Under normal conditions, healthy heart and liver cells have longer life span, suggesting that there may not be excess ROS, and that normal OXPHOS is occurring to form ATP. Unlike heart and liver cells, platelets have a short life span of 7 - 10 days. According to the hypothesis, under normal conditions platelets have a defective OXPHOS due to limited availability of ADP (due to compartmentalization in dense granules) resulting in the failure of ATP formation and releasing the energy to the surroundings along with the production of ROS. If this ROS production is not controlled by the antioxidants, it can induce early cell death by apoptosis leading to a shorter life span. Taken together, these events suggest that platelets are integral in producing heat to maintain body temperature under normal conditions.

The other blood cells, RBCs and WBCs, may not be capable of producing heat, but they live longer. The RBCs do not have mitochondria and make ATP only through glycolysis, which is then used for the function of carrying CO_2 and O_2. WBCs are little in number and so are less likely to produce sufficient heat. In addition, the stored ATP is used for the vital functions of the cells and may not be available for heat generation.

During exercise, platelet count is increased transiently through the effect of epinephrine [17] [18] [19] on spleen and accumulates near muscle cells and causes local increase in body temperature. This increase in body temperature causes sweating to reduce the temperature. Females have increased platelet counts and higher body temperature than males. Even though the difference is minor, it supports the hypothesis of platelets being a key player in body heat production.

There is a strong correlation between hypothermia and thrombocytopenia as evidenced by case reports of patients [29] [30] [31] and animal experiments in dogs [32] [33]. In both cases, first, they were exposed to cold temperature that caused a temporary sequestration of platelets by the liver and spleen leading to thrombocytopenia which in turn induced hypothermia. When the patients and dogs returned to normal temperature, they resume normal platelet count and body temperature.

Platelets produce heat and maintain body temperature in healthy individuals. Under pathological conditions, the situations are different. For example, during most viral infections [34], the platelet count decreased causing thrombocytopenia, but also leads to pyrexia. This observation contradicts the hypothesis. However, a possible explanation is that during such pathological conditions, the hypothalamus can induce an alternate mechanism that can provide heat to the body. In such conditions, the body induces natural uncouplers of OXPHOS such as uncoupling protein-1 (UCP) and adenine nucleotide translocase-1 (ANT) [15]. Both function as uncouplers of OXPHOS in normal cells with the release of heat and inhibition of ATP synthesis. This alternate mechanism can work for a shorter period of time with a minor damage by the production of ROS. Once the infection is clear, the hypothalamus region shuts down the alternate mechanism and the body regenerates the normal mechanism to produce heat. It is also important to note that the nonsteroidal pain relievers such as aspirin, paracetamol, and ibuprofen reduce the fever by inhibiting the platelet activity. This discussion highlights an area of biochemistry and physiology that is yet to be fully explored. The hypothesis was obtained as a result of extensive analyses of available evidence from the literature and has to be further confirmed with experiments.

Acknowledgements

The author acknowledges Renumathi Subramanian and Dhanalakshmi Anbukumar from Washington University, Praveen Subramanian from University of Kansas, Curie Marie Subramanian from Saint Louis University and Suriya Subramanian from University of Texas Southwestern Medical Center for their constant encouragements, critical readings and helpful suggestions for the preparation of the manuscript.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Melchinger, H., Jain, K., Tyagi, T. and Hwa, J. (2019) Role of Platelet Mitochondria: Life in a Nucleus Free Zone. *Frontiers in Cardiovascular Medicine*, **6**, Article 153. https://doi.org/10.3389/fcvm.2019.00153

[2] Sharda, A. and Flaumenhaft, R. (2018) The Life Cycle of Platelet Granules [Version 1; Referees: 2 Approved]. *F1000Research*, **7**, 236-247. https://doi.org/10.12688/f1000research.13283.1

[3] Kaushansky, K. (2005) The Molecular Mechanisms That Control Thrombopoiesis. *The Journal of Clinical Investigation*, **115**, 3339-3347. https://doi.org/10.1172/JCI26674

[4] Kaushansky, K. (2006) Lineage-Specific Hematopoietic Growth Factors. *The New England Journal of Medicine*, **354**, 2034-2045. https://doi.org/10.1056/NEJMra052706

[5] Patel, S.R., Hartwig, J.H. and Italiano Jr. J.E. (2005) The Biogenesis of Platelets from Megakaryocyte Proplatelets. *The Journal of Clinical Investigation*, **115**, 3348-3354. https://doi.org/10.1172/JCI26891

[6] Wojtukiewicz, M.Z., Sierko, E. and Hempel, D. (2017) Platelets and Cancer Angiogenesis Nexus. *Cancer Metastasis Review*, **36**, 249-262. https://doi.org/10.1007/s10555-017-9673-1

[7] De Geatano, G. (2001) Historical Overview of the Role of Platelets in Hemostasis and Thrombosis. *Heamatologica*, **86**, 349-356. https://pubmed.ncbi.nlm.nih.gov/11325638/

[8] Cooper, K.E. (1965) The Role of Hypothalamus in the Genesis of Fever. *Proceedings of the Royal Society of Medicine*, **58**, Article 740. https://doi.org/10.1177/003591576505800941

[9] Fitch-Tewfik, J.L. and Flaumenhaft, R. (2013) Platelet Granule Exocytosis: A Comparison with Chromaffin Cells. *Frontiers in Endocrinology*, **4**, Article 77. https://doi.org/10.3389/fendo.2013.00077

[10] Kulkarni, P.P., Ekhlak, M., Sonkar, V.K. and Dash, D. (2022) Mitochondrial ATP Generation in Stimulated Platelets Is Essential for Granule Secretion but Dispensable for Aggregation and Procoagulant Activity. *Haematologica*, **107**, 1209-1213. https://doi.org/10.3324/haematol.2021.279847

[11] Whiteheart, S.W. (2017) Fueling Platelets: Where Does the Glucose Come from? *Arteriosclerosis, Thrombosis and Vascular Biology*, **37**, 1592-1594. https://doi.org/10.1161/ATVBAHA.117.309841

[12] Mitchell, P. and Moyle, J. (1967) Chemiosmotic Hypothesis of Oxidative Phosphorylation. *Nature*, **213**, 137-139. https://doi.org/10.1038/213137a0

[13] Jastroch, M., Divakaruni, A.S., Mookerjee, S., Treberg, J.R. and Brand, M.D. (2010) Mitochondrial Proton and Electron Leaks. *Essays in Biochemistry*, **47**, 53-67. https://doi.org/10.1042/bse0470053

[14] Genova, M.L., Baracca, A., Biondi, A., Casalena, G., Faccioli, M., Falasca, A.I., Formiggini, G., Garbi, G. S., Solaini, G. and Lenaz, G. (2008) Is Super Complex Organization of a Respiratory Chain Required for Optimal Electron Transfer Activity? *Biochimica et Biophysica Acta*, **1777**, 740-746. https://doi.org/10.1016/j.bbabio.2008.04.007

[15] Demine, S., Renard, P. and Arnould, T. (2019) Mitochondrial Uncoupling: A Key Controller of Biological Processes in Physiology and Diseases. *Cells*, **8**, Article 795. https://doi.org/10.3390/cells8080795

[16] Vissenaekens, H., Smagghe, G., Criel, H., Grootaert, C., Raes, K., Rajkovic, A., Goeminne, G., Boon, N., Schutter, K.D. and Camp, J.V. (2021) Intracellular Quercetin Accumulation and Its Impact on Mitochondrial Dysfunction in Intestinal Caco-2 Cells. *Food Research International*, **145**, Article 110430. https://doi.org/10.1016/j.foodres.2021.110430

[17] Chamberlain, K.G., Tong, M. and Penington, D.G. (1990) Properties of the Exchangeable Splenic Platelets Released into the Circulation during Exercise Induced Thrombocytosis. *American Journal of Hematology*, **34**, 161-168. https://doi.org/10.1002/ajh.2830340302

[18] Schmidt, K.G. and Rasmussen, J.W. (1984) Exercise-Induced Changes in the *in Vivo* Distribution of ^{111}In-Labelled Platelets. *Scandinavian Journal of Haematology*, **32**, 159-166. https://doi.org/10.1111/j.1600-0609.1984.tb02172.x

[19] Bakovic, D., Pivac, N., Eterovic, D., Breskovic, T., Zubin, P. and Obad, A. (2013) The Effects of Low-Dose Epinephrine Infusion on Spleen Size, Central and Hepatic Circulation and Circulating Platelets. *Clinical Physiology and Functional Imaging*, **33**, 30-37. https://doi.org/10.1111/j.1475-097X.2012.01156.x

[20] Zouhal, H., Jacob, C., Delamarche, P. and Gratas-Delamarche, A. (2008) Catecholamines and the Effects of Exercise, Training and Gender. *Sports Medicine*, **38**, 401-423. https://doi.org/10.2165/00007256-200838050-00004

[21] Blino, G., Santimone, I., Minelli, C., Sorice, R., Frongia, B., Traglia, M., *et al.* (2013) Age- and Sex-Related Variations in Platelet Count in Italy: A Proposal of Reference Ranges Based on 40987 Subjects' Data. *PLOS ONE*, **8**, e54289. https://doi.org/10.1371/journal.pone.0054289

[22] Ittermann, T., Feig, M.A., Petersmann, A., Radke, D., Greinacher, A., Volzke, H., *et al.* (2019) Mean Platelet Volume Is More Important Than Age for Defining Reference Intervals of Platelet Counts. *PLOS ONE*, **14**, e0213658. https://doi.org/10.1371/journal.pone.0213658

[23] Kaikaew, K., van den Beukel, A., Neggers, S. and Themmen, A. (2008) Sex Difference in Cold Perception and Shivering Onset Upon Gradual Cold Exposure. *Journal of Thermal Biology*, **77**, 137-144. https://doi.org/10.1016/j.jtherbio.2018.08.016

[24] Mackowiak, P.A., Wasserman, S.S. and Levine, M.M. (1992) A Critical Appraisal of 98.6˚F, the Upper Limit of the Normal Body Temperature, and Other Legacies of Carl Reinhold August Wunderlich. *Journal of the American Medical Association*, **268**, 1578-1580. https://doi.org/10.1001/jama.1992.03490120092034

[25] Zarbock, A., Polanowska-Grabowska, R.K. and Ley, K. (2007) Platelet-Neutrophil Interactions: Linking Hemostasis and Inflammation. *Blood Review*, **21**, 99-111. https://doi.org/10.1016/j.blre.2006.06.001

[26] Afdhal, N., McHutchison, J., Brown, R., Jacobson, I., Manns, M., Poordad, F., *et al.* (2008) Thrombocytopenia Associated with Chronic Liver Disease. *Journal of Hepatology*, **48**, 1000-1007. https://doi.org/10.1016/j.jhep.2008.03.009

[27] Assinger, A., Kral, J.B., Yaiw, K.C., Schrottmaier, W.C., Kurzejamska, E., Wang, Y., *et al.* (2014) Human Cytomegalovirus-Platelet Interaction Triggers Toll-Like Receptor 2-Dependent Proinflammatory and Proangiogenic Responses. *Arteriosclerosis, Thrombosis and Vascular Biology*, **34**, 801-809. https://doi.org/10.1161/ATVBAHA.114.303287

[28] Koupenova, M., Vitseva, O., MacKay, C.R., Beaulieu, L.M., Benjamin, E.L., Mick, E., *et al.* (2014) Platlet-TLR7 Mediates Host Arrival and Platelet Count during Viral Infection in the Absence of Platelet-Dependent Thrombosis. *Blood*, **124**, 791-802. https://doi.org/10.1182/blood-2013-11-536003

[29] Vella, M.A., Jenner, C., Betteridge, D.J. and Jowett, N.I. (1988) Hypothermia-Induced Thrombocytopenia. *Journal of the Royal Society of Medicine*, **81**, 228-229. https://doi.org/10.1177/014107688808100414

[30] Chan, K.M. and Beard, K. (1993) A Patient with Recurrent Hypothermia Associated with Thrombocytopenia. *Postgraduate Medical Journal*, **69**, 227-229. https://doi.org/10.1136/pgmj.69.809.227

[31] Rashidi, A. (2012) Hypothermia-Induced Thrombocytopenia in an Elderly Woman. *Platelets*, **23**, 246-247. https://doi.org/10.3109/09537104.2011.604807

[32] Pina-Cabral, J.M., Amaral, I., Pinto, M.M., Guerra, E. and Paz, L.H. (1973/74) Hepatic and Splenic Platelet Sequestration during Deep Hypothermia in the dogs. *Haemostasis*, **2**, 235-244. https://doi.org/10.1159/000214026

[33] Hessel, E.A., Schmer, G. and Dillard, D.H. (1980) Platelet Kinetics during Deep Hypothermia. *Journal of Surgical Research*, **28**, 23-34. https://doi.org/10.1016/0022-4804(80)90078-5

[34] Assinger, A. (2014) Platelets and Infection—An Emerging Role of Platelets in Viral Infection. *Frontiers in Immunology*, **5**, Article 649. https://doi.org/10.3389/fimmu.2014.00649