



The Hypothetical Role of Erythrocytes in COVID-19: Immediate Clinical Therapys

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ABSTRACT

We suppose a hypothetical role of erythrocytes in COVID-19: Involvement of bone marrow; evidences of the presence of ferritins in the autoptic spleen; role of erythrocytes in the production of thrombosis; the reason of using chloroquine and heparin; the similar actions with HIV-1; protection of HIV patients and Thalassemic patients from Covid19; reason of increase of Kawasaki patients; At last the protective role of Methylene blue in COVID-19.

INTRODUCTION

COVID19 - The virus is made of genetic code (RNA or DNA), the capsid inside which it is encased and the envelope. The virus has an oxide-reductive capability by which it imposes allosterism of its proteins [1]. The COVID-19 virus enters the bone marrow (totipotent stem cells) and then follows the maturation line of the Dendritic Cells (DCs) [2] and leaves quantities of its Spike glycoprotein inside some red blood cells (presence of ferric iron in the CD69 macrophages of the bone marrow). Probably the Spike glycoprotein binds to the 1-beta chains of hemoglobin. A situation of suffering and oxidative stress of erythrocytes in COVID-19 is evidenced in some articles [3].

Regarding the Dendritic cells (DCs), they exist in two functionally and phenotypically distinct states, immature and mature [4]. The immature DCs (iDCs) act in the early hours of viral encounter as "Trojan horses" in HIV-1, because they capture HIV-1 in the mucosa and then, migrating to secondary lymphoid tissues, where stored HIV-1 could be transmitted to CD4⁺ T cells and contribute to the spread of infection [2,5,6]. We theorize that this situation occurs also for COVID-19, with the difference that in COVID-19 there is the participation of mature DCs that produces copious amount of cytokines (cytokines storm).

Decreased concentration of the oxygen in blood and oxidative stress

We believe the Spike glycoprotein enters the red blood cells, binds the beta chains of hemoglobin and sometimes but not always, it can interfere with the heme group with manifestation of Methemoglobinemia (values from 1.5% to 3% as in HIV-1 infection) [7]. If the Spike glycoprotein fails to interfere with the heme group there is no manifestation of methemoglobinemia, but in any case there is an oxidizing action on GSH that is inside erythrocytes [1]. This situation produces an oxidative stress that results a reduction of hemoglobin, a hyperferritinemia and

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a reduction of T4 Helper cells number, and production of ROS (reactive oxygen species) and RNS (reactive nitrogen species) [8]. We suppose that the Oxidative stress has negative effects on metabolism because Electron Transport Chain (Respiratory Chain) and Oxidative Phosphorylation do not produce ATP, the Beta-Oxidation of reserve fatty acids is not yet possible because there is not ATP, so that there is a decreased organism energy capacity, that is compensate by using albumin and also organic proteins as an energetic source (there is decreased albumin level in COVID-19 patients [9,10]), since the clinical data, now evident, show that COVID-19 patients have a great weight loss.

Hyperferritinemic syndromes

Usually this term “Hyperferritinemic syndromes” defines and includes four clinical conditions that are Macrophage Activation Syndrome (MAS), adult-Onset Still’s Disease (AOSD), catastrophic Anti-Phospholipid Syndrome (CAPS), and septic shock. In the study of Rosario, et al. [11] they hypothesize that huge level of ferritin in these four clinical conditions are not just a secondary product of the inflammatory process but rather that they are part of the pathogenic mechanism. Other authors, Colafrancesco, et al. [12] claim that the more severe form of COVID-19 and ”Hyperferritinemic syndromes” are all characterized by high serum ferritin and life-threatening hyper-inflammation sustained by a cytokines storm which eventually leads to multi-organ failure. They note that the epidemiological and molecular mechanism responsible for hyper-inflammation in COVID-19 patients has similarities with “Hyperferritinemic syndromes” and they would consider COVID-19 as a fifth member of this spectrum of inflammatory conditions [12].

Now we would like to point out that these syndromes often respond to similar therapies, so we believe that Methylene blue can have a crucial role in treatments of these pathologies, also because it was just used in cases of septic shock, but primarily because it is a powerful reducing agent and control the Oxidative Stress reducing hyper-ferritinemia.

Vasculitis, thrombosis and pneumonia

We theorize that once the Spike has consumed all the GSH and has transformed it into GSSG the red blood cell membrane undergoes charge variation because it activates a chain called BOAT1 which contains the ACE2 receptor. Once this receptor is activated, ACE2, that is an enzyme attached to the cell membranes of cells in the lungs, heart, arteries, kidneys, binds to it and an event of great contrast occurs, especially in the lungs, between ACE2 which is an antioxidant and the oxidizing Spike, (in fact Spike is a condenser of oxide/reductive potential), causing simultaneously, vasculitis, thrombosis and pneumonia (SARS-CoV 2).

Spleen

Having defined the behavior of COVID19 as similar to HIV-1 spread by air, it can be expected to find the presence of ferric iron Fe^{3+} and hemoglobin in the Cords of Billroth of the spleens of the deceased for the cause of COVID-19, as Ansovini - Balbolini and co-workers found in the spleens of deceased for the cause of HIV-1 [3]. In particular, the presence of ferric iron Fe^{3+} and hemoglobin in the Cords of Billroth shows that there is a hemoglobinopathy in HIV-1 infection [3], as we suppose also in COVID-19. Since it is difficult to find the comparison inside red blood cells, their final station, the spleen, provides the evidence. What is responsible for the oxidization of iron? We presume the Spike glycoprotein.

Chloroquine

Chloroquine binds to heme so that it prevents Spike to attack the heme on 1-beta chain of hemoglobin, but it is insufficient to contain the COVID-19 infection with important side effects [13].

Heparin

Heparin was used to prevent thromboembolic events but it has not the expected effect probably because cannot function to completely dissolve the thrombi made of aggregated red blood cells that are attached to the cell membranes in the lung cells and in other organs that have ACE2 enzyme in the cell membranes.

HIV

The HIV-1 attack site is 1-beta chains of hemoglobin, the same as that one of COVID19, so the COVID-19 Spike, which has some HIV-1-like proteins, fails to prevail, and positive HIV-1 individuals are protected from COVID-19 infection [14]. We also theorize that babies born to positive COVID19 mothers, like to HIV-1 positive mothers, rarely become infected because they have fetal hemoglobin without 1-beta chains, so both viruses, HIV-1 and COVID-19, have not their site attack.

Thalassemia

The reduced size of red blood cells does not allow the spike to bind stably so also Thalassemic individuals are protected from COVID-19 infection [15].

Kawasaki disease

In COVID19, as described, a contemporary triad of: vasculitis, thrombosis, pneumonia occurs. Vasculitis occurs in Kawasaki syndrome. This is one of the most important aspects to understand the link between COVID-19 and the totipotent blood cell. Confirming the difficulty of the Spike to join hemoglobin in young children due to the structural differences of the chains compared to adults,

there is evidence that COVID-19 infected young children, can develop, in the predisposed individuals, only Kawasaki syndrome, instead of a COVID-19 disease [16].

METHYLENE BLUE

Methylene blue can have a protective role or, at the first symptoms of COVID19, it can be therapeutic in order to avoid vasculitis [17]. We suppose that Methylene blue is the only aid that can prevent the attachment of ACE2 to the red blood cell membrane only to the red blood cells which have inside the Spike glycoprotein because it is a powerful reducing agent, so that it inhibits the activation of ACE2 receptors (BOAT1) in the erythrocytes by neutralizing the Spike action.

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