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Red Blood Cells and Their Immunoregulatory Role

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Highlights of the Study

- Red blood cells modulate innate and adaptive immune responses.
- Through their complement receptor 1, they bind bacteria, virus, or immunocomplexes, which macrophages take up from them.
- They release microvesicles that promote innate and adaptive immune responses.
- They inhibit the maturation and activity of the 6-sulfo-lactose-N-acetyl dendritic cells and promote the homeostasis and positioning of splenic dendritic cells.

Keywords
Red blood cells · Innate and adaptive immunity · Dendritic cells

Abstract
The physiological roles played by red blood cells (RBCs), i.e., oxygen transport to all cells and tissues, CO_2 delivery to the lungs, control of pH in blood, and ions transport into and out of the cell membrane, have been investigated extensively over the past decades. The roles mature and immature RBCs play, while in the blood vessels, when they come in contact with other blood and endothelial cells, are only partially known. Here we will focus on the ability of RBC to modulate innate and adaptive immune responses when they interact with cells or molecules encountered during their flow in the vessels. We will outline the possible clinical impact on treatment of some diseases, such as autoimmune diseases, inflammatory pathologies, or tumors, where immunotherapy can be applied.

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Background

During their life span, human red blood cells (RBCs) undergo a continuous turnover, and aged cells are destroyed in spleen. During their passage in the vessels and capillaries, RBCs are subjected to a remarkable physical stress and they come into contact with endothelial cells, platelets, and leukocytes. The latter interactions may impact the functions of lymphocytes and their transfer out of the blood vessels, on platelets, endothelial cells, and on macrophages and this has previously been reported [1–3]. Furthermore, even at various stages of development and differentiation from reticulocytes to mature RBCs, they can regulate the immune response [4].

Innate Immunity and the Interplay of RBCs with Other Cells Encountered during Their Passage through Vessels

The innate immunity can be mediated by RBC receptors expressed on the cell membrane or RBC-derived microparticles (MPs) in several intercellular contexts by links of

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their membrane receptors to the agonists. The engulfment and destruction of senescent RBCs by macrophages is dependent on the interaction between CD47, an integrin-associated glycoprotein of RBC membrane, and signal regulatory protein-alpha (SIRP-alpha), a signal regulatory protein on the macrophage membrane. The interaction CD47-SIRP-alpha prevents RBC phagocytosis, by inducing an inhibitory signal to macrophages [5]. On the contrary, senescent or damaged RBCs lacking CD47, or expressing CD47 with abnormal conformation, are phagocytized and cleared off [6, 7]. Furthermore, macrophages take up immunocomplexes or pathogens bound to complement receptor 1 (CR1) on red cells, and they are able to clear intracellular pathogens such as *Plasmodium falciparum*. In bacteremia, red cells remove the bacteria from blood stream by oxycytosis, mediated by oxygen released by RBC hemoglobin [1, 8, 9]. Among the RBC receptors, toll receptors-7 and -9 (TLR-7, TLR-9) should be mentioned. TLRs are protective immune sentinels that sense pathogen-associated molecular patterns such as unmethylated double-stranded CpG containing DNA fragments derived from bacteria, plasmodia, and mitochondria (TLR-9) and single-stranded RNA. TLR-7 binds lipoproteins, lipopolysaccharide, and flagellin. In innate immune myeloid cells, TLRs induce the secretion of inflammatory cytokines, thereby engaging lymphocytes to mount an adaptive, antigen-specific immune response that ultimately eradicates the invading microbes [10, 11]. Tollr-9, when it binds its agonists, can also cause negative effects since, besides innate immunity activation, it can cause anemia: indeed, RBCs binding CpG containing DNA fail to express CD47; thereby, they are subjected to macrophage phagocytosis [11].

MPs, that are pieces of the cell membrane released by RBCs (RBCs-MPs or R-MPs), are important players in different physiological processes as well. Proteins and lipids derived from RBCs are present on R-MPs and bind to monocytes, induce pro-inflammatory cytokines, and boost mitogen-driven T-cell responses; specifically, they amplify antigen-presenting cell (APC)-based induction of pro-inflammatory cytokines and chemokines from peripheral blood monocytes, promoting T cells activation [12–14]. Several previous reports have described the molecules of the MPs, which are derived from fresh or stored RBCs. The presence of several RBC antigens has been found in microvesicles from the stored RBCs [12–17].

The RBC antigens in microvesicles from stored RBCs can cause potential negative impact in various clinical conditions since they lead to potential deleterious effects in transfused recipients, including hypercoagulability, microcirculation impairment, and immunosuppression [17, 18].

In sickle cell disease, acid sphyngomyelinase derived from RBCs can induce release of inflammatory MPs. Sphyngomyelinase enhances RBC-derived MP generation. The MPs are internalized by myeloid cells and induce pro-inflammatory cytokine secretion and endothelial cell adhesion, promoting a potential crosstalk between circulating inflammatory cells and the MPs [18].

Finally, RBCs are important inter-organ communication systems with additional functions, including participation in the control of systemic NO metabolism, regulation of vascular tone, blood rheology, and viscosity. RBCs are relevant for redox balance, especially during hypoxic and ischemic conditions, and the production and release of nitric oxide (NO) bioactivity. RBCs produce nitric oxide through NO synthetase in a reaction where the enzyme is regulated by its substrate, arginine, calcium, and phosphorylation via phosphatidyl-3-kinase (PI3-kinase) [19]. In cases of hypoxia, the formation of free radicals, such as NO or reactive oxygen species, causes the conversion of nitric oxide (NO) to peroxynitrite, thereby diminishing the bioavailability of NO [20, 21]. Furthermore, hypoxic conditions induce an increase in sphingosine1-P (S1-P), which initiates a set of cytoprotective events via its cellular receptors. Cellular receptors for S1-P are present in erythrocytes and in other cells and tissues. Furthermore, platelets and erythrocytes are mediator of blood transport of S1-P. In RBCs, the efflux of S1-P is mediated by apolipoprotein M [22, 23].

RBCs and the Adaptive Immune Response

In 2006, a pioneer article [24] showed that RBCs can interact through their membrane glycoprotein CD47, with a subset of dendritic cells (DCs) (named SLAN DCs: 6-sulfo-lactose-N-acetyl). SLAN is an epitope of a DC membrane protein that, at variance with the majority of DCs, circulates in the blood. Majority of DCs are resident in lymphoid organs and are the conventional APCs, able to uptake, process, and present antigens to T cells, to activate the immune responses [25]. SLAN DCs can activate innate immune responses, through binding of many pathogens such as *Escherichia coli*, through glycophorin, and a subsequent macrophage-mediated clearing in the spleen [24].

SLAN DCs produce IL-12 [24], an inflammatory interleukin, when stimulated by lipopolysaccharide, tumor necrosis factor-alpha (TNF-alpha). Therefore, they are highly pro-inflammatory cells. Through IL-12, they promote the differentiation of T-helper cells in gamma interferon producing T cells, named T helper cells type 1 (Th1). They are also able to mediate antibody-dependent cellular cytotoxicity and stimulate

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the natural killer cells, which migrate in response to anaphylatoxins [25–27].

Specific combinations of receptors and ligands are temporally activated in tissues during the immune response and ensure the responding leukocytes' traffic to the correct location. P-selectin glycoprotein ligand-1 (PSGL-1) is on the cell membrane of most hematopoietic cells, such as DCs, and shows the epitope SLAN as well as SLAN DCs. PSLG-1 is a critical regulator of lymphocytes migration during homeostasis and disease [28] and binds its primary ligand, P-selectin, through biochemical modification (sulfation and glycosylation of tyrosine) [29]. Multiple partners of PSLG-1 can interfere with the role of T cells in immune response [30]. Indeed, the interaction of the SLAN epitope of the PSLG-1 glycoprotein with CD47 present on the RBC membrane can signal, through SIRP-alpha (signal regulatory protein-alpha), inhibition of the maturation of DCs and of production of IL-12. Then, besides the ability to inhibit the phagocytosis of senescent red cells by spleen macrophages, CD47 can also prevent the inflammatory activity and the Th1 immune response mediated by circulating SLAN DCs [24].

The study of Schäkel et al. [24] has led to further investigations, which have been cited by other researchers [31, 32]. Multiple types of DCs exist in different tissues, each with unique, but also overlapping, functions and molecular mechanisms, to induce different types of T-cell responses or the activation of monocytes and macrophages. For instance, at the psoriasis lesions, macrophages, expressing toll-like receptors-7 and -9 (TLRs-7 and -9) play a pathogenic role [33] and DCs play a crucial role in the development of psoriasis, an auto-immune disease [33].

Finally, it is noteworthy that homeostasis and positioning of splenic conventional dendritic cells type 2 (cDC2) is regulated by interaction between the RBC membrane protein CD55 (decay accelerating factor) and CD97 (ADGRE5, adhesion G-protein coupled receptor 5), a membrane receptor of cDC2: this interaction, allowing mechano-sensing of RBCs, promotes the homeostasis of DCs, their positioning in spleen, and the capture and antigen presentation to T cells. In the absence of CD55 on the RBC membrane, cDC2 are lost in the circulation [34].

Conclusion

Altogether, the studies, reported in this minireview, indicate a role of RBCs in innate and adaptive immune responses: in the adaptive ones, RBCs show two different interactions with either SLAN DCs (inhibition of their maturation, downregulation of inflammatory release of cytokines and of antigen specific response) or with conventional DC type 2 (positioning of CDC2 and antigen presentation activity). Investigations are still needed to clarify the molecular details of the complex interaction between lymphocytes, erythrocytes, macrophages, the different subsets of DCs, and the related biological effects.

However, these studies will have an impact on different types of immunopathologies. Among these, we can list: (1) modulation of the inflammatory responses; (2) modulation or inhibition of unwanted immune responses, such as those involved in psoriasis, an autoimmune disease; (3) stimulation of conventional DCs in many adaptive responses, and (4) immunotherapy, a treatment of many solid and hematological malignancies; this therapy requires the maturation and the subsequent APC activity by DCs to activate the anti-cancer function of T cells [35]. More recently, the chimeric antigen receptor T cells therapy (lymphocytes where T-cell receptor has been previously engineered and is able to identify specific antigens expressed on tumor cells) has been used in several tumor microenvironment [35]. The therapy requires efficient, functional DCs indicating their relevant role in regulating the T cell response to tumors and also the one played by RBCs in positioning and maintaining homeostasis of DCs.

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Statement of Ethics

Ethical approval was not required for this study.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

Angela Risso wrote a draft of the manuscript, collected the corresponding references, and designed the sections of the manuscript. Guglielmo Antonutto discussed the sections of the manuscript, contributed to the improvement of the draft and its style, and amended the format.

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