Blood Reviews xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

Review

Consequences of dysregulated complement regulators on red blood cells

Astrid J.F. Thielen[a], Sacha Zeerleder[a,b], Diana Wouters[a,*]

[a] Department of Immunopathology, Sanquin Research, Landsteiner Laboratory of the Academic Medical Center, University of Amsterdam, Plesmanlaan 125, 1066 CX Amsterdam, The Netherlands

[b] Department of Hematology, Academic Medical Center, University of Amsterdam, Meibegdreef 9, 1105 AZ Amsterdam, The Netherlands

ARTICLE INFO

Keywords:
Red blood cells
Complement activation
Regulation
Hemolysis
Anemia

ABSTRACT

The complement system represents the first line of defense that is involved in the clearance of pathogens, dying cells and immune complexes via opsonization, induction of an inflammatory response and the formation of a lytic pore. Red blood cells (RBCs) are very important for the delivery of oxygen to tissues and are continuously in contact with complement proteins in the blood plasma. To prevent complement activation on RBCs, various complement regulatory proteins can be found in plasma and on the cell membrane. RBCs are special cells without a nucleus and having a slightly different make-up of complement regulators than nucleated cells, as membrane cofactor protein (MCP) is not expressed and complement receptor 1 (CR1) is highly expressed. Decreased expression and/or function of complement regulatory proteins may result in unwanted complement activation and accelerated removal of RBCs. This review describes complement regulation on RBCs and the consequences when this regulation is out of balance.

1. Introduction

Red blood cells (RBCs) are the most common cells in our blood and are indispensable in the delivery of oxygen to tissues. RBCs have a biconcave form, do not have a nucleus, and under normal conditions RBCs have a life span of ~120 days. While circulating in the body, RBCs are continuously in contact with complement components in the blood plasma [1].

The complement system is part of our innate immune system and is very important in the clearance of pathogens, dying cells and immune complexes. The complement system consists of at least 30 circulating and membrane-associated proteins that are mainly synthesized by the liver. There are three distinct pathways of complement activation: the classical pathway (CP), which is activated by antibody-antigen complexes, pattern recognition molecules such as CRP or directly by structures on pathogens or apoptotic cells, the lectin pathway (LP) is activated by pathogen associated carbohydrate structures and the alternative pathway (AP) which is activated by the spontaneous hydrolysis of C3, that can form the AP-initiating C3 convertase (called tick-over mechanism), and only proceeds on unregulated surfaces. Both the CP and LP lead to the cleavage of complement proteins C4, C2 and the subsequent formation of the C3 convertase C4bC2a on the activating surface, while the AP leads to the formation of the C3 convertase C3bBb on the surface [1–5]. Both C3 convertases cleave more C3 molecules to opsonize foreign or damaged material for phagocytosis and eventually leading to clearance of cells by formation of the membrane attack complex (MAC) and the chemotaxis of leukocytes by anaphylatoxins contributing to the inflammatory response [1,2,6,7].

Since complement activation has potentially dangerous strong inflammatory effects and may lead to cell lysis, it is of utmost importance that complement activation is tightly regulated. Complement regulation must act specifically on healthy host cell surfaces, while leaving pathogen clearance intact. Next to complement regulation on host cell surfaces, soluble complement regulators also control complement activation in solution to prevent consumption of complement proteins in plasma. Dysregulation of the complement system, due to either inefficient regulation or overstimulation, can be detrimental for the host and contributes to the pathology of many diseases including autoimmune diseases, transfusion reactions, and complement mediated conditions like paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS) and age-related macular degeneration (AMD) [1,2,8,9]. This review focuses on complement regulation on RBCs and the consequences of complement regulation dysbalance on RBCs.

2. Complement regulators

Complement regulatory proteins can be found both in the fluid phase in plasma (such as factor H (FH) and its splice variant FH-like 1 (FHL-1), factor I (FI), C1 inhibitor (C1-INH) and C4b-binding protein

* Corresponding author.
E-mail address: d.wouters@sanquin.nl (D. Wouters).

https://doi.org/10.1016/j.blre.2018.01.003

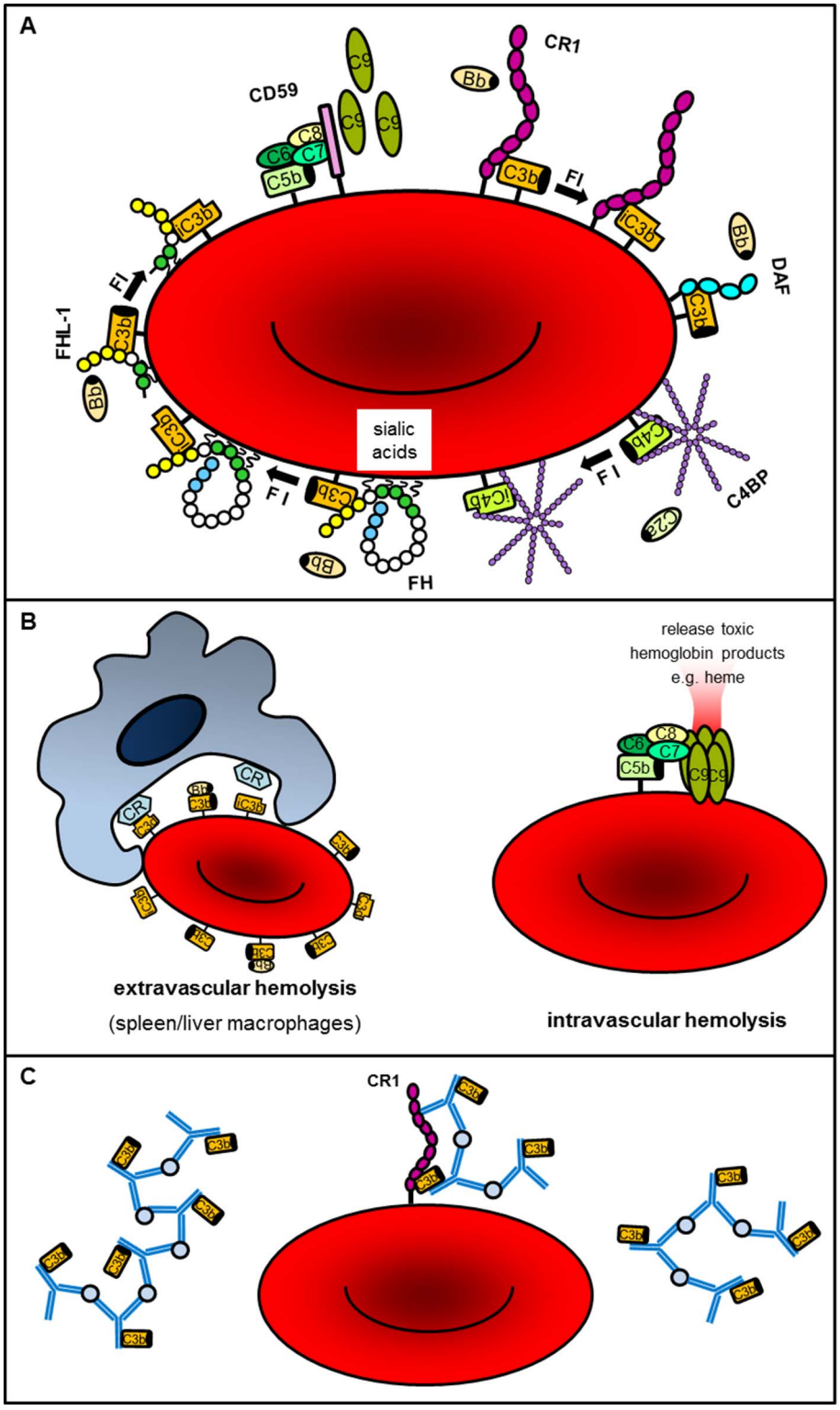

Fig. 1. Complement regulation on RBCs and consequences of dysregulation. (A) Membrane-bound complement regulators (DAF, CR1, CD59) and fluid phase complement regulators (C4BP, FH, FHL-1, FI) prevent further amplification of complement activation on RBCs. CR1 and DAF accelerates dissociation of the C3 convertase of all three complement activation pathways (C4bC2a and C3bBb). CR1 can also act as a co-factor for FI to inactivate both deposited C3b and C4b. FH and FHL-1 can bind to RBCs via sialic acids and accelerates the dissociation of the C3 convertase of the AP (C3bBb) and can inactivate deposited C3b together with FI, while C4BP accelerates the dissociation of the C3 convertase of the CP and LP (C4bC2a) and mainly inactivates deposited C4b together with FI. CD59 prevents the binding and polymerization of C9 and thus formation of the MAC. Lack of MCP expression on RBCs is the major difference as compared to complement regulation on nucleated cells. **(B)** Decreased expression and/or function of complement regulatory proteins results in opsonization of RBCs with the C3 convertase of all three complement activation pathways (C4bC2a and C3bBb) and degradation products (iC4b, C4d and iC3b, C3d) contributing to extravascular lysis due to clearance by spleen and liver macrophages and/or results in the formation of the MAC causing intravascular hemolysis of RBCs. Both ways of hemolysis contribute to the development of anemia. **(C)** Decreased expression and/or function of CR1 reduces immune adherence clearance that results in accumulation of immune complexes that contribute to a stronger inflammatory response and thus disease progression in patients.

(C4BP)) and on the cell surface of most human cells (complement receptor 1 (CR1/CD35), membrane cofactor protein (MCP/CD46), decay-accelerating factor (DAF/CD55), and CD59) [2,10]. Genes expressing several regulatory proteins are located in the same region on chromosome 1. Therefore, this region is also called the regulator of complement activation (RCA) gene cluster. The genes in this cluster show a particular structural organization as they consist of short consensus repeats (SCR) domains, also called sushi domains or complement control protein, with a length of ~60 amino acids. Genes of this cluster include CR1, MCP, DAF, FH and C4BP [11,12]. However, not all genes for complement regulatory proteins are located in this RCA cluster, as C1-INH and CD59 are located on chromosome 11 and the gene encoding for FI is located on chromosome 4 [13–15].

2.1. Fluid phase complement regulators

Fluid phase complement regulators are more pathway specific compared to membrane bound complement regulators, that have more