Immunobiology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Immunobiology

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

Complement genetics and susceptibility to inflammatory disease. Lessons from genotype–phenotype correlations

Santiago Rodríguez de Córdoba*

Centro Investigaciones Biológicas and Ciber de Enfermedades Raras, Ramiro de Maeztu 9, 28040 Madrid, Spain

ARTICLE INFO

Article history:
Received 18 February 2015
Accepted 6 May 2015
Available online xxx

Keywords:
Complement
Factor H
Factor H-related proteins
CFHRs
C3
Disease susceptibility

ABSTRACT

Different genome-wide linkage and association studies performed during the last 15 years have associated mutations and polymorphisms in complement genes with different diseases characterized by tissue damage and inflammation. These are complex disorders in which genetically susceptible individuals usually develop the pathology as a consequence of environmental triggers. Although complement dysregulation is a common feature of these pathologies, how the disease phenotype is determined is only partly understood. One way to advance understanding is to focus the research in the analysis of the peculiar genotype–phenotype correlations that characterize some of these diseases. I will review here how understanding the functional consequences of these disease-associated complement genetic variants is providing us with novel insights into the underpinning complement biology and a better knowledge of the pathogenic mechanisms underlying each of these pathologies. These advances have important therapeutic and diagnostic implications.

Introduction

Complement is a key component of our innate immunity capable of firing alarm signals in the presence of pathogens, immune complexes or apoptotic cells. Complement discriminates between host, altered host and pathogens for their elimination by opsonophagocytosis or destruction by direct cell lysis. Briefly, (i) complement activation by three independent activation pathways, classical (CP), lectin (LP) and alternative (AP), results in the formation of unstable protease complexes, named C3-convertases (AP, C3bBb; CP/LP, C4b2a) that cleave C3 to generate C3b; (ii) Convertase-generated C3b can form more AP C3-convertase, providing exponential amplification of the initial activation; and (iii) Clustering C3b molecules around the surface-bound C3-convertase generates the C5-convertase with the capacity to bind and cleave C5, triggering inflammation and initiating formation of the lytic membrane attack complex (MAC). Several regulatory proteins restrict complement activation to the surface responsible for its activation and avoid complete consumption after activation. These include factor H (FH), C4b-binding protein (C4BP), membrane cofactor protein (MCP, CD46), decay accelerating factor (DAF, CD55) and complement receptor 1 (CR1; CD35). Loss of complement regulation leads to the generation of pro-inflammatory components and/or damage to self-tissues, both situations resulting in pathology (Ricklin et al., 2010; Holers, 2008; de Cordoba et al., 2012; Ricklin and Lambris, 2013).

FH is the most important regulator of the AP. It is an abundant plasma glycoprotein composed of 20 repetitive units (short consensus repeats, SCRs) that accelerate the AP convertase decay and acts as cofactor for the factor I-mediated proteolysis of C3b; FH regulates complement in fluid phase and on cellular surfaces (Rodríguez de Córdoba et al., 2004). Importantly, while FH binds and inactivates promptly C3b in fluid phase, the inactivation of surface-bound C3b by FH is dependent on the chemical composition of the surface to which C3b is bound. In the presence of polyanions, like sialylated glycans, glycosaminoglycans or sulphated polysaccharides (heparins), and other FH ligands, the affinity of FH for surface-bound C3b increases as a consequence of the simultaneous recognition of these FH ligands and bound C3b by the same FH molecule (Morgan et al., 2011; Blaum et al., 2015; Morgan et al., 2012; Kajander et al., 2011). The regulatory activities of the FH molecule depend on three major functional domains, an N-terminal domain (SCRs 1–4) that sustains the cofactor and decay accelerating activities and two domains in SCRs 6–7 and SCRs 19–20 which are relevant for ligand and cell surface recognition. FHL-1, derived from the *CFH* gene via alternative splicing, includes only the N-terminal and the SCRs 6–7 functional domains and, therefore, has limited capacity to regulate complement on surfaces. As described, FH is a multifunctional protein and it should be expected that mutations that eliminate, completely or

* Correspondence to: Dept. Medicina Celular y Molecular, Centro de Investigaciones Biologicas, c/Ramiro de Maeztu 9, 28040 Madrid, Spain. Tel.: +34 918373112.
E-mail address: srdecordoba@cib.csic.es

http://dx.doi.org/10.1016/j.imbio.2015.05.015
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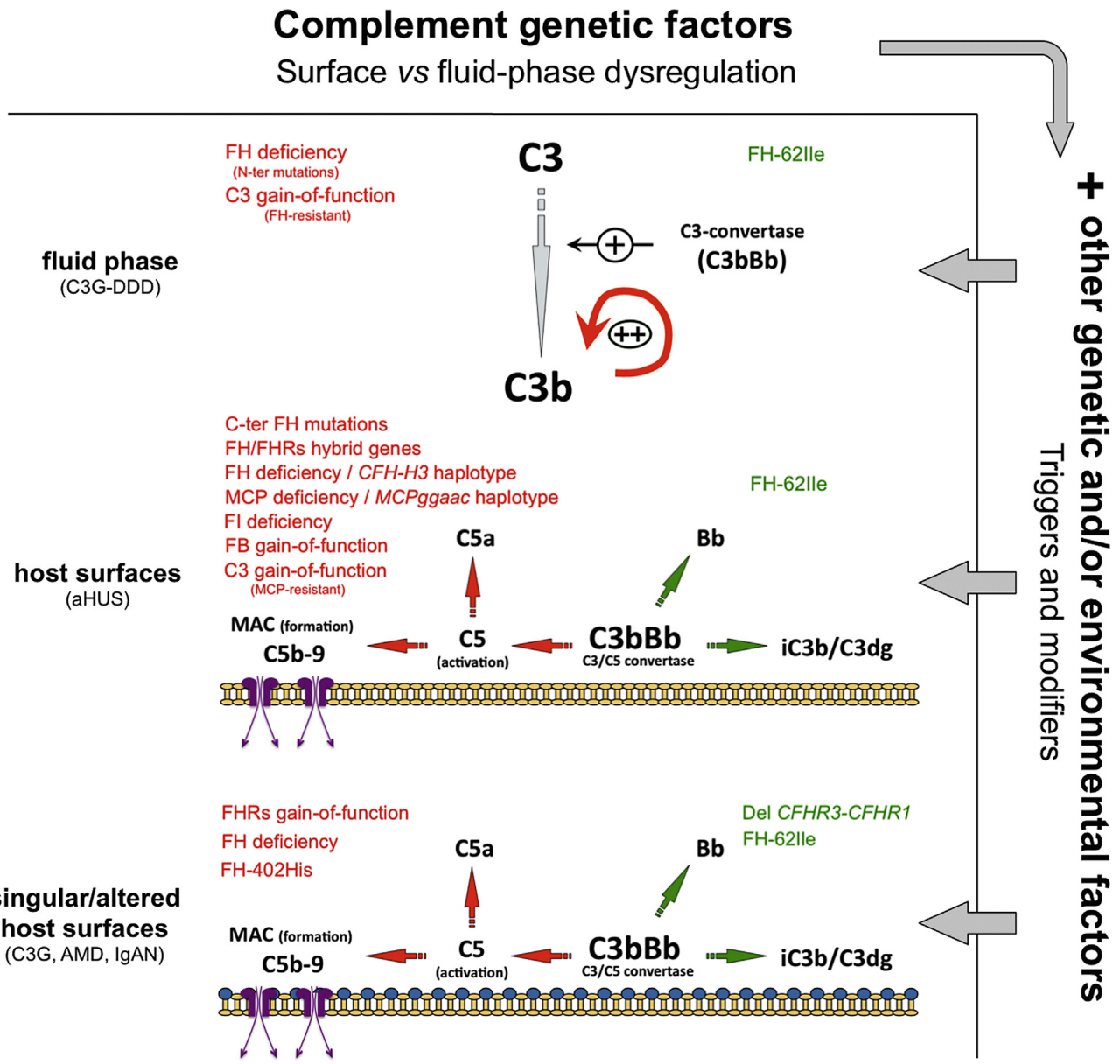

Fig. 1. Complement genetic variants and disease outcome. Figure depicts combinations of factors that determine the site of complement dysregulation and disease outcome. Only complement genetic variants are listed. Red, risk factors. Green, protective factors. Singular and altered host surfaces are terms used here in a wide and overlapping sense to refer, for example, to extracellular matrix and other cell surface components modified by aging, microbial and chemical agents, or by deposition of immune complexes (including those containing galactose deficient-IgA), or even to iC3b, C3dg opsonized surfaces. We like to suggest that on these singular and altered host surfaces an unbalanced FH/FHRs ratio causes complement dysregulation.

partially, all or some of these functional sites will cause specific FH dysfunctions with distinct pathological consequences.

Compelling evidence generated in recent years indicates that the complement regulatory activities of FH on surfaces are modulated by a group of evolutionarily and structurally related proteins, denominated FH-related proteins (FHRs) (Józsi et al., 2015). This set of proteins includes FHR-1, FHR-2, FHR-3, FHR-4 and FHR-5, of which FHR-1 has two major allelic variants, FHR-1*A and FHR-1*B, and FHR-4 has two isoforms, FHR-4A and FHR-4B. FHRs originated from FH by gene duplication events (Pérez-Caballero et al., 2001). They have retained, with different degrees of sequence conservation, the two domains in FH (SCRs 6–7 and SCRs 19–20) that are relevant for ligand and cell surface recognition (Józsi and Zipfel, 2008; Skerka and Zipfel, 2008; Zipfel, 2009). Although FHRs lack regions homologous with the complement regulatory domain of FH (SCRs 1–4), they were initially considered complement regulators. These early conclusions are currently being revised. The present view of the FHRs is that they are surface recognition molecules that, by competing with FH, provide improved discrimination of the surfaces where complement activation will take place (Józsi et al., 2015). We refer to this activity of the FHRs as complement de-regulation (Goicoechea de Jorge et al., 2013; Tortajada et al., 2013).

Here I will summarize our understanding of some mutations and polymorphisms in complement genes (particularly in *CFH, CFHRs* and *C3*) that illustrate the most relevant genotype–phenotype correlations and how this knowledge is helping us to decipher pathogenic mechanisms and is providing novel insights into complement biology.

CFH *mutations*

Atypical hemolytic uremic syndrome (aHUS), a thrombotic microangiopathy that affects mainly the kidney resulting in

Please cite this article in press as: de Córdoba, S.R., Complement genetics and susceptibility to inflammatory disease. Lessons from genotype–phenotype correlations. Immunobiology (2015), http://dx.doi.org/10.1016/j.imbio.2015.05.015