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The complement fitness Factor H: Role in human diseases and for immune escape of pathogens, like pneumococci

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ABSTRACT

Factor H is the central regulator of the alternative complement pathway and controls early activation of the complement cascade at the level of the C3 convertase. Mutations in the *Factor H* gene are associated with severe and diverse diseases including the rare renal disorders hemolytic uremic syndrome (HUS) and membranoproliferative glomerulonephritis (MPGN) also termed dense deposit disease (DDD), as well as the more frequent retinal disease age related macular degeneration (AMD). In addition, pathogenic microbes utilize host complement Factor H for immune evasion and these pathogens express specific surface receptors which bind host innate immune regulators. Sequence variations or mutations of one single gene, coding for the host regulator Factor H, form the basis for multiple, different disorders such as human renal and retinal diseases as well as infections. This association of Factor H but also of additional related complement components and regulators with the same diseases demonstrate an important role of complement, particularly of the alternative pathway, for tissue homeostasis. Disturbances of this central immune surveillance system lead to damage of autologous tissues and surfaces and result in autoimmune diseases. Remarkably, pathogenic microbes copy this mechanism of immune surveillance: they mimic the composition of host cell's, bind Factor H to their surface and engage acquired host Factor H for immune disguise.

1. Introduction

In the post genome era it is still important to understand the genetic mechanisms of human diseases and infection processes and to define in molecular terms how genetic mutations and sequence variations of individual genes modify the function of one single gene product and cause pathophysiology. Genetic mutations and sequence variations translate into functional disturbances that affect the fine tuned networks of proteins and cells. Understanding the molecular mechanisms that lead to cell, organ or immune dysfunction provides an ultimate goal for treating and preventing autoimmune diseases. Novel strategies depending on the identified mechanisms will be developed and used to modulate individual reactions in order to obtain the normal physiological reactions and to reestablish a healthy status. The identification of disease associated gene variations and gene mutations will result in precise diagnostic methods and also to the development of novel more efficient therapies.

The complement system forms one important barrier of innate immunity and maintains tissue homeostasis by recognizing and eliminating damaged and modified self structures, as well as foreign, invading microbes [1]. The individual complement components act in a cascade type manner and linked into a network form an important immune surveillance system. The activated complement system initiates a proteolytic cascade, that (i) generates activation products with pro-inflammatory and antimicrobial activity, (ii) marks modified self surfaces and foreign surfaces for phagocytosis, (iii) initiates membrane-damaging pores, and (iv) directs the adaptive immune response.

Based on the highly damaging potential the activation of this cascade is spatially regulated to direct the damaging activation products to the site of the foreign or modified surface. Several regulators exist which ensure that the activated system is properly controlled in terms of time and space [2,3]. The individual regulators are distributed in solution, but do also attach to biological self surfaces and additional regulators form integral membrane proteins. Under physiological conditions the complement system is activated at a constant, but low level, resulting in an immune

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surveillance system [4,5]. Apparently each single step of the complement cascade is controlled by multiple regulators, which display redundant activity, and show a different distribution.

Factor H is one central complement regulator that is found in the fluid phase and plasma and that binds to the surface of host cells and biological surfaces [6,7]. Factor H attaches to biological self surfaces, including the glomerular basement membrane of the kidney, the Bruch's membrane of the retina and likely also to other biological surfaces, however with relatively low affinity. At the surface Factor H forms a protective shield and aids in complement inhibition [8]. Factor H acts in combination with additional complement regulators and thus the surface attached Factor H assists the membrane anchored regulators. This surface activity is particularly relevant during local inflammation and complement stress and for damaged host cells.

Several pathogenic microbes copy this protective process and mimic the structure and the surface of host cells [9–11]. To this purpose pathogens express specific surface proteins which acquire the host regulator Factor H and multiple additional soluble host effector proteins. By attaching these host proteins to the microbial surface, pathogens make use of the self-protecting host regulatory system and e.g. utilize Factor H for immune evasion. Once recruited to the microbial surface, Factor H mediates immune and complement protection and contributes to serum resistance and tissue invasion of pathogens.

2. The complement system: a central innate immune effector cascade

The human complement system represents about 40 soluble and membrane bound proteins that are linked in a network-type interaction and provides the first defense line of innate immunity [1,3]. This complex network of proteins and the products generated during activation of the cascade have central functions in innate immune defense, including (i) recognition and elimination of microbes and foreign particles, (ii) clearance of immune complexes, (iii) removal of cellular debris as well as damaged self cells and particles, (iv) forming a central link between innate and adaptive immunity and (v) providing interaction with other host cascade systems, such as the coagulation system [1]. Complement activation occurs by multiple pathways and activation can be initiated by several mechanisms. The alternative pathway activation occurs automatically by default via the C3 tickover, classical pathway activation is triggered by immune complexes, and lectin pathway activation is initiated by carbohydrates on microbial surfaces [12]. In addition, proteases of the coagulation system initiate an extrinsic activation pathway. Once activated, the cascade progresses and generates inflammatory activation products, like the potent anaphylactic peptides C3a and C5a, soluble membrane attack complex (MAC)/sC5b-9 and membrane- or cell-damaging agents such as MAC/C5b-9. Based on this potent inflammatory response and membrane-damaging effects, complement activation is tightly regulated to ensure activation on the surface of foreign, non-self particles and to prevent activation on the surface of self cells.

The immune response is generally associated with inflammatory responses. Therefore, any reaction that ultimately results in the recognition and elimination of a foreign invading microbe represents a double-edged sword. The action of these potent damaging activation products must be restricted spatially and in terms of time. The newly generated, toxic activation products must be targeted to the surface of the foreign invader. However, in order to avoid tissue damage of self cells, in particular of host bystander cells must be protected which are positioned in direct vicinity of the invader. Thus, the host must ensure that the activation products are directed to the surface of the invader, but simultaneously host structures and cells must be protected. This duality of local restriction is mediated by the numerous regulatory proteins, which act in the fluid phase and also on the surface of self cells. The importance of this type of regulation for host integrity can be viewed from the fact that the number of regulators is actually larger than the number of the cascade components.

2.1. Continuous, low level activation of the alternative pathway

Complement is activated at a constant, low level and acts as an immune surveillance system. This low level, 'tick over' activation of the alternative complement pathway is caused by a spontaneous conformational change of C3 and when left uncontrolled results in further activation. Under physiological conditions, these initial reactions occur at a low rate and allow ample time for regulation.

In the absence of regulators, these initial steps progress and initiate a powerful amplification cycle, generating multiple C3b products and trigger further activation of the cascade. At the surface of a foreign invader, which usually lacks complement regulators, the amplified system progresses and the cascade amplifies (Fig. 1A). This results in release of anaphylatoxins (e.g. C3a and C5a), MAC formation, surface damage and ultimately in elimination and safe removal of a foreign or modified particle.

In contrast, intact host cells and in particularly bystander host cells, which are in direct vicinity of a foreign, complement activating microbe, are also attacked by the amplified system and in this situation maximal surface protection is required to maintain cellular integrity. In this situation of complement stress protection is mediated by the combined action of all available regulators (Fig. 1B). However, if the concerted action of all available complement regulators and/or complement components is not efficient, the triggered cascade will damage host surfaces. Thus, the situation of a defective or a reduced level of a regulator enhances the damaging effects.

2.2. Role of Factor H as a central inhibitor of the complement cascade

Complement Factor H is one of the central regulators of the complement cascade [2,6].

2.2.1. Inhibition of the complement cascade

Factor H is a plasma protein that is secreted primarily from the liver. However, additional extra hepatic expression e.g. by endothelial cells has been reported [13]. Factor H inhibits complement at the level of the C3 convertase, as the protein (i) prevents formation and inhibits assembly of the C3 convertase, (ii) enhances dissociation of a performed convertase (decay-accelerating activity) and (iii) acts as a cofactor for the serine protease Factor I, which cleaves and inactivates C3b (cofactor activity).

2.2.2. Domain structure of Factor H

Factor H, similar to other complement proteins, has a modular structure and is composed of repetitive domains termed complement control protein modules or short consensus repeat, SCRs. Factor H and the additional members of the Factor H plasma protein family [14] represent a unique group of immunologically related proteins whose individual members are exclusively composed of SCR domains.

Factor H has two central functional regions. The N-terminus, represented by SCRs 1-4, forms the central complement regulatory region which mediates cofactor activity and cleavage of C3b. Apparently, this N-terminal domain (SCRs 1-4) is sufficient and essential for complement regulation in fluid phase [15] (Fig. 2).