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Review Article

Applying complement therapeutics to rare diseases

Edimara S. Reis [a], Dimitrios C. Mastellos [b], Despina Yancopoulou [c], Antonio M. Risitano [d], Daniel Ricklin [a], John D. Lambris [a,*]

[a] Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, USA
[b] Division of Biodiagnostic Sciences and Technologies, INRASTES, National Center for Scientific Research 'Demokritos', Athens, Greece
[c] Amyndas Pharmaceuticals, Glyfada, Greece
[d] Hematology Department of Clinical Medicine and Surgery, Federico II University of Naples, Naples, Italy

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ABSTRACT

Around 350 million people worldwide suffer from rare diseases. These may have a genetic, infectious, or autoimmune basis, and several include an inflammatory component. Launching of effective treatments can be very challenging when there is a low disease prevalence and limited scientific insights into the disease mechanisms. As a key trigger of inflammatory processes, complement has been associated with a variety of diseases and has become an attractive therapeutic target for conditions involving inflammation. In view of the clinical experience acquired with drugs licensed for the treatment of rare diseases such as hereditary angioedema and paroxysmal nocturnal hemoglobinuria, growing evidence supports the safety and efficacy of complement therapeutics in restoring immune balance and preventing aggravation of clinical outcomes. This review provides an overview of the candidates currently in the pharmaceutical pipeline with potential to treat orphan diseases and discusses the molecular mechanisms triggered by complement involved with the disease pathogenesis.

Contents

Abbreviations: AChR, acetylcholine receptor; aHUS, atypical hemolytic uremic syndrome; AMD, age-related macular degeneration; AMR, antibody-mediated rejection; ANCA, anti-neutrophil cytoplasmic antibody; AP, alternative pathway; C1-INH, C1 esterase inhibitor; C3GN, C3 glomerulonephritis; C5aR, C5a receptor; C4BP, C4b binding protein; CAD, cold agglutinin disease; CCP, complement control protein domains; CP, classical pathway; CRIg, complement receptor of the immunoglobulin superfamily; DAF, decay accelerating factor; DDD, dense deposit disease; EMA, European medicine agency; FB, factor B; FD, factor D; FDA, Food and Drug Administration; FH, factor H; FI, factor I; GA, geographic atrophy; GBS, Guillain–Barré syndrome; GPCR, G-protein-coupled receptor; GPI, glycosyl-phosphatidyl-inositol; HAE, hereditary angioedema; HLA, human leukocyte antigen; HUS, hemolytic uremic syndrome; IRI, ischemia–reperfusion injury; IVIG, intravenous immunoglobulin; LRP, low density lipoprotein receptor-related protein; LP, lectin pathway; MAC, membrane attack complex; MASP, MBL-associated serine protease; MBL, mannose-binding lectin; MCP, membrane cofactor protein; MG, myasthenia gravis; MMN, multifocal motor neuropathy; MuSK, muscle-specific receptor tyrosine kinase; NMO, neuromyelitis optica; PIG-A, phosphatidyl-inositol glycan class A; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cells; RGD, arginine-glycine-aspartic acid; STEC, Shiga toxin-producing *Escherichia coli*; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; VEGF, vascular endothelial growth factor.

* Corresponding author at: Department of Pathology & Laboratory Medicine, University of Pennsylvania, 401 Stellar Chance, 422 Curie Blvd., Philadelphia, PA 19104, USA.
E-mail address: lambris@upenn.edu (J.D. Lambris).

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1. Introduction

The complement system is invariably considered one of the most ancient defense mechanisms of the body [1]. Since the discovery of the bactericidal properties of serum components more than a century ago, the perception of complement as part of immunity has changed considerably [2]. Initially regarded as a mere co-adjuvant in microbial elimination through opsonization and lysis, it is hard to assume that evolutionary forces would conserve such an intricate system comprising about 50 proteins to act entirely on microbial killing. Today, complement is seen not only as a first line of defense against pathogens but also as a modulator of acquired immunity, being the decisive factor that guides the quality and magnitude of cell activation and also orchestrates several important physiological and pathological processes, such as the clearance of foreign bodies, coagulation, tissue regeneration, and inflammation (Fig. 1) [2–4].

The biological functions of complement are elicited as a result of the activation of the classical, alternative, and/or lectin pathways (CP, AP, and LP, respectively). The initial components of each pathway serve as pattern recognition molecules: C1q fixes antigen-antibody complexes, mannose binding lectins (MBL) and ficolins bind to microbial carbohydrates, and molecules of C3b and properdin recognize self- and non-self-structures that are damaged or lack complement-regulatory proteins. The initial trigger for the CP and LP leads to subsequent activation of the components C2 and C4 and the formation of the C3 convertase, C4b2b (Fig. 2). The AP is continuously activated via the spontaneous hydrolysis of C3, resulting in a conformational change that allows the binding of factor B (FB). Upon cleavage of FB by the serine protease factor D (FD), the C3bBb complex is formed. This complex acts as the C3 convertase of the AP and plays a critical role in the amplification of the AP as a result of the continuous production of C3b molecules (Fig. 2), ensuring an immediate and effective response against danger signals. More recently, properdin has been identified as a pattern recognition molecule that is able to initiate the activation of the AP [5]. In addition, it also acts as a positive regulator of the C3bBb complex, favoring stable and longer activation of the AP. All three pathways converge

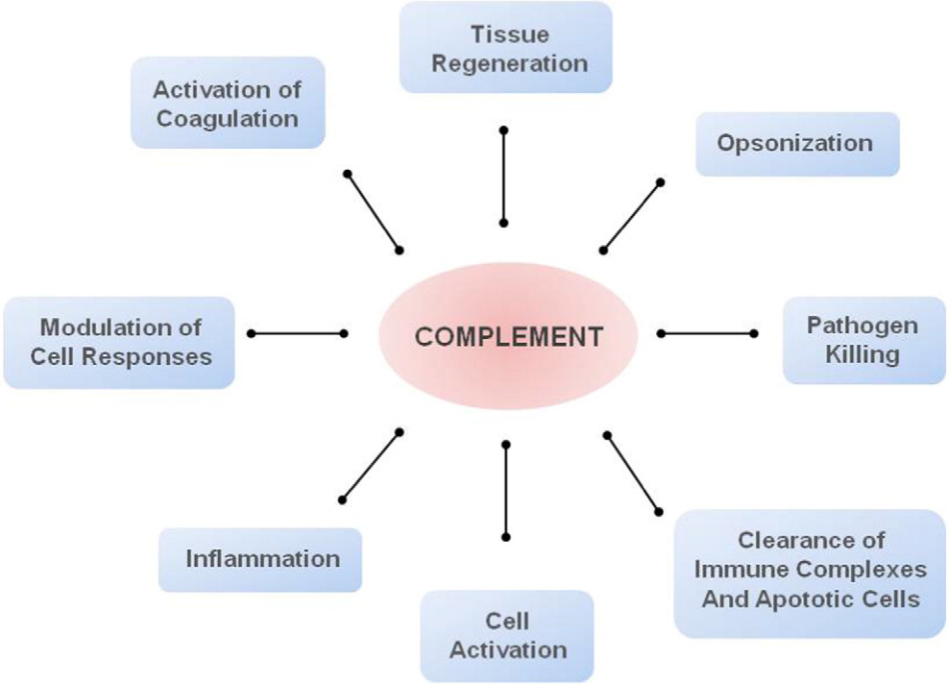

Fig. 1. Complement acts as a key mediator of several pathophysiological processes.