Review Article
Complement-related proteins and their measurements: the current status of clinical investigation

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Abstract

Complement has been considered to be a factor that protects the host against invading microorganisms during infection. However, in recent years, complement-related protein deficiency has been found to be involved in the onset of various diseases, such as autoimmune and inflammatory diseases. In Japan, C3, C4, and CH50 tests were generally performed only when a complement system examination was necessary and there were not enough examinations for other complement factors. Since the complement system has a very complicated activation pathway, at present, it is not well known which molecule must be measured to understand the pathological condition or pathogenesis in complement-related diseases. Furthermore, since the frequency of complement factor gene alleles also differs depending on race, data from foreign countries cannot be directly applied to Japanese populations. Under these circumstances, the Japanese Association for Complement Research (JACR) has prepared approximately 20 items for complement-related examinations, including the five categories of functional analysis, complement factors, complement regulators, activation products and autoantibodies.

I. Complement factors and the complement system

Complement was discovered as a serum protein system that assists the action of antibodies, and this system is currently known to include the main components of complement (C1 to C9) and other complement-related molecules (factor B and factor D). There are 8 types of humoral regulatory factors [complement factor I (CFI), complement factor H (CFH), C4 binding protein (C4bp), C1 inhibitor (C1-INH), properdin, C3a/C5a inhibitor, S protein, and clusterin] [1], four cell membrane proteins [CR1, MCP (CD46), DAF (CD55), and CD59] [2, 3] and seven complement receptors (C1qR, C3aR, C5aR, CR1, CR2, CR3, and CR4) [4]. Together, all proteins and their functions constitute the complement system.

II. Current status of measurement for complement abnormalities

Until recently, in Japan, special examinations for complement have been carried out by some groups from the Japanese Association for Complement Research (JACR) as volunteers [5]. Complement factor deficiencies are known to differ significantly depending on race, but there is not much specific information on the gene mutation frequencies of the complement regulatory factors in the Japanese population.

The JACR discussed a reconstruction of new complement examinations under the initiative of an academic society, "Comprehensive registration of complement-related diseases and establishment of treatment guidelines by building a new complement examination system" [6, 7]. This strategy was determined at the JACR board meeting. The examinations are divided into two parts: (1) complement factor and complement function measurements and (2) complement-related genetic analyses, mainly using blood. The current status and significance of each examination are outlined.

III. Complement factors and their functional measurements

Currently, in Japan, C3, C4, and CH50 are commonly measured when they are required for clinical evaluation. Until now, these three factors have been regarded as sufficient for complement examinations. However, these measurements cannot detect subtle and local complement activation in complement-related diseases. The activation pathway of the complement system (shown in Fig. 1) is very complicated, and unfortunately, at the present time, which factor analysis is appropriate for understanding the pathophysiology and which factor participates in the pathogenesis of complement-related diseases have not been fully determined. Moreover, since the allele frequencies

of complement genes vary depending on race, the genomic characteristics in foreign countries cannot be directly applied to the Japanese population.

Under these circumstances, the International Complement Society (ICS) classified the complement examination items into five categories (functional analysis, complement factors, complement regulators, activation products and autoantibodies) (Table 1) for the purpose of standardization of complement examinations and recommended that each member of society undergo approximately 20 complement-related examinations [8, 9, 10].

1) Functional analysis: CH50, ACH50, and lectin pathway analysis

There are three pathways in complement activation. First, a classical pathway (CP) is initiated by the formation of an antigen-antibody complex and its binding to C1q. Second, a lectin pathway (LP) is triggered by pattern recognition of a sugar chain by a lectin. Third, there is an alternative pathway (AP) in which activation is constantly occurring at a low level by hydrolysis [2, 11]. The AP is thought to play an important role as an amplification pathway of complement activation initiated by the CP and the LP. To measure the CP, CH50 is performed by observing hemolysis of sensitized erythrocytes by complements in a sample, and to measure AP, ACH50 is performed by observing hemolysis of rabbit erythrocytes [12, 13]. The CP requires calcium and magnesium ions, whereas the AP does not require calcium ions; therefore, the use of Mg-EGTA buffer can prevent hemolysis due to the CP. There are also ELISA kits that can measure the activation of the three pathways individually. For the CP, LP and AP assays, samples are placed in IgM-, mannan- and LPS-coated wells, respectively, activated by complement factors in the samples, and evaluated by detection of C5b-9 formation [14].

2) Complement factors: C3, C4, and C1q

In addition to the functional analysis mentioned above, measuring the protein concentrations of C3, C4, and C1q makes it possible to infer in which pathway and why abnormal complement activation is occurring in more detail.

In Japan, there was a period when all C1-C9 proteins were quantitatively measured previously, but now there are some negative opinions regarding the measurement of mere complement factors. For example, in atypical hemolytic uremic syndrome (aHUS), abnormal complement activation is involved locally, and the values of C3, C4, and CH50 are not markedly changed [15, 16, 17].

3) Complement regulators: CFH, CFI, and C1-INH (activity and protein)

Liquid phase regulators in complement activation include CFH, CFI, and C1-INH. CFH, which is present at high concentrations (500 μg/mL) in plasma, works in both the liquid and solid phases and attenuates the activity of C3 convertase in the alternative pathway and acts as a cofactor for factor I cleave C3b and C4b [18]. It is a multifunctional molecule that has the function of decay acceleration and plays a very important role in regulating complement activation. C1-INH binds to C1r, C1s, and mannose-binding lectin-associated serine proteases (MASP)-1, MASP-2, and MASP-3 in the liquid phase, inhibits the serine protease activity of these proteins, and controls the activation of the CP and the LP [19, 20, 21]. The activity of C1-INH is mainly examined, and quantification is performed when examining the disease type in more detail. Quantitating the protein levels of the complement regulatory factors is a sufficiently useful test in cases of complete loss of regulatory factors, but there are many genetic mutations with which the decrease in regulatory factor protein concentration is not significant [22, 23].

4) Activation products: C3dg, C3a, Bb (Ba), sC5b-9, and C5a

Activation products comprise C3dg, C3a, Bb (Ba), sC5b-9, and C5a and can be detected as complement activation in vivo in a sensitive manner. Their measurement is clearly important because C3a and C5a act as strong anaphylatoxins [24], and Bb (Ba) and sC5b-9 in blood indicate the results of complement activation in vivo [25]. The measurement of the complement activation degradation product is reasonable and is currently the most attractive strategy to explore. Particularly useful activation products for aHUS include Bb (Ba), C5a and sC5b-9, suggesting a transition to terminal complement complex (TCC) formation [17, 26, 27].

5) Autoantibodies: Anti-C1q, anti-C1-INH (G/A/M), anti-CFH, and C3 nephritic factor (C3Nef)

In addition, autoantibodies to complement factors are associated with the onset of complement-related disease and are listed as measurement items. Anti-C1q antibody causes systemic lupus erythematosus (SLE) [28], anti-Cl-INH antibody causes hereditary angioedema (HAE) [29, 30], anti-FH antibody causes aHUS [31, 32], and C3Nef stabilizes C3 convertase and activates complement due to C3 glomerulopathy[33, 34, 35]. When the level of autoantibodies to complement regulatory factors increases, the complement regulation system may malfunction, and thus complement activation may proceed. In the future, more autoantibodies to complement factors will be identified in association with some complement-related diseases of unknown etiologies.

Under these circumstances mentioned above, the JACR developed the following 11 items divided into the five categories proposed by ICS: (1) CH50; (2) C3, C4; (3) CFH, CFI, and C1-INH (activity and protein); (4) Ba, sC5b-9, and C5a; and (5) anti-CFH during the three years after 2015 and is now planning to prepare all 20 items recommended by ICS step by step.

IV. Genetic abnormalities in complement and their regulators

In addition to aHUS [36], AMD (age-related macular degeneration) [37] and C3 glomerulopathy [38, 39, 40]are included as examples of the complement-related diseases described above. Genetic abnormalities have been identified and reported[41, 42, 43, 44, 45, 46]. However, there are many complement-related diseases in the following fields: pediatrics, nephrology, hematology, neurology, ophthalmology, dermatology, and transplantation[47]. We believe that it is important to conduct complement gene research led by the JACR. In complement-related diseases, we analyzed 115 genes, including complement-related genes (85 genes) and coagulation/fibrinolytic system-related genes, as well as previously reported gene abnormalities (shown in Fig. 2). In the case of suspected hereditary angioedema (HAE), 136 genes, including 21 related genes, were further analyzed [48]. As a method, targeted exome sequencing of these complement-related genes was performed using next-generation sequencing (NGS). For data analysis, variation frequency analysis was performed with reference data from the Human Genetic Variation Database (HGVD) (Kyoto University)[49] and Exome Aggregation Consortium (ExAC)[50]. For genetic variation and disease data, the Human Gene Mutation Database was used[51, 52]. In addition, we are conducting some analytical studies on genetic variation and complement function using programs that predict three-dimensional structures. In addition, the genes that are thought to be particularly involved in aHUS (CFH, MCP, CFI, C3, CFB, THBD, PLG, and DGKE) are being reexamined using Sanger sequencing as another gene analysis method to supplement the NGS system. Although important information can be obtained from genetic analysis for the current complement-related diseases, it is extremely difficult to determine the pathological significance of the genetic variations by only genomic information.

V. Global standardization of complement measurements and future prospects

The methods of complement measurement include ELISA and the other testing systems using commercially available or noncommercial kits, and the protocols of the tests are different, making it difficult to compare the results from different laboratories. Strict complement testing requires even

more caution (usually complement test samples are required to be frozen as soon as possible and transported on dry ice). In particular, the measurement of complement activation degradation products is very difficult because complement is rapidly activated at room temperature. For these reasons, we consider it to be important to transport the samples to the JACR center laboratory with the utmost caution and to establish an intensive complement testing system.

In January 2016, the External Meeting on the Standardization of Complement Measurements was held in Budapest, Hungary. The meeting presented the lessons from External Quality Assessments (EQAs) 1-5, which were discussed during the five years from 2010 to 2015, and the results of EQA5 [53, 54]. Subsequently, EQA6/2016 was performed in October 2016. In EQA6/2016, the participants from each country registered the test items with INSTAND (An interdisciplinary, not-for-profit, scientific medical society, one of three reference institutions appointed by the German Medical Association and thus responsible for the organization of EQAs for quality control in medical laboratories), sent the test samples, and reported the measurement values. If each test result fell within the range of the reference value, a certificate was issued indicating that the result of the evaluation was valid. The JACR also participated in EQA6/2016 and received a certificate of validity for the quantitative tests for C3, C4, CH50, and sC5b-9 and for a qualitative test for anti-CFH.

Furthermore, as a next-generation complement protein test, we believe that a batch complement test using the multiplex system (Luminex) or a similar system is a possible candidate for future investigations. The advantage of the multiplex system is that multiple complement factors in the blood can be simultaneously quantified. Cytokines are also used as a quantitative and reproducible technique for complement-related disease, but at present, their measurement is in the research stage. Furthermore, each parameter is currently being evaluated with the overall pattern of all test values. That is, the test value pattern of a type of complement-related disease is obtained and can be used for the diagnosis of complement-related diseases. This is beyond the scope of this review, but it can indicate future prospects if a certain trend is present in each disease. The JACR believes that the global standardization of complement measurements and a multiplex test system will provide a scientific contribution for complement research and clinical benefits for complement-related diseases.

Statements

All papers must contain the following statements after the main body of the text and before the reference list:

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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Figure Legends

Fig. 1. Activation pathway of the complement system and target factors for standardization of complement-related examination

Fig. 2. Targets of complement gene testing (115 complement-related genes + disease-related genes)

Table 1. Examination system for complement-related proteins.

	Examination items
Functions	CH50, ACH50, lectin pathway activity
Components	C3, C4, C1q
Regulators	CFH, CFI, C1-inhibitor (activity and protein)
Activation products	C3dg, C3a, Bb(Ba), sC5b-9, (C5a)
Autoantibodies	Anti-C1q, Anti-C1 inhibitor (IgG/A/M), Anti-CFH, C3Nef

Underlined items are measured by the JACR at present
20 testing items to be standardized worldwide

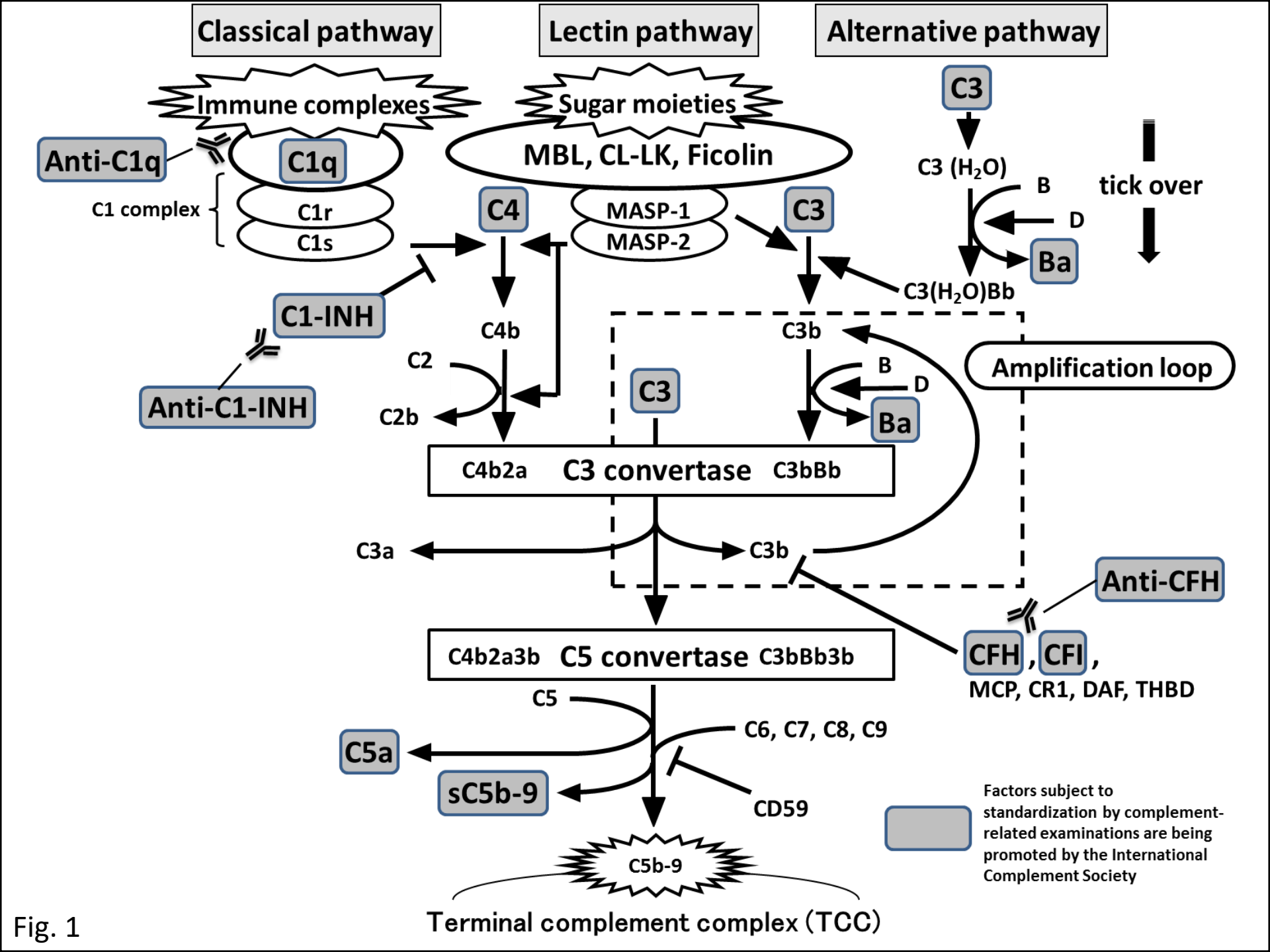
Classical pathway
Lectin pathway
Alternative pathway
Immune complexes
Sugar moieties
C3
Anti-C1q
C1q
MBL, CL-LK, Ficolin
C3 (H2O)
B
D
tick over
C1 complex
C1r
C1s
C4
MASP-1
MASP-2
C3
Ba
C1-INH
C3(H2O)Bb
C4b
C3b
C2
B
D
Amplification loop
Anti-C1-INH
C3
C2b
Ba
C4b2a C3 convertase C3bBb
C3a
C3b
Anti-CFH
C4b2a3b C5 convertase C3bBb3b
CFH , CFI ,
MCP, CR1, DAF, THBD
C5
C6, C7, C8, C9
C5a
sC5b-9
CD59
C5b-9
Terminal complement complex (TCC)
Factors subject to standardization by complement-related examinations are being promoted by the International Complement Society

Fig. 1

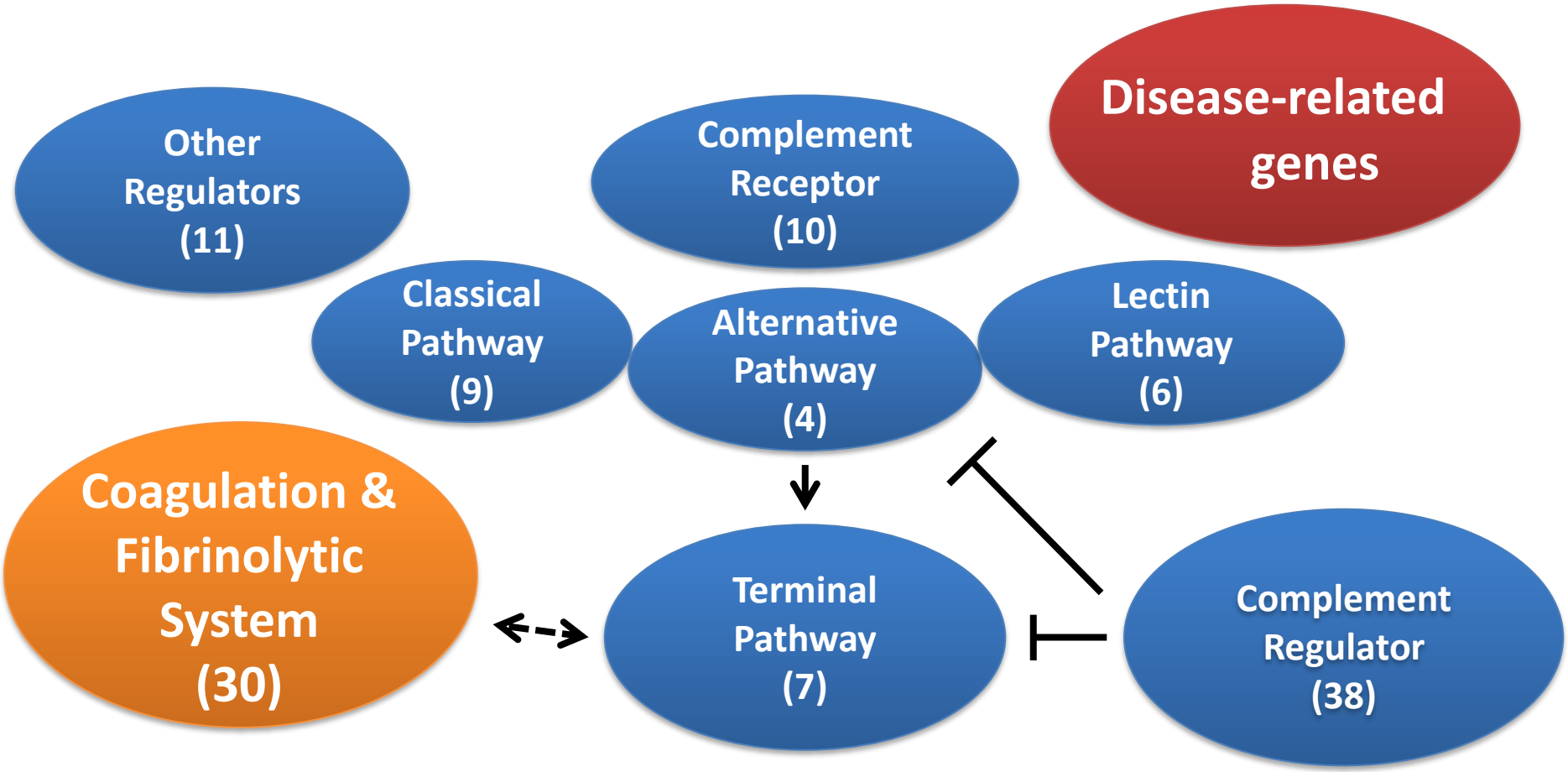
Other Regulators (11)
Complement Receptor (10)
Disease-related genes
Classical Pathway (9)
Alternative Pathway (4)
Lectin Pathway (6)
Coagulation & Fibrinolytic System (30)
Terminal Pathway (7)
Complement Regulator (38)

Fig. 2