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Therapeutic targeting of the complement system

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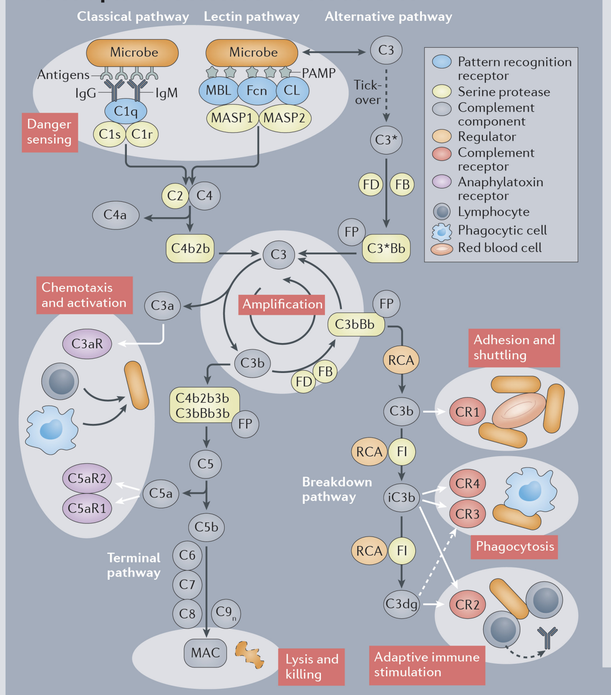
The human complement system constitutes a Janus-faced part of our immune machinery, which confers rapid protection against microbial intruders but can quickly turn against the host and contribute to inflammatory, immune-, age- and foreign body-related clinical complications[1]. The defence–offence profile often tilts unfavourably during ageing, traumatic insults or genetic dysregulation of the cascade. The list of disorders with known complement contribution is growing constantly, and with it the incentive to control complement activation therapeutically[1–3]. Since the introduction of complement-specific drugs in 2007, and the generally positive experience in the clinic, the interest in developing new therapeutic inhibitors has been growing constantly and has led to a cornucopious pipeline[2,3]. While the clinically available arsenal is currently limited to a few targets and mostly orphan and rare indications, it is expected that the recently sparked confidence and commercial interest will soon lead to a significant broadening of treatment options and, consequently, clinical conditions in which complement-targeted drugs will be applied[2]. New frontiers, such as applications in the therapy of cancer or neurological diseases are already on the horizon[4,5].

The complement cascade in host defence



Under physiological circumstances, complement acts as a pillar of host defence by assisting in the rapid recognition and elimination of microbial intruders[1,6]. Pattern recognition receptors sense danger (antibody-antigen complexes or pathogen-associated molecular pattern) and engage an enzyme-driven and self-amplifying cascade that leads to the opsonization of the microbe, attraction of immune cells, adhesion and shuttling to lymphoid organs, phagocytic uptake, stimulation of adaptive immune responses and direct killing through lysis. The generation of effector molecules such as the anaphylatoxins C3a and C5a helps orchestrate a comprehensive immune response[1,6].

Can and should we inhibit a host defence pathway?

Despite the early recognition that complement is a contributor to many clinical conditions, the development of therapeutic complement inhibitors was initially hindered by concerns about interfering with host defence functions[1,2]. Indeed, patients with complement deficiencies often face episodes of infection; however, with the strengthening of adaptive immunity during childhood the defence role of complement gradually subsides[7]. At the same time, ageing often imposes a risk for inadvertent complement activation that can trigger or exacerbate disease[1]. Alongside the positive clinical experience with complement inhibitors in the clinic and the realization that residual risks can largely be controlled by anti-infective strategies and the choice of administration regimen (systemic vs. local; acute vs. chronic), this led to a new confidence in the approach and a surge in complement-targeted therapeutics[2,3].

Targeting the initiation pathways

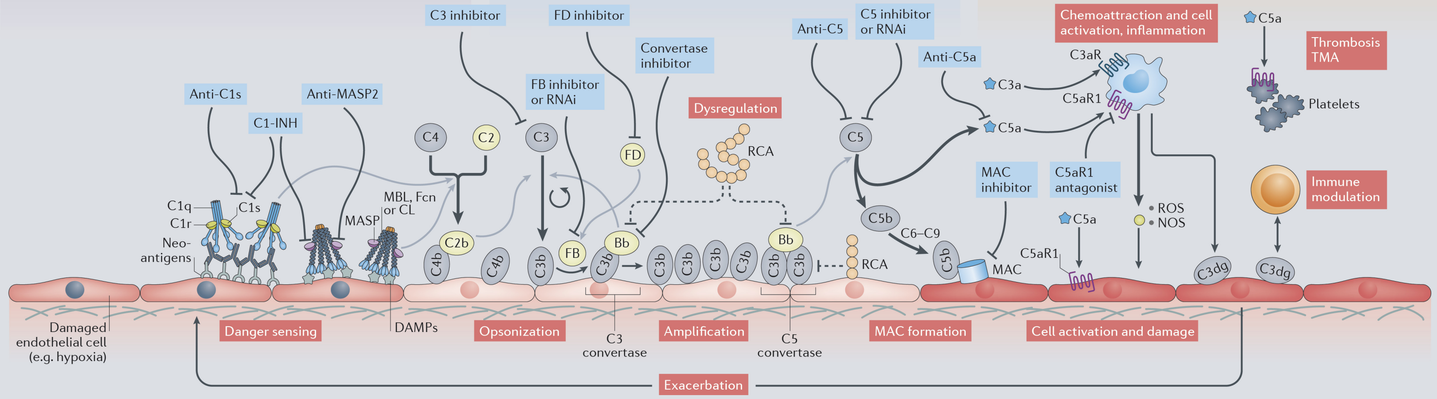
In some complement-related diseases, the complement response is triggered by one dominant pathway. Specific blockage of one pathway may offer the means of halting detrimental complement activation while keeping some of the defensive reactivity intact. However, the triggering pathway needs to be identified and the approach may be insufficient during a complex activation pattern[3]. The only clinically approved member of this category is C1 esterase inhibitor (C1-INH), which blocks C1s, C1r and MASPs but also other serine proteases. In fact, its approved indication (hereditary angioedoema) is not complement related, but trials in transplantation and other indications are ongoing[2]. Two therapeutic antibodies targeting the classical (anti-C1s) and lectin (anti-MASP2) pathways are in clinical development[2].

Targeting the amplification loop

Independent of the triggering pathway, a majority of the measurable complement response is often derived from the amplification loop of the alternative pathway[8]. When compared with CP/LP inhibition, central blockage may theoretically have a more profound impact on defence functions, although such risks can largely be mitigated. Inhibiting this loop confers a particularly attractive option in cases of complex, AP-specific and/or acute situations, since it effectively prevents opsonization and effector generation[2,3]. Currently, there is no approved member of this class but several candidates are in clinical development. Whereas FD inhibitors and FB RNAi prevent convertase formation, FB inhibitors and regulator-based convertase inhibitors block its activity. C3 inhibitors of the compstatin family prevent C3 activation by all convertases and reach beyond AP inhibition[2].

Targeting the effector pathways

Owing to their detrimental biological activity, the effectors of the terminal pathway (i.e. C5a and MAC) often contribute most visibly to the clinical manifestation of complement-mediated diseases[1]. Prevention of C5 activation via clinically available anti-C5 mAbs (eculizumab, ravulizumab) has proved effective in rare diseases of the haemolytic and inflammatory spectrum. Encouraged by this success, several C5 modulators (mAb, inhibitors, RNAi) are currently in clinical trials[2,3]. Moreover, specific blockage of the C5a–C5aR1 signalling axis is assessed using anti-C5a mAb and C5aR1 antagonists[2,5]. Finally, a MAC inhibitor based on the regulator CD59 is being evaluated. Of note, all inhibitors of effector functions leave upstream complement activation intact, which may have some benefits but may also lead to an accumulation of opsonized cells[2,3].



Excessive and erroneous complement activation

Whereas complement-mediated sensing is ideally directed against microbial intruders, there are other targets that can trigger an unwanted response[1]. This is particularly true for surfaces that are brought into contact with blood during medical procedures, such as biomaterials (e.g. haemodialysis filters) and cell or organ transplants[1]. In the latter case, the recognition of mismatch antigens (ABO, HLA) by natural antibodies induces the classical pathway and leads to hyperacute rejection. In addition, the unavoidable ischaemia–reperfusion injury (IRI) during transplant transfer typically causes exposure of damage-associated molecular patterns (DAMPs) that are sensed by the lectin pathway[1]. IRI is also a driving force during stroke or myocardial infarction. In many autoimmune diseases, such as myasthenia gravis (MG), autoimmune haemolytic anaemia (AIHA), or cold agglutinin disease (CAD), classical pathway activation is strongly involved[2]. In IgA nephropathy, the autoimmune trigger is mediated by aberrant glycans via the lectin pathway. During certain age-related diseases, accumulating debris may also trigger any of the initiation pathways[1]. Finally, in conditions related to systemic inflammatory response syndrome, an excessive complement response to the right target, i.e. microbes (sepsis) or injured cells (trauma) can start a vicious hyperinflammatory cycle[1].

Dysregulation and insufficient control

On healthy host cells, a panel of soluble or membrane-bound regulators of complement activation (RCA) keeps background and bystander activation in check[6]. However, any imbalance caused by missing or insufficiently active regulators may favour the development of complement-mediated diseases. The eyes and kidneys appear to be particularly affected by such dysregulation, even if systemic[1]. Age-related macular degeneration (AMD) is a typical example, in which the insufficient regulation of complement activity was found to be a major risk factor for the loss of retinal cells[11]. Poorly controlled fluid-phase activation of complement can lead to dense opsonin deposits in the kidney, manifesting in C3 glomerulopathy (C3G)[2]. Another complement-mediated kidney disease, atypical haemolytic uraemic syndrome (aHUS), is also caused by complement dysregulation but typically involves membrane-bound or membrane-directed regulators[12]. In most of these cases, more than one factor determines the susceptibility and onset of a disorder; this includes combinations of polymorphisms (termed 'complotype'), deletions or deficiencies, or autoantibodies against complement regulators[1].

Damaging effector functions and exacerbation

Regardless of which specific initiation pathway gets triggered, amplification of the response via the alternative pathway and the associated generation of effector molecules by the terminal and breakdown pathways are typically the routes that cause most damage and may exacerbate the disorder[1]. Perhaps the most profound example is sepsis, in which the release of the C5a anaphylatoxin is known as one of the major factors fuelling hyperinflammatory states that can lead to multi-organ failure and death[1]. The membrane-attack complex (MAC) is the main contributor to haemolytic disorders such as PNH, AIHA or CAD. Both C5a and MAC appear to be largely responsible for clinical manifestations of autoimmune diseases such as anti-neutrophil circulating antibody-associated vasculitis (AAV) or some forms of generalized myasthenia gravis and neuromyelitis optica[3]. In aHUS, the generation of C5-derived effectors is thought not only to cause tissue damage but also to contribute to thrombotic microangiopathies (TMA) in conjunction with platelet activation and haemolysis, which can serve as a second hit for the disorder[2]. Complement-related TMA is also observed in other disorders, e.g. as complication during haematopoietic stem cell transplantation (HSCT).

Selected inhibitors targeting complement[a]

Drug (Company)	Target	Indication	Status
Targeting pathway initiation			
C1-Inhibitor: Cinryze (Shire), Berinert (CSL), Cetor (Sanquin), Ruconest (Pharming)[b]	C1r, C1s, MASPs, other proteases	• Hereditary angioedoema • Kidney IRI • Sepsis • Kidney transplantation	• Approved • Phase II • Phase III • Phase II
Sutimlimab (Sanofi)	C1s	• Cold agglutinin disease • Immune thrombocytopenic purpura	• Phase III • Phase I
Narsoplimab (Omeros)	MASP-2	• aHUS, IgA nephropathy, HSCT-TMA • Lupus nephritis	• Phase III • Phase II
Targeting the alternative pathway and amplification loop			
APL-2/pegcetacoplan (Apellis)	C3	• AMD (GA), PNH, AIHA • Nephropathies	• Phase III • Phase II
AMY-101 (Amyndas)	C3	• Periodontal disease • Stroke, transplantation	• Phase II • Phase I
Mirococept	Convertase	Kidney transplantation	Phase II
LNP023 (Novartis)	FB	• C3G • PNH • IgA nephropathy, glomerulonephritis	• Phase II • Phase II • Phase II
IONIS-FB-LRx (Ionis/Roche)	FB	AMD (GA)	Phase II
Danicopan (Achillion)	FD	• PNH • C3G	• Phase II • Phase II
CLG561 (Alcon)	FP	AMD (GA)	Phase II
Targeting the terminal pathway effectors			
Soliris, Eculizumab (Alexion)[c]	C5	• PNH, aHUS • Generalized MG • Neuromyelitis optica	• Approved • Approved • Approved
Ultomiris, Ravulizumab (Alexion)	C5	• PNH • aHUS • Generalized MG	• Approved • Phase III • Phase III
ABP 959 (Amgen)	C5	PNH	Phase III
Nomacopan (Akari)	C5	• PNH • BP, AKC	• Phase III • Phase II
Pozelimab (Regeneron)	C5	PNH	Phase I
Crovalimab (Roche)	C5	PNH	Phase I
Tesidolumab (Novartis)	C5	PNH	Phase II
Zilucoplan (Ra)	C5	• Generalized MG • INMN, renal disorders	• Phase II • Phase I
Cemdisiran (Alnylam)	C5	IgA nephropathy	Phase II
Zimura (Iveric)	C5	AMD (GA), Stargardt	Phase II
IFX-1 (InflaRx)	C5a	HS, AAV	Phase II
Avacopan (ChemoCentryx)	C5aR1	• AAV • C3G, HS	• Phase III • Phase II
HMR59 (Hemera)	MAC	AMD (GA, CNV)	Phase I

For a comprehensive overview of drug candidates and clinical trials, the authors refer to Refs. 2 and 3. [a]For each company, the approved drugs or the candidate in furthest clinical development is shown. [b]Distinct C1-INH preparations are involved in the listed clinical trials. [c]Alongside the improved indications, eculizumab is also clinically evaluated in a series of other indications.

Abbreviations

AAV, anti-neutrophil antibody-associated vasculitis; aHUS, atypical haemolytic uraemic syndrome; AIHA, autoimmune haemolytic anaemia; AKC, atopic keratoconjunctivitis; AMD, age-related macular degeneration; AP, alternative pathway; BP, bullous pemphigoid; C1-INH, C1 esterase inhibitor; C3aR, C3a receptor; C3G, C3 glomerulopathy; C5aR, C5a receptor; CAD, cold agglutinin disease; CL, collectin; CNV, choroidal neovascularization; CP, classical pathway; CR, complement receptor; DAMP, damage-associated molecular pattern; FB, factor B; Fcn, ficolin; FD, factor D; FI, factor I; FP, properdin; GA, geographic atrophy; HLA, human leukocyte antigen; HS, hidradenitis suppurtiva; HSCT, haematopoietic stem cell transplantation; IMNM, immune-mediated necrotizing myopathy; IRI, ischaemia–reperfusion injury; LP, lectin pathway; MAC, membrane attack complex; MASPs, MBL-associated serine proteases; MBL, mannose-binding lectin; MG, myasthenia gravis; NOS, nitric oxide synthase; PAMP, pathogen-associated molecular pattern; PNH, paroxysmal nocturnal haemoglobinuria; RCA, regulators of complement activation; RNAi, RNA interference, ROS, reactive oxygen species; TMA, thrombotic microangiopathy.

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Competing interests statement

J.D.L. is the founder of Amyndas Pharmaceuticals, which is developing complement inhibitors for therapeutic purposes. J.D.L. and D.R. are inventors of patents or patent applications that describe the use of complement inhibitors for therapeutic purposes, some of which are developed by Amyndas Pharmaceuticals. J.D.L. is also the inventor of the compstatin technology licensed to Apellis Pharmaceuticals (that is, 4(1MeW)7W/POT-4/APL-1 and PEGylated derivatives such as APL-2/pegcetacoplan). D.C.M. declares no competing interests. The authors state that they are not affiliated with the companies sponsoring this poster and that this sponsorship does not imply that they are endorsing their clinical programs, objectives or corporate practices.

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