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Novel potential inhibitors of complement system and their roles in complement regulation and beyond

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ABSTRACT

The complement system resembles a double-edged sword since its activation can either benefit or harm the host. Thus, regulation of this system is of utmost importance and performed by several circulating and membrane-bound complement inhibitors. The pool of well-established regulators has recently been enriched with proteins that either share structural homology to known complement inhibitors such as Sushi domain-containing (SUSD) protein family and Human CUB and Sushi multiple domains (CSMD) families or extracellular matrix (ECM) macromolecules that interact with and modulate complement activity. In this review, we summarize the current knowledge about newly discovered complement inhibitors and discuss their implications in complement regulation, as well as in processes beyond complement regulation such cancer development. Understanding the behavior of these proteins will introduce new mechanisms of complement regulation and may provide new avenues in the development of novel therapies.

1. Complement system regulation at a glance

The complement system is an ancient innate immune-surveillance system classically described as providing the first line of defense against pathogens and mediating the clearance of host cells, but more recently has been shown to play an instrumental role in immunological and inflammatory processes during homeostasis (Ricklin et al., 2010; Freeley et al., 2016).

Over 50 serum circulating proteins, cell surface receptors and regulators comprise this large intricate effector system (Fig. 1). Complement initiation can be triggered through three distinct pathways (classical, lectin and alternative pathway) varying in the pattern recognition molecule (antibody-dependent, mannose-binding lectin/ficolins and spontaneous formation of C3b-like molecules). These cascades converge at its core component, complement factor C3, which after cleavage by C3-convertases generates anaphylatoxin C3a and opsonin C3b (Ricklin et al., 2010) (Fig. 1). Anaphylatoxins transduce inflammatory and chemotactic signals via interaction with their cognate receptors, whereas opsonins are the principal mediators of phagocytosis (Klos et al., 2009; Winkelstein, 1973). Subsequently, C5 is activated by C5-convertases yielding potent pro-inflammatory anaphylatoxin C5a and C5b, which can initiate formation of multi-protein pore, the membrane attack complex (MAC). MAC assembly can cause lysis of Gram-negative bacteria and eukaryotic cells, as well as exerting sub-lytic activities (Serna et al., 2016; Bayly-Jones et al., 2017).

It is critical that complement, a potentially highly harmful system is under tight control to avoid complement activation on host cells which may result in autoimmune disease due to an inappropriate inflammatory response (Ricklin et al., 2016). Such vital control is achieved through a spectrum of membrane-bound and circulating complement inhibitors. Membrane-bound complement inhibitors consist of the GPI-anchored decay-accelerating factor (DAF, CD55), membrane cofactor protein (MCP, CD46) and complement receptor 1 (CR1, CD35), whereas C4b-binding protein (C4BP) and factor H are soluble inhibitors, present in the plasma. Their mode of action includes the proteolytic inactivation of C3b/C4b by factor I (MCP, CR1, FH, C4BP)

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Abbreviations: AMOP, adhesion-associated domain present in MUC4 and other proteins; C4BP, C4b-binding protein; CCP, complement control protein; CR1, complement receptor 1; CR3, complement receptor 3; CS, chondroitin sulfate; CSMD, CUB and Sushi multiple domains; DAF, decay-accelerating factor; DAMPs, damage-associated molecular patterns; DRAGO, Drug-activated gene overexpress protein; DS, dermatan sulfate; ECM, extracellular matrix; EGF, epidermal growth factor; ER, endoplasmic reticulum; ERα, estrogen receptor α; FACIT, fibril-associated collagen; FH, factor H; FI, factor I; GAGs, glycosaminoglycans; Gal-1, Galectin-1; KS, keratan sulfate; LRRs, leucine-rich repeats; MAC, membrane attack complex; MCP, membrane cofactor protein; miRNAs, microRNA; MMP-13, matrix metalloprotease-13; NC4, N-terminal noncollagenous domain 4; PGs, proteoglycans; PRELP, proline/arginine-rich end leucine-rich repeat protein; SCR, short consensus repeats; shRNA, short hairpin RNA; SLRPs, small leucine-rich proteoglycans; SNPs, single-nucleotide polymorphisms; SO, somatomedin B-like domain; SUSD, sushi domain-containing; TNFα, tumor necrosis factor α; Treg, regulatory T cells; TSP-5, thrombospondin-5; TSP-3, thrombospondin type 3; UTR, untranslated region; VWD, von Willebrand factor type D domain

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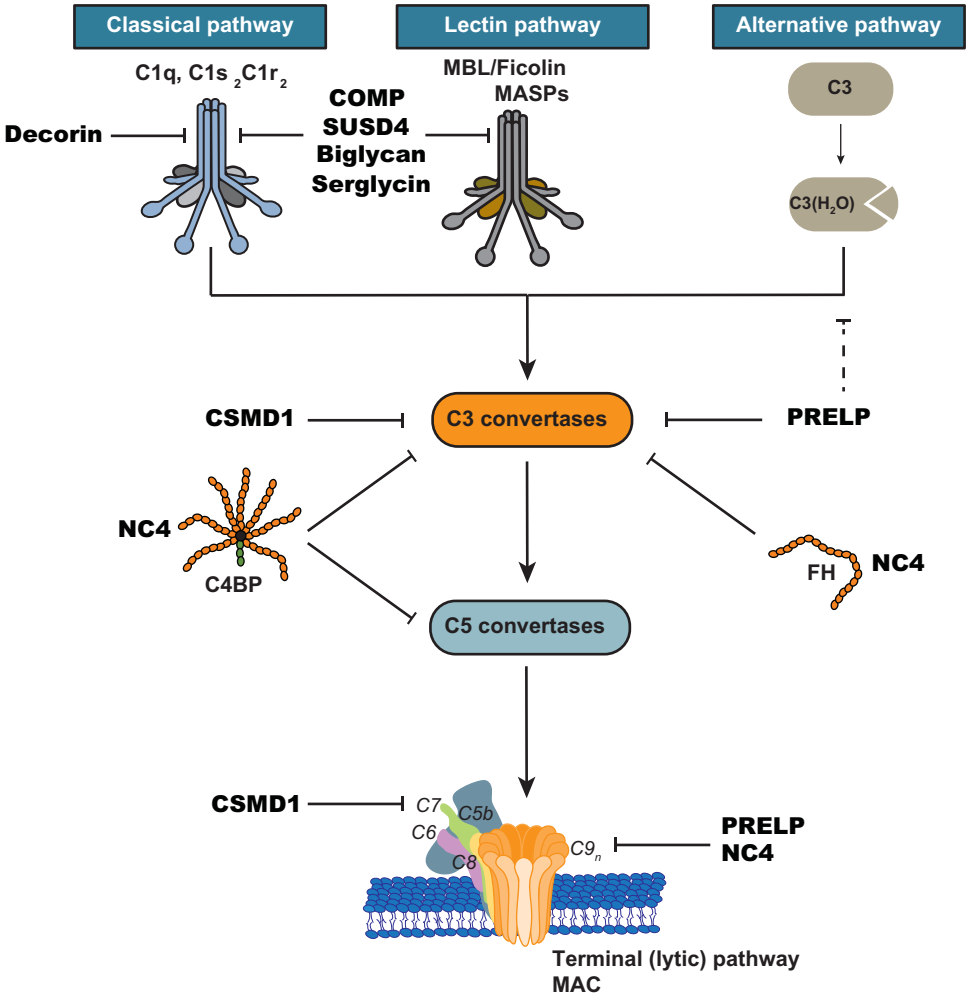

Fig. 1. Scheme of the complement cascade indicating sites of inhibition by novel complement inhibitors, such as CSMD1, SUSD4 and ECM proteins. The complement cascade can be triggered by three canonical pathways (classical, lectin and alternative) that all lead to the assembly of C3- and C5-processing enzymes termed 'convertases'. These multiprotein complexes are responsible for the proteolytic activation of the central components C3 and C5, and the release of their respective bioactive fragments, C3a and C3b, and C5a and C5b and finally formation of a lytic membrane attack complex (MAC), which disrupts membrane integrity. The cascade is tightly regulated by several inhibitors that can be either soluble or bound to cell surface.. The family of complement inhibitors has been extended in the recent years with new proteins containing CCP domains as well as components of ECM.

or convertase dissociation (DAF, CR1, FH, C4BP). Furthermore, C1-inhibitor provides efficient control of the C1 complex, while GPI-linked CD59 present on most cells is the crucial inhibitor of MAC (Zipfel and Skerka, 2009).

2. Proteins containing complement control protein domains

One common trait of many well-established complement inhibitors is the presence of multiple, consecutive complement control protein (CCP) domains, alternatively known as short consensus repeats (SCR) or Sushi domains. This trait raised the possibility that further proteins containing several such domains, such as CSMD1 or SUSD4 may regulate complement. In this review, their roles in regulating the complement cascade, as well as in other cellular processes are discussed.

2.1. Sushi domain-containing (SUSD) protein family

The SUSD protein family includes six different transmembrane proteins (SUSD 1-6), each containing one or multiple sushi (CCP) domains (Fig. 2). Our knowledge about SUSD proteins is restricted to a handful of published studies and database entries often relying on the predictions that are still waiting for direct experimental evidence. SUSD proteins are expressed by genes located on different chromosomes; these genes contain variable functional extracellular domains and different numbers of CCP repeats. Their tissue distribution and functions are also divergent. The least studied member of the group, SUSD1 (~82kDa), consists of an extracellular part of two sushi domains and three EGF-like domains, two of which have calcium ion binding sites. Additionally, it contains a transmembrane domain with a very short cytoplasmic extension. In man, SUSD1 is expressed in the brain, endocrine tissues, gastrointestinal tract, lung, and pancreas. Another protein of this family, SUSD2 (~90kDa) is composed of a somatomedin B-like domain (SO), adhesion-associated domain present in MUC4 and other proteins (AMOP), von Willebrand factor type D domain (VWD), and one sushi domain in the extracellular portion, with both domains essential in the membrane localization of the protein (Cheng et al., 2016). Like SUSD1, SUSD2 has a transmembrane part and a short cytoplasmic domain. SUSD2 is expressed in small amounts in many tissues such as adipose, adrenal gland, spleen, trachea, and uterus but dominantly in lung and kidney (Watson et al., 2013). SUSD3 (~27kDa) has an extracellular domain bearing one CCP domain but no other functional domains, transmembrane domain nor an intracellular domain. It is highly expressed in the brain, male and female reproductive tissues and endocrine tissues, with less expression observed in the spleen, bone marrow, adipose and soft tissues. SUSD3 is localized distinctly at the cell-to-cell borders and plays role in cell-to-cell adhesion. The SUSD4