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Review

An unexpected player in Gaucher disease: The multiple roles of complement in disease development

Manoj K. Pandey[a,c,**], Gregory A. Grabowski[a,c], Jörg Köhl[b,c,d,*]

[a] Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, 45229, USA
[b] Division of Immunobiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, 45229, USA
[c] The Department of Pediatrics of the University of Cincinnati College of Medicine, Cincinnati, OH, 45229, USA
[d] Institute for Systemic Inflammation Research, University of Lübeck, 23562, Lübeck, Germany

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ABSTRACT

The complement system is well appreciated for its role as an important effector of innate immunity that is activated by the classical, lectin or alternative pathway. C5a is one important mediator of the system that is generated in response to canonical and non-canonical C5 cleavage by circulating or cell-derived proteases. In addition to its function as a chemoattractant for neutrophils and other myeloid effectors, C5a and its sister molecule C3a have concerted roles in cell homeostasis and surveillance. Through activation of their cognate G protein coupled receptors, C3a and C5a regulate multiple intracellular pathways within the mitochondria and the lysosomal compartments that harbor multiple enzymes critical for protein, carbohydrate and lipid metabolism. Genetic mutations of such lysosomal enzymes or their receptors can result in the compartmental accumulation of specific classes of substrates in this organelle summarized as lysosomal storage diseases (LSD). A frequent LSD is Gaucher disease (GD), caused by autosomal recessively inherited mutations in *GBA1*, resulting in functional defects of the encoded enzyme, acid β-glucosidase (glucocerebrosidase, GCase). Such mutations promote excessive accumulation of β-glucosylceramide (GC or GL1) in innate and adaptive immune cells frequently associated with chronic inflammation. Recently, we uncovered an unexpected link between the C5a and C5a receptor 1 (C5aR1) axis and the accumulation of GL1 in experimental and clinical GD. Here, we will review the pathways of complement activation in GD, its role as a mediator of the inflammatory response, and its impact on glucosphingolipid metabolism. Further, we will discuss the potential role of the C5a/C5aR1 axis in GL1-specific autoantibody formation and as a novel therapeutic target in GD.

1. Introduction

The complement system exerts important functions as an effector of innate immunity. It senses pathogen or danger/damage associated molecular patterns (PAMPs or DAMPs) expressed on microbial invaders as well as damaged, altered or dying host cells by complement 1q

Abbreviations: ADA, anti-drug antibodies; AMPK, 5′ adenosine monophosphate-activated protein kinase; aHUS, atypical hemolytic uremic syndrome; AMD, age-related macular degeneration; APC, antigen presenting cells; AT, anaphylatoxin; BTK, Bruton's tyrosine kinase; C1q, complement 1q; C3a, complement 3a fragement of C3; C3aR, C3a receptors; C5a, complement 5a fragment of C5; C5aR1, C5a receptor 1; C5aR2, C5a receptor 2; CBE, conduritol B epoxide; CCL2, CC-chemokine ligand 2; CLEAR, Coordinated Lysosomal Expression and Regulation; CMIA, Complement-Metabolism-Inflammasome Axis; CNS, central nervous system; CR, complement receptor; CRIg, complement receptor of the immoglubin superfamily; CXCR5, C-X-C chemokine receptor Type 5; CSF-1, colony stimulating factor 1; CSF-2, colony-stimulating factor 2; DAG, diacylglycerol; DAMP, danger or damage-associatted molecular pattern; DC, dendritic cell; ERT, enzyme replacement therapy; FcγR, IgG Fc receptor; GAGs, glycosaminoglycans; GC/GL1, glucosylceramide; GD, Gaucher disease; GL1-IC, immune complexes comprising GL1 and GL1-specific autoantibodies; GLS, Greater Lysosomal System; GPCRs, G protein-coupled receptors; ICOS, induced costimulatory molecule; IFN-γ, interferon gamma; IL, interleukin; ITAM, immunoreceptor tyrosine-based activating motif; ITIM, immunoreceptor tyrosine-based inhibiting motif; LAL, lysosomal acid lipase; LAT, linker for activation of T cells; LGL1, lysoGL1 or glucosylsphingosine; LSD, lysosomal storage disease; MACs, multimolecular adaptor complexes; MAPK, mitogen-activated protein kinase; MBL, mannan-binding lectin; MiT, micropthalmia transcription; MMR, Mϕ mannose receptor; Mϕ, macrophage; MOs, monocytes; mTORC1, mammalian target of rapamycin complex 1; NF-κB, nuclear factor kappa B; NKT, natural killer T cells; NLRP3, nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing 3; PAMP, pathogen-associated molecular pattern; PD-1, programmed cell death-1; PI, phosphoinositide base; PI3K, phosphoinositide 3-kinase; PGP, pGlycoprotein; PLC-γ, phospholipase C gamme; PNH, paroxysmal nocturnal hemoglbinuria; PMN, polymorphonuclear cells; PRR, pattern-recognition receptor; ROS, reactive oxygen species; SREBP, sterol regulatory element binding protein; SRTs, substrate reduction therapies TCC, terminal complement complex; TFEB and TFE3, transcription factor EB or E3; T_{FH}, T follicular helper cells; Th, T helper; TLR, Toll-like receptor; Treg, regulatory T cells

* Corresponding author at: Institute for Systemic Inflammation Research, University of Lübeck, Ratzeburger Allee 160, Lübeck, 23562, Germany.
** Corresponding author at: Division of Human Genetics, Cincinnati Children's Hospital Medical Center, USA.
E-mail addresses: manoj.pandey@cchmc.org (M.K. Pandey), joerg.koehl@uksh.de (J. Köhl).

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(C1q), Mannan-bindig lectin (MBL) or ficolins, which initiates a series of proteolytic events eventually resulting in the cleavage and activation of several soluble complement components and their corresponding cellular receptors. This process facilitates and enhances the phagocytosis of pathogens and altered, damaged, or apoptotic host cells. Also, it may result in direct killing of pathogens. As we will outline below, it also intersects with other sensor and effector systems of innate immunity and regulates several adaptive immune responses. In addition to the important role of complement in the circulation, novel intracellular functions of complement have recently been uncovered in innate and adaptive immune cells that control nutrient uptake [1], cellular metabolism and nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing 3 (NLRP3) inflammasome activation [2] critical for T helper (Th) cell differentiation, cell survival [3] as well as processing of apoptotic cargo [4,5].

Many of these intracellular functions are mediated by the small cleavage fragments of C3, i.e. C3a and of C5, i.e. C5a, termed anaphylatoxins (AT) and their corresponding C3a receptor (C3aR), C5aR1 and C5aR2 (formerly C5L2) [6]. Traditionally, the ATs have been appreciated as mediators of inflammation that recruit and activate innate immune cells. The signaling pathways of the AT receptors cross-talk heavily with Toll-like receptors (TLRs) [7], C-type lectin receptors [8] and IgG Fc receptors (FcγR) [9]. The distinct AT activities from C3 and C5 were reported in the mid 60ies, which was almost at the same time when Brady et al. [10], discovered that a deficiency of the lysosomal enzyme GCase accounted for the accumulation of GL1 in macrophage (Mϕ) lineage cells, thereby initiating the many of morbid disease manifestations of GD. However, up to this day, this paradigm does not account for the propagation of the disease process, which seemed to be associated with multiple inflammatory responses. It took another 50 years to uncover a previously unknown link between the initiating genetic defect and the inflammatory propagation effects through the C5a/C5aR1 axis of the complement system [11].

2. Lysosomal storage diseases

Lysosomes are intracellular organelles initially described as acidic compartments whose major purpose was to degrade intra- and extracellular proteins, carbohydrates, complex oligosaccharides, mucopolysaccharides [a.k.a. glycosaminoglycans (GAGs)] and pathogens and to serve as a mechanism for compartmental delivery of its constituent proteins, lipids, and other compounds [12]. These two concepts provided the foundations for elucidating the pathophysiologies and development of therapies for the LSDs. These LSDs have been classified based on the compartmental accumulation of specific classes of substrates resulting from mutations in the genes encoding essential lysosomal enzymes/proteins or the receptors for their delivery to this organelle. Thus, the resultant LSD nomenclature includes glycoproteinoses/oligosaccharidoses, sphingolipidoses/lipidoses, mucopolysaccharidoses, glycogenosis, and others (see the Lysosomal disease section in [13] for detailed review). Each of over 60 LSDs and their variants have wild phenotypic variation and organ involvement.

From the initial concepts, lysosome function has evolved into a coordinated system, i.e., the Greater Lysosomal System (GLS), that is central to the regulation of cellular and organismal metabolism and has major roles in innate and adaptive immunity [14–16]. Consequently, the lysosome can no longer be considered to be a simple digestive vacuole, since it is a part of a complex organellar system (i.e., GLS) that senses and transduces signals based on specific tissue/cellular compositions (i.e., contextual dependence) that modulate major metabolic and immunological processes (Fig. 1). Indeed, this complexity was inherent in early findings that lysosomal acid lipase (LAL) cleavage of lysosomal cholesteryl esters was essential to efflux of free cholesterol from the lysosome and the subsequent feedback control of cholesterol synthesis regulation by the sterol regulatory element binding protein (SREBP) systems [17–19]. The definition of the CLEAR (coordinated lysosomal expression and regulation) system molecularly united the control of autophagy/lysosomes/lysosome-like organelles and lipid droplets, and their disruptions in disease. The molecular events that control the function(s) of this system, their diversity with cell/organ type, and spatial/temporal alterations in LSDs remain to be fully defined [20–22], e.g., the differences in Mϕ subtypes and contextual properties.

Transcription Factor EB (TFEB) and TFE3, members of the ancient micropthalmia transcription (MiT) factor family [23], are essential to the control of the GLS system [14,20,21,24,25] as well as immune functions in monocytes (MOs)/Mϕs [3] and T-cells [4]. Importantly, contextual aberrations for specific LSDs initiate the disease processes as well as interactions with the 5′ adenosine monophosphate-activated protein kinase (AMPK) system [20]. Sabatini and coworkers (reviewed in [26] and others [24,27,28]) expanded insights of the mammalian target of rapamycin complex 1 (mTORC1) role in the regulation of the TFEB/TFE3 system, to the central role of the lysosome in energy monitoring, lipid metabolism, and the innate immune system (Fig. 1). For the GLS diseases, the perturbations of these major systems are at least as important as the causative mutations, thereby highlighting the need to encapsulate LSDs into GLS diseases [29–31]. Indeed, unbiased lipidomic analyses indicate that the cellular responses may presage overt evidence of disease in specific disorders, and indicated that the stage for disease development may be set early [32].

The integration leading to the redefinition of LSDs as GLS diseases requires reconceptualization of these diseases as resulting from inert intracellular macromolecule accumulations to complex disorders having major contextual effects on specific cellular types and organs. The specific substrates that accumulate have distinct metabolic and immunological effects in specific tissues [33,34] from the dysregulated GLS. Indeed, these contextual disruptions of the lysosomal/autophagy/mitophagy and immune systems, currently well defined in T-cells, have further expanded the GLS to include the “Complement-Metabolism-Inflammasome Axis (CMIA)” (simplified for GD in Fig. 1) [15,16,32,35,36]. Not unexpectedly, these disruptions lead to pleomorphic effects, including, potentially mTORC1-independent macrophage/microglial activation of TFEB/TFE3 [3] and cyto-/chemokine storms (e.g., in GD and Niemann-Pick disease), dysmorphology and skeletal malformations (e.g., mucopolysaccharidoses), and/or neuroinflammation and neuronal apoptosis/necroptosis (e.g., neuronopathic GD, neuronal ceroid lipofuscinoses, and Krabbe disease [37]).

Embracing the complexities of the GLS diseases and elucidation of specific tissue, cellular, and disruptive molecular effects of the causative mutation(s) as well as the resultant dysregulated immunological and/or other responses in each GLS disease will provide additional therapeutic to address disease propagation. This is particularly relevant to the CNS involvement, because essential molecular and neuroinflammatory details are wanting [33,34]. The focus herein is on GD.

2.1. Gaucher disease

GD is caused by autosomal recessively inherited mutations in *GBA1,* which result in functional defects of the encoded lysosomal enzyme acid β-glucosidase (glucocerebrosidase, GCase). GCase cleaves the β-D-glucosidic bond from the glycosphingolipid substrates, GL1 (or GC), yielding β-D-glucose and ceramide, and its deacylated product, glucosylsphingosine (lyso-GL1 or LGL1), resulting in the formation of β-D-glucose and sphingosine (Fig. 2) [38]. GL1 is synthesized by the cis-Golgi enzyme, glucosylceramide synthase (UDP-glucose ceramide glucosyltransferase, GCS). LGL1 is derived from GL1 by the acid ceramidase hydrolysis of the fatty acid acyl chain (Fig. 2). These substrates preferentially accumulate in liver, lung, spleen, and bone marrow-residing MOs, Mϕs, and dendritic cells (DCs), leading to characteristic “Gaucher cells” that are engorged with these substrate. GL1 is the primary accumulated substrate [27]. GD can be divided into three clinically delineated categories, that is types 1, 2 and 3. The type 2 and 3 variants are quite rare in the “Western world” (< 1/100,000 live-

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