Editorial review

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Antibody equivalent molecules of the innate immune system: parallels between innate and adaptive immune proteins

Nades Palaniyar

Department of Laboratory Medicine and Pathobiology, Lung Innate Immunity Research Laboratory, Program in Physiology and Experimental Medicine, The Hospital for Sick Children and Institute of Medical Sciences, University of Toronto, Toronto, Ontario, Canada

Soluble pattern-recognition innate immune proteins functionally resemble the antibodies of the adaptive immune system. Two major families of such proteins are ficolins and collectins or collagenous lectins (*e.g.* mannose-binding lectin [MBL], surfactant proteins [SP-A and SP-D] and conglutinin). In general, subunits of ficolins and collectins recognize the carbohydrate arrays of their targets via globular trimeric carbohydrate-recognition domains (CRDs) whereas IgG, IgM and other antibody isotypes recognize proteins via dimeric antigen-binding domains (Fab). Considering the structure and functions of these proteins, ficolins and MBL are analogous to molecules with the complement activating functions of C1q and the target recognition ability of IgG. Although the structure of SP-A is similar to MBL, it does not activate the complement system. Surfactant protein-D and conglutinin could be considered as the collagenous non-complement activating giant IgMs of the innate immune system. Proteins such as peptidoglycan-recognition proteins, pentraxins and agglutinin gp-340/DMBT1 are also pattern-recognition proteins. These proteins may be considered as different isotypes of antibody-like molecules. Proteins such as defensins, cathelicidins and lactoferrins directly or indirectly alter microbes or microbial growth. These proteins may not be considered as antibodies of the innate immune system. Hence, ficolins and collectins could be considered as specialized 'antibodies of the innate immune system' instead of 'ante-antibody' innate immune molecules. The discovery, structure, functions and future research directions of many of these soluble proteins and receptors such as Toll-like and NOD-like receptors are discussed in this special issue of *Innate Immunity*.

Keywords: antibodies, innate immune antibodies, ante-antibodies, collectins, ficolins, peptidoglycan-recognition proteins, defensins, cathelicidins, agglutinin, gp-340, DMBT1, pentraxins, C1q, natural IgM, innate immune cells, apoptotic cell clearance, TLR, NLR

Abbreviations: A2M, alpha-2-macroglobulin; C, complement component proteins (C1q, C3, C4); CRD, carbohydrate-recognition domain; CRP, C-reactive protein; DAMPs, damage or danger-associated molecular patterns; DMBT1, deleted in malignant brain tumor 1; FReD, fibrinogen-related domain; GlcNAc, *N*-acetyl glucosamine; gp-340, agglutinin; LLR, leucine-rich repeat; MBL, mannose-binding lectin; NLR, NOD-like receptor; PAMPs, pathogen-associated molecular patterns; PGRP, peptidoglycan-recognition protein; PTX3, long pentraxin; SAP, serum amyloid P component; SP-A, surfactant protein A; SP-D, surfactant protein D; SRCR, scavenger receptor cystine-rich repeat; TLR, Toll-like receptor

Correspondence to: Nades Palaniyar, Department of Laboratory Medicine and Pathobiology, Institute of Medical Sciences, University of Toronto, 555 University Ave, Toronto, ON, Canada M5G 1X8. Tel: +1 416 813 7654 ext 2328. Fax: + 1 416 813 5771;
E-mail: nades.palaniyar@sickkids.ca

INTRODUCTION

The importance of innate immune proteins has been well appreciated in the last two decades. The structure and function of many soluble (extracellular and intracellular) and membrane-bound pattern recognition proteins have been established in the recent past. Many of these proteins bind various pathogen-associated molecular patterns (PAMPs). Genome sequencing has identified additional members to the family of innate immune proteins (*e.g.* collectin CL-11 and some members of peptidoglycan-recognition proteins or PGRPs). Currently, additional novel functions of these new and previously known innate immune proteins are actively being studied. Studies conducted by several research laboratories show that overall structure and functions of few innate immune proteins are homologous to the antibodies of the adaptive immune system.[1–9]

Comparison of collectins and ficolins with antibodies

Collectins have been considered as 'ante-antibodies' because these proteins evolutionarily pre-date antibodies and they can identify microbes before the host is able to make antibodies to specific pathogens.[10] I propose that it is worth considering ficolins and collectins as specialized 'antibodies of the innate immune system' instead of 'ante-antibody' innate immune molecules.

Collectins and ficolins are important families of pattern-recognition innate immune proteins that are present in the circulation, mucosal surfaces including the lungs, and many other tissues.[1,2,11] In many aspects, these proteins resemble pre-assembled, broad-spectrum antibodies of the adaptive immune system (Fig. 1). The trimeric carbohydrate recognition domains (CRDs) of the collectins are functionally homologous to the dimeric antigen-binding domains of the antibodies (Fab). The CRDs from each collectin is specific for particular carbohydrate termini, with some flexibility to accommodate related carbohydrates.[2] Formation of homo-oligomers further provides a high degree of avidity and selectivity to bind their target arrays. For example, the innate immune collectins SP-A and MBL can be compared to a fusion protein made of C1q and IgG. The number of target binding sites is typically 18 (6 trimers; octadecamer) for SP-A and MBL, whereas C1q can bind 12 or more targets through IgG (assuming 6 trimers, each trimeric C1q globular head binding to at least one IgG, and each IgG binding to 2 targets). The difference is that C1q recognizes pathogens via IgG in a two-step process whereas collectins identify their targets directly in a one-step process.[2,8,12] Different forms of MBL (*e.g.* MBL-A, MBL-C) and ficolins (*e.g.* ficolins 1, 2, 3 or L, H, M) may be compared to subclasses of antibody isotypes. Although MBL can activate complement via the lectin pathway, no such function has been identified for SP-A. Ficolins are another class of soluble innate immune proteins that can activate the complement system.[8,13,14] These proteins also fit the description of 'antibodies of the innate immune system'. The primary difference between the ficolins and the collectins, is that ficolins contain fibrinogen-related domains (FReDs) for carbohydrate recognition compared to the C-type lectin domains of the collectins.[2,8,13]

Compared to SP-A and MBL, other collectins such as SP-D and conglutinin orient their CRDs in multiple directions akin to IgM. These collectins can be considered as a giant version of IgM with fibrillar collagen like regions at the centre of the molecule (Fig. 1). Immunoglobulin M has 10 (pentamers) or 12 (hexamers) antigen-binding sites, whereas, dodecameric SP-D and conglutinin can bind 12 (4 trimeric CRDs) targets/molecule. Surfactant protein D can also assemble into an asterisk-like multimer, which provides >30 CRDs/molecule. No complement-activating function has been reported for SP-D or conglutinin. The structure and functions of other collectins, such as CL-11, CL-43, CL-46, CL-P1 and CL-L1, have not been extensively investigated. Based on the known characteristics of these proteins, they may be considered as different antibody isotypes of the innate immune system, but further studies are needed to understand their precise structures and functions.

Key proteins and their functions

Whitsett is a pioneer in the field of collectins and other surfactant proteins. He and his co-workers have conducted a large body of work on collectins and other lung proteins. In his article, he provides a timely, personal perspective on the discovery and functions of collectins and other surfactant proteins.[1] He describes how the generation of transgenic and knockout mice for many of these proteins has helped to establish their functions. These animal models and reagents have revealed novel functions for these proteins and, now, the therapeutic potential of these proteins has been explored in these animal models and in humans. He points out that understanding the functional regulation of these molecules *in vivo* are important for reaping their full therapeutic potentials.

Structure of collectins

Determining the structures of collectins is essential for understanding their biological functions and appropriate therapeutic use. Structures of many of these proteins have been initially determined by biochemical,

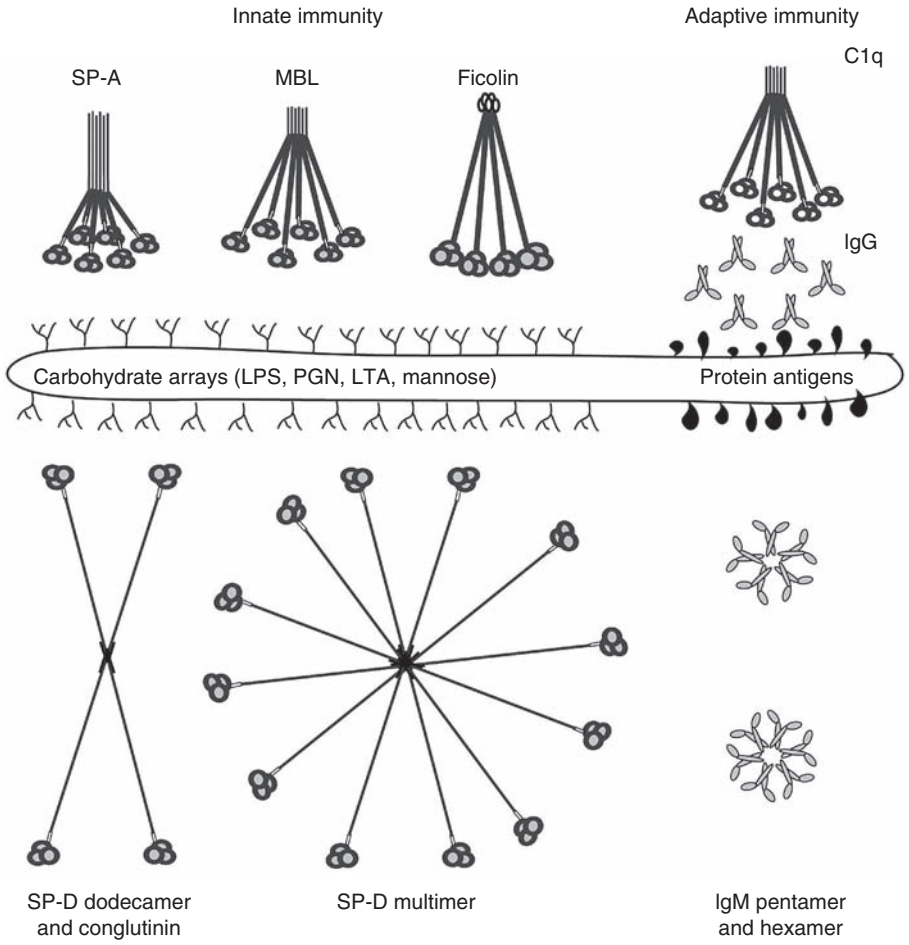

Fig. 1. Parallels between innate and adaptive immune systems. Collectins and ficolins can be considered as special isotypes of specialized pre-assembled, broad-spectrum, anti-carbohydrate 'antibodies of the innate immune system'. Ficolins and collectins SP-A and MBL are analogous to C1q+IgG. However, ficolins and MBL, but not SP-A, activate complement. Surfactant protein D and conglutinin are analogous to collagenous giant IgMs. These molecules do not activate complement. Collectins and ficolins of the innate immune system (left) recognize microbial surface (elongated oval) carbohydrate arrays (branched structures) by their trimeric CRDs, whereas antibodies of the adaptive immune system (right) typically bind protein antigens (solid irregular-sized structures) via their dimeric antigen-binding domains or Fab domains. Antibodies of the innate immune system provide protection against several microbes (bacteria, fungi, virus) throughout the life of the host organism. In contrast, antibodies of the adaptive immune system are generated to pathogenic micro-organisms and effective during subsequent infections. Dimension of SP-D is ~100 nm, and all the other immune proteins are drawn relatively to this scale.

biophysical and electron microscopy methods. Several research groups, including Reid, Crouch, Palaniyar, their colleagues, and others have revealed the structure of SP-A and SP-D by electron microscopy.[15–21] Initially, detailed structural studies have been conducted on the serum collectin MBL.[22] Subsequently, group efforts by Reid, Hakansson, Greenhough and their co-workers in the UK, and McCormack, Crouch, Hartshorn, Head, and Seaton in the US have helped to resolve several high-resolution structures of the CRDs of both SP-A and SP-D.[2,23–26] In this issue, Seaton and her collaborators discuss the relevance of CRD structures in determining the carbohydrate-binding specificities.[2] It is clear that, like antibodies, collectins also recognize and aggregate various microbes and other target molecules, and enhance their clearance by phagocytes. However, unlike antibodies, each collectin molecule can recognize different microbial pathogens because many pathogens contain dense repeating carbohydrate arrays made primarily of a few basic types (*e.g.* mannose, *N*-acetyl glucosamine [GlcNAc], glucose, other hexoses, pentoses or relevant modified carbohydrates).[2] These features emphasize that collectins can be considered as broad-spectrum, giant, anti-carbohydrate antibodies of the innate immune system.

Defensins, LL-37, A2M, C3 and C4

In addition to collectins, other antimicrobial peptides such as defensin and cathelicidins are also present in the lungs and several other organs. Hartshorn and his

co-workers have been studying the role of defensins and defensin:collectin interactions in microbial killing and clearance.[3,27] In this issue, Tecle *et al*.[3] provide a concise and critical evaluation of these proteins in innate immunity, with particular relevance to the lungs. Interestingly, these peptides can also modulate various steps of the inflammatory response. However, functions of defensins and cathelicidins (LL-37) suggest that these proteins do not fit the description of typical antibody-like molecules.

Lactoferrin is considered as an innate immune protein as it indirectly reduces the growth of the microbial pathogens, particularly by chelating metal cations. Alpha-2-macroglobulin (A2M) is also considered as an innate immune protein because it can neutralize the proteases from many microbial pathogens and immobilize them via thiol-ester bonds in its cage-like structure.[28–30] The thiol-ester-based mode of action of A2M is similar to that of the opsonic proteins C3 and C4 of the complement system. Alpha-2-macroglobulin and iC3b are recognized by specific collectins, and these interactions may provide additional links between the innate and adaptive immune systems.[29–31] However, these proteins cannot be considered as innate immune antibodies.

Agglutinin gp-340/DMBT1

Agglutinin or gp-340 is another innate immune protein found in many mucosal surfaces, and can identify and agglutinate number of microbial pathogens. Holmskov, Reid, and co-workers have identified that gp-340 interacts with SP-D.[4] This lung protein was later confirmed as the protein deleted in malignant brain tumour 1 (DMBT1) or salivary agglutinin. Madsen *et al*.[4] review the current state of the knowledge of this scavenger receptor cystine-rich (SRCR) repeat containing-protein. Recent studies have provided additional information about this protein. Although this protein has a putative transmembrane domain in the genomic DNA, only soluble forms have been identified to date. Gp-340 has anti-inflammatory effects in the intestine and it can affect lipopolysaccharide (LPS)-triggered, Toll-like receptor (TLR)4-mediated nuclear factor (NF)-κB signaling to hinder bacterial infection via aggregation. Gp-340 can also interact with IgA and SP-A.[4,32] This protein may be considered as an antibody isotype of the innate immune system.[4]

Peptidoglycan-recognition proteins

The PGRPs are another group of soluble innate immune proteins. These proteins preferentially recognize Gram-positive and Gram-negative bacterial peptidoglycan. They are mostly secreted and are either directly bactericidal or hydrolyze peptidoglycan. Therefore, these proteins could also be considered as a specific innate immune antibody isotype. Dziarski and co-workers have been extensively studying the structure and functions of these proteins.[5,33] They describe the key features of this class of innate immune proteins and compare and contrast the structures and functions of various PGRPs.[5]

Chemical modification of collectins

Functions of many innate immune proteins are affected by structural modifications. For example, the oligomeric state of collectins has been suggested to regulate whether these proteins behave as a pro- or anti-inflammatory proteins.[34] Interestingly, post-translational modifications appear to alter the structure and functions of collectins. Atochina-Vasserman, Gow, Beers, and others have identified specific chemical modifications of SP-D and potential functional consequences.[6,35] Their article details the key chemical modifications of collectins under various biological and pathological conditions.[6]

Collectin–immune cell interactions

Wright and co-workers have been studying various functional aspects of collectins including SP-A. Work from Wright and other laboratories indicate how collectins, such as SP-A and SP-D, could interlink the innate and adaptive immune systems. These collectins are known to interact with, and modulate the functions of, different cells, such as type II epithelial cells, macrophages, neutrophils, eosinophils, mast cells, T-cells and dendritic cells.[7,36–41] An article by Ledford *et al*.[7] provides an update of the current understanding of the roles of these proteins in modulating allergic airway diseases with particular reference to collectins interacting with immune cells such as T cells and dendritic cells. Classical antibodies can interact with specific receptors present on various cells and modulate immune functions. Whether different collectins interact with different immune cells needs to be determined. This new information may allow the comparison of different collectins to various isotypes of antibodies.

Clearance of dying cells

An article by Litvack and Palaniyar summarizes the role of collectins, IgM and other soluble proteins that are involved in recognizing and clearing dying cells.[8] Palaniyar and colleagues have identified that collectins, particularly SP-D, effectively recognize novel targets and soluble proteins (*e.g*. antibodies, decorin, A2M,

DNA, RNA).[29,42–44] It is becoming clear that collectins such as SP-A, SP-D and MBL play an important role in recognizing apoptotic cells and nucleic acids, and their clearance.[42,45] Surfactant protein A also interacts with IgG and complement proteins such as C1q.[46,47] Interestingly, C1q and natural IgM can directly recognize molecular patterns present on certain cells under specific biological situations; for example, they recognize damage- or danger-associated molecular patterns (DAMPs) of dying cells.[48–50] Therefore, collectins may further regulate or utilize the complement system for effective immune surveillance and regulation of tissue inflammation. Notably, collectins modulate multiple immune functions and autoimmune diseases such as systemic lupus erythematosus.[1,7,8,36] Once again, like specific antibodies, collectins may also exert other tissue-specific immune functions.

Pentraxins (C-reactive protein [CRP], serum amyloid P component [SAP], long pentraxin [PTX3]) are another notable class of soluble innate immune proteins.[51] These proteins often form small pentameric structures and specifically recognize carbohydrate, certain lipids, and chromatin. These proteins are important in recognizing apoptotic cells and their components for effective clearance. Many of these proteins can directly interact with C1q to exert additional functions such as complement activation.[8] Hence, pentraxins can fit the description of innate immune antibodies.

Toll-like and NOD-like receptors

Toll-like receptors are membrane proteins and have been extensively studied in the last few decades. This family of proteins has leucine-rich repeat (LLR) domains that recognize numerous microbial ligands including LPS, PGN, flagellin, DNA and RNA. These receptors regulate signaling pathways and cytokine profiles of cells. CD14 is one of the well-studied, membrane-bound proteins but it lacks a cytoplasmic signaling domain; hence, it interacts with other receptors for downstream signalling. Collectins can interact with TLRs and CD14 and regulate signaling pathways.[9,52,53] NOD-like receptors or NLRs are intracellular signalling molecules that have LLR domains. The NLRs are known for binding to peptidoglycan. These proteins are considered to reside both in epithelial and hematopoietic cells. Jeyaseelan and co-workers have been investigating several signalling pathways mediated by these receptors.[54] Balamayooran *et al*.[9] describe the recent advances in the role of innate immune pattern-recognition receptors in the context of pathogen recognition. These proteins cannot be directly considered as antibodies. The TLRs particularly represent a true cellular receptor of innate immune system.

Summary and Future Directions

In conclusion, certain soluble innate immune proteins represent the antibody equivalents of the innate immune system. Ficolins and the serum collectin MBL can be considered as antibodies with C1q-like complement activating functions (Fig. 1). Although SP-A is structurally similar to MBL, it is functionally different. Surfactant protein D and conglutinin can be compared to an IgM-like antibody that has collagenous arms. This arrangement may be analogous to a flattened version of C1q with antigen recognition sites at the globular domain. Gp-340, PGRP and pentraxins may also be considered as innate-immune antibody-like proteins. However, defensins, cathelicidins and lactoferrin do not fit the description of the antibodies of the innate immune system. The TLRs represent true cellular receptors, and do not fit the description of soluble antibodies. Additional research work and discussions are necessary to clearly establish the parallels between the soluble innate immune proteins to different antibody isotypes (IgG, IgM, IgA, IgE and IgD), and subclasses (*e.g*. IgG1, IgG2, *etc*.). I believe that it would be worth examining collectins and ficolins in the context of 'antibodies of the innate immune system' to explore their functions further.

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