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REVIEW

Ficolins and infectious diseases

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Ficolins are serum complement lectins, with a structure similar to mannose-binding lectin (MBL) and lung surfactant protein (SP)-A and SP-D. Ficolins activate the lectin complement system and play important roles in host innate immunity. Ficolins are members of the collectin family of proteins, which act as pattern recognition receptors (PRRs). They are soluble oligomeric defense proteins with lectin-like activity, and are able to recognize pathogen-associated molecular patterns (PAMPs), which are carbohydrate molecules on the surface of pathogens, and of apoptotic, necrotic, and malignant cells. Upon binding to their specific PAMPs, ficolins may trigger activation of the immune system either (1) by initiating activation of complement via the lectin pathway, (2) by a primitive type of opsonophagocytosis, or (3) by stimulating secretion of the inflammatory cytokines interferon (IFN)-γ, interleukin (IL)-17, IL-6, and tumor necrosis factor (TNF)-α, and production of nitric oxide (NO) by macrophages, thus limiting the infection and concurrently orchestrating the subsequent adaptive immune response. Recently, a number of reports have shown that dysfunction or abnormal expression of ficolins may play crucial roles in viral and bacterial diseases and in inflammation. This review summarizes the reports on the roles of ficolins in the infectious diseases, and provides insight into ficolins as novel innate immune therapeutic options to treat these diseases.

KEYWORDS L-ficolin; H-ficolin; M-ficolin; virus; bacteria

INTRODUCTION

The complement system plays a crucial role in protecting against invading microorganisms, and acts through three activation pathways: the classic, alternative, and lectin pathways. The lectin pathway of complement activation is the most recently discovered of the three complement pathways. Mannose-binding lectin (MBL) and ficolins represent the first components of the lectin branch of the complement system. The anti-microbial activity of MBL has been widely studied, and it recognizes many different microorganisms, including fungi, bacteria, viruses, and protozoa (Dommett R M, et al., 2006; Jack D L, et al., 1998). Both MBL and the recently identified ficolins act as pattern recognition receptors (PRRs). These are soluble oligomeric defense proteins with lectin-like activity, and are able to recognize pathogen-associated molecular patterns (PAMPs), which are carbohydrate molecules on the surface of pathogens and of apoptotic, necrotic, and malignant cells. PRRs are either secreted or membrane-bound. Secreted PRRs are also called opsonins, and include MBL, ficolins, C-reactive protein (CRP), and serum amyloid protein (SAP) (Medzhitov R, 2007; Medzhitov R, et al., 2002). PRRs recognize charged ligands and facilitate elimination of their ligands by phagocytes, and also mediate removal of apoptotic cells. PRRs serve several important roles in the innate immune response, including opsonization, phagocytosis, induction of apoptosis, and activation of cascades of complement, coagulation, and inflammation (Medzhitov R, et al., 2002).

The ficolins were originally identified as transforming growth factor (TGF)-1-binding proteins on porcine uterine membranes (Ichijo H, et al., 1993). Several members of the ficolin family have been identified to date, including human L-ficolin-2/P35 (FCN2 or ficolin 2) (Matsushita M, et al., 1996), M-ficolin (FCN1 or ficolin 1) (Endo Y,

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et al., 1996; Lu J, et al., 1996), and H-ficolin/Hakata antigen (FCN3 or ficolin 3) (Akaiwa M, et al., 1999), the mouse ficolins A and B (Fujimori Y, et al., 1998) (Table 1), the pig ficolins α and β, and the tachylectins 5A/5B (TL 5A/5B) from the horseshoe crab *Tachypleus tridentatus* (Gokudan S, et al., 1999). All ficolins function as recognition molecules, and trigger either the lectin pathway of complement or other effector mechanisms, following binding to several ligands.

Human L-ficolin is mainly synthesized in the liver and secreted into blood circulation. H-ficolin is expressed in the lung and liver, and can also be found in serum. Another human ficolin, M-ficolin, is a secretory protein from neutrophils and monocytes in peripheral blood and from type II alveolar epithelial cells in lung. Ficolins and MBL are associated with MBL-associated serine proteases (MASPs) and with small MBL-associated protein (sMAP), a truncated protein of MASP-2, and both ficolins and MBL activate the lectin pathway of complement (Matsushita M, et al., 2001; Zhang X L, et al., 2008). Ficolins act as pattern recognition molecules that specifically bind to many clinically important microorganisms. They also function as opsonins when binding to certain types of oligosaccharides on the surfaces of pathogens via their lectin activity (Liu Y, et al., 2005; Matsushita M, et al., 2001; Matsushita M, et al., 1996).

MOLECULAR STRUCTURES OF FICOLINS

All ficolins are oligomeric defense proteins assembled from a collagen-like domain (CLD) and fibrinogen-like (FBG) domains, which are able to sense danger signals such as pathogens or apoptotic cells (Figure 1). The polypeptide chains then radiate out in a sertiform structure, giving ficolins the typical "bouquet"-like appearance. The FBG domain forms a globular structure similar to the carbohydrate-recognition domain (CRD) of C-type lectin.

L-Ficolin is encoded by the *FCN2* gene, which is localized to chromosome 9 (9q34), and was first cloned and described as a type of lectin with a similar structure and function to MBL (Endo Y, et al., 1996), and is reported to play an important role in innate immunity. L-ficolin (with molecular weight of 35 kDa) has lectin- like activity for N-acetyl-D-glucosamine (GlcNAc), lipopolysaccharides, 1,3-β-D glucan, lipoteichoic acid (LTA), and various acetylated compounds (Lynch N J, et al., 2004; Matsushita M, et al., 2001). Its binding specificity differs from that of MBL (Kilpatrick D C, et al., 2012) in that L-ficolin mainly binds to GlcNAc residues next to galactose at the non-reducing terminal of the oligosaccharide, whereas MBL binds mainly to mannose.

Human H-ficolin is structurally similar to C1q and MBL (Holmskov U, et al., 2003; Zhang X L, et al., 2008). H-ficolin coded by the *FCN-3* gene localized to 1p36.11 and is composed of structural subunits similar to that of L-ficolin (Figure 1). Each subunit (trimer) contains a CLD and three C-terminal recognition domains (FBG-like domains) binding to acetyl groups on microbial surfaces (Schlapbach L J, et al., 2009; Sugimoto R, et al., 1998). H-ficolin has a shorter collagen domain than the other two ficolins.

M-ficolin is encoded by the *FCN1* gene, localized to chromosome 9. Similar to the structures of L-ficolin and H-ficolin, M-ficolin consists of a number of subunits, each containing a collagen-like strand and three C-terminal recognition domains. M-ficolin binds to microbial surfaces that express N-acetyl-D-glucosamine or N-acetyl-galactosamine, and to sialic acid residues (Liu Y, et al., 2005; Teh C, et al., 2000). Human M-ficolin is also a

Table 1. Expression, sugar specificity, and target pathogens of ficolins in human and mouse

Species	Ficolin	Tissues of origin	Tissues of presentation	Sugar specificity	Gene localization	Complement activation
Human	L-ficolin (ficolin-2)	Liver	Serum	GlcNAc/ManNAc>>GalNAc/CysNAc/GlyNAc, acetylcholine, elastin, corticosteroids, 1,3-β-D-glucan, LTA	9q34	Yes
	H-ficolin (ficolin-3)	Liver, type II alveolar cells	Serum, bronchus, alveolus, bile	GlcNAc, GalNAc, fucose, glucose, PSA	1p36.11	Yes
	M-ficolin (ficolin-1)	Monocytes	Monocyte surface, serum	GlcNAc-BSA, GalNAc-BSA, SiaLacNAc-BSA	9q34	Yes
Mouse	Ficolin-A	Liver and spleen	Serum	GlcNAc, GalNAc	2A3	Yes
	Ficolin-B	BM and spleen	Peritoneal macrophages	GlcNAc, GalNAc, SiaLacNAc, fetuin	2A3	No

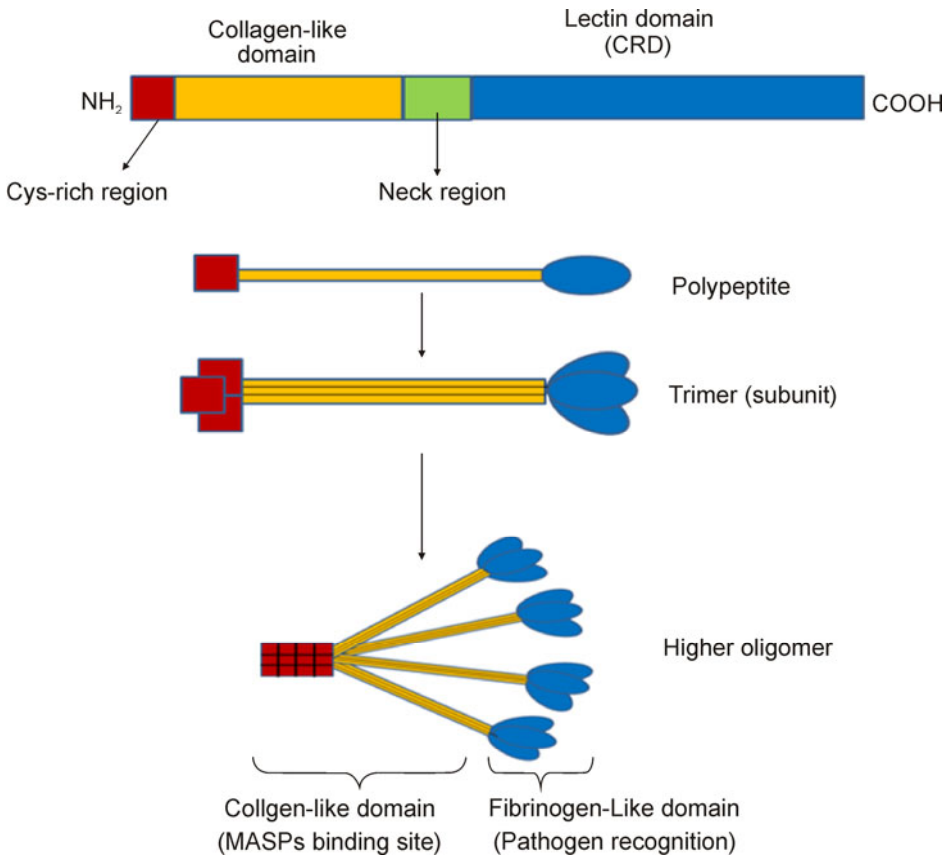

Figure 1. Ficolins are oligomers (12-mer, 4 × 3) of structural subunits, each of which is composed of three identical 35-kDa polypeptides. Each subunit (trimer) contains a collagen-like domain and three C-terminal recognition domains (fibrinogen-like domains). Three identical polypeptide chains assemble into the structural subunits (trimers), which in turn associate into higher oligomeric forms.

secretory protein that activates the lectin complement pathway, is present in a highly mobilizable subset of human neutrophil granules, and associates with the cell surface (Matsushita M, 2010; Rorvig S, et al., 2009) (Table 1).

FICOLINS AND VIRAL DISEASES

Recently, an increasing number of reports have shown that dysfunction or abnormal expression of ficolins play crucial roles in many clinically important viral diseases.

Ficolins and Hepatitis C Virus

Hepatitis C virus (HCV) infects 170 million people worldwide, and about 80% of infected individuals develop chronic hepatitis, with a risk of progression to cirrhosis and hepatocellular carcinoma. A recent study showed that activating the lectin pathway of complement could contribute to HCV infection (Hu Y L, et al., 2013). In patients with chronic HCV (CHC), the protein concentrations of L-ficolin were found to be significantly higher in patients with CHC who had abnormal alanine aminotransferase (ALT) levels (>40 U/L), compared with patients who had normal ALT (≤40 U/L) or with healthy controls. The mean level of L-ficolin in patients with CHC was about 6.0–7.2 μg/ml, while that of healthy donors was about 4.5–4.6 μg/ml. After therapy, the concentrations of L-ficolin decreased to normal, and were positively correlated with the ALT and HCV RNA levels. Patients who had high L-ficolin levels in early follow-up serum samples obtained rapid favorable viral response. These findings suggest that L-ficolin has a high correlation with hepatic inflammation and rapid viral response, indicating that L-ficolin has an anti-HCV effect *in vivo* (Hu Y L, et al., 2013; Liu J, et al., 2009).

HCV contains two highly glycosylated envelope proteins, E1 and E2, and L-ficolin has been shown to bind to these two envelope proteins (Liu J, et al., 2009). L-ficolin was shown to interact with the ectopic expression of the HCV E1 or E2 glycoproteins in a dose-dependent manner. However, if the E1 or E2 glycoproteins were pretreated with N-glycanase or if E1-expressing or E2-expressing cells were pretreated with the N-glycosy-

lation inhibitor 1-deoxynojirimycin (DNM), L-ficolin could not bind to E1 or E2. Therefore, the interaction between L-ficolin and the HCV E1 and E2 glycoproteins is attributable to the N-glycans of E1 and E2 (Liu J, et al., 2009). After binding to the N-glycans of E1 and E2 of HCV, L-ficolin triggers C4 deposition to activate the complement lectin pathway in HCV-infected hepatocytes (Endo Y, et al., 2011; Liu J, et al., 2009). L-ficolin can also effectively bind to and inhibit JFH1 HCVcc (HCV cell culture) infection of Huh7.5.1 cells *in vitro* (our unpublished data), which is consistent with the anti-HCV effects of L-ficolin observed in an *in vivo* study (Hu Y L, et al., 2013). These reports suggest beneficial therapeutic effects for the innate immune molecule L-ficolin against HCV infection

Ficolins and Hepatitis B Virus

Infection with hepatitis B virus (HBV) may cause acute or chronic disease, resulting in chronic inflammation and cirrhosis. Hoang et al. recently demonstrated that L-ficolin levels and *FCN2* haplotypes contributed to hepatitis B infection outcome in Vietnamese patients (Hoang T V, et al., 2011). The Vietnamese patients with acute hepatitis B had higher serum L-ficolin levels compared with patients with hepatocellular carcinoma (HCC) or liver cirrhosis (LC), asymptomatic HBV carriers, or healthy donors (Hoang T V, et al., 2011). After screening the genotype of the Vietnamese cohort, comprised of 423 clinically classified patients with HBV and 303 healthy controls, for functional single nucleotide polymorphisms in the promoter region (-986G>A, -602G>A, -4A>G) and in exon 8 (+6424G>T) by real-time PCR, no significant differences were observed either in genotype or in allelic distribution between patients and controls, or within the patient group.

Ficolins and influenza A virus and other viruses

Influenza A virus (IAV) is an important human pathogen that causes worldwide epidemics yearly, and pandemics sporadically. IAV bears two surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA), both of which play crucial roles in the ability of the virus to replicate in susceptible target cells. Both L-ficolin and H-ficolin have been reported to be able to inhibit IAV infection both *in vitro* and *in vivo* (Pan Q, et al., 2012; Verma A, et al., 2012). The level of H-ficolin in blood is about 20 μg/ml, which is higher than that of the other two ficolins. H-ficolin was shown to have a role in innate defense against IAV in the airway and to contribute to the rarity of viremia in IAV infection (Verma A, et al., 2012). L-ficolin recognized and bound to HA and NA, and to different subtypes of IAV, and these interactions were found to be competitively inhibited by N-acetyl-D-glucosamine (GlcNAc) (Pan Q, et al., 2012). In addition, the binding of L-ficolin and ficolin A led to the activation of the lectin complement pathway (Pan Q, et al., 2012). L-ficolin was found to block influenza viral infections both *in vitro* and also *in vivo* (using ficolin A knockout mice), possibly by interacting with the carbohydrates of HA and NA (Pan Q, et al., 2012). Therefore, these data may provide new immunotherapeutic strategies, based on the innate immune molecule L-ficolin, against IAV.

It was found that recombinant chimeric lectin (RCL), prepared by replacing the MBL collagenous domain with that from L-ficolin, had superior antiviral activities compared with MBL alone (Chang W C, et al., 2011). Chimeric proteins containing the N-terminal domains of L-ficolin and the CRD of MBL strongly inhibited both Ebola virus and IAV (Chang W C, et al., 2011; Michelow I C, et al., 2010), and the RCL could also bind to Nipa, Hendra, and Ebola viruses (Chang W C, et al., 2011). The chemic lectin of MBL and L-ficolin is effective in improving H1N1 infection by down-regulating pro-inflammatory molecules and up-regulating anti-inflammatory molecules (Takahashi K, et al., 2013).

Human immunodeficiency virus (HIV) is also another important pathogen. Recently, we found that L-ficolin protein could recognize and bind to HIV via interaction with the N-glycans of viral envelope glycoprotein gp120, subsequently activating the lectin complement pathway (unpublished data). However, cytomegalovirus (CMV) disease was not associated with MBL or ficolins in HIV-infected patients with CMV (Egli A, et al., 2013). In addition, the porcine plasma ficolin reduced the infectivity of porcine reproductive and respiratory syndrome virus (Keirstead N D, et al., 2008).

FICOLINS AND BACTERIAL DISEASES

Many reports have shown that ficolins play crucial roles in many clinically important bacterial diseases.

Ficolins and *Mycobacterium tuberculosis*

Tuberculosis (TB) is a disease caused by *Mycobacterium tuberculosis* and remains a major global health problem. It was reported recently that L-ficolin (ficolin-2) serum levels of 107 patients with pulmonary TB were much lower than those of 107 healthy controls (Luo F, et al., 2013). *In vitro* analysis showed that L-ficolin bound to the virulent *M. tuberculosis* H37Rv strain much more strongly than to the non-virulent *M. bovis* BCG and *M. smegmatis* bacteria. L-ficolin bound to the surface glycolipid portion of H37Rv, and blocked H37Rv infection in human lung A549 cells. Opsonophagocytosis was also promoted by L-ficolin. Administration of exogenous L-ficolin had a marked protective effect against virulent *M. tuberculosis* H37Rv infection in both C57BL/6J and BALB/c mice. Ficolin-A (mouse L-ficolin-like molecule)

knockout mice exhibited increased susceptibility to H37Rv infection. These new findings will contribute to the development of ficolins as a new immunotherapy molecule against TB, and they indicate that L-ficolin insufficiency is associated with higher susceptibility to infection in humans (Luo F, et al., 2013).

Ficolins and Gram-negative bacteria

L-ficolin can bind to carbohydrates on the surface of bacteria via the FBG domain. L-ficolin was shown to bind to Gram-negative bacteria, such as the rough type of *Salmonella typhimurium* TV119, and *Pseudomonas aeruginosa* (Kilpatrick D C, et al., 2009). Taira et al. reported that L-ficolin bound to *S. typhimurium* (TV119), a Ra chemotype strain having an exposed GlcNAc at the non-reducing termini of the polysaccharide, whereas it did not bind to LT2, a smooth-type strain of *S. typhimurium* with additional O-polysaccharides covering GlcNAc (Taira S, et al., 2000). Binding of L-ficolin to *S. typhimurium* (TV119) enhanced the clearance of pathogens with surface GlcNAc, suggesting that L-ficolin serves as an opsonin, increasing phagocytosis by polymorphonuclear leukocytes or monocytes, but has no opsonic activity towards LT2. This result suggests that L-ficolin has a function in innate immunity against certain pathogenic organisms by acting as an opsonin. L-ficolin formed a functional complex with the MASPs and sMAP by immunoprecipitation using L-ficolin antibody, and the complex subsequently activated the complement system, showing that L-ficolin could mediate clearance of pathogens effectively by complement activation and complement receptor-mediated phagocytosis (Matsushita M, et al., 2000).

M-ficolin and H-ficolin have been shown to bind to carbohydrate structures on Gram-negative bacteria (Akaiwa M, et al., 1999; Liu Y, et al., 2005). They present affinity for GlcNAc and bind to *S. typhimurium, S.almonella minnesota*, and *Escherichia* spp.

Ficolins and Gram-positive bacteria

Both L-ficolin and M-ficolin have been demonstrated to be associated with Gram-positive bacterial infectious diseases. L-ficolin was shown to activate the lectin complement pathway through binding to carbohydrate on the bacterial surface, and it enhanced the opsonic activity of polymorphonuclear neutrophils (Aoyagi Y, et al., 2005). Binding of L-ficolin to type III group B streptococci or *Staphyloccus aureus* leads to activation of the lectin pathway (Lynch N J, et al., 2004). Another human ficolin, M-ficolin, was found to be localized in secretory granules in the cytoplasm of neutrophils, monocytes, and type II alveolar epithelial cells in the lung. M-ficolin was shown to bind to *S. aureus* (Gram-positive bacteria) and *S. typhimurium* LT2 (Gram-negative bacteria) (Frederiksen P D, et al., 2005; Liu Y, et al., 2005). M-ficolin bound to several neoglycoproteins bearing GlcNAc, N-acetylgalactosamine, and sialyl-N-acetyllactosamine, suggesting that M-ficolin can recognize the common carbohydrate residues found in microbes (Frederiksen P D, et al., 2005; Liu Y, et al., 2005). Kjaer et al's goup (Kjaer T R, et al., 2011) demonstrated that M-ficolin specifically bound to sialic acids in the capsule of *Streptococcus agalactiae*. Porcine ficolin was also reported to bind to the *Actinobacillus pleuropneumoniae* serotype 5B (Nahid A M, et al., 2006). Studies to date have shown that the only Gram-positive bacterium to which H-ficolin binds is *Aerococcus viridans* (Tsujimura M, et al., 2001).

Ficolins and inflammation

Ficolins are reported to stimulate expression of inflammatory cytokines by macrophages. Our research group recently demonstrated that L-ficolin could defend against virulent *M. tuberculosis* H37Rv infection at least partially by activating Jun kinase (JNK) phosphorylation and stimulating the secretion of interferon (IFN)-γ, interleukin (IL)-17, IL-6, and tumor necrosis factor (TNF)-α, and nitric oxide (NO) production by macrophages (Luo F, et al., 2013)(Figure 2).

Munthe-Fog reported a patient with a history of severe recurrent infections, who was homozygous for the FCN3+1637delC mutation and had no detectable H-ficolin in their serum, suggesting that complete lack of H-ficolin is a novel immunodeficiency associated with inflammatory disease (Munthe-Fog L, et al., 2009). Schaffer reported that H-ficolin concentrations were slightly reduced in patients with Crohn's disease (CD) or ulcerative colitis compared with healthy controls. Patients with CD who had high titers of anti-*Saccharomyces cerevisiae* antibodies (ASCA) had significantly lower H-ficolin concentrations compared with patients who had low or negative ASCA levels (Schaffer T, et al., 2013). High concentrations of H-ficolin in the placentas of pre-eclamptic pregnant women were accompanied by low levels of serum H-ficolin (Wang C C, et al., 2007).

M-ficolin levels correlated with the number of neutrophils in the blood of healthy blood donors and of patients with rheumatoid arthritis (RA) (Ammitzboll C G, et al., 2012). It was recently reported that there was a 30-fold increase in M-ficolin concentrations in the synovial fluid of patients with chronic active RA compared with those of patients with osteoarthritis, suggesting that M-ficolin is involved in the pathogenesis of RA (Ammitzboll C G, et al., 2012). These data demonstrate that increased circulating M-ficolin levels are associated with higher disease activity in patients with RA.

system either by initiating activation of complement via the lectin pathway, by a primitive opsonophagocytosis,

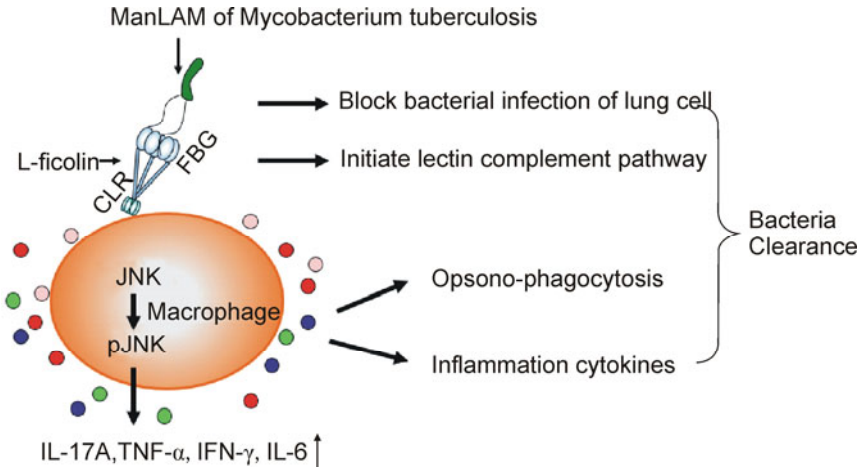

Figure 2. Hypothetical model of the mechanisms mediated by L-ficolin, stimulating secretion of inflammatory cytokines by macrophages during *Mycobacterium tuberculosis* infection (modified from Luo et al. 2013; doi:10.1371/journal.pone.0073859.g007)

Table 2. Ficolins and infectious diseases

	Roles of ficolins during viral and bacterial infection	References
Viral infection		
Ficolins and HCV	L-ficolin binds to viral N-glycans, and triggers complement lectin pathway activation; L-ficolin serum concentrations were positively correlated with ALT and HCV RNA levels after therapy *in vivo*	(Hu Y L, et al., 2013; Liu J, et al., 2009)
Ficolins and HBV	Higher serum L-ficolin levels were observed in patients with acute HBV compared with patients with HCC or healthy donors	(Hoang T V, et al., 2011)
Ficolins and IAV and other viruses	L- and H-ficolins bind to HA and NA glycoproteins and different subtypes of influenza A virus, and inhibit virus infection both *in vitro* and i*n vivo*	(Chang W C, et al., 2011; Michelow I C, et al., 2010; Pan Q, et al., 2012; Verma A, et al., 2012)
Bacterial infection		
Ficolins and MTB	L-ficolin binds to the surface glycolipid portion of H37Rv, and blocks H37Rv infection	(Luo F, et al., 2013)
Ficolins and Gram-negative bacteria	L-, M-, and H-ficolins bind to Gram-negative bacteria, such as the rough type of *Salmonella typhimurium* TV119, and *Pseudomonas aeruginosa* via the FBG domain, and serve as opsonins, increasing phagocytosis	(Akaiwa M, et al., 1999; Frederiksen P D, et al., 2005; Kilpatrick D C, et al., 2009; Liu Y, et al., 2005; Matsushita M, et al., 2001; Taira S, et al., 2000)
Ficolins and Gram-positive bacteria	Both L-ficolin and M-ficolin bind to Gram-positive bacteria, such as streptococci (GBS) and *Staphylococcus aureus*, and lead to activation of the lectin pathway. H-ficolin binds to the Gram-positive bacterium *Aerococcus viridans*	(Aoyagi Y, et al., 2005; Kjaer T R, et al., 2011; Lynch N J, et al., 2004; Tsujimura M, et al., 2001)

FBG, fibrinogen-like; HA, hemagglutinin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; GBS, group B streptococci; IAV, influenza A virus; MTB, *Mycobacterium tuberculosis*; NA, neuraminidase.

DISCUSSION

An increasing body of data suggests that ficolin is an important aspect in host innate defenses against viral and bacterial diseases (Table 2), while defective or abnormal expression will cause the pathogenic activities of these organisms. Ficolins may trigger activation of the immune

or by stimulating the secretion of IFN-γ, IL-17, IL-6, TNF-α and NO production by macrophages, thus limiting the infection. These results will provide insight into ficolins as novel innate immune therapeutic options to treat many infectious diseases.

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