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Soluble defense collagens: Sweeping up immune threats

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ABSTRACT

Soluble defense collagens form a group of secreted proteins that are primarily involved in host defense. All defense collagens contain a globular recognition domain contiguous to a collagen-like triple helical domain. They are oligomeric proteins, assembled in multiples of three subunits due to their collagen domains. Members of this group include collectins such as surfactant protein A and D (SP-A, SP-D), and mannan-binding lectin; C1q, the first component of the complement system; adiponectin; and ficolins. All are secreted to tissue cavities or serum. Soluble defense collagens are specialized to respond to infection, triggering the initiation of the complement cascade and/or enhancing phagocytosis of pathogens by macrophages. However, once inflammation is established, C1q, collectins, ficolins, or adiponectin can influence macrophage responses, thereby contributing to resolve the inflammation. In addition, some members of this group of proteins (SP-A, C1q, and adiponectin) modulate tissue-repair functions of macrophages. This review will focus on the molecular mechanisms by which these proteins efficiently defend against immune threats and contribute to tissue repair.

1. Introduction

The term 'defense collagens' distinguishes a growing family of proteins, involved in host defense, from structural collagens that constitute the extracellular matrix. They are highly conserved across mammalian species and include i) integral membrane proteins such as class A scavenger receptors (SR-A1, SR-A3-5, and MARCO) (Zani et al., 2015; PrabhuDas et al., 2017) and ii) proteins secreted to tissue cavities and/or serum (Tenner, 1999; Fraser and Tenner, 2008). In this review, we will focus on human secreted defense collagens, which display a wide range of binding properties to immune targets and cell surface receptors through their globular head regions and collagen-like domains. These soluble pattern recognition molecules serve to identify pathogen-associated molecular patterns (PAMPs) (Medzhitov and Janeway, 2002) and danger-associated molecular patterns (DAMPs) (Matzinger, 1994; Venereau et al., 2015).

The human soluble defense collagens considered in this review are enumerated in Table 1. They include three sets of defense collagens: (a) members of the collectin family (CL): surfactant protein A and D (SP-A and SP-D), mannan-binding lectin (MBL), collectin liver-1 (CL-L1 aka CL-10), collectin kidney-1 (CL-K1 aka CL-11), and the heterotrimeric CL-LK formed by the combination of CL-K1 and CL-L1 polypeptides (Casals et al., 2018); (b) two members of the C1q and TNF-related proteins (CTRP) family: C1q, the first subcomponent of the complement classical activation pathway, and adiponectin (Kishore et al., 2004; Ressl et al., 2015); and (c) members of the ficolin family: M-ficolin (ficolin 1), L-ficolin (ficolin 2) and H-ficolin (ficolin 3) (Matsushita, 2010).

SP-A and SP-D are secreted to the airway mucosa by alveolar epithelial type II cells and nonciliated bronchiolar cells. They are also detected in the trachea and nasal mucosa, where they provide immune protection (Casals et al., 2018). SP-A and SP-D are also present in other extra-pulmonary mucosal surfaces and tissues, such as the middle ear, the ocular system (cornea, conjunctiva, and tear fluid), the digestive,

ABBREVIATIONS: Axl, AXL receptor tyrosine kinase; CL-, collectin; CR, complement receptor; CRD, carbohydrate recognition domain; CTRP, C1q/TNF-related protein; DAMPs, damage-associated molecular patterns; FBG, fibrinogen-like globular domain; gC1q, globular complement factor C1q domain; LAIR-1, leukocyte associated immunoglobulin like receptor 1; LPS, lipopolysaccharide; LRP1, low density lipoprotein receptor related protein 1; MASP, mannan-binding lectin-associated serine protease; MBL, mannan-binding lectin; Mertk, c-mer proto-oncogene tyrosine kinase; PAMPs, pathogen-associated molecular patterns; PS, phosphatidylserine; RELM, resistin-like molecule alpha; ROS, reactive oxygen species; SHP-1, Src-homology 2 domain-containing protein tyrosine phosphatase; SIRP-α, Signal regulatory protein α; SLE, systemic lupus erythematosus; SP-, surfactant protein; SR, scavenger receptor; TLR, toll-like receptor

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Table 1
Expression and secretion of human soluble defense collagens.

Protein name	mRNA expression	Protein detection	Levels in serum	References
SP-D	Alveolar epithelial type II cells, bronchiolar Club cells, trachea, and other mucosal epithelia	Lung, alveolar fluid, and other mucosal epithelia	0	Wright (2005), Ordonez et al. (2017), Ujma et al. (2017)
CL-L1 (CL-10)	Hepatocytes, epithelial cells of different tissues	Serum, liver, kidney, lung, digestive tract, adrenal glands, and other secretory and mucosal epithelia	~ 0.5 μg/ml	Troldborg et al. (2017), Hansen et al. (2018)
CL-K1 (CL-11)	Hepatocytes, epithelial cells of different tissues	Serum, liver, kidney, lung, digestive tract, adrenal glands, and other secretory and mucosal epithelia	~ 0.5 μg/ml	Yoshizaki et al. (2012), Troldborg et al. (2017), Hansen et al. (2018)
SP-A	Alveolar epithelial type II cells, bronchiolar Club cells, trachea, and other mucosal epithelia	Lung, alveolar fluid, and other mucosal epithelia	0	Wright (2005), Ordonez et al. (2017), Ujma et al. (2017)
MBL	Hepatocytes	Serum	0.05-8 μg/ml (dependent on MBL2 genotype)	Garred et al. (2003) Heitzeneder et al. (2012)
C1q	Myeloid cells	Serum, tissue cavities	80 μg/ml	Thielens et al. (2017), Reid (2018)
Adiponectin	Adipocytes	Serum, adipose tissue	~ 10-15 μg/ml	Atzmon et al. (2008) Wang and Scherer (2016) Zhang et al. (2017)
L-ficolin (ficolin 2)	Liver	Serum, liver	5 μg/ml	Matsushita (2010), Garred et al. (2016)
M-ficolin (ficolin 1)	Peripheral blood leukocytes, bone-marrow-derived cells, spleen, and lung	Serum, alveolar fluid, neutrophils, monocytes, macrophages	0.3 μg/ml	
H-ficolin (ficolin 3)	Liver (bile duct epithelial cells and hepatocytes); lung (ciliated bronchial and alveolar epithelial type II cells)	Serum, liver, bronchi, and alveolar fluid	25 μg/ml	

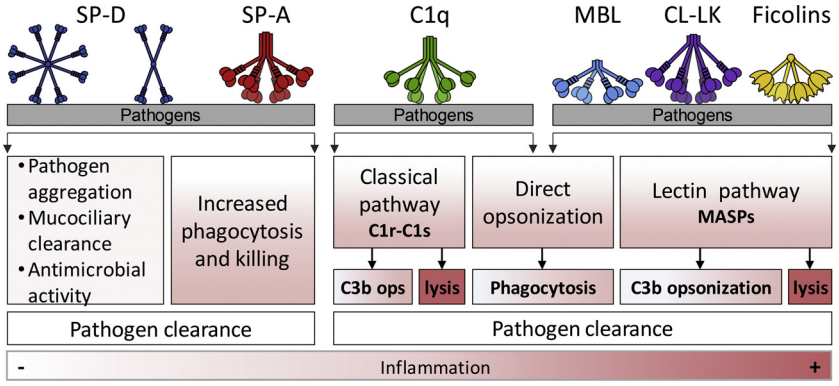

Fig. 1. Mechanisms used by soluble defense collagens to respond to infection. C1q triggers the initiation of the complement cascade by the classical pathway. MBL, CL-K1, CL-LK, and ficolins do so by the lectin pathway, leading to pathogen opsonization by C3b, and to phagocytosis and/or lysis by membrane attack complex formation. C1q, MBL, CL-LK, and ficolins also directly opsonize pathogens for phagocytic clearance. SP-A and SP-D do not activate complement, but they enhance pathogen aggregation and mucociliary clearance, bacterial killing, and phagocytosis. The inflammation triggered by these processes is depicted in light or dark shading according to the color bar.

urinary and reproductive tracts, the skin, the brain, and the synovial fluid (Ujma et al., 2017). However, SP-A and SP-D are not secreted to the serum. MBL is secreted by hepatocytes to the serum (Heitzeneder et al., 2012), and CL-L1 and CL-K1 are present in the serum and several tissues, with high expression in secretory and mucosal epithelia, similar to SP-D (Hansen et al., 2018). In circulation, the majority of CL-K1 forms part of the heteromeric protein CL-LK (Hansen et al., 2016). C1q is expressed and secreted mainly by myeloid cells, including monocytes, macrophages, dendritic cells, and microglial cells, and also by epithelial, endothelial, and mesenchymal cells, fibroblasts, and trophoblasts (Thielens et al., 2017; Reid, 2018). C1q is secreted to the local environment and the serum, where it has the highest concentration of the defense collagens found in serum. Adiponectin, with multiple functions in whole body metabolism, is specifically expressed in adipose tissue and is secreted to the serum (Wang and Scherer, 2016). Adiponectin plasma levels show sexual dimorphism since women have significantly higher adiponectin levels than men (Atzmon et al., 2008). Ficolins are secreted to the serum and to tissue cavities showing tissue-dependent distribution. mRNA of L-ficolin is mainly expressed in the liver and is secreted to serum. H-ficolin mRNA is expressed in the liver and lung. In the liver, H-ficolin is secreted by epithelial bile duct cells to the bile and by hepatocytes to the serum. In the lung, H-ficolin is secreted to the airways by bronchial epithelial cells and type II alveolar epithelial cells. M-ficolin is secreted by neutrophils, monocytes/macrophages, and alveolar type II cells, and it is found in plasma at very low concentrations (Matsushita, 2010). With respect to chromosomal location, this family of proteins maps to different chromosomal locations. MBL, SP-A1, SP-A-2, and SP-D map to the long arm of chromosome 10; the genes for CL-L1 and CL-K1 are on chromosomes 8 and 2, respectively; the genes for M- and L-ficolin are located on chromosome 9, whereas H-ficolin is on chromosome 1; the three genes for C1qa, C1qb, and C1qc polypeptides are on chromosome 1, while adiponectin is located on chromosome 3.

Most soluble defense collagens are specialized to respond to infection. C1q triggers the initiation of the complement cascade by the classical pathway and MBL, CL-K1, CL-LK, and ficolins do so by the lectin pathway (Walport, 2001a, b; Fujita, 2002; Garred et al., 2016). Complement activation promotes the phagocytosis of pathogens or their direct lysis via the membranolytic attack complex (MAC) formation (Fig. 1). The activation of the complement cascade releases opsonic C3b and iC3b fragments that mediate noninflammatory uptake of pathogens by phagocytic cells, but also releases anaphylatoxins C3a and C5a that are potent mediators of inflammation, recruiting leukocytes to the site of infection. Some regulatory molecules prevent generation of C3a, C5a, and MAC (Zipfel and Skerka, 2009). C1q, MBL, CL-LK, and

ficolins also have non-complement activation-related functions. They recognize pathogens and lead to their clearance by phagocyte activation (Fig. 1). On the other hand, SP-A and SP-D do not activate the complement cascade, which could be detrimental to the delicate alveolar epithelium and other vulnerable body interfaces (Watford et al., 2000). However, they constantly survey the extracellular environment for pathogens and quickly activate several mechanisms involved in pathogen clearance without inducing strong inflammatory responses. They bind to some microorganisms, which results in either bacterial aggregation and mucociliary clearance and/or bacterial killing in synergy with antimicrobial factors; They also enhance phagocytosis of pathogens by tissue macrophages (Wright, 2005; Coya et al., 2015; Ordonez et al., 2017; Casals et al., 2018) (Fig. 1). With respect to adiponectin, there are no reports to date indicating that this protein participates in the clearance of pathogens.

Once infection is being efficiently fought, inflammation must be resolved to avoid collateral tissue damage. Soluble defense collagens, including adiponectin, contribute to resolution of inflammation by limiting macrophage pro-inflammatory activation, promoting clearance of dead cells (Bohlson et al., 2014), and enhancing tissue-repair functions. This review will focus on common structural elements of soluble defense collagens and on the molecular mechanisms by which these proteins influence macrophage activation and may contribute to tissue repair and tissue homeostasis.

2. Common structural elements of soluble defense collagens

Fig. 2 highlights the domain organization and high-order oligomers of human soluble defense collagens. They are assembled in three or multiples of three subunits, which are made up of three identical polypeptides, except in the case of C1q, human SP-A, and CL-LK. C1q trimers are assembled from three quite similar polypeptide chains (A, B, and C) (Thielens et al., 2017). In human SP-A, unlike other mammalian SP-A except that of baboons, there are two functional genes, resulting in some differences in the corresponding proteins (SP-A1 and SP-A2) (Floros and Hoover, 1998; Garcia-Verdugo et al., 2002). CL-LK trimers are composed of two CL-K1 and one CL-L1 polypeptide chains (Hansen et al., 2016).

The primary structure of each polypeptide chain consists of an N-terminal segment containing cysteine residues involved in oligomerization, followed by a collagen-like region, and a globular domain that in collectins and ficolins contains a carbohydrate recognition domain (CRD). The CRD of collectins uses calcium ions to coordinate with the hydroxyl groups of their carbohydrate ligands (Drickamer, 1999). However, the CRD of ficolins is a fibrinogen-like globular (FBG) domain that binds calcium, but the ion does not participate directly in saccharide binding (Garlatti et al., 2007). The globular recognition domains of C1q and adiponectin do not contain a CRD. They assemble in a similar way, exhibiting a compact, almost spherical trimeric assemblage, held together mainly by non-polar interactions, with a Ca^{2+} ion bound at the top (Shapiro and Scherer, 1998; Gaboriaud et al., 2003).

A structural domain, which is present in collectins but not in ficolin and CTRP families, is the structure of the neck domain between the collagen-like domain and the globular domains. The X-ray crystallographic data for MBL (Weis and Drickamer, 1994), SP-D (Hakansson et al., 1999), SP-A (Head et al., 2003), and CL-K1 (Venkatraman Girija et al., 2015) demonstrated the existence of an α-helical coiled-coil structure in the neck region. The amino acid sequence of this region is characterized by a heptad repeat pattern a-b-c-d-e-f-g-d, where residues "a" and "d" are hydrophobic amino acids. These hydrophobic amino acids at every turn of the helix form the interior of the coiled-coil and stabilize this structure. The α-helical coiled-coil structure is one of the collectin domains essential for trimerization, together with the collagen-like region and the interchain disulfide cross-linkage at the N-terminal region. Researchers believe that the formation of trimers in collectins occurs in a zipper-like fashion along the C-terminal to N-terminal axis (Hakansson and Reid, 2000). Trimerization of C-terminal globular domains, likely by the trimeric α-helical coiled-coil, takes place before the triple-helix folding that aligns the polypeptide chains for disulfide bond formation at the N-terminal segment. In the case of ficolins, C1q, and adiponectin, the domains essential for trimerization are those outside the globular heads (the collagen-like domain and the N-terminal segment, which contains cysteine residues) (Endo et al., 2007; Garlatti et al., 2010b; Thielens et al., 2017; Reid, 2018).

Except for the globular domain, the domain organization of human soluble defense collagens is drawn to scale in Fig. 2. The collagenous region of these proteins varies considerably in length or number of Gly-X-Y triplets (where X is often a proline, and Y is frequently a hydroxylysine or a hydroxyproline). SP-D contains 59 triplets, C1q 25, SP-A 23, adiponectin 22, CL-L1 20, MBL 18, CL-K1 16, and L-, M-, and H-ficolins 16, 15, and 11 triplets, respectively. The collagen sequence in MBL, SP-A, and C1q is interrupted once, giving rise to a kink in the collagen structure (Voss et al., 1988; Casals and García-Verdugo, 2005; Jensenius et al., 2009; Thielens et al., 2017). For SP-A and C1q, in which their collagen-like domain contains a sequence irregularity (kink) near the middle of the collagen structure, lateral association of

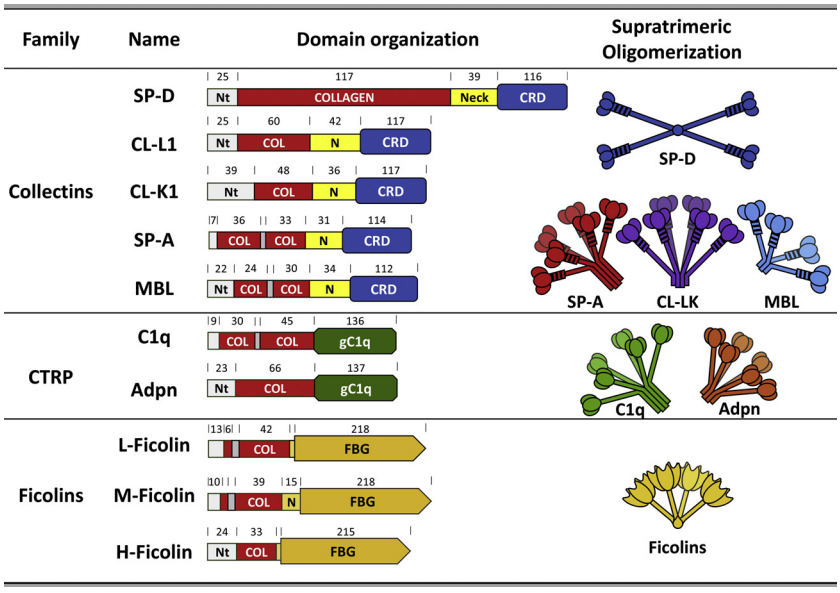

Fig. 2. Domain organization and overall structures of human soluble defense collagens. The domain organization of polypeptide chains is drawn to scale, except for the globular domain. The number of amino acids covering each domain is shown. Interruptions in the collagen domain of SP-A, MBL, C1q, and L- and M-ficolins are indicated. The schematic structures of high-order oligomers represent interpretations of electron microscopy and atomic force microscopy studies. Except for SP-D, which assembles in cruciform-shaped oligomers of four trimers, most proteins form umbelliform-shaped structures of six trimers for SP-A, C1q, and adiponectin, and four trimers for MBL and ficolins. The supratrimeric oligomerization of CL-L1, CL-K1, and CL-LK have not yet been characterized, but it is thought that they form umbelliform-shaped structures composed of 4–6 trimers. Nt, N-terminal domain; COL, collagen-like domain; N, neck; Adpn, adiponectin.

six trimers forms the microfibril end piece in the N-terminal half below the kink. Above the kink, approximately half-way along the collagen-like region, individual collagen triple helices diverge at a bend to form six individual branches, each terminating in three globular heads (Fig. 2). It is believed that the kink functions as a hinge that permits flexible movements of the collagen stalks, modulating the position of their adjacent globular heads (Voss et al., 1988; Reid, 2018). In the case of MBL, the interruption of the collagenous repeat results in a kink in only 30% of the trimers. Most of the trimers spread out from the N-terminal hub in a flexible conformation like that of ficolins (Jensenius et al., 2009). L- and M-ficolin also show a 6 amino acid-interruption of the collagen sequence but just at the beginning of the sequence, after the first two Gly-X-Y triplets, followed by 14 and 12 triplets, respectively (Endo et al., 2007). Thus, trimers spread out from the N-terminal hub without bending (Fig. 2).

The collagen-like regions are modified by hydroxylation of certain proline and lysine residues in the endoplasmic reticulum before the formation of collagen triple helix. Hydroxyproline residues have an essential role in providing the collagen triple helices with thermal stability and affect both the arrangement of disulfide bonding and the extent of oligomerization (Garcia-Verdugo et al., 2003; Jensen et al., 2007a, b). Hydroxylation and O-glycosylation of the lysine residues within the collagenous domain take place in SP-D (Leth-Larsen et al., 1999), C1q (Shinkai and Yonemasu, 1979; Reid, 1979; Pflieger et al., 2010), MBL (Jensen et al., 2007a, b), and adiponectin (Wang et al., 2002). The glycosides attached to hydroxylated lysines are glucosylgalactosyl groups. O-glycosylation seems to aid proper protein folding. Importantly, three lysine residues of the collagen-like domain of C1q, located above the kink, are completely unmodified (Pflieger et al., 2010). These lysine residues (LysA59, LysB61, and LysC58) are fully available and in an appropriate position to interact with the C1r and C1s protease partners of C1q. Functional analysis of rC1q variants, which carry mutations of LysA59, LysB61, and/or LysC58 in the collagen-like stems, demonstrates that LysB61 and LysC58 play a key role in the interaction with C1s-C1r-C1r-C1s (Bally et al., 2013). On the other hand, the collagen domain of SP-D is characterized by an N-linked glycosylation in Asn-70 with a complex type bi-antennary structure in which no sialic acid residues are present (Leth-Larsen et al., 1999).

Trimers of collectins, ficolins, C1q, or adiponectin are assembled intracellularly into complex supratrimeric structures (Fig. 2). Electron microscopy and atomic force microscopy techniques help us to understand the supratrimeric oligomerization of soluble defense collagens. SP-D displays a cruciform-shaped structure with a maximum of four trimers joined N-terminally (Crouch et al., 1994). Other non-human collectins like bovine conglutinin and CL-46 also form cruciform oligomers of four trimers (Holmskov et al., 2003). SP-D may also form oligomers of the cruciform tetramers that resemble a cart wheel or 'fuzzy balls' (Holmskov et al., 2003; Arroyo et al., 2018). By contrast, SP-A, MBL, C1q, adiponectins, and ficolins form supratrimeric structures that resemble the form of an umbel. These umbelliform- or sertiform-shaped structures show a prominent form of six trimers for SP-A (Voss et al., 1988; Hickling et al., 1998; Sanchez-Barbero et al., 2005, 2007), C1q (Voss et al., 1988; Bally et al., 2013), and adiponectin (Radjainia et al., 2008). The most prominent oligomer of MBL contains four trimers, but oligomers of 3, 5, and 6 trimers were also shown for MBL (Jensenius et al., 2009). Oligomers of L, M, and H-ficolins also contain four trimers (Ohashi and Erickson, 1997). The majority of CL-K1 in the circulation is in the form of the heterotrimeric collectin CL-LK, whose size and supratrimeric oligomerization type have not yet been characterized. It is thought that, like other collectins, CL-LK may oligomerize into umbelliform-shaped structures composed of 2, 4, 5, or 6 trimers (Hansen et al., 2016).

The manner in which trimers are assembled into oligomers (umbelliform vs. cruciform) and the length of the collagen domains of the monomeric subunits determine the size of fully assembled defense collagens. For instance, the size of MBL is approximately 13 nm, whereas that of SP-D is about 100 nm (Crouch et al., 1994), which is consistent with the SP-D function of agglutinating pathogens. Agglutination enhances mucociliary removal by the respiratory tract and prevents attachment of pathogens to cell surfaces, avoiding microbial colonization and invasion. Supratrimeric oligomerization of soluble defense collagens appears to be needed for many of their functions since oligomerization increases the functional affinity of the globular domain for their ligands and facilitates multivalent binding. For instance, mutations in the collagenous region of human MBL compromise assembly of higher order oligomers, resulting in reduced ligand binding capacity and thus reduced capability to activate the complement. This leads to recurrent infections and susceptibility to autoimmunity and carcinogenesis (Larsen et al., 2004; Liu et al., 2012). Likewise, SP-A exists in smaller oligomeric forms in allergic patients (Hickling et al., 1998), and only the high order oligomeric form of adiponectin (6 trimers), but not the lower oligomeric form (2 trimers), possesses anti-inflammatory, anti-atherogenic and anti-diabetic functions in mice and humans (Wang et al., 2008; Wang and Scherer, 2016).

The collagen-like domains do not function only as scaffolding that amplifies the ligand binding activities of globular domains. Collagenic domains confer high tensile strength, stability and relative resistance to proteolysis to the overall structure. Moreover, the collagen-like domains are involved in binding to receptors in immune cells or to specific serine proteases that trigger the initiation of the complement cascade upon activation. For instance, the $C1r_2$–$C1s_2$ binding site in C1q is in the middle of the C-terminal portion of the collagen-like region, close to the kink and out from the microfibril-like region (Bally et al., 2013). Similarly, MBL, ficolins, CL-K1, and CL-L1 interact with their associated proteases (MASPs) in their collagenic arms (Garred et al., 2016). Interactions between C1q-MASP2 and MBL-C1r/s tetramer have also been reported in vitro. Ficolin-A-C1rs and C1q-MASP-1 complexes are also formed (Phillips et al., 2009). However, these proteases are not associated with the lung collectins, SP-A and SP-D, and adiponectin. The collagen-like triple helical domains of C1q, MBL, CL-LK, and ficolins are not always masked by their associated proteases ($C1r_2$–$C1s_2$ or MASPs), and thus their entire collagen-like regions are available for interaction with receptors on cell surfaces involved in phagocytosis and clearance of microorganisms and dead cells (apoptotic/necrotic) (Table 2). Collagen-dependent functions of most soluble defense collagens have a dual capacity to promote pathogen elimination and control inflammation.

With respect to the globular heads of soluble defense collagens, the CRD of collectins belongs to the mannose/glucose-binding C-type lectins that contain a highly conserved sequence [Glu-Pro-Asn] in their CRDs, although human SP-A contains a different sequence: Glu^{195}-Pro^{196}-Ala^{197} (Drickamer, 1999). Collectins recognize a wide variety of carbohydrates present in the surface of several microorganisms (mainly mannose and N-acetyl-glucosamine) (Veldhuizen et al., 2011). However, they do not usually detect carbohydrates that decorate the mammalian glycoproteins, such as galactose and sialic acid. Collectins also bind a broader repertoire of ligands, including proteins, nucleic acids, and lipids (Casals, 2001; Palaniyar et al., 2004; Wright, 2005; Nakamura et al., 2009; Saenz et al., 2010). Despite their similar CRDs, collectins show significant differences in ligand preferences, which likely extend the range of innate immune surveillance.

The FBG of L-, M-, and H- ficolins bind N-acetylated glycans such as N-acetyl-glucosamine and N-acetyl-galactosamine. Moreover, they broadly recognize polysaccharide ligands, including peptidoglycan, lipoteichoic acid of Gram-positive bacteria, and fungal 1,3-β-D-glucan as well as acetylated, phosphorylated, and sulfated molecules (Bidula et al., 2019). With respect to C1q, functional studies indicate that its globular heads bind a wide range of self- and non-self-ligands, including the Fc region of immunoglobulins, non-immunoglobulin targets such as C-reactive protein, lipopolysaccharides, bacterial porins, phosphatidylserine (PS), and DNA. The globular head of C1q recognizes a broad spectrum of bacterial and viral surface proteins, as well as altered self-

Table 2
Common receptors for two or more soluble defense collagens.

Receptor	Protein name (domain)	Biological function	References
cC1qR, receptor for the collagen tail of C1q (aka calreticulin)	• C1q (collagen and globular heads) • MBL (collagen, MASPs binding site) • SP-A (collagen) • SP-D • CL-K1 • Ficolins (collagen, MASPs binding site) • Adiponectin	• Efferocytosis	Dong et al. (2017), Lacroix et al. (2009), Ogden et al. (2001), Pagh et al. (2008), Paidassi et al. (2011), Takemura et al. (2007), Vandivier et al. (2002)
gC1qR, receptor for the globular head of C1q (aka p33)	• C1q (globular heads) • MBL	• Attachment and phagocytosis of pathogens	Brudner et al. (2013), Peerschke and Ghebrehiwet (2007)
LRP1 (CD91) aka α-2-macroglobulin receptor	• C1q (collagen and globular heads) • MBL (collagen, MASP binding site) • L-ficolin	• Phagocytosis of microbial and apoptotic material	Duus et al. (2010a,b)
CR1 (CD35)	• C1q (collagen and globular heads) • MBL (collagen, MASPs binding site) • Ficolins (collagen, MASPs binding site)	• Possible role in the phagocytosis of opsonized particles or immune complexes	Jacquet et al. (2013, 2018)
α2β1 and β1 integrin	• C1q • MBL • SP-A	• Activation of mast cells	Edelson et al. (2006)
LAIR-1 (CD305) aka inhibitory Ig-like leukocyte-associated receptor	• C1q (collagen) • MBL • SP-D (collagen)	• Restriction of dendritic cells' differentiation and activation • Anti-inflammatory action on neutrophils • Polarization of monocytes to an anti-inflammatory phenotype (in complex with RAGE and HMGB1)	Olde Nordkamp et al. (2014a, 2014b), Son and Diamond (2015), Son et al. (2016)
Myo18A (CD245) aka SPR210[1]	• SP-A (collagen) • C1q	• Enhance alternative activation of macrophages and promote tissue repair • Promote phagocytosis of microorganisms	Sever-Chroneos et al. (2011), Minutti et al. (2017a)
SIRP-α (CD172a)	• SP-A (globular heads) • SP-D (globular heads) • CL-K1	• Blocks production of pro-inflammatory mediators in macrophages (SP-A and SP-D) and retinal pigment epithelial cells (CL-K1)	Gardai et al. (2003), Fournier et al. (2012), Dong et al. (2017)
TLR4 CD14 MD-2 TLR2	• SP-A (globular heads) • SP-D (globular heads) • MBL	• Inhibit binding of TLR ligands to immune cells and downregulate pro-inflammatory activation	Garcia-Verdugo et al. (2005), Sano et al. (1999), Sorensen (2018), Wang et al. (2011, 2013, 2019), Yamada et al. (2006)
CR3 (CD11b/CD18) aka Mac-1, αMβ2 integrin	• C1q (collagen) • SP-A (N-linked sugars, CRD, and neck)	• Complement receptor-mediated phagocytosis and efferocytosis	Gil et al. (2009), Ma et al. (2012)

elements (apoptotic cells, amyloid, and prion proteins) (Gaboriaud et al., 2011; Thielens et al., 2017). Adiponectin, as a member of the CTRP family, is involved in a range of biological processes such as protection against systemic inflammation, clearance of dead or damaged cells, energy homeostasis, and tissue regeneration (Kishore et al., 2004; Ouchi et al., 2011). Adiponectin shares some ligands with C1q, such as DAMPs released by damaged cells, which bind to both the collagen regions and globular heads of these proteins. Adiponectin deficiency, as well as C1q and MBL deficiency, leads to increased systemic inflammation, possibly due to a defect in the uptake of apoptotic cells (Takemura et al., 2007; Monticielo et al., 2008; Stegert et al., 2015).

3. Role of soluble defense collagens in the resolution of inflammation

In addition to efficiently clearing infection (Fig. 1), soluble defense collagens share the ability to resolve the inflammation by limiting macrophage pro-inflammatory activation and promoting clearance of apoptotic cells (Fig. 3).

3.1. Downregulation of inflammation

With respect to macrophages and monocytes, soluble defense collagens influence cell responses to limit inflammation by several mechanisms. First, they block the interaction of TLR ligands with their receptors. This effect can be exerted by i) direct binding to TLR2, TLR3, TLR4, the TLR co-receptor MD2, and CD14, as demonstrated for SP-A, SP-D, and MBL (Garcia-Verdugo et al., 2005; Wang et al., 2011, 2013; Liu et al., 2014; Casals et al., 2018; Wang et al., 2019); or ii) direct interaction with TLR ligands, as shown for SP-A, SP-D, and H-ficolin, which bind to the TLR4 ligand LPS (Michalski et al., 2015; Casals et al., 2018); and for MBL, which binds to the TLR3 ligand poly(I:C) (Liu et al., 2014). Second, they modify macrophage response to TLR ligands by modulating signaling cascades. For example, SP-A and adiponectin enhance the expression of negative regulators of TLR-signaling, such as IRAK-M (Nguyen et al., 2012; Zacharioudaki et al., 2009), and inhibit activation of NFκB, ERK, and other signaling molecules (Henning et al., 2008; Mandal et al., 2010; Casals et al., 2018). C1q also inhibits the activation of NFκB heterodimers p50/p65 through activation of inhibitory homodimers p50/p50 and CREB (Fraser et al., 2007). Third, they promote the activation of the SHP-1-dependent signaling pathway that blocks proinflammatory mediator production. Inhibitory SHP-1 phosphatase is activated by binding of SP-A and SP-D to the SIRP-α receptor through their globular heads (Gardai et al., 2003), as well as by binding of C1q to the inhibitory receptor LAIR-1 through C1q collagen tails (Son and Diamond, 2015; Son et al., 2016). Fourth, through binding to IFN-γ, SP-A suppresses IFN-γ interaction with its IFN-γR1

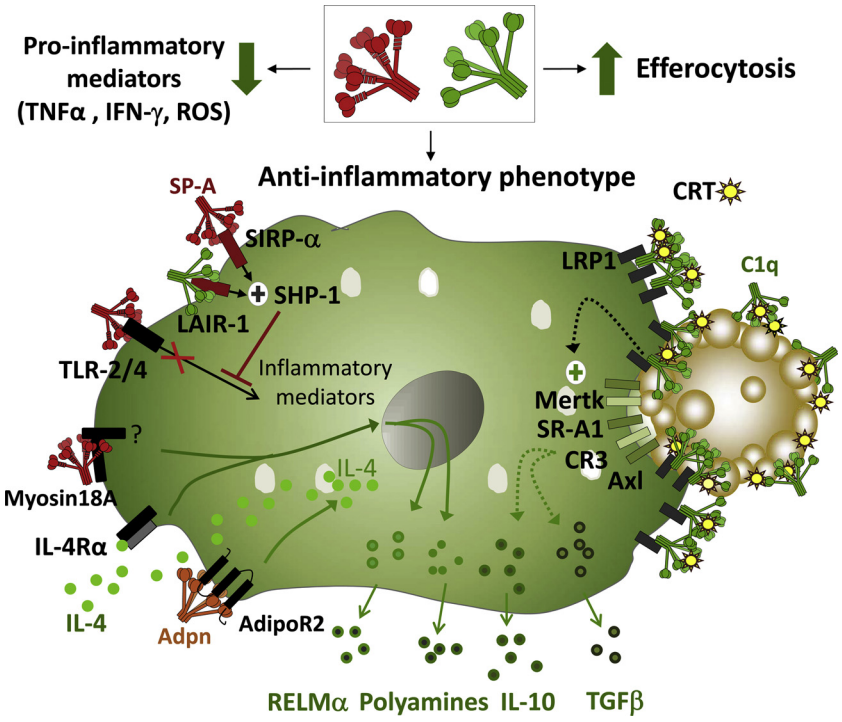

Fig. 3. Soluble defense collagens promote resolution of inflammation. This group of proteins shares the ability to downregulate inflammation and facilitate the clearance of dying cells. For clarity in drawing, two members of this family — SP-A (dark red) and C1q (light green) — are drawn to show the molecular mechanisms by which these proteins influence macrophage responses to limit inflammation. For example, they bind to TLRs, blocking the binding of TLR ligands, and promote the activation of SHP-1-dependent signaling pathway, which blocks proinflammatory mediator production. They enhance the expression of anti-inflammatory cytokines, and receptors involved in efferocytosis (Mertk, SR-A1, or CR3). In addition, they recognize DAMPs exposed by dying cells such as calreticulin (CRT), acting as a bridging molecule by binding to macrophage receptors involved in cell uptake (such as LRP1). Adiponectin (Adpn)/AdipoR2 interaction is also shown. Some soluble defense collagens also stimulate IL-4Rα-mediated macrophage activation toward an anti-inflammatory resolving phenotype involved in tissue repair.

receptor and inhibits activation of human and murine alveolar macrophages (Minutti et al., 2016). In addition, C1q and adiponectin inhibit LPS-induced inflammasome activation (Benoit et al., 2012; Kim et al., 2017), and SP-D, SP-A, and adiponectin reduce the production of reactive oxygen species (ROS) (Yoshida et al., 2001; Crowther et al., 2004; Kim et al., 2014).

Besides limiting inflammation, soluble defense collagens contribute to enhance alternative activation of macrophages toward an anti-inflammatory and resolving phenotype (Fig. 3). Adiponectin promotes alternative macrophage activation (Ohashi et al., 2010) and secretion of anti-inflammatory cytokines (Park et al., 2008). The anti-inflammatory effect of adiponectin seems to be exerted through the expression of IL-4 by macrophages and subsequent activation of STAT6 upon binding of adiponectin to its receptor AdipoR2 (Mandal et al., 2011). C1q and MBL also promote macrophage activation to a resolving phenotype since both C1q and MBL enhance the expression of anti-inflammatory cytokines such as IL-10 or IL-1R antagonist (Fraser et al., 2006, 2009), which may be due in part to C1q-mediated activation of the inhibitory transcription factor CREB (Fraser et al., 2007). C1q also promoted alternative macrophage activation during clearance of oxLDL (Spivia et al., 2014). It is believed that the anti-inflammatory role of C1q parallels its capability to enhance the clearance of apoptotic cells by macrophages (Benoit et al., 2012; Hulsebus et al., 2016; Thielens et al., 2017), which leads to the production of IL-10 and TGFβ (Greenlee-Wacker, 2016). Finally, we have recently shown that SP-A and C1q enhance IL-4-induced alternative activation and proliferation of macrophages through binding to myosin 18A (Minutti et al., 2017a). The possible anti-inflammatory effect of CL-L1 and CL-K1 on monocytes or macrophages has not yet been studied, and further studies are needed to determine their contribution in the resolution of inflammation.

Defense collagens also modulate the activation of immune cells other than monocytes and macrophages. With respect to dendritic cells, it has been reported that C1q has an essential role in these cells' uptake of antigens to elicit antigen presentation (Ho et al., 2017). The inhibition of dendritic cell maturation and activation was demonstrated for C1q (Santer et al., 2010; Teh et al., 2011; Santer et al., 2012), MBL (Dean et al., 2011; Xu et al., 2015), adiponectin (Tsang et al., 2011; Tan et al., 2014), SP-A (Brinker et al., 2003), and SP-D (Liu et al., 2010). Downregulation of dendritic cell maturation and activation contributes to the protective effect of C1q (Mascarell et al., 2017), SP-A, and SP-D (Wang and Reid, 2007; Liu et al., 2010) in mouse models of allergic asthma. With respect to eosinophils, adiponectin, SP-D, and SP-A inhibit eosinophil recruitment and/or degranulation, limiting inflammation in allergic mouse models (von Bredow et al., 2006; Medoff et al., 2009; Ledford et al., 2012). Regarding neutrophils, SP-D inhibits ROS in a neutrophilic cell line by binding to the inhibitory receptor LAIR-1 via SP-D collagen tails (Olde Nordkamp et al., 2014b), and adiponectin also reduces activation of neutrophils and ROS production, which is associated with increased AMPK phosphorylation and decreased p47(phox) phosphorylation in phagocytes (Chedid et al., 2012). In contrast, C1q and MBL seem to enhance ROS production by neutrophils (Goodman et al., 1995; Li et al., 2012). With respect to lymphocyte differentiation, it has been shown that C1q indirectly promotes differentiation of the regulatory T cell subset and inhibits the Th1 and Th17 subsets via polarizing antigen presenting cells (reviewed in Thielens et al., 2017). SP-A and SP-D also inhibit T cell proliferation and activation (Kunzmann et al., 2006; Mukherjee et al., 2012a; Sorensen, 2018), and SP-A induces the differentiation of Treg cells via TGFβ (Mukherjee et al., 2012b). Moreover, MBL and CL-K1, as well as C1q, have recently been shown to suppress T cell proliferation through binding to calreticulin expressed on the surface of T lymphocytes (Zhao et al., 2017).

3.2. Clearance of apoptotic cells

Soluble defense collagens are also efficient sensors of altered self-signals, so-called DAMPs. Dying cells are a rich source of DAMPs, as they expose a large variety of otherwise intracellular molecules on the cell surface when the membrane of the dying cell loses integrity (Matzinger, 1994). By recognizing DAMPs exposed by dying cells, soluble defense collagens take part in the process of clearing apoptotic cells. The phagocytic clearance of dying cells (efferocytosis) by macrophages and other phagocytes is essential during embryonic development and to maintain tissue homeostasis and self-tolerance (Poon et al., 2014).

With respect to DAMPs, SP-A, SP-D, MBL, CL-K1, C1q, and L-Ficolin recognize DNA by their globular heads (Jiang et al., 1992; Tissot et al.,

2003; Palaniyar et al., 2003, 2004; Jensen et al., 2007a, b; Paidassi et al., 2008a; Garlatti et al., 2010a; Henriksen et al., 2013); most of them recognize calreticulin (see Table 2); and SP-A, MBL and C1q bind to PS, the canonical marker of apoptotic cells (Kuroki et al., 1997; Kilpatrick, 1998; Paidassi et al., 2008b; Jakel et al., 2010; Tan et al., 2010). Soluble defense collagens bind to apoptotic cells and serve as bridging molecules, linking the apoptotic cell to the phagocyte. This requires the interaction of these proteins with membrane receptors on the phagocyte membrane.

A common receptor for C1q, MBL, and SP-A was characterized by Malhotra et al. (1990a, b) and subsequently identified as calreticulin (Sim et al., 1998). Paradoxically, calreticulin does not have a transmembrane domain nor a membrane anchor. Calreticulin is normally localized in the lumen of the endoplasmic reticulum, but it is also detected on the cell surface of phagocytes and viable or apoptotic cells (Gardai et al., 2005; Feng et al., 2018). It was demonstrated that activated macrophages secrete calreticulin, which binds to the surface of viable or dying cells and marks them for removal by phagocytosis (Feng et al., 2018). However, viable cells seem to be protected from engulfment by repelling signals expressed on the cell surface, such as CD31, CD200, and CD47 (Gardai et al., 2005; Chao et al., 2011). It has been proposed that calreticulin acts as a recognition ligand by binding and activating LDL-receptor-related protein 1 (LRP1 aka CD91) on the engulfing cell (Gardai et al., 2005). However, no direct interaction between isolated LRP1 and calreticulin has yet been demonstrated (Donnelly et al., 2006; Duus et al., 2010a; Frachet et al., 2015). By contrast, the collagenous arms of soluble defense collagens bind directly to CD91 and calreticulin (see Table 2), mediating phagocytic uptake of apoptotic cells. This suggests that LRP1 may serve as a docking platform for recognition of calreticulin exposed on the surface of dying cells, which depends on soluble defense collagens (Fig. 3). Nevertheless, cell surface-anchored calreticulin interacts not only with bridging molecules (C1q, adiponectin, MBL, SP-A, SP-D, CL-K1, ficolins) but also with other molecules involved in efferocytosis such as PS on apoptotic cells and scavenger receptors on phagocytes (Frachet et al., 2015), suggesting that calreticulin-mediated efferocytosis could be regulated by complex multimolecular interactions.

Another receptor that may be involved in clearance of dead cells is myosin 18A (CD245), also known as SPR-210 (surfactant protein receptor 210 kDa) (Chroneos et al., 1996). This protein was first purified from the macrophage cell line U937 and later identified as myosin 18A (Yang et al., 2005). It is normally located inside the cells as part of the cytoskeleton (Tan et al., 2008; Dippold et al., 2009; Ng et al., 2013) and on the cell surface of different tissue macrophages when stimulated with IL-4, and on other leucocyte populations (Minutti et al., 2017a; De Masson et al., 2016). The interaction between SP-A and myosin 18A takes place through the collagen tail of SP-A (Borron et al., 1998; Minutti et al., 2017a). C1q also binds to myosin 18A (Minutti et al., 2017a), probably by its collagen domains, although direct binding studies are lacking. Experiments using blocking antibodies against myosin 18A revealed that the SP-A/myosin 18A axis is involved in the uptake of bacteria, and probably dead cells, by macrophages (Sever-Chroneos et al., 2011). Myosin 18A does not have a transmembrane domain; it might therefore function as an adaptor molecule during the recognition of altered-self material by SP-A or C1q. Although the transmembrane receptor that recognizes SP-A/C1q associated with myosin 18A has yet to be discovered, the group of Zissis Chroneos identified a functional association of myosin 18A with the phagocytic SR-A1 (Sever-Chroneos et al., 2011; Yang et al., 2015). Furthermore, it has been shown that myosin 18A co-localizes with integrin β1 (Byron et al., 2012), which is another receptor for some soluble defense collagens (C1q, MBL, and SP-A) (Zutter and Edelson, 2007). Interestingly, integrin α2β1 interacts with calreticulin at the surface of various cells (Elton et al., 2002).

With respect to receptors for complement components that coat the surface of apoptotic cells and facilitate ingestion by macrophages, CR1 (CD35) and CR3 (*aka* Mac-1, integrin αMβ2) are phagocytic receptors involved in the recognition of C3b and iCb3 fragments and several soluble defense collagens (see Table 2). Complement may be activated in a controlled manner on the surface of damaged or apoptotic cells to proceed until C3b surface deposition (Zipfel and Skerka, 2009). Opsonized apoptotic cells can be removed by binding to CR1 and CR3 on phagocytes. As indicated above, these receptors are also involved in the recognition of soluble defense collagens (Table 2). It was recently demonstrated the predominant role of C1q, rather than C1 activation and C3b deposition, on clearance of early apoptotic cells, since C1s inhibition did not impact C1q binding to dying cells and uptake of dying cells (Colonna et al., 2016). Direct binding of CR3 to C1q (Ma et al., 2012) and SP-A (Gil et al., 2009) has been demonstrated. The collagenous tail of SP-A augments CR3-mediated phagocytosis (Gil et al., 2009). On the other hand, CR1 interacts with MBL (Ghiran et al., 2000) and L-ficolin (Jacquet et al., 2013) near the MASP binding site in their collagenous tails. At the same time, MBL, SP-A, and ficolins can bind to dying cells by their globular heads. CR1 interacts with both collagen stalks and globular heads of C1q (Klickstein et al., 1997; Jacquet et al., 2018).

Another mechanism by which soluble defense collagens promote efferocytosis is by enhancing the expression of PS receptors on macrophages: AXL receptor tyrosine kinase (Axl) and c-mer proto-oncogene tyrosine kinase (Mertk). C1q and adiponectin enhance the expression of Mertk by activating AMPK phosphorylation and the nuclear retinoid X receptor on macrophages (Galvan et al., 2012, 2014). Consequently, C1q and adiponectin promote Mertk-dependent clearance of apoptotic cells. In addition, SP-A and MBL increase the expression of SR-A1 (Ono et al., 2006; Kuronuma et al., 2004), which interacts with Mertk and is thought to promote Mertk signaling during apoptotic cell uptake (Todt et al., 2008) (Fig. 3). SP-A also enhances the expression of other phagocytic receptors such as CD36 (Dodd et al., 2016), mannose receptor (Beharka et al., 2002, 2005), and CR3 (Gil et al., 2009).

Alterations in the normal clearance of apoptotic cells and immune complexes cause high levels of DAMPs and autoantigens that are presented inappropriately to the immune system, promoting inflammation and autoimmune diseases (Grumach and Kirschfink, 2014). Deficiencies of C1q and MBL are associated with the development of the autoimmune pathology systemic lupus erythematosus (SLE) (Monticielo et al., 2008; Stegert et al., 2015). Complete genetic deficiency of C1q is strongly associated with SLE, and subtle variations in the abundance and activity of the protein (i.e. partial deficiency, point mutations, or auto antibodies against C1q) predispose to the development of SLE symptoms (Frachet et al., 2015). Low levels of MBL, due to *MBL-2* gene polymorphisms or anti-MBL autoantibodies, are associated with susceptibility to autoimmune diseases and SLE (Monticielo et al., 2008). Interestingly, low levels of CL-L1, CL-K1, and M-ficolin have also been found to be associated with SLE (Troldborg et al., 2018). Auto-antibodies against L- and H-ficolin have been found in SLE patients, correlating with disease activity (Colliard et al., 2018; Plawecki et al., 2016), and H-ficolin deficiency is linked to different diseases, including SLE (Troldborg et al., 2019). Similarly, it has been shown that adiponectin deficiency leads to high accumulation of apoptotic cells, systemic inflammation, and autoimmune phenotype in *lpr* mice, which are already susceptible to autoimmunity since they exhibit impaired uptake of dead cells (Takemura et al., 2007). In contrast, high levels of serum adiponectin and H-ficolin are often found in SLE patients (Dini et al., 2017; Hein et al., 2015; Li et al., 2016). Therefore, the causes and consequences of altered levels of CL-L1, CL-K1, adiponectin, and ficolins in SLE have yet to be determined.

4. Role of soluble defense collagens in tissue repair

After inflammation declines, macrophages actively sustain tissue formation and remodeling so that the injured tissue returns to normality. Tissue repair activities of macrophages at these stages are associated with type II cytokine activation through the IL-4Rα receptor.

Global and cell-specific myeloid cell disruption of the IL-4Rα gene was shown to cause tissue repair deficiencies in the skin (Knipper et al., 2015), lung, and liver (Minutti et al., 2017a; Chen et al., 2012) in different models of injury. Mechanistically, it has been proposed that IL-4Rα-activation of macrophages induces the secretion of growth factors like IGF-1 (Han et al., 2016) and the production of repair factors such as collagen type I, alpha 1 (Col1a1), which forms the extracellular matrix; resistin-like molecule alpha (RELMα), which serves to cross-link collagen with fibrils; and arginine-derived polyamines, which are necessary for collagen synthesis and cell proliferation (Mantovani et al., 2013; Knipper et al., 2015; Minutti et al., 2017b; Krljanac et al., 2019). Furthermore, IL-4Rα signaling instructs macrophage proliferation, resulting in the local expansion of this effector population (Jenkins et al., 2011).

Our group has recently reported that IL-4 and IL-13 may not be sufficient for the activation of tissue macrophages and that involvement of local tissue signals is also required (Minutti et al., 2017a). SP-A, in the lung, and C1q, in the liver, enhance IL-4Rα-dependent alternative activation, proliferation, and tissue-repair functions of resident macrophages through binding their collagen domains to the myosin 18A receptor (Minutti et al., 2017a) (Fig. 4). IL-4 drives production of these tissue factors (SP-A and C1q) and expression of their myosin 18A receptor on the macrophage surface for full IL-4-dependent activation and proliferation. Loss of function studies using SP-A- and C1qa-deficient mice demonstrated that SP-A and C1q are necessary to promote tissue repair during lung and liver infection with the parasite *N. brasiliensis* and the Gram positive bacterium *Listeria monocytogenes*, respectively (Minutti et al., 2017a). SP-A and C1q are tissue specific since SP-A, but not C1q, enhances IL-4-dependent effects on alveolar macrophages, and C1q has effects on peritoneal and liver macrophages. These tissue-specific functions are likely determined by distinct as yet unknown myosin 18A co-receptors.

To guarantee efficient repair, macrophages must also diminish their inflammatory response, which otherwise impairs the process (Vannella and Wynn, 2017). As indicated above, defense collagens downregulate inflammation and efficiently encourage the clearance of apoptotic cells (Fig. 3). Importantly, it was recently shown that IL-4Rα-dependent tissue repair requires concomitant recognition and clearance of apoptotic cells by macrophages (Bosurgi et al., 2017). The authors identified the PS receptors, Axl and Mertk, to be essential for promoting IL-4Rα-induced tissue repair. Deletion of PS receptor genes *Mertk* and *Axl* impairs IL-4-dependent induction of macrophage proliferation and tissue repair genes in the lung, after *N. brasiliensis* infection, and the gut, in a model of colitis. Control studies indicate that $Axl^{-/-}Mertk^{-/-}$ doubly deficient macrophages show normal induction of genes for pattern recognition receptor, cell adhesion, and chemotaxis in response to IL-4 (Bosurgi et al., 2017). This study provided the first example of how our body restricts macrophage tissue repair activities to the damaged site.

The activation of tissue repair in macrophages requires integration of several external signals from the tissue environment: i) IL-4/IL-13 cytokines; ii) soluble defense collagens; and iii) dying cells and their subsequent uptake (Fig. 4). Intriguingly, there is a link between IL-4 and tissue factors (SP-A or C1q), since IL-4 increases SP-A, C1q, and myosin 18A levels. There is also a connection between tissue factors and efferocytosis, since C1q increases the expression of Mertk, and SP-A increases the expression of SR-A1, which promotes Mertk signaling (Kuronuma et al., 2004; Ono et al., 2006; Todt et al., 2008; Galvan et al., 2012, 2014). In addition, SP-A and C1q act as bridging molecules in the efferocytic process. These data suggest that the activation of a tissue repair program in macrophages could be regulated by a complex process of integrated multimolecular signaling (Fig. 4).

With respect to adiponectin, IL-4 also increases the secretion of adiponectin by adipocytes (Lizcano et al., 2017), and adiponectin enhances secretion of IL-4 by peritoneal macrophages through binding to its receptor (adipoR2) (Mandal et al., 2011), resulting in the induction of arginase and other markers of alternative activation (Ohashi et al., 2010). Moreover, adiponectin promotes proliferation of IL-4-activated macrophages through activation of PI3K upon binding to the GPI-anchored protein T-cadherin (Hui et al., 2015). Intriguingly, adiponectin exerts anti-fibrogenic functions on hepatic stellate cells, the major fibrogenic cell type in the liver (Higashi et al., 2017). Adiponectin attenuates liver fibrosis by inducing nitric oxide production (via the adipoR2/AMPK/NF-κB pathway) and inhibits hepatic stellate cell proliferation. In addition, adiponectin increases TIMP-1 secretion, which binds to the CD63/1-integrin complex to decrease FAK activity and stellate cell migration (reviewed in Higashi et al., 2017). These adiponectin antifibrotic actions support its role in tissue repair.

The contribution of other soluble defense collagens in tissue repair is scarcely known. Using SP-D-deficient mice, Horsnell's group showed that *N. brasiliensis* infection of SP-D-deficient mice results in profound impairment of host innate immunity and ability to resolve infection, another function attributed to IL-4Rα-activated macrophages. The authors showed that SP-D also enhanced IL-4Rα-mediated macrophage activation in the lung (Thawer et al., 2016), and IL-4 increases the expression of SP-D in the lung (Ikegami et al., 2000; Haczku et al.,

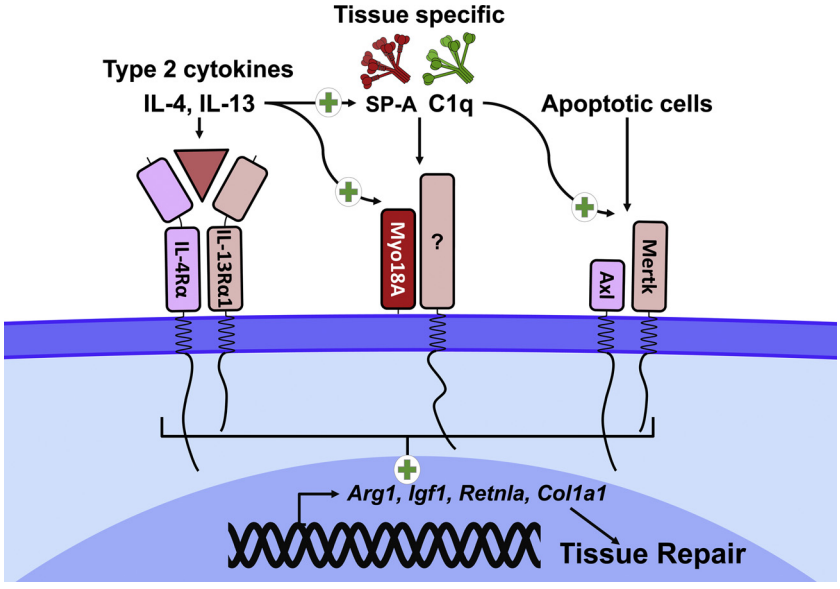

Fig. 4. The activation of tissue repair in macrophages requires integration of several external signals from the tissue environment: 1) Type 2 cytokines, through IL-4Rα, induce the expression of key tissue repair factors in macrophages (*Arg1, Retnla, Col1a1, and Igf1)*. IL-4 also enhances the production of tissue-specific factors (C1q in the liver and SP-A in the lung) and the expression of myosin18A on the cell surface of macrophages. 2) C1q and SP-A enhance the production of tissue repair factors induced by IL-4. 3) The recognition and uptake of apoptotic cells through Mertk and Axl receptors amplify the gene signature induced in macrophages by IL-4/13. C1q increases the expression of Mertk, and SP-A increases the expression of SR-A1, which boosts Mertk signaling, promoting efferocytosis. *Arg1*, arginase 1; *Retnla*, resistin-like molecule alpha; *Col1a1*, collagen type I, alpha 1; *Igf1*, insulin-like growth factor 1.

2006). Despite the fact that ficolins belong to the fibrinogen-related proteins, which are a group of extracellular molecules with important roles in tissue repair for many of its members (Zuliani-Alvarez and Midwood, 2015), there are no data yet on the implication of ficolins in this process.

Macrophages clear dying cells and promote tissue regeneration, but overactivated macrophages responding to tissue damage may cause exaggerated repair responses and fibrotic lesions (Gieseck et al., 2018). In this vein, we found that C1q significantly amplifies peritoneal fibrosis induced by a lactate dialysate; it does so by promoting an anti-inflammatory peritoneal macrophage phenotype driven by lactate and dependent on HIF1α (Minutti et al., 2017a). C1q had been previously shown to promote fibrosis in aging skeletal muscle through activating Wnt signalling, resulting in impairment of muscle regeneration due to decreased proliferation of myocyte precursors parallel to increased proliferation of fibroblasts and increased collagen release from fibroblasts (Naito et al., 2012). This indicates that C1q can exacerbate fibrosis in cells other than macrophages. Another example of the participation of C1q in tissue remodeling and repair may be inferred from its recently discovered role in the central nervous system. As reviewed by Tenner and colleagues (2018), C1q is a key mediator of synapse elimination by "tagging" weak or immature synapses for elimination by adjacent microglia (a process called synapse pruning) in the healthy developing brain. However, aberrant synapse pruning could mediate pathological synapse loss in neurodevelopmental and neurodegenerative disorders, such as Alzheimer's disease (Tenner et al., 2018). Further studies should be done to explore the implication of soluble defense collagens in protection from or aggravation of chronic diseases that are associated with dysregulated tissue repair and remodeling.

5. Concluding remarks

Three decades ago, it was thought that proteins containing collagen domains were present only in the extracellular matrix and have only a structural role. However, it was recognized at the end of the 1980s that the type 1 scavenger receptor, whose trimeric structure includes a fibrous extracellular collagenous domain, participates in host defense activities by recognizing and mediating the endocytosis of pathogens (Krieger et al., 1993). The collagen domain of the scavenger receptor was considered as molecular flypaper for high affinity binding of specific polyanions. In the same period, it was proved that several proteins secreted to serum and tissue cavities (such as C1q, MBL, SP-A, and conglutinin) contained short collagen domains and were also involved in host-defense (Reid, 1979; Drickamer et al., 1986; Haagsman et al., 1987; Voss et al., 1988; Thiel and Reid, 1989). All these proteins have a selectively sticky surface and were involved in clearing the extracellular space of debris, including pathogenic material. This growing family of proteins is of great clinical interest for various diseases.

Apart from their collagen domains, one common physical property of these proteins is their high-order oligomerization in umbelliform- or cruciform-shaped structures composed of trimeric units. Such oligomerization is integral to these proteins' biological functions and must be under substantial selection pressure. It is evident that these proteins have evolved to use protein oligomerization as a tool for the control and execution of many of their distinct functions. Oligomerization confers structural and functional advantages. It improves stability and control over the accessibility and functional affinity of their binding regions (globular and collagen-like domains). Moreover, it facilitates multivalent binding to their ligands. However, unwanted oligomerization of proteins can also lead to the formation of pathogenic structures, suggesting that structure-function studies of these proteins in pathological states should be intensively explored. In addition, the expression of the functionally active recombinant form of these proteins and the generation of point mutation variants would aid understanding, at the molecular level, of the functions of these complex and versatile proteins.

C1q, MBL, and adiponectin deficiency lead to increased systemic inflammation, possibly due to a defect in the uptake of apoptotic cells (Takemura et al., 2007; Monticielo et al., 2008; Stegert et al., 2015). Inherited deficiency of H-ficolin results in chronic disabling infections (Munthe-Fog et al., 2009; Schlapbach et al., 2011). Decreased SP-A/-D levels are commonly observed in lung diseases (Ledford et al., 2014; Sorensen, 2018). However, SP-A/-D decrease may be a consequence of the diseased lung environment as proteins are partially degraded, oxidized, and present in smaller oligomeric forms. Much of what we know about the protective role of SP-A and SP-D, and other defense collagens, has arisen from studies using gene-deficient mice in murine models of several diseases.

Besides protecting from invading pathogens, soluble defense collagens are involved in controlling inflammation. They modulate macrophages toward an anti-inflammatory resolving phenotype and reduce the activation of immune cells other than macrophages. Soluble defense collagens detect and promote the uptake of dying cells caused by tissue damage and are key factors for macrophage-driven repair programs that restore homeostasis. Identification of the key receptors involved in these processes will aid to elucidate the tissue-specific role of these proteins. Moreover, this will allow the generation of cell-targeted gene-deficient mice to complete more sophisticated studies. Efforts in understanding the molecular and cellular mechanisms that govern macrophage-driven repair programs in health and disease will aid in the development of macrophage-directed therapeutic targets.

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