AIM/CD5L: a key protein in the control of immune homeostasis and inflammatory disease

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RECEIVED FEBRUARY 26, 2015; REVISED APRIL 9, 2015; ACCEPTED APRIL 12, 2015. DOI: 10.1189/jlb.3RU0215-074R

Abstract

CD5L, a soluble protein belonging to the SRCR superfamily, is expressed mostly by macrophages in lymphoid and inflamed tissues. The expression of this protein is transcriptionally controlled by LXRs, members of the nuclear receptor family that play major roles in lipid homeostasis. Research undertaken over the last decade has uncovered critical roles of CD5L as a PRR of bacterial and fungal components and in the control of key mechanisms in inflammatory responses, with involvement in processes, such as infection, atherosclerosis, and cancer. In this review, we summarize the current knowledge of CD5L, its roles at the intersection between lipid homeostasis and immune response, and its potential use as a diagnostic biomarker in a variety of diseases, such as TB and liver cirrhosis. J. Leukoc. Biol. 98: 173–184; 2015.

Introduction

The immune system serves to protect the host from pathogenic and sterile insults. In both types of aggression, a variety of cellular and protein systems contributes to a coordinated response that seeks to resolve the infection and/or recover homeostasis. CD5L is an emerging key component among the repertoire of immune effectors. It was identified in 1997 as a macrophage-secreted protein, hence its original name, Sp. Given its antiapoptotic role on leukocytes, it was later termed AIM and apoptosis inhibitor-6 [2]. Research in the last decade has shown that this protein plays myriad additional functions, ranging from the modulation of leukocyte migration and inflammatory responses to the control of lipid metabolism. In this review, we will refer to this molecule as CD5L to comply with the Human Genome Organisation Gene Nomenclature. We will provide an overview of the current knowledge of CD5L, covering basic aspects, such as its cloning, evolution, and tissue and cellular expression, as well as its role in leukocyte biology and pathology. Furthermore, current data supporting the capacity of CD5L to serve as a diagnostic marker in several diseases of inflammatory origin will be discussed.

CD5L: Basic Aspects

Cloning

In 1997, Gebe et al. [1] screened a cDNA library comprising human spleen mRNA and discovered that the 2 longest isolated clones—of 1804 and 2152 bp—encode for a 347 aa polypeptide. The coding sequence had the features of a secreted protein, and so, it was named Sp (Fig. 1). Analysis of the primary sequence of hCD5L revealed 19 hydrophobic amino acids at its amino terminal end that act as a secretory signal sequence. N-Terminal sequencing of 2 distinct recombinant forms of the protein, namely CD5L-Ig fusion protein produced by COS (CV-1 in Origin with SV40 genes) cells [1] and a CD5L form synthesized by HEK cells [3], respectively, confirmed that these 19 amino acids are absent in the mature protein. This secretory signal sequence is followed by 3 cysteine-rich domains, each ~100 aa in length, followed by an in-frame stop codon (Fig. 1). Sequence comparison with several other proteins revealed that the 3 cysteine-rich domains show significant homology to the SRCR domain.

Evolutionary Insights

The SRCR domain consists of 90–110 residues containing 6–8 cysteines with a well-conserved disulfide bond pattern [3, 4]. SRCR domains are present in >30 different secreted and/or membrane-anchored proteins. Examples of proteins containing SRCR domains are scavenger receptor A 1/II, MARCO, CD163, and DMBT1 [5], among others. Many of these proteins are found on cells associated with the immune system, and some of them have

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The online version of this paper, found at www.jleukbio.org, includes supplemental information.
been implicated in the development and regulation of innate and adaptive immune responses. Interestingly, sequences containing SRCR domains are highly conserved and have been identified in representatives of a variety of animal phyla, from *Ciona*, sea urchin, or *Caenorhabditis elegans* to amphioxus, lamprey, teleost, or mammals [6, 7]. The genes that encode SRCR domain-containing proteins are easy to predict from genome sequences, but conversely, they are difficult to classify in a particular family of proteins. Moreover, it is still not clear whether the SRCR domain originated from a single ancestral gene very early in the evolution or arose independently several times [6, 7].

Besides the presence of 3 SRCR domains and an N-terminal peptide, CD5L has an additional important feature: it lacks a transmembrane domain. With these 3 premises, we searched for CD5L orthologous genes along the evolutionary tree and found CD5L orthologs in several mammalian species (Table 1). More specifically, we found a high degree of conservation between the primate sequences (identities ranging from 74 to 99%), having nonsynonymous/synonymous substitution ratios below 1, which indicated evolutionary constrain, and also between the placental mammalian sequences (identities ranging from 47 to 99%). Interestingly, we detected that cow CD5L, despite having 51% identity and a predicted signal peptide, shows an extra SRCR domain (methods for these alignments are detailed in Supplementary information). The amino acid number is shown below each sequence, and the observed MWs for each protein, according to refs. [3, 8, 9], are indicated.

Expression in cells and tissue

Regarding tissue expression, Northern blot analysis identified 3 distinct RNAs hybridizing to hCD5L in bone marrow, spleen, lymph node, thymus, and fetal liver but not in nonlymphoid tissues (~2.4, 2.1, and 1.8 kb in length) [1]. The authors found that the sequence of the 3 hCD5L mRNA transcripts differed in their 3′ regions, which were of different lengths, and differed in the number of AUUUUA elements. They suggested that these AU-rich elements participate in regulating hCD5L mRNA stability [1]. Interestingly, subsequent cloning and Northern blot analysis of mCD5L revealed a unique band of 1.9 kb, strongly expressed in the spleen and liver and weakly in the lung [2, 8]. In these initial studies, mCD5L mRNA was also detected by RT-PCR in the thymus and by in situ mRNA hybridization in the thymus, spleen, and liver tissues. In addition, bacillus Calmette Guérin-induced granulomas, which harbor large numbers of infiltrating macrophages, were found in the liver [2]. It was proposed that the lack of variation in the presence of AU-rich elements explained the single mRNA encoding for mCD5L. In this regard, it was suggested that whereas the tissue distribution of CD5L mRNA transcripts is similar in human and mouse, the abundance of these transcripts may be differentially regulated in the 2 species [8].

At the protein level, hCD5L and mCD5L share a high level of sequence identity (68%), and their predicted sizes on the basis of amino acid sequences are similar (~37 kDa). However, SDS-PAGE and WB analysis show that the molecular weights of the human and mouse proteins differ. This observation is attributable to different posttranslational modifications (Fig. 1). In humans, 2 forms were defined at 38 and 40 kDa, resulting from distinct sialic acid content [3]. Accordingly, the primary sequence of hCD5L contains a potential region of O-linked glycosylation in a Pro-Ser-Thr-rich polypeptide, separating SRCR domains 1 and 2 [3]. In the mouse, the larger molecular weight (55 kDa) of the protein can be explained by other posttranslational modifications [1, 9]. In this regard, whereas hCD5L contains no N-linked glycans, the mCD5L sequence presents 3 putative N-glycosylation sites, 2 of which were verified to bind to N-glycans [9].

It has been hypothesized recurrently that differences in glycosylation patterns between human and mouse proteins result in 3-domain criteria, but only the turkey homolog has a predicted signal peptide. Interestingly, we detected annotated fish CD5L orthologs (e.g., medaka, *Oryzias latipes*, or stickleback *Gasterosteus aculeatus*), but they showed an expansion in the number of SRCR domains (from 5 to 16 SRCR domains), which did not match with our 3 main criteria for CD5L identification. Even the putative homologous of CD5L in sea lamprey (*Perkinsus marinus*), showing the highest identity, did not meet the main criteria of its mammalian counterparts. Likewise, we could not find CD5L orthologs in *Drosophila melanogaster*, *Ciona intestinalis*, *Ciona savignyi*, C. elegans, *Strongylocentrotus purpuratus*, *Branchiostoma floridae*, or *Branchiostoma belcheri*. Overall, these preliminary analyses may suggest that CD5L could be an innovation of the mammalian lineage. Alternatively, other vertebrates may have homologous CD5L proteins with variations in the structural characteristics, as we have observed in cow and some avian, reptilian, or fish sequences. Additional functional data will be necessary to clarify this issue.

**Table 1**

<table>
<thead>
<tr>
<th>Species</th>
<th>CD5L orthologous genes along the evolutionary tree and found predicted orthologs in other mammals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td></td>
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<tr>
<td>Mouse</td>
<td></td>
</tr>
<tr>
<td>Cat</td>
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</tr>
<tr>
<td>Chicken</td>
<td></td>
</tr>
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<td>Pig</td>
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<td>Fish</td>
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<tr>
<td>Lamprey</td>
<td></td>
</tr>
<tr>
<td>Teleost</td>
<td></td>
</tr>
<tr>
<td>Mammals</td>
<td></td>
</tr>
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<td><em>Ciona</em></td>
<td></td>
</tr>
<tr>
<td><em>Caenorhabditis</em></td>
<td></td>
</tr>
<tr>
<td><em>Branchiostoma</em></td>
<td></td>
</tr>
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</table>

(continued from previous page)
in distinct functional activities. Accordingly, in the present review, we will distinguish between data on mCD5L and hCD5L or refer to both as CD5L. Regarding the relevance of glycosylation in mCD5L function, the mutation of 2 N-glycosylation sites in the protein was found to affect its secretion and enhance its lipolytic activity in adipocytes (see below) [9]. Further studies will be required to determine whether this differential glycosylation also influences other functional aspects of CD5L biology.

Regulation of expression

Various studies that use experimental models and/or human sample analysis have revealed 2 cellular sources of CD5L, namely epithelial cells in the lung and to a higher extent, tissue macrophages. Macrophages are the main source of CD5L in the organism, and CD5L expression is up-regulated under inflammatory conditions of infectious origin, such as endotoxin-induced fulminant hepatitis [10], heat-killed *Corynebacterium parvum* injection [11], LM infection [12], as well as in the course of cardiovascular and metabolic pathologies, such as in atherosclerotic lesions [13], and in the adipose tissue of obese mice [14]. However, in contrast to tissue macrophages, in vitro-cultured macrophages do not apparently express CD5L unless previously activated with specific stimuli. In this regard, in early studies, mCD5L mRNA expression was lost in freshly isolated thioglycollate-activated peritoneal macrophages after 16 h of culture in plastic dishes, and its expression could not be reinduced by PMA, LPS, or IFN-γ [2, 12]. These data suggested that other factors within the tissue are required for mCD5L gene expression. However, our later results indicated that cellular hCD5L mRNA and protein levels are increased in 2 in vitro settings, namely in MTB infection of THP1 macrophages [15] and in cultured human monocyte-derived macrophage by maturation with M-CSF or with GM-CSF [16]. These data reinforced the notion that CD5L expression is tightly regulated in cells and tissues.

CD5L expression is positively controlled by LXR [12, 17], a transcription factor that belongs to the nuclear receptor family and that plays key roles in lipid homeostasis [18]. Two LXR isoforms have been defined, namely LXRα and LXRβ, both activated by oxysterols and specific intermediates in the cholesterol biosynthetic pathway (revised in ref. [19]). LXRα is expressed in

### TABLE 1. CD5L members from different species

<table>
<thead>
<tr>
<th>Species</th>
<th>Common name</th>
<th>Accession number</th>
<th>Identity with hCD5L (%)</th>
<th>Number of SRCR domains</th>
<th>Predicted signal peptide</th>
</tr>
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<tr>
<td>Homo sapiens</td>
<td>Human</td>
<td>O43866</td>
<td>–</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>Pan troglodytes</td>
<td>Chimpanzee</td>
<td>H2Q0B2</td>
<td>99</td>
<td>3</td>
<td>+</td>
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<tr>
<td>Pan paniscus</td>
<td>Bonobo</td>
<td>XP_008972736.1</td>
<td>99</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>Pongo abelii</td>
<td>Orangutan</td>
<td>H2N5A1</td>
<td>95</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>Gorilla gorilla</td>
<td>Gorilla</td>
<td>G3R058</td>
<td>98</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>Nomascus leucogenys</td>
<td>Gibbon</td>
<td>G1RRC5</td>
<td>96</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>Macaca mulatta</td>
<td>Macaque</td>
<td>F7FUB7</td>
<td>91</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
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<td>Vervet monkey</td>
<td>XP_007974830.1</td>
<td>90</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>Papio anubis</td>
<td>Baboon</td>
<td>A0A096NR27</td>
<td>90</td>
<td>3</td>
<td>+</td>
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<td>Langur</td>
<td>XP_010879556.1</td>
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<td>3</td>
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<td>Callithrix jacchus</td>
<td>Marmoset</td>
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<tr>
<td>Otolemur garnetti</td>
<td>Bushbaby</td>
<td>H0WRR4</td>
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<tr>
<td>Phoropus vanryphus</td>
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<td>3</td>
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<tr>
<td>Mus musculus</td>
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<td>Q9QV4K4</td>
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<td>3</td>
<td>+</td>
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<td>Rattus norvegicus</td>
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<td>Equus caballus</td>
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<td>F7BXD8 (fragment)</td>
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<tr>
<td>Camelus ferus</td>
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<tr>
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<tr>
<td>Bos taurus</td>
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<tr>
<td>Sarcoptes harrisi</td>
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<td>57</td>
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<tr>
<td>Monodelphis domestica</td>
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<tr>
<td>Ovis aries</td>
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<td>Pelodiscus sinensis</td>
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<td>Melanagrapsus gallopavo</td>
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<tr>
<td>Gallus gallus</td>
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<td>32</td>
<td>4</td>
<td>–</td>
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<tr>
<td>Ficedula albicollis</td>
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<td>U3K326</td>
<td>12</td>
<td>9</td>
<td>–</td>
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<tr>
<td>Anas platyrhynchos</td>
<td>Duck</td>
<td>U3S20</td>
<td>16</td>
<td>9</td>
<td>–</td>
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<tr>
<td>Oryzias latipes</td>
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<td>5</td>
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<tr>
<td>Gasterosteus aculeatus</td>
<td>Stickleback</td>
<td>G3Q5G5</td>
<td>11</td>
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<tr>
<td>Astyanax mexicanus</td>
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<td>16</td>
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<td>Lamprey</td>
<td>S4RUM0 (fragment)</td>
<td>44</td>
<td>5</td>
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</tr>
</tbody>
</table>

*a.n.d, nondetermined; protein fragments without N terminus, thus without signal peptide.*
tissues with a high metabolic activity, including liver, adipose, and macrophages, whereas LXRα is ubiquitously expressed [19]. Of the 2 isoforms, LXRα is selectively involved in the regulation of CD5L expression [12]. To regulate gene expression positively, LXRα form heterodimers with another member of the nuclear receptor family, the RXR. CD5L expression is induced in macrophages by natural LXR ligands, including 25-hydroxycholesterol and oxLDL, and by synthetic LXR agonists (TO901317 and GW3966) [12, 16, 17, 20], with synergistic induction of CD5L expression resulting from the combined activation by LXR and RXR agonists [12, 17]. Initial studies identified a potential LXR response element at position 5 kb upstream of the CD5L transcriptional start site [12]. In addition, CD5L is a target gene for SREBP-1a, a transcription factor that positively regulates lipogenic genes [21]. A functional SREBP-responsive element corresponding to an E-box element was identified at position −507 in the CD5L promoter [21]. More recently, it has been shown that the transcription factor MaB is required for the induction of CD5L by agonist-activated LXR/RXR through a MaB response element at position −54 in the CD5L promoter [22]. MaB expression is indeed up-regulated upon LXR activation through direct and indirect mechanisms, depending on the cellular context [21–23]. These observations would suggest that CD5L expression is coordinately regulated by a complex transcriptional network, including LXR/RXR, MaB, and SREBP-1 transcription factors.

Epithelial cells have been described to be an additional cellular source of CD5L. This finding came from massive expression analysis of the genes implicated in tumorigenesis and emphysema in the lung in association with pulmonary inflammation that occurs in lac−/− mouse. In that study, overexpression of the mRNA encoding CD5L was detected in lung tissue from lac−/− mice compared with WT animals. Interestingly, subcellular fragmentation revealed that the CD5L mRNA derived from ATII cells and not cells purified from the BAL (containing 95% macrophages) [24]. This work set the foundations for the generation of a transgenic mouse model overexpressing mCD5L in ATII cells, which resulted in an increased incidence of lung adenocarcinoma [25] (see more details in Pathophysiological implications section).

Cell-surface receptors for CD5L

Recent evidence obtained in vitro and in vivo support the involvement of scavenger receptor CD36 as a bona fide cell-surface receptor for CD5L [14]. In those studies, nonexpressing adipocytes internalized rmCD5L—a process that was drastically decreased in the presence of CD36-neutralizing antibodies. Moreover, cellular uptake of systemically administered rmCD5L was markedly lower in CD36-deficient mice compared with WT mice [14]. Internalized rmCD5L colocalized with early endosomes but not with late or recycling endosomes, thereby suggesting that CD5L could be transported into the cytosol during endosome maturation. In addition, rmCD5L was internalized by macrophages through CD36, indicating that this surface molecule may serve as a cellular receptor for CD5L endocytosis in several cell types [14].

CD36 is an 88 kDa transmembrane glycoprotein expressed in a wide variety of cell types, such as microvascular endothelial cells; “professional” phagocytes (including macrophages, dendritic cells, and microglia); retinal pigment epithelial cells; erythroid precursors; hepatocytes; adipocytes; cardiac and skeletal myocytes; and specialized epithelial cells of the breast, kidney, and gut [26]. Accumulating evidence shows that CD36 recognizes many types of ligands, including thrombospordin [27]; Plasmodium falciparum [28]; bacterial cell-wall components [29]; phosphatidylserine and oxidized phosphatidylserine on the surface of apoptotic cells [30]; and additional endogenous ligands, such as oxLDL [31], among others. The multivariate ligand recognition of CD36 allows it to exert several functions, depending on the cell type. Importantly, the capacity of CD36 to internalize modified lipoproteins (e.g., oxLDL), which facilitates cholesterol accumulation in macrophages, links the activity of this receptor to the initiation and perpetuation of atherosclerosis. Furthermore, CD36 is intimately involved in the regulation of fatty acid uptake across the plasma membrane and the subsequent metabolism of this substrate [32]. Thus, it has been proposed that CD36 expression and function influence susceptibility to certain metabolic diseases, such as obesity, insulin resistance, and fatty liver disease [33, 34]. In phagocytes, CD36 is also involved in phagocytosis and the development of an inflammatory response upon pathogen aggression [29, 35, 36]. By analogy with membrane protein CD14, it has been suggested that CD36 functions as an accessory protein to present bacterial and modified host proteins to some TLRs [37–41]. Whether the interaction of CD5L with CD36 modulates the binding of CD5L ligands and/or any of its activities remains to be elucidated. Likewise, the biochemical nature of the CD36–CD5L interaction is still unknown.

In addition, given the observation that thymocytes and NKT cells—in which CD5L is also active [2, 11]—do not express CD36, distinct cell types may have alternative receptors for CD5L. In this regard, recent findings have highlighted the interaction of CD5L with the molecules CD55, Gm, CD59, and factor H [42]. The interaction of CD5L with CD55, Gm, CD59, and factor H was demonstrated by coimmunoprecipitation assays in cellular lysates from transfected HEK293 T cells [42]. These are membrane-bound (CD55, Gm, and CD59) and soluble (factor H) RCAs. The complement system is an essential constituent of host innate immunity that involves around 50 players, including pattern recognition molecules, protein components, proteases, and cell-surface receptors. It constitutes a central mechanism of immune surveillance that fights against pathogens and also against altered homeostasis of healthy and damaged host cells. To prevent self-reactivity, RCA protects host cells from complement attack [43]. CD5L binding to the RCA blocked RCA activity and allowed immune recognition of cancer cells (see Pathophysiological implications section) [42]. These findings open a wide perspective on the functional relationship between CD5L and the complement system.

Presence in blood

In blood, CD5L circulates in high concentrations (~10 μg/ml) [3, 44], in association with IgM [3, 8], and the plasma levels of both proteins are positively correlated [45–47]. The IgM–CD5L interaction was discovered initially upon CD5L detection in IgM but not in IgG or IgA fractions of human serum [48]. The interaction was later demonstrated in direct binding studies that use rCD5L and FCS-free hybridoma-produced IgM mAb [3, 46]. Further interaction studies with rCD5L showed that each of the 3 SRCR domains of CD5L binds
to the Fc region of IgM. Although there is no direct interaction between CD5L and the J-chain, the latter appears to be required for the binding of CD5L to IgM. Therefore, CD5L may bind circulating but not cell-surface IgM [46].

Further analysis showed that circulating mCD5L is stabilized in serum as a result of its interaction with IgM, a process that protects mCD5L from renal excretion [46]. This notion was reinforced with a model of intravenous injection of a synthetic Fc portion of the IgM heavy chain into mice lacking circulating IgM. Synthetic IgM-Fc associated with endogenous mCD5L, protecting mCD5L from renal excretion and preserving the levels of circulating mCD5L [44].

**ROLES IN LEUKOCYTE FUNCTION**

CD5L has been implicated in the modulation of many important aspects of leukocyte function. These are explained below and summarized in Fig. 2.

**Leukocyte apoptosis**

Apoptosis is a programmed form of cell death that is considered a key component of various physiologic processes. In fact, inappropriate apoptosis occurs in many human pathologic conditions, including atherosclerosis, autoimmune disorders, and cancer [49].

mCD5L was named AIM initially, in accordance with its antiapoptotic effects in vivo and in vitro. In CD5L-deficient mice, before thymic selection, CD4/CD8 DP thymocytes were more susceptible to apoptosis induced by dexamethasone and irradiation. In vitro, rmCD5L significantly inhibited cell death of DP thymocytes and CD95/Fas-cross-linking-mediated apoptosis of the monocyte-derived cell line J774A.1 [2]. Later, apoptotic function of mCD5L was corroborated in CD5L-deficient mice, which showed a reduction of T and NKT cells in liver granulomas compared with WT mice when challenged with heat-killed C. parvum [11]. In addition, administration in vitro of rmCD5L significantly inhibited apoptosis of liver NKT and T cells obtained from mice injected with C. parvum [11]. Altogether, these observations suggested that mCD5L had the capacity to rescue these cell types from programmed cell death.

In line with the previous findings, mCD5L also contributes to protecting macrophages against apoptosis induced by various pathogen, namely *Bacillus anthracis*, *Escherichia coli*, *Salmonella typhimurium*, and LM [12, 17, 20]. Moreover, in humans and mice, CD5L produced by macrophages was identified as a factor that protects these phagocytic cells from the apoptotic effects of diverse agents, such as anisomycin [17], cycloheximide [16], cigarette smoke extract [50], and oxidized lipids [13, 16]—the latter facilitating the progression of atherosclerotic disease (see Pathophysiological implications section).

![Figure 2. The many roles of CD5L in inflammation.](image)
Given all of these observations, mCD5L and hCD5L forms can be defined as apoptosis inhibitors that support the survival of macrophages and other cell types when challenged by various apoptosis-inducing insults of infectious origin and chemical compounds.

**Autophagy and inflammation**

Autophagy is a highly conserved cellular degradation process found in eukaryotes ranging from yeast to mammals, and it serves to recycle obsolete damaged or superfluous cell components into basic biomolecules. In this regard, autophagy drives a flow of biomolecules in a continuous degradation-regeneration cycle [51]. During the last decade, autophagic dysfunction has been associated with a broad variety of human pathologies, from cancer to infectious and metabolic diseases. Thus, the modulation of autophagy may represent a pharmacological target for drug development and therapeutic intervention for various human disorders [52, 53].

Autophagy controls inflammation through regulatory interactions with innate-immune signaling pathways through the removal of endogenous inflammasome activators and through effects on the secretion of immune mediators [54]. CD5L has been shown to influence the monocyte inflammatory response. On the one hand, hCD5L inhibits monocyte TNF [55, 56] and IL-1β production, while enhancing IL-10 secretion [57] upon TLR2 and TLR4 stimulation. We have revealed recently that the macrophage anti-inflammatory pattern induced by CD5L is mediated through enhanced autophagy mechanisms in this cell type [57]. Examination of autophagy markers in THP1 macrophages and peripheral blood monocytes reinforced this notion. In this regard, hCD5L increased cellular LC3-II content, LC3 puncta, as well as LC3-Lysotracker Red colocalization. Furthermore, electron microscopy analysis showed an increased presence of cytoplasmic autophagosomes in THP1 macrophages overexpressing hCD5L. Silencing experiments indicated that the receptor CD36 was required for hCD5L-induced autophagy, thereby revealing a novel function for the CD36-CD5L axis in the induction of macrophage autophagy and in the control of cellular homeostasis. These observations suggest that the modulation of CD5L-CD36 activity may offer therapeutic options for severe inflammatory conditions associated with deregulated autophagy.

**B cell proliferation**

hCD5L was described initially as a novel, secreted protein, produced in lymphoid tissues, that may regulate monocyte activation, function, and/or survival [1]. This suggestion was based on the results of cell-binding studies that use an hCD5L-murine Ig fusion protein, which showed that hCD5L binds to peripheral blood monocytes but not to T or B cells. This finding is in apparent contrast with the evidence provided by Yusa et al. [58], who showed that when in combination with TGF-β, hCD5L inhibits LPS-induced proliferation in B lymphocytes. These authors proposed that CD5L exerts distinct functions depending on the target cell types and/or its combined effects with other cytokines [58].

**PATHOPHYSIOLOGICAL IMPLICATIONS**

The involvement of CD5L in modulating the activity of macrophages and other cell types may have consequences on the outcome of serious pathologies. In this regard, CD5L has been implicated in several diseases that are highly relevant for human health, mostly of inflammatory origin, ranging from infection and obesity to cancer.

**Antimicrobial responses**

Infectious diseases are a major cause of morbidity and mortality worldwide. The mammalian innate-immune system is a remarkable complex of cellular and biochemical processes that enable efficient detection and elimination of pathogens that threaten host viability. However, although the generation of a potent immune response is crucial for the containment and eradication of microbial infection, excessive or inappropriate inflammation may be harmful to the host and may result in immunopathology or autoimmunity [59, 60]. Like other members of the SRCR superfamily, such as MARCO [61], DMBT1/salivary agglutinin glycoprotein/gp340 [62], CD6 [63], CD163 [64, 65] and CD5 [66], CD5L is able to bind bacterial components. hCD5L and mCD5L proteins bind to and aggregate Gram-negative and -positive bacteria [55, 56] and to saprophytic and pathogenic fungi [55]. Moreover, hCD5L has been found to act as a PRR for LPS and LTA, and competition-binding studies revealed that the binding of hCD5L to LPS and LTA is mediated by 2 independent sites [56]. In addition to its pathogen-binding properties, CD5L exerts antimicrobial activities. In this regard, initial evidence showed that mCD5L increases macrophage phagocytosis of latex beads [10]. Later, in vitro studies by our group indicated that hCD5L enhances the mycobactericidal activity of macrophages, thus actively participating in the macrophage response against MTB. CD5L expression peaked in the early phase of infection, thereby inducing the synthesis of vitamin D-dependent antimicrobial peptides and subsequent autophagy mechanisms that led to mycobacterial killing. These data thus demonstrated that hCD5L plays a role in the host response against MTB [15].

Moreover, mice that do not express functional LXRs displayed increased susceptibility to infection with the intracellular bacteria LM, mainly because of altered macrophage function, accelerated apoptosis, and defective bacterial clearance [12]. Loss of regulation of CD5L expression upon LM administration greatly contributed to the increased macrophage apoptosis and higher susceptibility to infection in the LXR-deficient mice. In another experimental model of LM infection, transient overexpression of Ch25h, the enzyme that synthesizes the LXR natural ligand 25-hydroxycholesterol, promoted the survival of LM-infected cells through mCD5L induction but increased susceptibility of the host to infection [20]. In this scenario, infected mice showed higher bacterial loads in liver and spleen, which correlated with increased bacterial content in macrophages infected in vitro. Thus, these results apparently contradicted the findings described previously in LXR-deficient mice. The authors suggested that these discrepancies reflect different effects of constitutive versus transient changes in macrophage apoptosis, supported by the notion that increased survival of LM-infected macrophages by transient Ch25h overexpression at the time of infection.
intensifies the disease. Furthermore, 25-hydroxycholesterol influences immune response independently of LXRα, which may help to explain the differences between these 2 models [67]. Interestingly, mCD5L inhibited LPS-induced macrophage death, in part, by blocking caspase-1 cleavage. The authors proposed that these events could be part of a strategy evolved by the pathogen to maintain a protected cellular environment for its replication and to prevent immune activation by pyroptotic death of macrophages. Overall, these studies revealed new intersection points between metabolic and inflammatory pathways, in which CD5L plays a central role and also highlighted the delicate balance between cell survival and cell death required for the host to resist infection.

Inflammation
A model of LPS-induced hepatitis in mice was used to assess the involvement of mCD5L in the progression of inflammation in vivo. Mice overexpressing mCD5L were immunized by heat-inactivated Propionibacterium acnes and challenged with intravenous injection of LPS. In these studies, the antiapoptotic action of mCD5L was linked to increased numbers of liver-infiltrating macrophages and hence, increased inflammation [10]. The authors also showed that mCD5L promotes macrophage phagocytosis and thus, hypothesized that CD5L-dependent support of macrophage survival and phagocytic activity results in efficient clearance of dead cells and infectious or toxic reagents in hepatitis.

Atherosclerosis
Atherosclerosis is an inflammatory pathology characterized by an accumulation of fat deposits and cellular debris within the arterial wall. Two major factors contributing to the pathophysiology of atherosclerosis are hyperlipidemia and inflammation. LDL is a major extracellular carrier of cholesterol, and as such, it plays key physiologic roles, distributing cholesterol to peripheral tissues through the circulatory system. However, under conditions of hyperlipidemia, specific components of LDL become oxidized (oxLDL) or otherwise modified, and these modifications substantially alter the function of these components. Modified LDL particles cause alterations in the endothelium and are chemotactic for monocytes, facilitating monocyte migration and subsequent differentiation into macrophages. Furthermore, they are avidly taken up by macrophages via scavenger receptors to generate lipid-rich foam cells. The accumulation of these cells and subsequent proinflammatory reactions in the artery wall lead to the development of atherosclerotic lesions, which may obstruct the arterial lumen and/or eventually rupture and thrombose, causing myocardial infarction or stroke [68, 69].

In humans and mice, CD5L is highly expressed in lipid-laden macrophages at atherosclerotic lesions. In this regard, the induction of CD5L expression supports macrophage survival within the artery wall and is thus associated with atherogenesis [13]. Indeed, in mice with a double deficiency in CD5L and LDLR, the development of atherosclerotic lesions induced by a high-fat, high-cholesterol diet was markedly reduced compared with LDLR-deficient mice [13]. Accordingly, a recent report showed that MafB, which directly regulates CD5L expression, also participates in the acceleration of atherosclerosis by inhibiting foam-cell apoptosis [22].

In addition to its antiapoptotic effects, CD5L participates in other key aspects of atherogenesis. We have demonstrated recently that hCD5L increases macrophage foam cell formation. Together with the finding that rhCD5L binds to oxLDL, we hypothesized that CD5L serves as a soluble protein that transfers oxLDL to CD36 and showed that hCD5L does promote CD36-mediated oxLDL uptake [16]. Furthermore, hCD5L may contribute to macrophage-endothelial cell adhesion to endothelial ICAM-1 by enhancing the expression of the integrins LFA-1 and macrophage 1 antigen [16].

Chronic kidney disease
CD5L may also have an additional role related to vascular damage—this time, localized in the small arteries and arterioles in the kidney, causing nephrosclerosis. This is one of the main pathologies underlying chronic kidney disease, and it may lead to ischemic changes in the glomeruli and interstitium, consequently compromising renal function. In a rat model of nephrosclerosis, immunohistochemistry analysis showed CD5L strongly expressed in macrophages that infiltrated the diseased kidney [70]. Furthermore, treatment with drugs that inhibited kidney damage and lowered macrophage infiltration reduced CD5L expression in renal tissue, thus suggesting the that CD5L expression is critical for the progression of nephrosclerosis [70].

Obesity-associated inflammatory diseases
Obesity is closely associated with insulin resistance—a condition that triggers and/or accelerates multiple metabolic disorders, including type 2 diabetes, cardiovascular diseases, and fatty liver dysfunction. Insulin resistance is caused, in part, by chronic, low-grade inflammation in adipose tissue of the obese [71]. This subclinical state of inflammation is dependent mainly on the innate-immune system. Activation of TLRs expressed on adipocytes by fatty acids leads to the production of inflammatory adipokines and the recruitment of classically activated inflammatory macrophages (M1 macrophages) into the adipose tissue of obese subjects, enhancing the chronic, subacute, inflammatory stage [72, 73].

In studies focused on analyzing the putative role of CD5L in inflammation and obesity, mCD5L was shown to induce lipolysis in adipose tissue after its internalization into adipocytes through CD36 [74]. Once in the cytosol, mCD5L binds to FASN, a metabolic enzyme that is highly expressed in adipose tissue and that catalyzes the synthesis of saturated fatty acids, such as palmitate, from acetyl-CoA and malonyl-CoA precursors. Through the interaction between mCD5L and FASN, the former remarkably reduced the enzymatic activity of the latter, thereby decreasing the amount of saturated fatty acids in adipocytes [14]. This response ablated transcriptional activity of peroxisome proliferator-activated receptor γ, a master transcription factor for the differentiation of adipocytes, leading to diminished gene expression of lipid-droplet-coating proteins, including fat-specific protein 27 and Perilipin, which are indispensable for triacylglycerol storage in adipocytes [74]. These events resulted in decreased lipid droplet size, lower numbers of mature adipocytes, and decreased weight and fat mass induced by a high-fat diet in mice—findings that are physiologic relevant for the prevention of obesity [14, 74]. However, this CD5L-dependent
lipolytic response also induced an efflux of free fatty acids from adipose cells, which stimulated chemokine production in surrounding adipocytes through TLR4 activation, concomitant with an infiltration of inflammatory macrophages [75]. Supporting these observations, the progression of obesity-associated inflammation was prevented locally and systemically in obese, CD5L-deficient mice as a result of the abolished infiltration of inflammatory macrophages. Likewise, whole-body glucose intolerance and insulin resistance were ameliorated in obese CD5L null mice. Thus, the absence of mCD5L apparently prevented insulin resistance in obese mice [75]. Consequently, the regulation of hCD5L levels has been proposed as a potential therapeutic strategy to treat inflammatory diseases associated with obesity, such as the metabolic syndrome [76].

Winer et al. [77] suggested that obesity in humans often increases the serum levels of multiple autoantibodies, thus causing autoimmune diseases. In accordance, pathogenic IgG antibodies, including a unique profile of autoantibodies, have been found in obese humans and mice. In this context, it was demonstrated recently that mCD5L modulates the homeostasis of IgM in obese mice fed a high-fat diet, subsequently contributing to autoantibody production [46]. In that study, the mCD5L-IgM association inhibited IgM binding and internalization by follicular dendritic cells through the Fcα/μ receptor. The authors proposed that this response prolongs the presence of the IgM immunocomplexes on the surface of splenic follicular dendritic cells and may increase IgM-dependent antigen presentation to germinal center B cells, thereby enhancing the development of long-lived plasma cells that produce high-affinity IgG autoantibodies [46]. Whether CD5L is also associated with the pathogenesis of other autoimmune diseases remains to be seen.

COPD

Macrophages are key cellular mediators of immune defense and inflammation in the lung. Among these cells, AMs are the most abundant population [78]. Although they are essential for pulmonary host defense, they are also involved in enhanced inflammation in COPD [78], which is characterized by airflow limitation that is not fully reversible, and it is a major cause of chronic morbidity and mortality worldwide [79]. AM resistance to apoptosis has been implicated in the pathogenesis of this disease. In this regard, the numbers of AMs, including those positive for CD5L, were found to be increased significantly in the lungs of a mouse model of COPD [50]. CD5L expression was demonstrated at mRNA and protein levels in AMs isolated from the BAL. In vitro, conditioned medium containing CD5L protected U937 macrophage cells from the apoptotic effects of cigarette smoke extract. These studies support the notion that CD5L participates in resistance to apoptosis in COPD-associated AMs.

Cancer

Several reports have pointed to the contribution of CD5L to 2 highly prevalent malignancies, namely lung adenocarcinoma and hepatocellular carcinoma. Interestingly, by modulating immune responses, CD5L may have opposite effects on the outcome of these conditions, thereby promoting lung and inhibiting liver cancer.

Lung adenocarcinoma. In a transgenic mouse model of specific overexpression of CD5L in myeloid cells, myeloid cell apoptosis was inhibited [80]. These mice also displayed systemically increased myeloid cell proliferation. Interestingly, CD5L overexpression led to lung inflammation and the formation of bronchoalveolar adenocarcinoma, thus lowering animal survival significantly. At the molecular level, it was observed that oncogenic signaling pathways (i.e., increased phospho-Stat3-, phospho-Erk1/2-, and phospho-p38-positive cells) were activated in blood and lung macrophages, dendritic cells, and neutrophils of these mice [80]. Similar effects were observed upon CD5L overexpression in A549 epithelial cells in vivo [25]. These mice also presented malignant transformation of the lung as a result of decreased epithelial cell apoptosis and enhanced proinflammatory cytokine/chemokine amounts in lung and serum [25].

Hepatocellular carcinoma in steatosis. A recent study has shown that circulating mCD5L prevented HCC that arose in a steatotic liver in obese mice [42]. Under these conditions, mCD5L accumulated on the surface of tumor hepatocytes. There, CD5L interacted with the negative RCA molecules CD55, CD59, and Crry, leading to RCA inactivation and subsequent C3 activation and/or membrane-attack complex deposition. The final outcome was induced necrotic death of tumor hepatocytes, which could then be removed by bystander Kupffer cells. Accordingly, CD5L-deficient mice were highly susceptible to steatosis-associated HCC development. When fed a high-fat diet for 1 yr, all CD5L-deficient mice developed multiple liver tumors, which were confirmed HCC upon histologic examination. In contrast, mice with normal mCD5L expression did not develop these tumors after the same dietary challenge [42]. The specific mechanism of RCA inactivation and whether CD5L has the capacity to eliminate other types of tumor cells remain unknown. Interestingly, the authors of that study also observed that CD5L interference with RCA activity was specific for tumor cells, as normal hepatocytes internalized mCD5L through CD36, with concomitant modulation of intracellular lipid metabolism, as described for adipocytes [42]. These results support the use of CD5L as a therapy to target and destroy liver cancer cells specifically through activation of the complement system.

CD5L AS A DISEASE BIOMARKER

Biomarkers have gained significant clinical value in medical practice and have been introduced recently into clinical patient management for the diagnosis, treatment stratification, and prognosis of diverse pathologies. As mentioned, hCD5L is detected in serum in relatively high amounts (micrograms/milliliter range), and a large-scale analysis in a healthy population revealed higher levels in women than in men (mean 6.06 ± 2.1 µg/ml in women; 4.99 ± 1.8 µg/ml in men) [47]. Interestingly, hCD5L peaked in women in their 20s and decreased with age (mean 6.75 ± 2.05 µg/ml at 20 yr old; 4.91 ± 1.57 at 70 yr old) [47]. Moreover, plasma levels of CD5L are altered in several conditions that arise in an inflammatory context. In this regard, we have seen that mCD5L plasma levels increase up to 10-fold in mice infected with MBT, 3 wk after infection, coinciding with peak CFU numbers in spleen and lung [15]. Likewise, septic shock induction with LPS and zymosan
<table>
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<td>↑↑</td>
<td>None</td>
<td>None</td>
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<td>↓</td>
<td>None</td>
<td>Antiapoptotic role; preventing stress-induced apoptosis</td>
<td>[92]</td>
</tr>
</tbody>
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2D-PAGE, 2-dimensional-PAGE; MS, mass spectrometry; n, number of cases; TS, Turner syndrome; CLI, critical limb ischemia; 2D-DIGE, 2D difference gel electrophoresis; iTRAQ, isobaric tag for relative and absolute quantitation; 2DLC, 2D liquid chromatography; 2DE, 2D electrophoresis. ▲, Decreased; †, increased.
modulates mCD5L plasma levels in mice, resulting in increased levels, 24 h postinjection [55].

Several proteomic studies that use human plasma/serum and synovial and BALF have highlighted hCD5L protein as a putative biomarker for a number of inflammatory conditions (Table 2). The list of conditions is increasing steadily, ranging from AD [85] to KD [86] and osteoarthritis [91]. Interestingly, most of the studies focused on the value of hCD5L as a biomarker of liver disease [93].

In the liver, chronic inflammation causes high morbidity and mortality worldwide. Hepatitis virus infection, alcohol abuse, and NAFLD are the main etiologies associated with this disease. In this context, continuous inflammation as a result of liver damage leads to hepatic fibrosis, which frequently brings about cirrhosis and ultimately, HCC [93]. The determination of a plasma biomarker of liver fibrosis or HCC would be of great relevance for the clinical management of these patients. In this context, proteomic analysis based on 2-dimensional gel electrophoresis identified elevated levels of hCD5L in the sera of individuals with liver cirrhosis related to HCV infection compared with healthy control serum, and this protein was proposed as a potential biomarker for assessing liver fibrosis [81]. A later study confirmed that serum levels of hCD5L are indicators of advanced liver fibrosis in HCV [84]. Furthermore, on the basis of its proposed role in immune system regulation, hCD5L was thought to be most likely associated with viral infection rather than cirrhosis [81]. In the context of HCV infection, a study on 19 HCV-positive patients that included 7 with cirrhosis and 5 with HCC suggested that CD5L might be a useful biomarker for early diagnosis of HCC in HCV cirrhotic patients [83]. A more recent report showed that certain combinations of hCD5L indexes normalized to liver-marker score distinguished HCC patients from non-HCC patients (mostly HCV) and thus, could be applicable for HCC diagnosis [47]. However, a proteomic approach applied in different stages of NAFLD identified and further validated hCD5L as an up-regulated serum biomarker for cirrhotic NAFLD but discarded hCD5L as a surveillance tool for HCC in these patients [82]. These studies suggest that blood levels of hCD5L may serve as a biomarker of liver cirrhosis in HCV and NAFLD and HCC only in HCV. Future studies are required to confirm the potential of hCD5L as a biomarker of liver damage/HCC and of other inflammatory diseases. Moreover, significant alterations of hCD5L levels point to a functional implication of this protein in these pathologies—a question that deserves further investigation.

CONCLUDING REMARKS

Research during the last decade has provided a wealth of information on CD5L that places this molecule at the crossroads of immunity and metabolism. However, important questions, such as the mechanism(s) induced by CD5L to inhibit cellular apoptosis remain unanswered. Through its multiple activities, mostly in leukocytes but also in adipocytes and epithelial cells, CD5L may affect the modulation of diseases of high prevalence, such as atherosclerosis, obesity, and liver cancer. Given our increasing understanding of CD5L function, strategies involving anti-/pro-CD5L compounds could provide the basis for novel therapies in these pathologic settings. CD5L has an added value in its potential use as a biomarker of disease. The presence of this protein in human fluids facilitates its use as a diagnostic and prognostic biomarker of various aspects of pathology. Future studies will reveal the therapeutic and biomarker utility of this versatile molecule.

ACKNOWLEDGMENTS

This work was supported by grants from the Fundación la Marató de TV3 (MTV3 20133610) and also from the Spanish Ministry of Health, Instituto de Salud Carlos III, and FEDER funds (FIS PI10/1565, PI13/1906; all to M.R.S.). M.R.S. and N.R. are supported by Miguel Servet (CPII14/00021) and Ramón y Cajal (RYC-2010-06210) fellowships, respectively.

DISCLOSURES

The authors do not have any conflicts of interest to declare.

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Access the most recent version at doi:10.1189/jlb.3RU0215-074R

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