ACCSCIENCE PUBLISHING

Microbes & Immunity

PERSPECTIVE ARTICLE

SRCR proteins uncovered: Their crucial role in inflammation

Maria Carolina Silva[1†], Rita P. Pinto[1,2†], Liliana Oliveira[1,3], and Alexandre M. Carmo[1,3*]

[1]i3S - Institute for Research and Innovation in Health, University of Porto, Porto, Portugal

[2]Department of Medical Sciences, University of Aveiro, Aveiro, Portugal

[3]Institute of Molecular and Cell Biology, University of Porto, Porto, Portugal

Abstract

The scavenger receptor cysteine-rich (SRCR) superfamily comprises a highly conserved group of extracellular soluble and membrane-attached glycoproteins that function as pattern recognition receptors against a diverse range of pathogenic determinants. While considerable attention has been devoted to their roles in microbial recognition, this perspective aims to emphasize the significant, yet previously overlooked, anti-inflammatory properties of circulating SRCR proteins, which may be even more crucial for immune regulation. In addition, we examine SRCR cell surface proteins that, despite exhibiting limited microbial recognition, have demonstrated potential in mitigating inflammation through their soluble forms released during infectious and inflammatory conditions. Collectively, the paper emphasizes the dual roles of these proteins in infection control and the regulation of inflammatory responses, spotlighting their therapeutic potential in managing inflammatory diseases and enhancing host defense mechanisms.

Keywords: Scavenger receptors; Pattern recognition receptors; Inflammation; Microbial recognition; Immune homeostasis

[†]These authors contributed equally to this work.

***Corresponding author:**
Alexandre M. Carmo
(acarmo@i3s.up.pt)

Citation: Silva MC, Pinto RP, Oliveira L, Carmo AM. SRCR proteins uncovered: Their crucial role in inflammation. *Microbes & Immunity*. 2025;2(2):46-52. doi: 10.36922/mi.5741

Received: November 1, 2024

Revised: December 20, 2024

Accepted: January 6, 2025

Published online: January 17, 2025

Copyright: © 2025 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

The scavenger receptor cysteine-rich (SRCR) superfamily is primarily known for its ability to recognize and bind various endogenous ligands, including lipids, proteins, and carbohydrates, while also serving as pattern recognition receptors (PRRs) that identify microbial components to initiate immune responses and enhance innate immunity against infections.[1] Among the various members of the SRCR superfamily, several have distinct binding characteristics toward particular microbes. CD5 antigen-like (CD5L) and soluble scavenger protein with 5 SRCR domains (SSC5D), which contain three and five SRCR domains, respectively, are known to recognize pathogen-associated molecular patterns (PAMPs) from Gram-positive and Gram-negative bacteria, as well as pathogenic and saprophytic fungal species, promoting the aggregation of these microorganisms to limit their dissemination.[2-4] SSC4D, composed of four SRCR domains, engages directly with various Gram-negative and Gram-positive bacterial species and also several protozoan parasites.[5] Finally, deleted in malignant brain tumors 1 (DMBT1), a secreted

glycoprotein primarily expressed by macrophages, interacts with various types of bacteria and viruses.[6]

Although the anti-inflammatory potential of individual SRCR proteins has been recognized for years, their collective significance in inflammation modulation has often been overlooked. Emerging evidence suggests that most, if not all, SRCR proteins possess crucial anti-inflammatory properties that may operate independently or alongside microbial targeting. These insights underscore the important functions of SRCR proteins in controlling inflammation and facilitating tissue repair, revealing their multifaceted roles in immune defense and the resolution of inflammatory responses.

2. Circulating SRCRs

Soluble SRCRs play a pivotal role in modulating inflammation, displaying distinct functional characteristics that influence immune responses (Figure 1). The inflammation-reducing properties of DMBT1 are well-documented, and its presence in the lungs, saliva, intestinal surfaces, amniotic fluid, and newborn meconium indicates its critical role in regulating inflammatory responses.[6] DMBT1 enhances classical complement pathway activation by interacting with complement proteins, particularly C1q, thereby shaping an anti-inflammatory immune response.[7] DMBT1 significantly influences the production and secretion of pro-inflammatory cytokines, such as interleukin (IL)-6, aiding in the regulation of inflammatory processes.[8] Furthermore, it has been shown to promote vascular endothelial growth factor (VEGF) while suppressing IL-6 production in alveolar tissues, indicating its capacity to mediate the transition from inflammation to tissue regeneration.[8] This dual capability establishes DMBT1 as a valuable clinical marker for managing inflammatory conditions.

Upregulation of DMBT1 occurs in various inflammatory states, including chronic nasal polyposis and cigarette smoke exposure, and is particularly pronounced

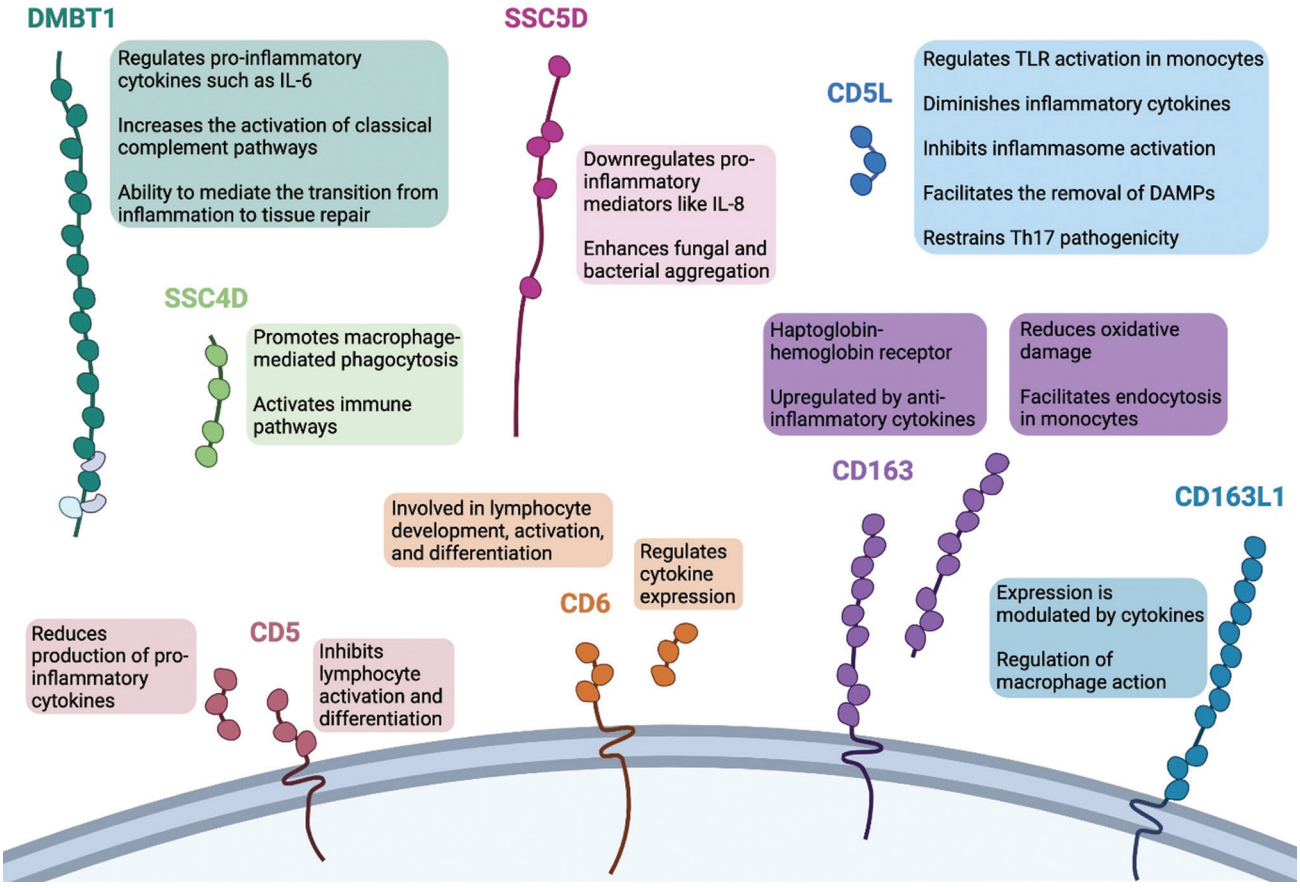

Figure 1. Schematic representation of selected scavenger receptor cysteine-rich (SRCR) superfamily soluble and membrane-anchored members and their anti-inflammatory properties. More details and corresponding literature references can be found in the main text. Figure created using Biorender.com. https://BioRender.com/k15w818.

Abbreviations: SRCR: scavenger receptor cysteine-rich; DAMPs: Damage-associated molecular patterns; DMBT1: Deleted in malignant brain tumors 1; IL: Interleukin; SSC4D: SRCR family member with 4 domains; SSC5D: SRCR family member with 5 domains; TLR: Toll-like receptor.

in the inflamed intestinal mucosa of patients with Crohn's disease and ulcerative colitis, where its levels correlate with disease activity.[9] This upregulation is mediated through nuclear factor kappa B (NF-κB) activation in response to nucleotide-binding oligomerization domain-containing protein 2 (NOD2) stimulation, emphasizing its significance in intestinal inflammation. Remarkably, patients with risk-promoting *NOD2* mutations demonstrate significantly reduced DMBT1 levels in inflamed tissues compared to those with wild-type *NOD2*. In addition, stimulation of Toll-like receptor 4 (TLR4) with lipopolysaccharide (LPS) leads to an increase in DMBT1 expression, facilitated by NF-κB activation. DMBT1 functions to inhibit bacterial invasion and counteract LPS-induced TLR4-mediated NF-κB activation, acting as an extracellular homeostatic element that sustains a balanced immune response.[10] This dynamic indicates a self-regulatory mechanism in which DMBT1 not only suppresses inflammation but also helps combat infections, akin to the functions of secretory IgA. This emphasizes DMBT1's role in anti-inflammatory immune exclusion within an evolutionary context.[6]

While information on the biological functions of SSC4D and SSC5D remains limited, emerging data indicate that both proteins may also have important contributions in resolving inflammation. SSC4D enhances macrophage-mediated phagocytosis and activates immune pathways, thereby supporting a balanced inflammatory response.[5] Likewise, SSC5D plays a crucial role in regulating inflammation by downregulating pro-inflammatory mediators, such as IL-8, effectively mitigating inflammatory responses and reducing overall inflammation.[3]

Among the soluble SRCR proteins, CD5L stands out for its significant anti-inflammatory potential. Primarily produced by macrophages, CD5L recognizes bacterial cell wall components, enhancing antimicrobial responses while simultaneously modulating inflammation.[11] The role of CD5L in clearing biological debris from dead or necrotic cells has been recognized for some time.[12] Recent research has increasingly underscored its importance in regulating lipid biosynthesis and its involvement in various inflammatory conditions, including atherosclerosis, obesity, nephropathy, and autoimmune diseases.[11] In addition, CD5L has been identified as one of the proteins with reduced levels in coronavirus disease 2019 (COVID-19) patients experiencing severe disease.[13] As such, CD5L may serve as a valuable biomarker for assessing inflammation severity and as a potential therapeutic target to mitigate excessive immune activation in critically ill COVID-19 patients.

Studies suggest that CD5L exerts anti-inflammatory effects by lowering levels of inflammatory cytokines and aiding in the clearance of damage-associated molecular patterns (DAMPs) that exacerbate symptoms, particularly in the context of autoimmune arthritis.[14] Conversely, in models such as aortic aneurysm, the administration of an anti-CD5L antibody resulted in decreased CD5L expression and improved survival rates by mitigating inflammatory cytokines, reinforcing its context-dependent actions.[15]

CD5L is also pivotal in modulating TLR activation in monocytes, where it inhibits the production of pro-inflammatory cytokines such as tumor necrosis factor (TNF), IL-1β, and IL-6 whereas promoting the secretion of the anti-inflammatory cytokine IL-10.[16] In addition, by binding to microbial cell wall components, CD5L signals immune cells to reduce inflammation and helps to restrain the pro-inflammatory activity of non-pathogenic Th17 cells.[17] It has also been shown to inhibit NOD-like receptor protein 3 inflammasome activation, thereby decreasing airway inflammation and Th2 immune responses.[18]

Nevertheless, the precise role of CD5L in inflammation is complex and can lead to conflicting effects depending on the disease context. One illustrative example of this complexity is evident in experimental sepsis models, where the effects of recombinant CD5L (rCD5L) administration vary significantly depending on the timing of delivery. When given concurrently with cecal ligation and puncture (CLP) induction, increased mortality is observed, suggesting that early treatment may suppress inflammation to a degree that undermines the beneficial immune response.[19] In contrast, administering rCD5L a few hours after sepsis onset shows protective effects by significantly reducing colony-forming units (CFUs) in both the peritoneum and blood, thereby improving survival rates.[20] However, if rCD5L were solely effective at inactivating pathogens, it would be expected to perform better in the initial model when the microbial load is low. Thus, the increased mortality seen with early administration indicates that its protective benefits extend beyond direct pathogen control, highlighting the significance of timing in its therapeutic application during sepsis.

These observations emphasize the intricate and multifaceted roles of CD5L, highlighting its critical function in modulating inflammatory responses beyond merely controlling pathogens. Transcriptomic profiling of CD5L-knockout mice in the context of CLP revealed a pronounced inflammatory response, reflecting the dysregulated immune responses often seen in sepsis.[20] Collectively, these findings suggest that CD5L may evolve into a valuable therapeutic agent in sepsis, in which the timing of administration is crucial for managing inflammation while preserving essential early immune responses. Ultimately, the anti-inflammatory properties of

CD5L may indeed surpass its antimicrobial effects, offering promising opportunities for therapeutic applications.

3. Cell-surface SRCRs and their cleavage products

While soluble SRCR proteins play pivotal roles in microbial recognition and anti-inflammatory responses, cell-surface receptors such as CD5, CD6, CD163, and CD163 antigen-like 1 (CD163L1) offer a contrasting yet complementary function. These receptors, primarily located on immune cells, exhibit unique dynamics in their engagement with microbial components. While their direct microbial recognition is less pronounced than soluble SRCRs, especially for T-cell antigens such as CD5 and CD6,[4,5,21] their significance emerges when proteolytic cleavage occurs during infections or inflammation.

CD5 is a transmembrane protein primarily expressed in mature T cells and a subset of B cells, characterized by three consecutive SRCR domains. It plays a crucial role in inhibiting T-cell signaling.[22] In various biological contexts, membrane-bound CD5 undergoes cleavage, resulting in the release of soluble CD5 (sCD5). The ectodomain of CD5 specifically interacts with several fungal species by recognizing β-glucans,[23] key components of fungal cell walls. In mouse models of fungal septic shock, administration of recombinant sCD5 led to significant reductions in pro-inflammatory cytokines such as IL-6 and IL-1β, indicating its therapeutic potential in mitigating inflammation and enhancing survival during infections.[23]

Similarly, CD6 is primarily expressed in T cells and some B cells, and also functions as an inhibitory receptor.[24] The ectodomain of CD6 can identify PAMPs, including lipoteichoic acid derived from Gram-positive bacteria and LPS from Gram-negative bacteria,[25] and also recognize saprophytic, non-pathogenic fungal species.[23] Cell-surface CD6 expression can be downregulated through proteolytic cleavage, which contributes to the homeostatic control of ongoing immune responses by increasing T-cell susceptibility to apoptosis and reducing their responsiveness to proliferative stimuli.[26]

Elevated circulating levels of soluble CD6 (sCD6) and sCD5 are observed in patients with primary Sjögren's syndrome.[27] Recently, an increase in CD6 plasma levels has been found to be associated with microbiota modulation of inflammation in psoriatic arthritis.[28] Indeed, CD6 has been investigated as a potential therapeutic target, with itolizumab, a humanized anti-CD6 monoclonal antibody, being explored for the treatment of inflammatory diseases such as psoriasis, rheumatoid arthritis, and complications related to COVID-19.[29-31]

Like CD5L, CD6 has also been utilized in therapeutic animal models of sepsis with relative success. Although the effects of extracellular rCD6 have not been evaluated when administered concurrently with CLP induction, it shows effectiveness when given 1 h after induction onset.[32] However, its efficacy declines if administered later (at 3 or 6 h), resulting in generally less favorable outcomes. This highlights the critical importance of timing in therapeutic interventions.

CD163, predominantly expressed on macrophages and monocytes, functions as an anti-inflammatory receptor that scavenges haptoglobin-hemoglobin complexes and interacts with various pathogens, including viruses and bacteria. Its expression is upregulated by glucocorticoids and anti-inflammatory cytokines such as IL-10, whereas pro-inflammatory signals such as TNF-α and interferon-gamma (IFN-γ) can lead to its suppression.[33] Proteolytic shedding of CD163 releases soluble CD163 (sCD163), which influences immune responses and is elevated in several inflammatory and infectious diseases, including sepsis[34] and COVID-19,[35] making it a valuable biomarker.[33] Similar to its membrane-bound form, sCD163 aids in the clearance of unbound hemoglobin, reducing oxidative damage. CD163 has emerged as a highly promising therapeutic target due to its selective expression on macrophages. As such, drug delivery systems such as liposomes and antibody-drug conjugates targeting CD163 were used in models of LPS-induced inflammation[36] and cancer, where targeting tumor-associated macrophages inhibits tumor growth.[37]

CD163L1 is prominently expressed and colocalizes with CD163 in various macrophage subsets; however, its expression is low or absent in alveolar macrophages, monocytes, glia, and Kupffer cells.[38] Unlike other scavenger receptors, CD163L1 has not been demonstrated to function as a PRR, as it does not interact with any clinically isolated bacterial strains, indicating a distinct mechanism of action. Its expression is upregulated by anti-inflammatory inducers such as IL-10 and macrophage colony-stimulating factor while being suppressed by pro-inflammatory mediators such as LPS, TNF-α, and IFN-γ.[39] The inflammation-resolving effects of CD163L1 are likely attributable to its regulatory function in macrophages and its response to specific cytokines rather than direct interactions with pathogens.

4. Conclusion

SRCR proteins, particularly the soluble members such as CD5L, DMBT1, SSC4D, and SSC5D, play vital roles in microbial recognition and the regulation of inflammatory responses. Their functions as PRRs not only enhance the

immune response to pathogens but also confer significant anti-inflammatory effects that contribute to homeostasis within the immune system. CD5L, in particular, underscores the complementary roles of these proteins, demonstrating pronounced anti-inflammatory activities that complement their microbial recognition capabilities.

Furthermore, the contributions of cell-surface molecules such as CD5, CD6, CD163, and CD163L1 highlight the complexity of the SRCR family, especially within the contexts of infection and inflammation. While these surface proteins may display limited microbial recognition capabilities due to their location on cell membranes, their proteolytic cleavage during inflammatory or infectious conditions generates soluble forms, which can exert critical regulatory influences on inflammation and immune responses.

Overall, the interplay between soluble and membrane-bound SRCR proteins highlights their therapeutic potential in addressing inflammatory disorders and infectious diseases. Future research focused on elucidating the detailed mechanisms governing these proteins will pave the way for innovative therapeutic strategies, enhancing our ability to modulate immune responses and improve host defense against pathogens effectively. As our understanding deepens, SRCR proteins may become essential targets for developing cutting-edge treatments that exploit their multifaceted roles in immune regulation.

Acknowledgments

None.

Funding

This work was supported by National Funds through Fundação para a Ciência e a Tecnologia (FCT), I.P., under the projects 2022.04792.PTDC and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Individual Research Grant to L.O.

Conflict of interest

The authors declare they have no conflict of interest.

Author contributions

Conceptualization: Liliana Oliveira, Alexandre M. Carmo
Visualization: Maria Carolina Silva, Liliana Oliveira
Writing – original draft: Maria Carolina Silva, Rita P. Pinto
Writing – review & editing: Liliana Oliveira, Alexandre M. Carmo

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

1. Martínez VG, Moestrup SK, Holmskov U, Mollenhauer J, Lozano F. The conserved scavenger receptor cysteine-rich superfamily in therapy and diagnosis. *Pharmacol Rev*. 2011;63(4):967-1000.

   doi: 10.1124/pr.111.004523

2. Martínez VG, Escoda-Ferran C, Tadeu Simões I, *et al*. The macrophage soluble receptor AIM/Api6/CD5L displays a broad pathogen recognition spectrum and is involved in early response to microbial aggression. *Cell Mol Immunol*. 2014;11(4):343-354.

   doi: 10.1038/cmi.2014.12

3. Miró-Julià C, Roselló S, Martínez VG, *et al*. Molecular and functional characterization of mouse S5D-SRCRB: A new group B member of the scavenger receptor cysteine-rich superfamily. *J Immunol*. 2011;186(4):2344-2354.

   doi: 10.4049/jimmunol.1000840

4. Bessa Pereira C, Bockova M, Santos RF, *et al*. The scavenger receptor SSc5D physically interacts with bacteria through the SRCR-containing N-terminal domain. article. *Front Immunol*. 2016;7:416.

   doi: 10.3389/fimmu.2016.00416

5. Cardoso MS, Santos RF, Almeida S, *et al*. Physical interactions with bacteria and protozoan parasites establish the scavenger receptor SSC4D as a broad-spectrum pattern recognition receptor. *Front Immunol*. 2021;12:760770.

   doi: 10.3389/fimmu.2021.760770

6. Alharbi AF, Sheng N, Nicol K, Stromberg N, Hollox EJ. Balancing selection at the human salivary agglutinin gene (DMBT1) driven by host-microbe interactions. *iScience*. 2022;25(5):104189.

   doi: 10.1016/j.isci.2022.104189

7. Reichhardt MP, Meri S. SALSA: A regulator of the early steps of complement activation on mucosal surfaces. *Front Immunol*. 2016;7:85.

   doi: 10.3389/fimmu.2016.00085

8. Muller H, Nagel C, Weiss C, Mollenhauer J, Poeschl J. Deleted in malignant brain tumors 1 (DMBT1) elicits increased VEGF and decreased IL-6 production in type II lung epithelial cells. *BMC Pulm Med*. 2015;15:32.

   doi: 10.1186/s12890-015-0027-x

9. Renner M, Bergmann G, Krebs I, *et al*. DMBT1 confers

mucosal protection *in vivo* and a deletion variant is associated with Crohn's disease. *Gastroenterology*. 2007;133(5):1499-1509.

doi: 10.1053/j.gastro.2007.08.007

10. Rosenstiel P, Sina C, End C, *et al*. Regulation of DMBT1 via NOD2 and TLR4 in intestinal epithelial cells modulates bacterial recognition and invasion. *J Immunol*. 2007;178(12):8203-8211.

doi: 10.4049/jimmunol.178.12.8203

11. Sanchez-Moral L, Rafols N, Martori C, Paul T, Tellez E, Sarrias MR. Multifaceted roles of CD5L in infectious and sterile inflammation. *Int J Mol Sci*. 2021;22(8):4076.

doi: 10.3390/ijms22084076

12. Arai S, Miyazaki T. A scavenging system against internal pathogens promoted by the circulating protein apoptosis inhibitor of macrophage (AIM). *Semin Immunopathol*. 2018;40(6):567-575.

doi: 10.1007/s00281-018-0717-6

13. Di Flora DC, Dionizio A, Pereira H, *et al*. Analysis of plasma proteins involved in inflammation, immune response/complement system, and blood coagulation upon admission of COVID-19 Patients to hospital may help to predict the prognosis of the disease. *Cells*. 2023;12(12):1601.

doi: 10.3390/cells12121601

14. Yasuda K, Shimodan S, Maehara N, *et al*. AIM/CD5L ameliorates autoimmune arthritis by promoting removal of inflammatory DAMPs at the lesions. *J Autoimmun*. 2024;142:103149.

doi: 10.1016/j.jaut.2023.103149

15. Fujii T, Yamawaki-Ogata A, Terazawa S, Narita Y, Mutsuga M. Administration of an antibody against apoptosis inhibitor of macrophage prevents aortic aneurysm progression in mice. *Sci Rep*. 2024;14(1):15878.

doi: 10.1038/s41598-024-66791-7

16. Sanjurjo L, Amezaga N, Aran G, *et al*. The human CD5L/AIM-CD36 axis: A novel autophagy inducer in macrophages that modulates inflammatory responses. *Autophagy*. 2015;11(3):487-502.

doi: 10.1080/15548627.2015.1017183

17. Wang C, Yosef N, Gaublomme J, *et al*. CD5L/AIM regulates lipid biosynthesis and restrains Th17 cell pathogenicity. *Cell*. 2015;163(6):1413-1427.

doi: 10.1016/j.cell.2015.10.068

18. Weng D, Gao S, Shen H, *et al*. CD5L attenuates allergic airway inflammation by expanding $CD11c^{high}$ alveolar macrophages and inhibiting NLRP3 inflammasome activation via HDAC2. *Immunology*. 2022;167:384-397.

doi: 10.1111/imm.13543

19. Gao X, Yan X, Yin Y, *et al*. Therapeutic targeting of apoptosis inhibitor of macrophage/CD5L in sepsis. *Am J Respir Cell Mol Biol*. 2019;60(3):323-334.

doi: 10.1165/rcmb.2018-0272OC

20. Oliveira L, Silva MC, Gomes AP, *et al*. CD5L as a promising biological therapeutic for treating sepsis. *Nat Commun*. 2024;15(1):4119.

doi: 10.1038/s41467-024-48360-8

21. Oliveira L, Carmo AM. Response: Commentary: The scavenger receptor SSc5d physically interacts with bacteria through the SRCR-containing N-terminal domain. *Front Immunol*. 2017;8:1004.

doi: 10.3389/fimmu.2017.01004

22. Tarakhovsky A, Kanner SB, Hombach J, *et al*. A role for CD5 in TCR-mediated signal transduction and thymocyte selection. *Science*. 1995;269(5223):535-537.

doi: 10.1126/science.7542801

23. Vera J, Fenutría R, Cañadas O, *et al*. The CD5 ectodomain interacts with conserved fungal cell wall components and protects from zymosan-induced septic shock-like syndrome. *Proc Natl Acad Sci U S A*. 2009;106(5):1506-1511.

doi: 10.1073/pnas.0805846106

24. Oliveira MI, Goncalves CM, Pinto M, *et al*. CD6 attenuates early and late signaling events, setting thresholds for T-cell activation. *Eur J Immunol*. 2012;42(1):195-205.

doi: 10.1002/eji.201040528

25. Sarrias MR, Farnos M, Mota R, *et al*. CD6 binds to pathogen-associated molecular patterns and protects from LPS-induced septic shock. *Proc Natl Acad Sci U S A*. 2007;104(28):11724-11729.

doi: 10.1073/pnas.0702815104

26. Carrasco E, Escoda-Ferran C, Climent N, *et al*. Human CD6 down-modulation following T-cell activation compromises lymphocyte survival and proliferative responses. *Front Immunol*. 2017;8:769.

doi: 10.3389/fimmu.2017.00769

27. Ramos-Casals M, Font J, García-Carrasco M, *et al*. High circulating levels of soluble scavenger receptors (sCD5 and sCD6) in patients with primary Sjögren's syndrome. *Rheumatology* (*Oxford*). 2001;40(9):1056-1059.

doi: 10.1093/rheumatology/40.9.1056

28. Kragsnaes MS, Jensen JRB, Nilsson AC, *et al*. Dynamics of inflammation-associated plasma proteins following faecal microbiota transplantation in patients with psoriatic arthritis and healthy controls: Exploratory findings from the FLORA trial. *RMD Open*. 2024;10(1):e003750.

doi: 10.1136/rmdopen-2023-003750

29. Falcon Lincheta L, Saumell Napoles Y, Gray Lovio OR, *et al*.

Long-term therapy with itolizumab is safe and effective for patients with moderate to severe psoriasis: Results from an expanded-access program. *Int Immunopharmacol*. 2024;134:112225.

doi: 10.1016/j.intimp.2024.112225

30. Rodriguez PC, Prada DM, Moreno E, *et al*. The anti-CD6 antibody itolizumab provides clinical benefit without lymphopenia in rheumatoid arthritis patients: Results from a 6-month, open-label Phase I clinical trial. *Clin Exp Immunol*. 2018;191(2):229-239.

doi: 10.1111/cei.13061

31. Loganathan S, Athalye SN, Joshi SR. Itolizumab, an anti-CD6 monoclonal antibody, as a potential treatment for COVID-19 complications. *Expert Opin Biol Ther*. 2020;20(9):1025-1031.

doi: 10.1080/14712598.2020.1798399

32. Martinez-Florensa M, Consuegra-Fernandez M, Aranda F, *et al*. Protective effects of human and mouse soluble scavenger-like CD6 lymphocyte receptor in a lethal model of polymicrobial sepsis. *Antimicrob Agents Chemother*. 2017;61(1):e01391-16.

doi: 10.1128/AAC.01391-16

33. Etzerodt A, Moestrup SK. CD163 and inflammation: Biological, diagnostic, and therapeutic aspects. *Antioxid Redox Signal*. 2013;18(17):2352-2363.

doi: 10.1089/ars.2012.4834

34. Mierzchala-Pasierb M, Lipinska-Gediga M, Lewandowski L, Krzystek-Korpacka M. Alterations in serum concentration of soluble CD163 within five study days from ICU admission are associated with in-hospital mortality of septic patients-A preliminary study. *Int J Environ Res Public Health*. 2023;20(3):2263.

doi: 10.3390/ijerph20032263

35. Volfovitch Y, Tsur AM, Gurevitch M, *et al*. The intercorrelations between blood levels of ferritin, sCD163, and IL-18 in COVID-19 patients and their association to prognosis. *Immunol Res*. 2022;70(6):817-828.

doi: 10.1007/s12026-022-09312-w

36. Thomsen KL, Moller HJ, Graversen JH, *et al*. Anti-CD163-dexamethasone conjugate inhibits the acute phase response to lipopolysaccharide in rats. *World J Hepatol*. 2016;8(17):726-730.

doi: 10.4254/wjh.v8.i17.726

37. Etzerodt A, Moulin M, Doktor TK, *et al*. Tissue-resident macrophages in omentum promote metastatic spread of ovarian cancer. *J Exp Med*. 2020;217(4):e20191869.

doi: 10.1084/jem.20191869

38. Moeller JB, Nielsen MJ, Reichhardt MP, *et al*. CD163-L1 is an endocytic macrophage protein strongly regulated by mediators in the inflammatory response. *J Immunol*. 2012;188(5):2399-2409.

doi: 10.4049/jimmunol.1103150

39. Gonzalez-Dominguez E, Samaniego R, Flores-Sevilla JL, *et al*. CD163L1 and CLEC5A discriminate subsets of human resident and inflammatory macrophages *in vivo*. *J Leukoc Biol*. 2015;98(4):453-466.

doi: 10.1189/jlb.3HI1114-531R