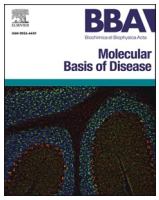
BBA - Molecular Basis of Disease 1871 (2025) 167761

Contents lists available at ScienceDirect

BBA - Molecular Basis of Disease

journal homepage: www.elsevier.com/locate/bbadis



Review

Sepsis and high-density lipoproteins: Pathophysiology and potential new therapeutic targets

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ARTICLE INFO

Keywords:
ApoA-I_{Milano}
High-density lipoproteins
LPS
Sepsis
Toll-like receptor

ABSTRACT

In 2020, sepsis has been defined a worldwide health major issue (World Health Organization). Lung, urinary tract and abdominal cavity are the preferred sites of sepsis-linked infection. Research has highlighted that the advancement of sepsis is not only related to the presence of inflammation or microbial or host pattern recognition. Clinicians and researchers now recognized that a severe immunosuppression is also a common feature found in patients with sepsis, increasing the susceptibility to secondary infections. Lipopolysaccharides (LPS) are expressed on the cell surface of Gram-negative, whereas Gram-positive bacteria express peptidoglycan (PGN) and lipoteichoic acid (LTA). The main mechanism by which LPS trigger host innate immune responses is binding to TLR4-MD2 (toll-like receptor4-myeloid differentiation factor 2), whereas, PGN and LTA are exogenous ligands of TLR2. Nucleotide-binding oligomerization domain (NOD)-like receptors are the most well-characterized cytosolic pattern recognition receptors, which bind microbial molecules, endogenous by-products and environmental triggers. It has been demonstrated that high-density lipoproteins (HDL), besides their major role in promoting cholesterol efflux, possess diverse pleiotropic properties, ranging from a modulation of the immune system to anti-inflammatory, anti-apoptotic, and anti-oxidant functions. In addition, HDL are able at i) binding LPS, preventing the activating of TLR4, and ii) inducing the expression of ATF3 (Activating transcription factor 3), a negative regulator of the TLR signalling pathways, contributing at justifying their capacity to hamper infection-based illnesses. Therefore, reconstituted HDL (rHDL), constituted by apolipoprotein A-I/apolipoprotein A-I_{Milano} complexed with phospholipids, may be considered as a new therapeutic tool for the management of sepsis.

1. Introduction

The term "sepsis" encompasses a complex clinical syndrome. Sepsis is the result of a detrimental or noxious host response to infection [1]. Diverse evidence highlighted that, besides the importance of discovery the underlying pathogenic mechanisms of the sepsis development, it is crucial to understand the fundament principles regulating microbial-host interactions. Clinical studies have demonstrated that different therapeutic strategies have been succeeded in significantly reducing the death rate from sepsis-related diseases and septic shock [2].

It has been shown that, when a physiological host response to microbe-based infections is exaggerated and then not controlled, sepsis develops. In 1992, it has been coined the first definition of sepsis (namely, Sepsis-1): "sepsis is a systemic inflammatory syndrome in response to infection which, when associated with acute organ dysfunction, such as acute renal failure, is said to be severe", by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) [3]. A 2001 collaborative unit, identifying restrictions with this definition, added new diagnostic criteria (Sepsis-2) [4]. Finally, the Third International consensus definitions for Sepsis and Septic Shock (Sepsis-3) stated that: "sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, whereas septic shock should be defined as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase the mortality" [2].

Nowadays, sepsis still affects a shocking high number of patents, reaching around 48.9 million cases of sepsis and 11 million sepsis-related deaths per year worldwide in 2017 [5]. As a consequence, in 2020, the World Health Organization (WHO) declared sepsis a worldwide health priority [6].

The preferred sites of sepsis-linked infection are the lung (43 %), the urinary tract (16 %), the abdominal cavity (14 %), the head (14 %) and the blood stream/other sites (13 %) [7]. Additionally, research has highlighted that the advancement of sepsis is not only related to the

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https://doi.org/10.1016/j.bbadis.2025.167761
Received 14 October 2024; Received in revised form 19 January 2025; Accepted 25 February 2025
Available online 3 March 2025

presence of inflammation or microbial or host pattern recognition. Indeed, sepsis impacts on tunica intima, immune cells, coagulation cascade and nervous system, this latter effect due to a direct action on microglial cells and neurons [8–11]. Finally, sepsis is characterized by the presence of a cytokine storm, mainly constituted by tumour necrosis factor (TNF), Type I interferons (IFNs), Interleukin-1 (IL-1), IL-6, IL-8 and IL-10 [12]. Nevertheless, diverse clinical studies using anti-inflammatory treatment approaches to control and halting this excessive inflammation have been unsuccessful [13]. Consequently, clinicians and researchers now recognized that a severe immunosuppression, caused by excessive lymphocytes apoptosis, is also a common feature found in patients with sepsis, increasing the susceptibility to secondary infections [14]. Specifically, it has been demonstrated that thymocytes (aka precursors of T cells) apoptosis is a major mechanism of lymphocyte depletion in sepsis [15].

The challenger ahead lies in identifying new diagnostic tools that allow to recognize patients with features that will have a higher probability to take advantage from a therapeutic approach based on a peculiar biological phenotype [16]. This "predictive enrichment of the treatment population", together with the "precision medicine" - that is, pharmacological interventions taking patient-unique phenotype into account – could enhance the odds of demonstrating the desired effects [14]. In parallel, the technological and methodological enhancements in zebrafish model, applied to the sepsis research, should provide novel insights and therapeutic breakthroughs aiming at significantly improving clinical outcomes [17].

High-density lipoproteins (HDL), besides their major role in promoting cholesterol efflux, possess diverse pleiotropic properties protecting the body from exogenous harmful chemicals of biologicals or support at repairing a damage caused by detrimental compounds [18]. Indeed, HDL modulate the activation of immune cells (mainly T cells), influence the expression of pro-inflammatory/anti-inflammatory molecules, and prevent oxidation and endothelial dysfunction [19,20].

This review aims at giving an overview of the pathophysiology of the sepsis and the interplay with HDL. Moreover, the role played by the apolipoprotein A-I_{Milano} (apoA-I_M) and apoA-II (apolipoprotein that, together with apoA-I, represents the main protein of HDL) in the hepatic expression of genes related to "inflammatory response and response to molecule of bacterial origin" and "antigen processing and presenting and inflammatory response" pathways, respectively, is also discussed [21].

2. Pathophysiology of sepsis

2.1. Microbial components involved in sepsis pathology

A major achievement in the sepsis field, especially from a therapeutic point of view, has been achieved when the bacterial components, triggering the septic process, have been identified. These bacteria motifs, named pathogen-associated molecular patterns (PAMPs), bind to specific pattern recognition receptors (PRRs), localized in cells of the innate immune system [i.e., monocytes, macrophages and dendritic cells (DCs)] as well as in fibroblasts, and epithelial and endothelial cells [22–24]. In Gram-negative bacteria, lipopolysaccharides (LPS), aka, endotoxins, play a dominant role. The term "endotoxin" was coined in 1892 [25]. Notwithstanding the etymology of the word "endotoxins", these molecules dwell on the surface of the cells and are not located inside the bacteria [26]. Chemically, LPS are constituted by a hydrophilic heteropolysaccharide covalently linked to a hydrophobic lipid A portion, which attaches the LPS to the external face of the outer membrane of the Gram-negative bacteria. In vitro and in vivo studies recognized the free lipid A as the portion causing the biological effects of LPS [27]. Based on their bacterial origin, the molecular composition of endotoxins widely differs in number of fatty acids, and atom of carbons, type of sugars, presence of phosphate groups, and charges. Of note, an important correlation between structure and bioactivity has been observed [27].

Conversely, no endotoxins have been found into Gram-positive bacteria, but their membranes present peptidoglycan (PGN) and lipoteichoic acid (LTA). However, up-to-now it is still unclear if these molecules display a crucial role in the pathogenesis of clinical sepsis [28]. Of note, it is strengthened that Gram-positive bacteria secrete powerful exotoxins, and it has been demonstrated that diverse are involved in septic shock [29]. These Gram-positive exotoxins play a dramatic crucial role because they display the properties of superantigens, i.e., a family of non-glycosylated low-molecular-weight exoproteins [30,31]. These proteins are unusually resistant to heat and desiccation, and generally resistant to proteolysis and acid [31,32]. For these characteristics some superantigens have been classified as "agents of bioterrorism". These superantigens share two diverse activities: 1) pyrogenicity and 2) enhancement (by up to 10^6-fold) of susceptibility to lethal shock induced by LPS [33,34], crucial in human illness [35]. This interplay could, at least in part, justify the life-threatening nature of the clinical picture of the shock illness [35]. Specifically, Marrack and Kappler coined the term "superantigen" to stress the peculiar manner these pyrogenic toxins promote T cell proliferation [30]. Indeed, superantigens are able to connect, acting like a bridge, the TCR (T cell receptor) on T lymphocytes with major histocompatibility complex class II (MHC II) molecules on antigen-presenting cells (APCs), in a quite non-specific manner, causing a dramatic proliferation of T cells and activation of DCs and macrophages [31,36–38].

2.2. Host response to microbial components

Diverse types of molecules can act as PAMPs, and among them, LPS, PGN, LTA, bacterial lipoproteins and nucleic acid (i.e., CpG DNA, dsDNA, dsRNA) are the more characterized [1]. Conversely, four divergent types of PRR families have been identified up-to-now. Toll-like receptors (TLRs) and C-type lectin receptors (CLRs) are transmembrane proteins, whereas Retinoic acid-inducible gene (RIG)-I-like receptors (RLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) are cytoplasmic proteins. The binding of PAMPs to PRRs actives these receptors (with the exception of some NLRs), eventually leading to the upregulation of the synthesis of genes, engaged in the inflammatory responses as well as the activation of adaptive immunity and cellular metabolism [23]. However, this physiological reaction is a double-edged sword because may determine i) the clearance of the bacteria by effector cells and complement systems or ii) the uncontrolled release of pro-inflammatory cytokines, causing tissue damage, organ failure, and death (i.e. sepsis or septic shock) [39]. Of note, excessive inflammation causes the release of damage-associated molecular patterns (DAMPs, also known as alarmins [40]) able at binding and activating PRRs, leading to a "malignant cycle" involving a pathological immune activation and organ dysfunction [41].

The main mechanism by which LPS trigger host innate immune responses is via the binding to TLR4-MD2 (myeloid differentiation factor 2) complex localized in lipid rafts on the membrane of monocytes, macrophages and DCs [42]. Of note, lipid rafts, defined as "small, heterogenous, highly dynamic, sterol and sphingolipid-enriched domains that compartmentalize cellular processes", play a key role in the correct localization of the receptors/ligands implicated in cellular signalling, namely TLRs and antigen presentation and signal transduction molecules [43,44]. It has been demonstrated that triggers causing cholesterol depletion are able to modify the lipid raft activities [45]. Indeed, lipid rafts disruption, for example via cholesterol depletion with cyclodestrin, normalized the response to LPS [46] as well as hindered antigen presentation and T cell activation [47]. Similar results were obtained using HDL and apoA-I, known agents able to promote cholesterol efflux from cell membranes [48–50].

Two fundamental molecules, the LPS-binding protein (LBP) and the co-receptor CD14, guarantee the efficient and specific transfer of LPS to the TLR4-MD2 complex [51]. LBP is a hepatic acute phase glycoprotein

which is included into the lipid-binding protein/lipid-transfer protein family, along with bacterial/permeability increasing protein (BPI), cholesteryl ester transfer protein (CETP), and phospholipid transfer protein (PLTP) [52]. While, CD14 is biologically active as either a glycosylphosphatidylinositol (GPI)-anchored membrane protein (mCD14) on myeloid cells or as a secreted soluble protein (sCD14) in the serum. Therefore, the sCD14 enables constitutively CD14 negative-cells, such as epithelial and endothelial cells, to retort to LPS [53]. It has been demonstrated that the serum levels of LBP and sCD14 sharply increase during sepsis [54,55]. Ryu et al. demonstrated that specific TLR4 domains are required for efficient LPS transfer from CD14 to MD2 [56]. Eventually, the LPS induces the recruitment of a M-shaped receptor multimer formed by two copies of the TLR4/MD2/LPS complex set up in a symmetrical fashion [57]. This dimerization is necessary to trigger the initiation of distinct signal pathways, leading to the phosphorylation/activation of the transcription factors, nuclear factor kappa B (NF-kB) and interferon regulatory factor 3 (IRF3), and the mitogen-activated protein kinases (MAPKs) (Fig. 1) [23].

Gram-positive cell-wall structures are exogenous ligands of TLR2 [58]. Upon the binding with ligands, TLR2 becomes a M-shaped heterodimer with either TLR1 or TLR6 (Fig. 1) [59]. It has been demonstrated that the activation of these TLR1/TLR2 or TLR6/TLR2 complexes

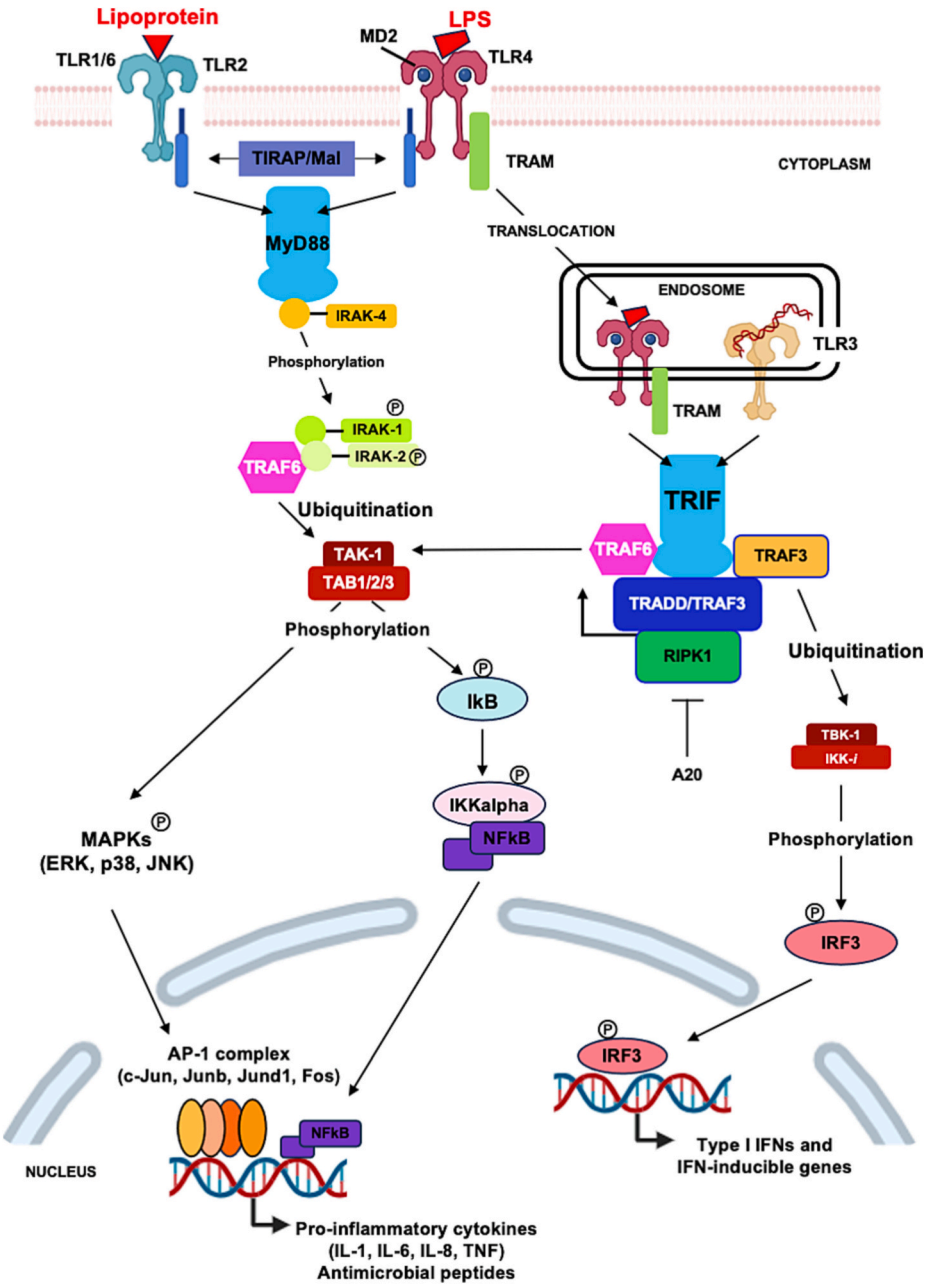

Fig. 1. Toll Like Receptor 1/6 (TLR1/6), TLR2, TLR3, TLR4 and signalling pathway. Lipoproteins and LPS are recognized on the cell surface by a M-shaped heterodimer of TLR1/6 and TLR2, and by a multimer composed of two copies of the TLR/MD2 complex, respectively. Ligand stimulation recruits MyD88 and TIRAP/Mal to the TLRs, eventually leading to the AP-1 complex and NF-kB translocation to the nucleus, where they drive the gene expression of diverse pro-inflammatory cytokines and antimicrobial peptides. Conversely, dsRNA are ligands of TLR3 present in the endosome. In this latter intracellular organelle, following LPS triggering, translocate TLR4 together with TRAM. The stimulation of the endosome's TLRs actives a TRIF-dependent signalling, which, through NF-kB and IRF3 activation, promotes pro-inflammatory cytokines and type I IFNs, respectively. Please refer to the text for meaning of the all abbreviations used in the figure. [Created in BioRender.com].

promotes the gene expression of diverse pro-inflammatory proteins in macrophages and DCs [23].

3. Toll-like receptor signalling pathways

TLRs, together with IL-1 receptors (IL1Rs), are part of the TIR (Toll/inteleukin-1 receptor) superfamily [60]. All these receptors contain the conserved cytosolic region, called TIR domain, through which they signal and active common signalling pathways. The diversity in the signalling pathways stimulated by the single TLRs is, in part, clarified by the TIR domain-containing adaptor molecules associated to TLRs [61]. Five TIR-domain-containing adaptors have been recognized up-to-now: MyD88 (Myeloid differentiation primary response 88), TRIF (TIR domain-containing adaptor inducing IFN-beta; aka TICAM1), TIRAP/MAL (MyD88-adapter-like protein), TRIF-related adaptor molecule (TRAM), and Sterile-alpha and Armadillo motif-containing protein (SARM) [61]. TLRs signalling include two different pathways, one using MyD88 and the other using TRIF, respectively [23,62] (Fig. 1). More in details, upon the activation of TRL2/4, the TIR domain of MyD88 catches the TLR2/4-TIR domain allowing the recruitment of MyD88 to TLR2/4 receptor [63] (Fig. 1). Additionally, TLR2/TLR1/6 and TLR4 signalling needs TIRAP/MAL to connect TLRs with MyD88. This step permits the recoverment and activation of IL-1R-associated kinase (IRAK)-4, a serine/threonine kinase containing an N-terminal death domain (DD), also present in the MyD88 adapter. IRAK-4 phosphorylates IRAK-1 and 2 [64]. These two phosphorylated IRAKs then dissociate from MyD88 and active tumour-necrosis factor-receptor-associated factor (TRAF)-6, that acting as an E3 ubiquitin ligase, containing two ubiquitin-conjugating enzymes, able to activate the complex formed by transforming growth factor-beta (TGF-beta)-activated kinase 1 (TAK1), TAK-1-binding protein 1 (TAB1), TAB2 and TAB3 [65] (Fig. 1). This activated complex phosphorylates the protein kinase, i.e. the inhibitory subunit beta of NF-kB kinase (IKKbeta, aka IkB kinase), and three MAPKs, including ERK, p38 and c-Jun-N-terminal kinase (JNK) [66–68]. In turn, IkB kinase phosphorylates the inhibitory subunit alpha (IKKalpha), which results in ubiquitination and dissociation of IKKalpha from NF-kB. The activated NF-kB is then translocated into the nucleus [66–68] (Fig. 1). Simultaneously, the phosphorylated MAPKs induce the formation of the AP-1 transcription factor complex, formed by c-Jun, Junb, Jund1 and Fos, and its translocation to the nucleus [66–68]. In the nucleus, these transcription factors bind to response elements and mediate the gene expression of cytokines, chemokines and anti-microbial-peptides [23,69] (Fig. 1).

On the contrary, TLR3, recognized by microbial nucleic acids and endogenous nucleic acids produced in pathogenic states, uses only the adaptor molecule TRIF [70] (Fig. 1). Of note, TLR4 signals both MyD88- and TRIF-dependent pathways. Differently from TLR3, TLR4 needs the TRAM-adaptor molecule to activate TRIF [71,72]. TRIF is involved in two distinct pathways aiming at activating NF-kB and MAPKs: 1) the TRAF6-dependent and 2) the receptor interacting serine/threonine kinase 1 (RIPK1)-dependent signalling pathways [73]. Indeed, upon TLR3/4 activation, TRIF may directly associate with and activate TRAF-6 by TRAF-binding sequences included in its N-terminal portion [74] (Fig. 1). Conversely, TRIF may recruit the signalling complex formed by the adaptor molecules, TRADD (TNF receptor 1-associated death domain) and TRAF3, and the kinase RIPK1, or directly bind and activate TRAF3 [23]. Subsequently, TRADD binds to RIPK1 and, stimulating the ubiquitination of RIPK1, facilitates the full induction of NF-kB and MAPK signalling pathways [75] (Fig. 1). While, when activated, TRAF-3 works as an E3 ubiquitin ligase by activating two IKK-related kinases, TANK-binding kinase 1 (TBK1) and IKK-*i* (aka, IKK-epsilon) [76,77]. Eventually, TBK1 and IKK-*i* phosphorylate IRF3, which migrates to the nucleus leading to the induction of type I IFNs and expression of IFN-inducible genes. [78] (Fig. 1). This pathway is sometimes indicated as the MyD88-independent pathway [71].

4. Nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) signalling pathway

NLRs are the most well-characterized cytosolic PRRs, that are activated by viruses and bacteria PAMPs, endogenous by-products of tissue damage and environmental compounds [79]. Upon activation, they influence diverse cell activities (such as, proliferation, apoptosis, autophagy and tissue repair) through signalling pathways. NOD1 and NOD2 are two NLRs, activated by specific bacterial ligands, that play seminal roles in both host defence and tissue homeostasis [80]. Structurally, NOD1 and NOD2 are characterized by a C-terminal leucin-rich repeat (LRR) domain fundamental for ligand sensing, a central nucleotide-binding domain (NBD) and an N-terminal caspase activation recruitment domain (CARD) (Fig. 2). Of note, one and two CARD are present into the NOD1 and NOD2, respectively [81,82] (Fig. 2). In addition, NOD1 is ubiquitously expressed in cells [83], whereas NOD2 has been detected primarily in immune (i.e., monocyte/macrophages and DCs) and epithelial (i.e., Paneth cells and keratinocytes) cells [84,85].

The activation of NOD1 and NOD 2 requires the association with the membranes, even though they are cytosolic receptors [86,87]. This association needs an intact LRR domain [87]. It has been recently demonstrated that S-palmitoylation is fundamental for the correct membrane targeting as well as downstream signalling [88]. Additionally, in this study the authors found that this reaction is mediated by the ZDHHC5 enzyme, constitutively localized into phagosomes [88]. Altogether, these data highlighted that both the existence of ZDHHC5 and its enzymatic activity are crucial for the physiological attachment of NOD1 and NOD2 to the plasma membrane and phagosomes (Fig. 2) [88,89].

Upon sensing their ligands, a conformational change of both NOD1 and NOD2 takes place, determining the homo-oligomerization of two NOD molecules, necessary for recruiting the adapter proteins TRAF2 and RIPK2, this latter presents an N and C-terminal CARD, able to interact with the homotypic CARD-CARD. This step leads to the ubiquitination of RIPK2 within its kinase domain, and subsequently to the activation of NF-kB, MAPKs and IRF3/7 pathways (Fig. 2). Additionally, autophagy in diverse cell types is induced by NOD1 and NOD2 pathway [90]. Of note, the induction of autophagy does not require RIPK2 and downstream signalling, but it rather requires the interaction with ATG16L1, an autophagy regulator, at the plasma membrane (Fig. 2) [91,92]. This interaction promotes the retirement of the microorganisms into autophagosomes, eventually stimulating their clearance (Fig. 2) [92].

5. Negative regulation of patter recognition receptor's signalling pathways

Keeping in mind that TLR activation could represent a life-threatening process, it is not surprising that these signalling pathways are under tight downregulation. Specifically, during acute infection, soluble TLRs, synthesized both in blood and tissues, may represent the primary level of negative regulation, preventing overreaction of the host response to microorganisms (Fig. 3) [93]. Once the TLR signalling have been activated, constitutively expressed or induced intracellular regulators can hamper TLR pathways (Fig. 3) [69]. Otherwise, nuclear transcriptional repressors, modulating gene expression, are also present and classified as basal repressors and inducible repressors [94]. Of note, basal repressors alt the gene expression of the primary response, whereas inducible repressors hinder the expression of genes involved in the secondary inflammatory response [94]. Additionally, this regulation may be mediated by reducing the number of TLRs, through the down-regulation of the gene expression of TLRs, or by the degradation of TLR proteins [95–97]. Finally, TLRs may act as death receptors by inducing cell death, therefore ensuring the apoptosis of over-reactive cells [98–100].

The intracellular/membrane-bound negative regulators include MyD88s, IRAK-M, SOCS1, NOD2, PI3K, A20, TOLLIP, ST2, SIGIRR, TRAILR, nuclear basal repressor and ATF3 (Figs. 3 and 4) [69].

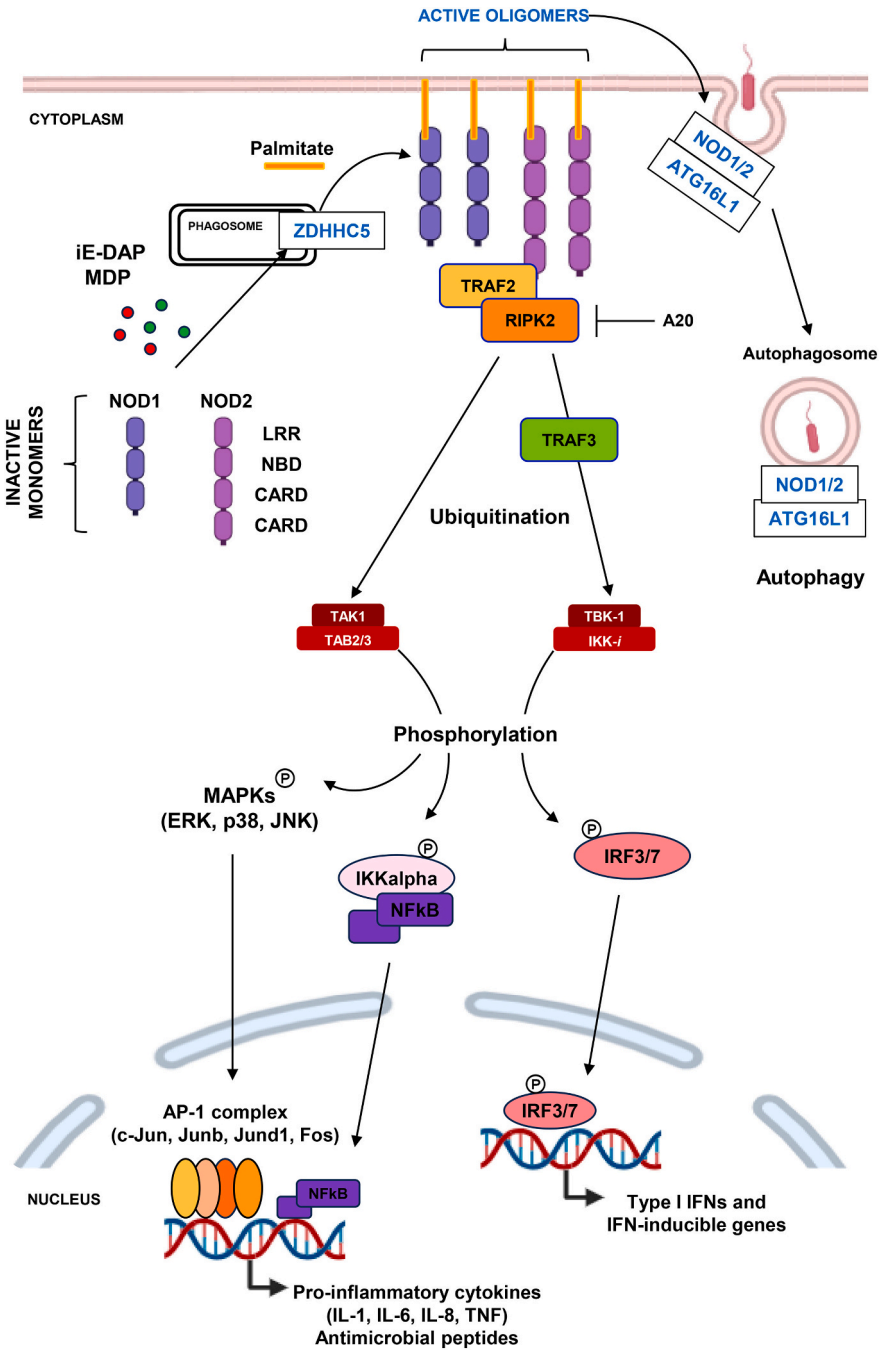

Fig. 2. Nucleotide-binding oligomerization domain (NOD) 1 and NOD2 signalling pathway. NOD 1 and NOD 2 are activated by fragments of peptidoglycan (PNG), such as iE-DAP and MDP. Upon sensing their ligands, a homo-oligomerization of two molecules of NOD1 or NOD2 occurs, together with the association with the plasma membrane mediated by a S-palmitoylation reaction catalysed by the ZDHHC5 enzyme, constitutively localized into phagosomes. This conformational change is necessary for recruiting the adapter proteins TRAF2 and RIPK2 and the following NF-kB and MAPKs activation. NOD1 and NOD2 can also induce autophagy, through the interaction with the autophagy regulator ATG16L1. Please refer to the text for meaning of the all abbreviations used in the figure. [Created in BioRender.com].

The short form of MyD88 (MyD88s), lacking the interdomain, hinders the phosphorylation of IRAK1/2 by IRAK4 (Fig. 3). Therefore, these kinases cannot assemble to the receptor complex [101–103]. IRAK-M is a kinase-deficient component of the TLR/IRAK family. Studies have shown that its expression is significantly up-regulated by LPS. The underlying mechanism is not completely elucidated yet. However, it has been reported that IRAK-M might: 1) hamper the dissociation of IRAK-1 and IRAK-4 from the TLR complex, eventually preventing IRAK-1/TRAF-6 downstream signalling (Fig. 3) [104]; 2) stabilize the MAPKs (Fig. 3) [105]; 3) downregulate the non-canonical NF-kB pathway [106].

Class IA phosphatidylinositol 3-kinases (PI3Ks) are heterodimers containing a p85 regulatory subunit and a p110 catalytic subunit. Growth factor receptor tyrosine kinases (RTKs) as well as TLRs ligands are able to turn-on the enzymatic activity of PI3Ks [107]. They catalyse the phosphorylation of the 3′-hydroxyl group of phosphatidylinositol-4,5-bisphosphate (PI-4,5-P_2) to form the phosphatidylinositol-3,4,5-trisphosphate (PIP_3), leading to the recruitment/activation of 3-phosphoinositide-dependent kinase (PDK1) and protein serine/threonine kinase (AKT) (Fig. 4) [108]. It has been demonstrated that AKT

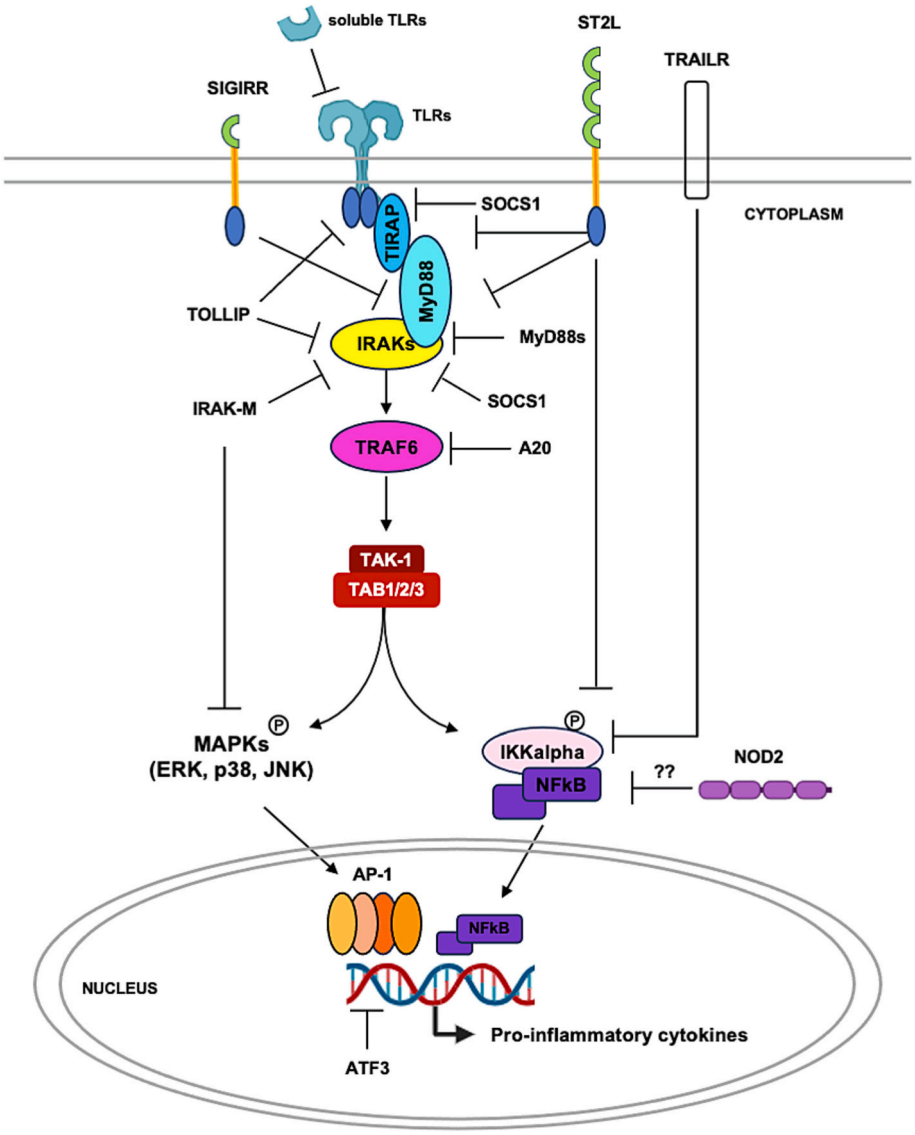

Fig. 3. Negative regulation of TLR signalling pathways. Toll-like receptor (TLR) signalling pathways are under tight negative regulation, which is achieved at multiple levels. The first line of negative regulation is represented by soluble TLRs produced in blood and tissues, following by intracellular/membrane bound (constitutively expressed or induced) negative regulators and nuclear transcriptional repressors. Please refer to the text for meaning of the all abbreviations used in the figure. [Created in BioRender.com].

promotes the phosphorylation of the serine/threonine kinase mTOR (mechanistic target of rapamycin) (Fig. 4) [109]. Then, the activated form of mTOR phosphorylates the p70 S6 kinase (S6K) [110] which, eventually, promote the synthesis and phosphorylation of hypoxia-inducible factor 1 (HIF1) alpha [111–114]. The phosphorylated form of HIF-1alpha migrates to the nucleus where it binds to aryl hydrocarbon receptor nuclear translocator (ARNT, aka HIF-1beta), forming the transcription factor HIF-1 (Fig. 4). The heterodimer HIF-1, interacting with p300/CBP [CREB (cyclic AMP-response element-binding protein) binding protein], attaches with the hypoxia response elements (HREs) present into the HIF target genes. Eventually, this interaction actives the synthesis of inducible nitric oxide synthase (iNOS), vascular endothelial growth factor (VEGF), erythropoietin (EPO), glucose transporter 1 (GLUT1), glycolytic enzymes, and diverse HIF target genes (such as, IL-10) linked to the enhancement of cell survival (Fig. 4) [115,116]. Indeed, IL-10 is a potent anti-inflammatory cytokine which actives STAT3, thus inhibiting inflammatory responses [117,118]. Additionally, the activated AKT phosphorylates glycogen synthase kinase 3beta (GSK3beta) and Forkhead Box protein O1 (FOXO1), preventing their nuclear translocation. Eventually, this phosphorylation/inhibition determines a reduction in MAPKs/NF-kB-dependent transcription of inflammatory genes, such as TNF, IL-1, IL-6 and IL-12 (Fig. 4) [119–123]. This was observed in mice lacking proteins activated by the PI3K pathway [124,125], as well as in experimental studies using pharmacological inhibition of AKT [120]. However, even though all TLRs can activate the PI3K signalling, the underlying mechanism is not clear yet. One candidate is the B-cell adapter for PI3K (BCAP), a large cytosolic protein containing four YxxM motifs (crucial for the p85 PI3K subunit phosphorylation) and a TIR domain (Fig. 4). Indeed, macrophages lacking BCAP produce higher amount of pro-inflammatory cytokines compared to wild-type macrophages, and BCAP knock-out mice shown an increased susceptibility to LPS toxicity assays compared to wild-type animals [126–128]. Recent data also demonstrated that macrophages lacking BCAP incubated with TLR ligands secrete a higher concentration of inflammatory proteins and, importantly, do not stimulate the expression of genes associate with the macrophage-reparative transition [129].

A20 (aka TNFAIP3) is a deubiquitinating protein that inhibit NF-kB-

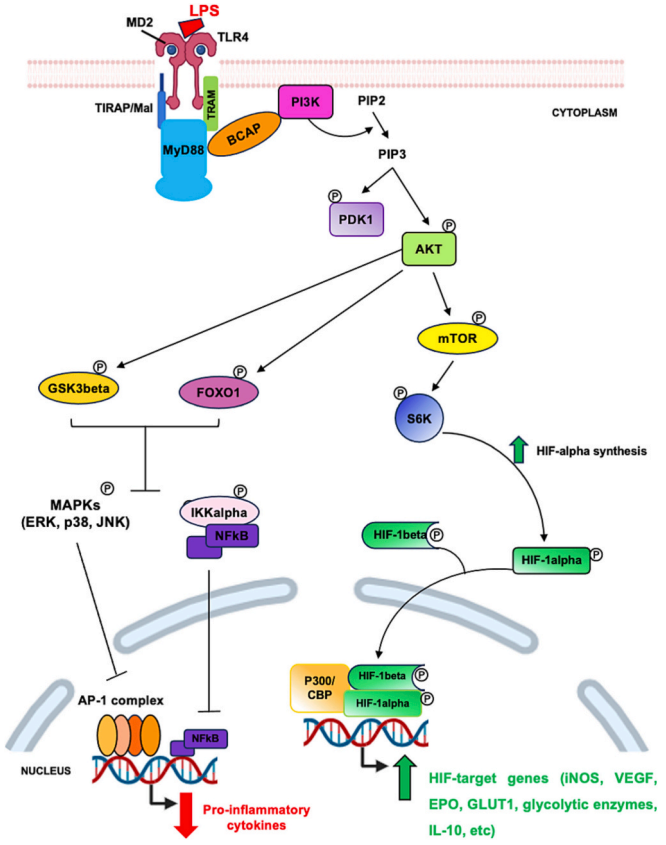

Fig. 4. Schematic representation of the PI3K-AKT pathway. TLR's ligands actives the PI3K-AKT signalling pathway in a BCAP-dependent mechanism. Eventually leading to the inhibition of pro-inflammatory gene expression, through the phosphorylation of GSK3beta and FOXO1, and the enhancement of hypoxia inducible factor 1 (HIF)-target gene expression, mediated by phosphorylation/activation of serine/threonine kinase mammalian target of rapamycin (mTOR). Please refer to the text for meaning of the all abbreviations used in the figure. [Created in BioRender.com].

dependent gene expression, induced by diverse immune-activating triggers, such as TNF, IL-1 and antigens, and in response to the activation of TLRs and NOD2 [130]. Different experimental studies have demonstrated that A20 inhibits NF-kB activity by deubiquitinating specific NF-kB signalling proteins, i.e., RIPK1, RIPK2 and TRAF6 [131,132], which disrupt specific protein-protein interaction (Figs. 1, 2 and 3). Since TRAF6 is shared by all the TLR pathways and RIPK2 is the adapter protein involved in the NOD1/2 signalling, A20 may influence both TLRs and NOD1/2 signalling pathways (Figs. 3 and 2).

Toll-interacting protein (TOLLIP) is a multifunctional intracellular protein, that is essential to diverse signalling pathways crucial to different human diseases, i.e., pathways leading to the expression of IL-1, IL-13, LPS, and TGF-beta [133–136]. Of note, recent data have shed new light about the fundamental role exerted by TOLLIP in inflammatory responses, autophagy and vacuole trafficking [137]. It has been demonstrated that, by acting through diverse pathways, TOLLIP mediates pro- as well as anti-inflammatory functions, influenced by the cellular context. TOLLIP modulates the MyD88-dependent NF-kB pathways in two diverse ways: (1) binding to IL-1R1, TLR2 and TLR4 after LPS activation, thus hindering TLR-mediated immune responses [138,135,139]; 2) interacting with PTEN-induced putative kinase 1 (PINK1), eventually preventing the autophosphorylation of IRAK-1 and IRAK-2, but without promoting their degradation, thus dampening downstream signalling activation (Fig. 3) [140–142]. Conversely, TOLLIP, when stimulated with low-dose LPS, acts as an adaptor protein, migrating from lysosomes to mitochondria, where it stimulates the mitochondrial reactive oxygen species and spreads chronic inflammation [143–145].

Activating transcription factor 3 (ATF3) is another negative regulator that can be up-regulated by TLR stimulation as well as a plenty of different triggers [146–148]. It is an element of the CREB family of basic leucine zipper (bZIP) transcription factor, which binds to CREB-ATF binding sites in the promoter regions of target genes, eventually leading to chromatin remodelling and inhibition of transcription-factor binding [146]. Therefore, ATF3 promotes a negative-feedback circuit to restrict the excessive production of pro-inflammatory cytokines, including TNF, IL-6 and IL-12p40 (Fig. 3) [147]. Additionally, ATF3 builds a regulatory loop with NF-kB and C/EBPs (CCAAT/enhancer-binding proteins) at some LPS-inducible genes [148,149], and it has been predicted that it can associate with the p50 subunit of NF-kB, and with c-Jun and Fos (subunits of AP-1 complex) (Fig. 3) [146].

6. Lipoproteins and sepsis

The liver has essential functions in sepsis because is considered the second line of defence in eliminating invading microorganisms, reducing the spread of infections [150]. It is well known that the first line of defence are the gut and the associate local immune system [151]. Under physiological conditions, hepatocytes, Kupffer (resident macrophages) and hepatic stellate cells are trained to eliminate antigens transported to the liver, via portal vein, from the gut lumen [152]. However, during microbial infection the altered gut epithelial barrier permeability facilitates microbial pathogens translocation into the blood stream, and then to the liver [152]. As a consequence, the hepatic cells become able to promote immunogenic responses and trigger the synthesis of about 30 acute-phase proteins (APPs) [such as, serum amyloid A-1 (SAA1), C-reactive protein, LBP, alpha1-antitrypsin, alpha2-macroglobulin, orosomucoid 2 (ORM2), hepcidin, haptoglobin, fibrinogen, plasminogen, tissue plasminogen activator (tPA), PA inhibitor 1 (PAI1)] [153] and different inflammatory proteins (i.e., IL-8 and CXCL1), aiming at recruiting additional cells (mainly neutrophils and monocytes) [152,154]. Of note, in physiological conditions, in the liver diverse mechanisms guarantee repression of immune responses, aiming at preventing inadvertent immune activation, exaggerated inflammation or autoimmunity [152]. For instance, SAA1 and CXCL1 synergically stimulate the recruitment of myeloid-derived suppressor cells (MDSC), aiming at preventing outrageous inflammation [155], through the release of IL-10 and TGF-beta. In addition, these cytokines promote the activation of T regulatory (T reg) cells, and the expression of arginase-1 and iNOS, eventually, suppressing the involvement of $CD4^+$ and $CD8^+$ T cells [156].

Lipids, such as free fatty acids, triglycerides, free cholesterol, cholesteryl esters, phospholipids, sphingolipids and glycolipids, have insignificant aqueous solubility. Therefore, their transport into and through the tissues necessitates the binding with the so-called apolipoproteins. Plasma lipoproteins, aka the complexes formed by lipids and apolipoproteins, include chylomicrons, chylomicrons remnants, very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and HDL [157–160]. They dispense lipids to the organs, particularly liver, for energy, metabolism, specialized molecule synthesis, and as structural components of cells. These lipoproteins are taken-up by cells and tissues by specific receptors [161], but are remodelled in plasma by transfer proteins. Even though the scientific population stated that the receptors recognize protein as primary ligand, while the lipid transfer proteins mainly recognize lipid, the net difference between receptors and transfer proteins is still not very clear [162,163]. Seminal for lipid metabolism are CETP, PLTP, microsomal triglyceride transfer protein (MTTP), ATP-binding cassette transporter 1 (ABCA1), fatty acid transporter/scavenger receptor class B member 2 (CD36/SR-B2), and scavenger receptor class B member 1 (SR-BI). Specifically, CETP is a glycoprotein secreted from the liver that circulates in plasma, mainly associated to HDL. It promotes the transfer of triglycerides from apoB-containing,

triglyceride-rich lipoproteins to HDL particles, and at the same time the transfer of cholesteryl esters from HDL to apoB-containing, triglyceride-rich lipoproteins. [164]. PLTP promotes the movement of phospholipids and free cholesterol from triglyceride-rich lipoproteins to HDL [165]. MTTP is the fundamental lipid-transfer protein that moves phospholipids and triglycerides to nascent apoB for the assembly of chylomicrons and VLDL [166]. ABCA1 is a lipid-transfer molecule fundamental in HDL biosynthesis and cellular cholesterol homeostasis [167,168]. Its enzymatic activity allows the transfer of phospholipids and free cholesterol from the cytoplasmic to the exofacial side of the plasma membrane. Of note, the efflux of these lipids from the cells and the generation of nascent/discoidal HDL particles necessitates the membrane-solubilizing proprieties of the amphipathic alpha-helices present in the main apolipoprotein component of HDL, such as the apoA-I () [167]. This process is the first step in the reverse cholesterol transport, by which excess cholesterol is removed from the peripheral tissues, and transfer to the liver for excretion [20]. CD36 is a co-transporter of membrane fatty acids [169,170], either from the extracellular and intracellular space, and a macrophage receptor for oxidized LDL (oxLDL) [171]. CD36 displays many functions in lipid metabolism and signalling, and it has been indicated as a pivotal membrane protein involved in whole-body homeostasis [169]. Indeed, CD36, found in lipid rafts [172,173], acts as a crucial co-factor of the TLR2-TLR6 heterodimers. Consequently, mice lacking of CD36 are more susceptible to infection caused by the Gram-positive bacterium *Staphylococcus aureus* compared to wild-type animals [174], and macrophages lacking of a functional Cd36 showed an impaired secretion of TNF, when incubated with TLR2-TLR6 ligands, such as LTA and diacylated lipopeptide MALP2 [175]. In addition, CD36 is involved in the inflammatory responses to oxLDL and amyloid-beta fibrils, facilitating the formation of the TLR4-TLR6 heterodimer [176,177]. CD36 interacts with TLR2-TLR6 and TLR4-TLR6 through a mechanism that is not fully characterized, but diverse experimental data demonstrated that the carboxyl terminus of CD36 play a seminal role in the formation of the TLR4-TLR6 heterodimer [176]. Furthermore, it has been observed that the assembly between CD36 and TLR4-TLR6 as well as the formation of a signalling-competent TLR2-TLR6-CD36 complex [174] is marked dampened when the activity of the Lyn tyrosine kinase is inhibited [178]. Finally, since CD36 undergoes palmitoylation to be correctly located to lipid rafts, its physiological functions are also influenced by its right placement to membrane microdomains [179]. SR-BI is a lipid-transfer protein involved in the bidirectional transfer of cholesterol and cholesteryl esters to HDL, without the uptake and lysosomal breakdown of these particles [180,181]. This process has been named selective cholesteryl ester uptake [182]. For this reason, SR-BI has been identified as the "first" HDL receptor, being its uptake/efflux of cholesteryl esters primarily from HDL [183].

As well-demonstrated, cholesterol and its diverse metabolites play complex biological functions, many of which are disrupted during sepsis. The specific contribution of cholesterol depletion to the sepsis-related abnormalities is still an open question. However, there is sufficient evidence suggesting a direct association between cholesterol deficiency and sepsis progression [184].

6.1. HDL as modulators of LPS-induced inflammation

HDL are defined as a vast, heterogeneous and dynamic group of nanoparticles constituted by a broad variety of lipid and proteins [185]. According to the new classification system proposed by Rosenson et al. [186], HDL have been divided into five subclasses based on their physical and chemical characteristics: very large HDL (namely HDL2b, particle diameter 9.7 to 12.9 nm), large HDL (namely HDL2a, particle size 8.8 to 9.7 nm), medium HDL (namely HDL3a, particle size 8.2 to 8.8 nm), small HDL (namely HDL3b, particle size 7.8 to 8.2 nm), and very small HDL (namely HDL3c, particle size 7.2 to 7.8 nm), this latter comprises pre-beta, discoidal, or nascent HDL. A detailed description of the composition and diverse physiological functions of HDL can be found in several recent reviews [18,20,187–189]. Of note, the pleiotropic functions of HDL are strongly influenced by particle size and structural variety, as demonstrated by large-scale proteomic and lipidomic characterization of HDL, that revealed >200 individual lipid species [190] and over 250 proteins [191]. In detail, the HDL proteomic analysis identified the presence of predominant apolipoproteins, including apoA-I, apoA-II, apoCI/CII/CIII, remodelling enzymes, and low amounts of seminal proteins, such as apoM, complement and coagulation factors, protease inhibitors and APPs. It has been demonstrated that apoM is a lipid carrier responsible of the transport of the sphingosine-1-phosphate (S1P), a lysophospholipid molecule included in different physiological activities [192]. Indeed, the apoM-S1P axis seems to play a seminal role in vascular homeostasis [192,193]. The lipidomic analysis of the HDL revealed the presence of phospholipids, free and esterified cholesterol, sphingolipids, triglycerides, these latter differing in the fatty acid content [194]. Of note, S1P functions as an extracellular as well as an intracellular signalling molecule [195], whereas sphingomyelin (SM) exert a double functions, being the main structural phospholipid and a master regulator of cholesteryl ester content, because inhibits the activity of lecithin:cholesterol acyltransferase (LCAT) by reducing the fluidity of the membranes [196,197]. This protein/lipid heterogeneity of HDL translates into distinct biological activities of HDL sub-populations. Indeed, small, dense, lipid-poor HDL3 are the best promoter of cellular cholesterol efflux, mediated by ABCA1 [198], exhibit more potent antioxidative and anti-inflammatory functions [199], and a stronger ability at protecting endothelial cells from apoptosis compared to large, light, lipid-rich HDL2 [200,201]. In line with these data, Kontush et al. by performing lipidomic analyses, have demonstrated that the HDL3c are characterized by a higher amount of S1P but a lower content of SM compared to HDL2b [202]. The authors also observed that this HDL3c contained more apoA-I. In addition, small HDL3 strongly lowered apoptosis in endothelial cells and prevented LDL oxidation [202]. Mechanistically, the reduced amount of SM in the HDL3 could rise the fluidity of its external side, enhancing the selective cellular uptake of lipids, such as S1P. The source of S1P is mainly from platelets, erythrocytes, monocytes, as well as endothelial and mast cells [203–205]. Furthermore, the antiatherogenic property of S1P presupposes the contact of HDL with cellular surfaces mediated by SR-BI, and then its intracellular/extracellular activity can be activated. The exact mechanism and signalling pathway of the internalized S1P are not completely clarified. Conversely, the extracellular signalling is mediated by the activation of membrane S1P receptors (S1PRs). It has been demonstrated that S1P is involved in vascular maturation, lymphocyte trafficking, endothelial barrier integrity, cell proliferation and survival, as well as protection from apoptosis and reduction of the expression of vascular adhesion molecules in endothelial cells. Moreover, overexpression of S1PR1 reduced the differentiation of CD4+ T cells to Treg cells by activating the Akt-mTOR signalling pathway [206]. On the contrary, T reg isolated from mice lacking of S1PR1 are characterized by an altered phenotype with increased Treg activation and differentiation, eventually resulting in a higher susceptibility to experimental autoimmune encephalomyelitis compared to Treg derived from wild-type animals [207]. Consistent with this pathway, it can be speculated that this complicated nature is strongly associated to the peculiar pattern of S1PR expression [192].

In addition, experimental and clinical data have demonstrated that HDL are bio-complex exerting a unique interplay between composition and activity. Therefore, HDL display diverse functions that defend the body from exogenous harmful chemicals of biologicals or support at repairing a damage caused by detrimental compounds. HDL perform these protective functions through three principal mechanisms: 1) cholesterol transport [19,187]; 2) interaction with different cells [18]; 3) neutralization of bio-danger [20]. Indeed, HDL proved efficacy in host defence, by scavenging and limiting endotoxin toxicity, and in the control of the immune cell response, by modifying the cholesterol content of the plasma membrane lipid rafts [188,189]. HDL seize dangerous

molecules, such as LPS, LTA, oxidized lipids, as well as diverse hydrophobic chemical substances [20]. It has been showed that HDL are able to neutralize LPS via directly binding the lipid A moiety, seizing it from interacting and activating TLR4 [184,208–211]. Moreover, Han Y-H recently demonstrated that the gut generates the small dense HDL3 enriched of LBP, paraoxonase 1 (PON1), alpha1-antitrypsin, and apoM [186,212]. These HDL3 reach the portal blood, where bind and mask LPS, through the LBP. Therefore, once in the liver LPS are not able to interact with the Kupffer cells via TLRs, avoiding the induction of proinflammatory and profibrotic genes. Nevertheless, acyloxyacyl hydrolase is able to inactivate the LPS bound to the HDL3 [212]. Moreover, this study showed that HDL3, isolated from human peripheral blood, are more potent suppressor of inflammatory genes compared to HDL2 in a concentration- and TLR4-dependent manner, when the trigger-agents are LPS [212]. Indeed, HDL3 more strongly bind LPS compared to HDL2, and HDL2-bound LPS are readily shuttled to LDL or VLDL, where LPS bioactivity is not neutralized. While, most HDL3-bound LPS remained associated to HDL3, and then inactivated [212]. The authors indicated that this intestinal mechanism is part of a "disease tolerance" strategy aiming at protecting the hepatic tissue from intestine-derived dangers [212]. In line with these data, a recent study recognized apoM as the "HDL-component" able at binding LPS with high affinity, promoting liver endotoxin neutralization and clearance [213]. This latter process averts the signalling of TLR4, thus suppressing the activation of downstream pathways, and the expression of pro-inflammatory proteins [23,69]. In addition, the docking simulations performed in this study showed that LPS associated with apoM in a pocket site different from that used by S1P. However, it is not known if LPS and S1P bind to apoM simultaneously [213]. Of note, collaborative and secondary analyses of clinical trials indicated that HDL3 but not HDL2 concentrations associate with a more favorable prognosis [214,215].

Of note, sepsis greatly impacts HDL metabolism that results in an acute and marked drop of the serum concentration of HDL-cholesterol [216–218]. Observational clinical studies showed that decreases in HDL-cholesterol and HDL lipoproteins (mainly apoAI) directly correlated with a higher chance of multiorgan failure, of being hospitalized for longer time, and mortality [219–222]. Experimental data have demonstrated that a deficiency in HDL results into a higher death rate caused by caecal ligation and puncture-induced sepsis, as well as reduced LPS neutralization and clearance [223,224]. Guo et al. have identified a novel function of HDL, aka modulation of thymocyte apoptosis in sepsis, in two different knock-out mouse models, i.e., apoA-I and SR-BI null mice [225]. These authors using HDL isolated from SR-BI knock-out mice demonstrated that the excessive accumulation of unesterified cholesterol renders them dysfunctional, such as unable to regulate the apoptosis and proliferation/differentiation of thymocytes [225]. In line with these data, a recent study investigated the function of SR-BI in monocytes/macrophages [226]. The results showed that SR-BI deficiency in the macrophages was associated with accelerated atherosclerosis progression, mainly caused by a low amount of apoptotic macrophage detected into the plaques [226]. In addition, these authors highlighted that the decreased propensity of macrophages to become apoptotic cells was caused by the increased gene expression of AIM (apoptosis inhibitor of macrophage), following a STA3-dependent mechanism [226]. Of note, it has been demonstrated that these effects also control 1) the p38-MAPK dependent apoB expression in intestinal absorptive cells and 2) the endothelial-NO synthesis promoted by HDL [227]. Wang et al. have demonstrated that liver specific SR-BI KO mice (AlbCreSR-BI$^{fl/fl}$), a model with impaired reverse cholesterol transport, were significantly more prone to polymicrobial sepsis compared to wild-type animals [228]. They found that sepsis in these AlbCreSR-BI$^{fl/fl}$ mice caused a marked rise in both the free cholesterol concentrations and the free cholesterol/cholesteryl ester ratio. This free cholesterol diffuses from lipoproteins to red blood cells, making these latter more prone to rupture, leading to haemolysis and septic death [228]. Of note, probucol treatment by normalising free cholesterol concentration and free cholesterol/cholesteryl ester ratio, rescued septic AlbCreSR-BI$^{fl/fl}$ mice [228].

Finally, a recent systematic review and meta-analysis stated that mortality is related to reduced concentrations of total cholesterol, HDL-cholesterol and LDL-cholesterol, rather than to triglyceride levels in patients with sepsis [229]. Taylor et al. confirmed these data and speculated that HDL-components could represent early markers of disease, suggesting that oncoming studies should take into account the wide heterogeneity of HDL [230]. Therefore, HDL supplementation may represent a potential therapeutic tool for these patients. However, more evidence should be provided, both in experimental and clinical studies, to translate HDL therapy into new guide-line for the management of sepsis, particularly in at-risk groups [229].

6.2. HDL and the immune system

HDL mediate potent anti-inflammatory effects in immune cells by inhibiting the NLRP3 (NLR family pyrin domain containing 3) inflammasome activation in response to cholesterol crystals in different ways [231]. The mature NLRP3 inflammasome consists of NLR, pro-caspase-1, and the adaptor protein ASC (apoptosis-associated speck-like protein containing caspase associated recruitment domain). Its activation is a multistep process that eventually results in the production of caspase-1, which then cuts pro-IL-1beta or pro-IL-18 into the active forms IL-1beta or IL-18, respectively [232]. The results of this study showed that HDL binds directly to cholesterol crystals, but do not dissolve them or prevent their phagocytosis. In addition, HDL treatment reduced (1) lysosomal rupture; (2) mRNA levels of *pro-IL-1beta* and *NLRP3*; (3) protein concentration of pro-caspase-1 and caspase-1; (4) the levels of the inhibitory subunit IKKalpha. Conversely, a transcriptional induction of *ATF3*, a negative regulator of the TLR signalling pathways, was observed [231,233]. It has been also demonstrated that, under hypoxic conditions, reconstituted HDL (rHDL) activate the PI3K/Akt pathway, via SR-BI, inducing the gene transcription of HIF-target proteins, namely VEGF, eventually promoting angiogenesis (Fig. 5) [234]. In line with these data, Song GJ et al. demonstrated that the anti-inflammatory effects of HDL are regulated by the macrophage expression of SR-BI. Indeed, SR-BI expression is up-regulated by HDL, together with the abolishment of LPS-induced NF-kB activation (Fig. 5) [235]. These latter studies allow the speculation of the mechanism behind the suppression of NLRP3 inflammasome activation by HDL. Indeed, as reported in the paragraph #5, the activation of PI3K/Akt signalling pathway also leads to a decrease of the NF-kB/MAPK-dependent transcription of pro-inflammatory genes (Fig. 4) [107,108,117–119]. Furthermore, it is of seminal importance to keep in mind that the defence strategy of the immune system relies on the combined action of innate and adaptive components, which recognize and target pathogens for containment, destruction or elimination, aiming at limiting the negative effects on host homeostasis [236]. However, immune-drive protection to infection is associated with a defence strategy, namely "disease tolerance", that identified an adaptive mechanism that restrains "damage to functions and structures" enforced upon the host during an infection, in absence of any effects on pathogen load [236,237]. The primary feature "disease tolerance" is tissue damage control, which is orchestrated by stress and/or damage responses. If these "control systems" fail, programmed cell death will start, leading to tissue injury and eventually organ dysfunction and disease. Divergent types of stress and damage caused straight by microorganisms (that is, virulence) or indirectly by host immune-drive resistance responses, that is immunopathology, sustain the stress and damage responses. Cholesterol crystal deposition and hypoxia are included in the stress and damage triggers, respectively. Therefore, based on the reported studies performed by Thacker et al. [231] and Tan et al. [234], HDL can be regarded as a tool to promote disease tolerance to infection.

As discussed earlier (see subheading 2.2), several receptors with key

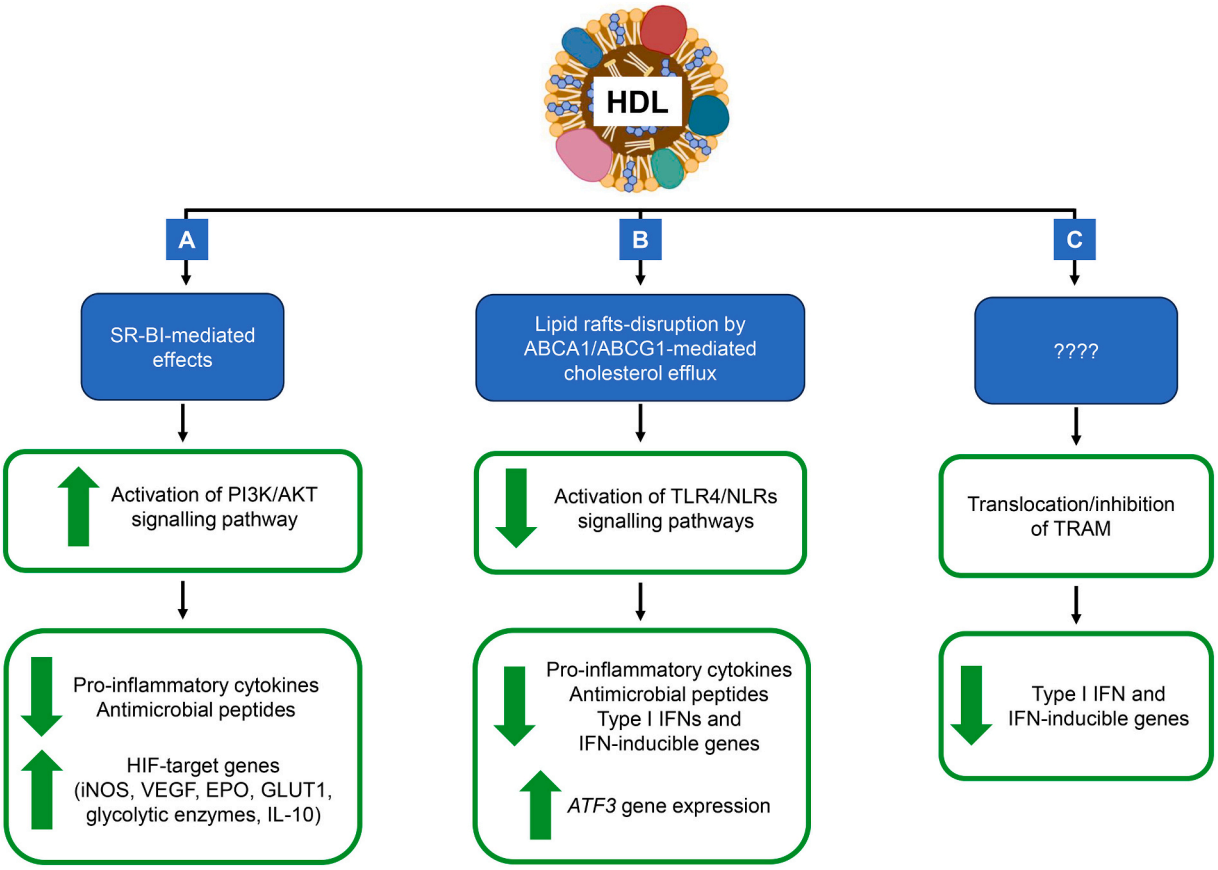

Fig. 5. Schematic representation of the anti-inflammatory/immunomodulatory functions of HDL. A) HDL activate the PI3K-AKT pathway, eventually leading to the inhibition of pro-inflammatory gene expression and the enhancement of hypoxia inducible factor 1 (HIF)-target gene expression. B) The removal of cholesterol from lipid rafts can decrease TLR4/NLRs pathways activation, leading to the inhibition of pro-inflammatory cytokines, antimicrobial peptides, Type I IFNs and IFN-inducible genes expression and the transcriptional induction of *ATF3*. C) Through an unknown mechanism, involving removal of the TRAM from the inner-cell membrane to intracellular compartments, HDL inhibit the LPS-stimulated Type I IFN response. Please refer to the text for meaning of the all abbreviations used in the figure. [Created in BioRender.com].

immunological activities (namely, TLRs and T and B cell receptors) have been identified within the lipid rafts [42]. Cholesterol depletion of lipid rafts, with cyclodestrin, HDL or apoA-I, altered the response of monocytes, macrophages and DCs challenged with inflammatory stimuli [48–50,238]. Indeed, this alteration of the composition of the lipid rafts normalized the response to LPS, by negatively modulating the activation of the TLR's signalling pathway. Eventually, reducing the antigen presentation and activation of T cell, and the secretion of pro-inflammatory proteins [43–45]. These data were also confirmed by Wang et al. [239]. In this study, HDL and apoA-I inhibited the ability of APCs to stimulate T cell activation by promoting cholesterol efflux, and ensuring a functional alteration of the lipid rafts in these cells (Fig. 5) [239]. A recent review described the new connections between HDL and $CD4^+$ T cells, highlighted that HDL promoting cholesterol efflux in T cells and DCs, may affect antigen presentation by decreasing MHC-II and lipid raft formation [189]. Indeed, HDL- or apoA-I-mediated increase of cholesterol efflux in DCs lowered their potential to activate T cells [239,240]. In addition, DCs lacking of ABCA1 and ABCG1 proteins exhibited impaired cholesterol efflux and enhanced $CD4^+$ T cell activation and Th1 and TH17 cell polarization [240,241]. Conversely, the direct interactions of HDL and $CD4^+$ T cells cause a reduce activation, proliferation, and cytokine production. Moreover, the interaction of HDL with Treg cells reduces oxidative stress and improves their metabolism and survival [189]. In line with this analysis, mice lacking of both ABCA1 and ABCG1 (main player in the active cholesterol efflux) presented a significant reduction of HDL-cholesterol concentration, a massive myocardial and spleen accumulation of inflammatory macrophages foam cells and neutrophils in diverse tissues, mimicking a classical myeloproliferative disorder [242–244]. Moreover, macrophages isolated from ABCA1/ABCG1-deficient mice expressed more TLR4/MD2 complex as well as lipid rafts, indicating that they elicit a stronger reaction to microbial stimuli or other TRL4 ligands compared to wild-type macrophages [242–244]. An autoimmune phenotype was instead observed in LDLR/apoAI double KO mice, characterized by enlarged spleens and peripheral lymph nodes, these latter filled up of immune cells (such as, T and B cells, macrophages, and DCs) [245]. The phenotype of these two genetically modified mouse models has been partially rescued by crossing the ABCA1/ABCG1 KO animals with mice over-expressing apoA-I or treating the LDLR/apoAI double KO mice with subcutaneous injections of lipid-free apoA-I, thus increasing the concentrations of apoA-I and HDL [241,245]. Conversely, Suzuki et al. demonstrated that HDL can also inhibit the inflammatory response of macrophages through an unknown mechanism, that involve the transfer of the TRAM, a key adaptor molecule that activates TRIF in endosomal compartments, from the membrane to intracellular space, thereby impairing subsequent signalling by TLR4, namely LPS-stimulated type I INF response (Fig. 5) [50]. Of note, signalling by TRAM requires endocytosis of TLR4, as represented in Fig. 1. The authors proposed that HDL exert this activity in a way independently from cholesterol-removal [50]. However, this complex interplay is not completely known or some aspects are still controversial, at least in part due to the highly heterogeneity of the HDL. Therefore, oncoming experimental and clinical trials remain warranted, if we want to use these interactions as additional diagnostic tools [189].

6.3. HDL dysfunction

It has been extensively demonstrated that HDL can become dysfunctional, losing their protective properties and paradoxically acquiring detrimental functions in chronic diseases, such as coronary heart disease (CHD), diabetes, kidney chronic disease (KCD), rheumatic and autoimmune diseases, or during infections [246,247]. These clinical data indicate that these modifications are frequently associated to systemic inflammation, suggesting a developmental role for HDL in the innate immune response, since the major danger to human longevity has ever derived from microbial infections. HDL dysfunctions are characterized by reduced abilities to: 1) promote cholesterol efflux from macrophages; 2) hinder LDL oxidation; 3) modulate apoptosis; 4) stimulate nitric oxide (NO) production and endothelial adhesion molecule's expression [246,247]. Data from diverse inflammatory-based pathologies demonstrated that structural changes in HDL have been directly correlated with the generation of dysfunctional HDL. In details, it has been observed that HDL incorporate SAA1, LBP, alpha1-antitrypsin, symmetric dimethylarginine, or fibrinogen. These changes result in HDL particles deprived of apoA-I, apoM, PON1 and cholesterol, but enriched of triglycerides, phospholipids, lipid peroxides, matrix metalloproteinase-9 (MMP-9), and platelet-activating factor acetylhydrolase (PAF-AH), which dampen their antioxidant capacity [246,248]. The low concentration of apoM impairs its ability to bind both LPS and S1P, thus negatively impacting on the HDL-mediated promotion of endotoxin neutralization and clearance, and vascular protection, respectively [192,193,249]. Translating these data on the clinical field, HDL isolated from patients with CHD or CKD hinder NO production, and exerted pro-oxidative and pro-inflammatory actions [250,251]. Indeed, these dysfunctional HDL by interacting with the lectin-like oxidized LDL receptor, LOX1, and the TLR2/4 promote the phosphorylation of inhibitory sites in endothelial NOS, resulting in the dampening of the NOS activity [250,251]. Sini et al. shown that HDL from patients with coronary artery disease facilitate lipid gathering in human monocyte-derived macrophages by upregulating the expression of CD36, and suppressing the expression of both ABCG1, the primary transporter of cholesterol to mature HDL, and SR-BI, causing a failure of the lipid efflux pathway [252]. In contrast, this effect was not observed using HDL from healthy subjects [252]. Furthermore, in these macrophages was also activated the ERK/MAPK signalling pathway, which in turn lead to lipid accumulation along with NF-kB-mediated proinflammatory response and subsequent release of TNF and MMP-9 [252]. In line with these data, a prospective pilot study suggested that HDL from older septic patients shown a reduced cholesterol efflux capacity and are more prone to oxidation compared to HDL from healthy older subjects [253]. Yang et al. confirmed the presence of significant changes in the composition of HDL obtained from septic-acute respiratory distress syndrome (ARDS) patients and demonstrated that these abnormal HDL exacerbated pulmonary endothelial dysfunction and acute lung injury in a mouse model of polymicrobial sepsis [254]. Finally, Madsen et al. found that, in subjects from the Copenhagen General Population Study the relation between HDL and all-cause death rate or risk of infectious disease was U-shaped. Of note, both high and low HDL cholesterol levels being correlated with high death rate/high risk [255,256]. They also discovered that this association was still present when considering only mortality from sepsis [256].

7. HDL therapy for sepsis

A double “take home message” come from these data, such as: 1) HDL quality rather than HDL-cholesterol levels does make a difference and 2) does exist an “ideal HDL-cholesterol concentration range”. These conclusions are strengthened by diverse observations that administration of rHDL, containing apoA-I or apoA-I mimetic peptide, as well as the transgenic expression of apoA-I in animals, proved efficacy in preventing or reducing the atherosclerotic plaque burden [256,257,20,259,260]. Therefore, rHDL and/or synthetic HDL, initially thought as innovative cardiovascular drugs, have also been indicated as a promising therapeutic strategy for the management of infection diseases [208,261,262]. Specifically, transgenic mice overexpressing human apoA-I, with a two-fold-rise in plasma HDL concentrations, displayed more endotoxin bound to HDL, reduced concentration of TNF and mortality compared to wild-type animals [263,264]. Similarly, rHDL containing full length apoA-I proved efficacy in suppressing LPS-induced TNF secretion and adhesion of leukocytes to endothelial cells, via CD11bCD18 and *E*-selectin-ICAM pathways, in macrophages and human polymorphonuclear leukocytes, respectively [265,266]. Endotoxin neutralization, reduced release of pro-inflammatory mediators and oxidative stress, and improved survival was also observed in different models of endotoxemia using rHDL containing full length apoA-I or L/D-4F mimetic peptides [267–270]. Furthermore, Tanaka et al. [271] evaluated the potential therapeutic effects of CSL-111, a rHDL containing apoA-I purified from human plasma [272], in three diverse models of sepsis. The infusion of CSL-111 increased the survival rate in all the mouse models used. It reduced inflammation in both plasma and lung, and significantly decreased bacterial count at 24 h after the sepsis in plasma, liver, and lung, and macrophages infiltration in lung compared to the saline-treated animals [271]. In line with these data, rHDL containing the 22A apoA-I mimetic peptide, namely ETC-642 [273], ameliorate organ functionality and 7-day survival in septic animals, neutralizing LPS as well as significantly reducing TLR4-NF-kB signalling and inflammatory cytokines secretion [274]. Finally, the effect of CER-001, a negatively charged lipoprotein, where a recombinant human apoA-I is complexed with two phospholipids [275], was assessed in a swine model of acute kidney injury induced by LPS [276]. CER-001 increased medial survival, reduced serum levels of TNF, MCP-1 (monocyte chemoattractant protein 1) and IL-6, complement activation and endothelial dysfunction in endotoxemic pigs. Moreover, CER-001 stimulated the excretion of LPS through the bile and prevented liver and renal parenchyma damage [276]. Taken together, these results strengthened the data showing small dense HDL3, mirrored by rHDL, having dramatic impact on LPS neutralization as well as on the TLR/NLR signalling pathways [189,212]. Aiming at translating from bench to bedside these in vitro and in vivo positive results, a seminal human study was performed by Pajkrt et al. [277]. The results demonstrated that intravenous infusion of rHDL downregulated the expression of CD14 on monocytes, and, being this latter a crucial co-receptor for LPS, decreased the secretion of TNF, IL6, and IL8 caused by LPS [277]. Furthermore, an open-label Phase 2a pilot clinical trial showed that intravenous infusions of CER-001 determined a normalization of the serum concentration of apoA-I together with an increase of the LPS neutralization, and clinical prognosis, regardless of the kind and degree of sepsis. In addition, CER-001 treatment lowered the serum concentration of TNF, MCP-1, IL-6, and sTREM-1, justifying the observed rise in survival/prognosis as well as the reduced rate of the onset and/or progression to severe acute-kidney injury. Lastly, in a sub-group of CER-001-treated patients a lowered permanence in intensive unit care, and necessity for organ support during the 30-day study period was observed, compared to standard of care (SOC)-treated subjects [276]. Unfortunately, studies performed with these types of rHDL or apoA-I peptides were characterized by a common limitation, i.e., the lack of clinical translatability, caused by low level of purity, endotoxin contamination, and extremely short half-life [278,272,279,280]. The short half-life required very high doses of rHDL/apoA-I peptides (from 45 to 500 mg/kg depending on the animal model used) to reach the therapeutic effect, increasing the risk of toxicity [20,263,265,267]. While, high pure second-generation rHDL proved efficacy at much lower doses, i.e. 7.5 mg/kg in mice [274]. Therefore, aiming at developing new therapeutical tools for sepsis management, this second-generation of rHDL guarantees a better regulation of the production process, resulting in a safer and less expensive end product, compared to HDL obtained from serum or rHDL containing recombinant apoA-I.

The apoA-I_M, where a cysteine replaced an arginine at residue 173, is the first mutation of apoA-I discovered in 1974 in Italy [281–284]. ApoA-I_M is present in the plasma as homodimer (apoA-I_M-apoA-I_M), or heterodimer with apoA-II (apoA-I_M-apoA-II) [282]. Carriers of ApoA-I_M, all heterozygous, are characterized by a lipid/lipoprotein phenotype at high-risk for the development of cardiovascular disease, namely, high levels of triglycerides and very low concentrations of HDL, but, surprisingly, they do not present a higher risk of premature CVD compared to non-carrier individuals [19]. By using rHDL containing apoA-I_M, diverse experiments have shown that apoA-I_M is more potent compared to wild-type apoA-I in stimulating cholesterol efflux, preventing the oxidation of LDL, and lowering markers of inflammation and plaque instability [282,285–287]. Moreover, pre-treatment with rHDL containing recombinant apoA-I_M significantly improved liver and renal failure, and lung injury in a rat-model of LPS-induced sepsis. These effects were associated with a marked suppression of the expression of TNF, IL-1, and IL-6, adhesion molecule ICAM-1, and of lipid peroxidation, and a rise of total antioxidant capacity [288]. Of note, in human apoA-I_M carriers, HDL2 are almost undetectable, and the presence of small HDL3b particles, enriched in apoA-II and cholesterol ester-poor, was observed [289]. Moreover, it has been demonstrated that sera from apoA-I_M subjects contain a sole HDL particle, a small spherical apoA-I_M-apoA-I_M-containing HDL, explaining the high capacity of apoA-I_M serum in stimulating ABCA1-mediated cell cholesterol efflux [290]. Nascent-discoidal apoA-I_M-apoA-I_M HDL slowly convert into larger spherical HDL, characterized by an elevated stability conferred due to the presence of the disulfide-linked dimer [291]. Indeed, kinetic studies performed in apoA-I_M carriers demonstrated a normal apoA-I_M-apoA-I_M production rate together with a remarkable delay in apoA-I_M-apoA-I_M catabolism, eventually supporting the longer elimination half-life of apoA-I_M compared to normal apoA-I [292]. Finally, small, dense, lipid-poor HDL3, enriched in S1P but poor in SM, are better acceptors of cholesterol mediated by the ABCA1-dependent pathway [198,202]. Altogether, these data allow the speculation that apoA-I_M could represent a stronger positive modulator of sepsis, compared to normal apoA-I, for at least two reasons: 1) enhanced cholesterol efflux capacity, meaning a higher efficiency in cholesterol depletion of lipid rafts [48–50,198]; 2) increased binding of LPS, due to a higher content of S1P [202]. However, the pathways explaining this increased activity of apoA-I_M versus apoA-I are not still elucidated, consequently to the lack of in vivo models to directly compared these two apolipoproteins. Aiming at overcoming this gap, a recent experimental study, by using unique mouse models, aka A-I_M k-in, hA-II/A-I_M k-in, A-I k-in, hA-II/A-I k-in, and the microarray methodology, studied the underlying molecular mechanisms of the apoA-I_M carrier's phenotype and the apoA-I_M higher efficacy [21]. Bioinformatic analysis highlighted that the expression of apoA-I_M or apoA-II represent a crucial factor of the liver concentrations of diverse genes associated to "inflammatory response and response to molecule of bacterial origin" and "antigen processing and presenting and inflammatory response", respectively (Figs. 5 and 6) [21]. Specifically, Jun, Tollip, Tlr6, Myd88, Irak2, and Cd36 were the most down-regulated differentially expressed genes (DEGs) in A-I k-in versus A-I_M k-in mice. STRING analysis demonstrated that these genes were included in the "inflammatory response" as well as "response to molecule of

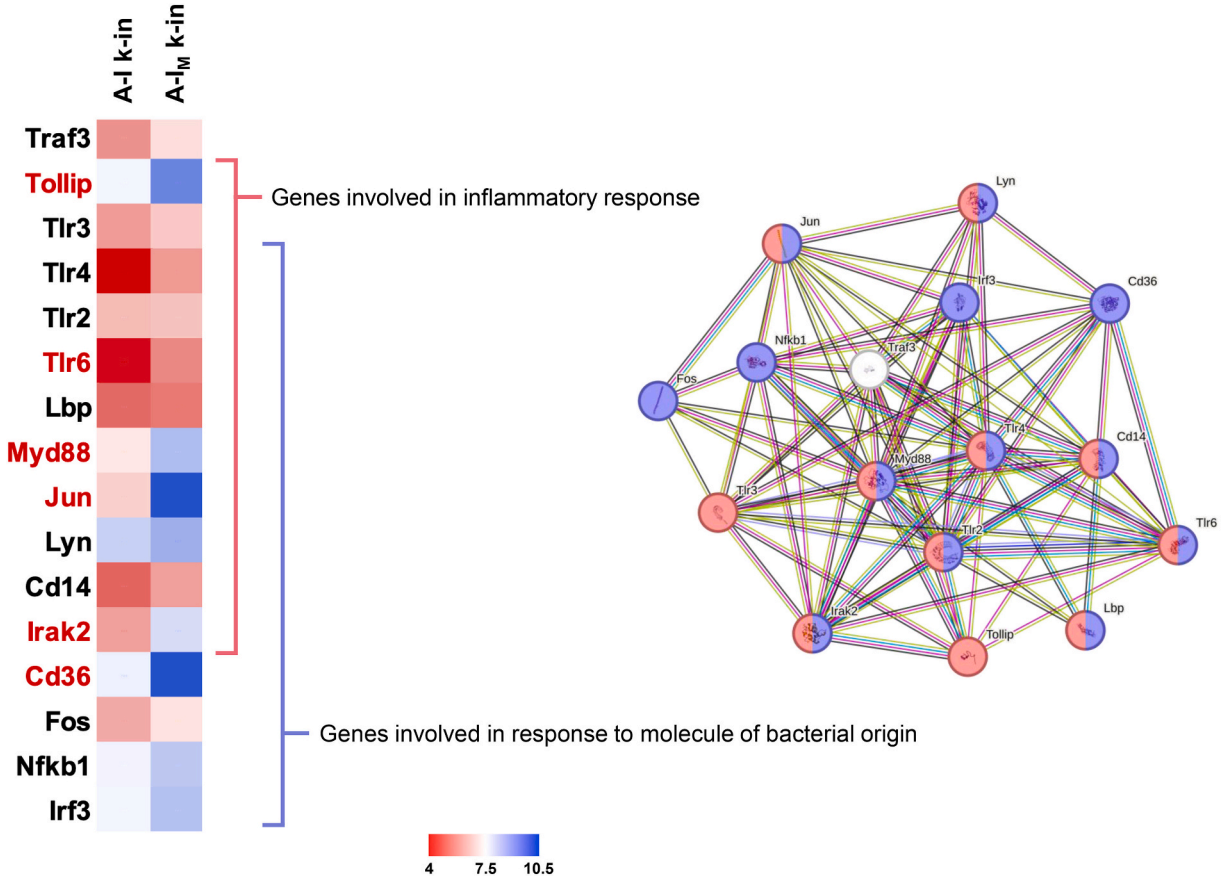

Fig. 6. Comparisons analyses of down-regulated DEGs in A-I versus A-I_M k-in mice. (A) Heat map and list of genes involved in "inflammatory response" and in "response to molecule of bacterial origin" biological functions (Gene Ontology). (B) Protein-protein association networks by STRING analyses of Jun, Tollip, Tlr6, Myd88, Irak2, and Cd36-related genes. Nodes are coloured by pathway membership (red, inflammatory response; blue, response to molecule of bacterial origin) and edges are coloured by meaning of interactions. The log2 colour scale abundance for gene expression, and the fixed saturation limits were indicated. Please refer to the text for meaning of the all abbreviations used in the figure.

bacterial origin" biological processes (Gene Ontology) (Fig. 6). Akt and Atf3, two negative regulators of TLRs signalling pathways (see Figs. 3 and 4), were also significantly down-regulated in A-I k-in compared to A-I_M k-in animals. As previously reported, under hypoxic conditions, rHDL activates the PI3K/Akt pathway, via SR-BI, inducing the transcription of genes, such as VEGF, eventually promoting angiogenesis (Fig. 4) [234]. Additionally, treatment of immune cells with HDL is able to hamper the transcriptional responses of pro-inflammatory cytokine genes by promoting the gene expression of Atf3 and, eventually, the Atf3-dependent chromatin remodelling [231,233,293]. Of note, all these DEGs are major players of the host defence against infection diseases. Therefore, these data support the previously reported results highlighting greater anti-inflammatory properties and an increased capacity of halting bacterial infections of apoA-I_M compared to apoA-I [21]. On the other hand, the co-expression of apoA-I and apoA-II, that is in hA-II/A-I k-in mice, caused an up-regulation of genes involved in "antigen processing and presenting" and "inflammatory response" biological processes (Fig. 7) [21]. Of note, Cd74 (the cell membrane receptor of the cytokine macrophage migration inhibitory factor – MIF), histocompatibility 2, class II antigen A, beta 1 (H2-Ab1), histocompatibility 2, class II antigen a, alpha (H2-Aa), and histocompatibility 2, class II antigen E beta (H2-Eb1) were the most upregulated in the "antigen processing and presenting" pathway ($p < 0.0005$, Fig. 7). While, Chemokine (C-C motif) ligand 6 and the APPs, Orm2, Saa1, 2, 3 and 4, were found in the group of most down-regulated DEGs in A-I k-in versus hA-II/A-I k-in, and involved in the "inflammatory response" biological process ($p < 0.05$) (Fig. 7). It has been demonstrated that, both the MIF/CD74 receptor pathway and the above-mentioned histocompatibility antigens have been related to the resolution-phase macrophage subtype, seminal in protecting against injuries and promoting resolution of inflammation, and eventually tissue repair and healing [294,295]. Whereas, Ccl6 and Orm2, Saa1, 2, 3, and 4 are involved in sepsis protection by promoting inflammatory/immune responses (Fig. 7) [296,297]. By looking at these results, it can be speculated that apoA-II may play a "promoter-like" role of the apoA-I biological activities [21].

8. Conclusions and prospectives

Nowadays, sepsis still affects a shocking high number of patients. Therefore, there is an urgent necessity at developing diagnostic methods with the aim of identifying patients with peculiarities rising the probability to take advantage from a therapeutic intervention based on their biological phenotype. In addition, the "precision medicine" - that is, pharmacological interventions taking patient-unique phenotype into account – could enhance the odds of demonstrating the desired effects in subgroups of patients with sepsis. HDL may represent a biological marker to be measured routinely, because they can be regarded as an early predictor of illness. However, since their diverse pleiotropic functions are strongly related to particle size and structural diversity, future research should take into account the metabolic and functional heterogeneity of HDL, when considering the management of sepsis patients. Indeed, the baseline serum cholesterol level (total, HDL, or LDL) together with the subclassification of HDL-cholesterol into HDL3-cholesterol and HDL2-cholesterol, by ultracentrifugation, could be

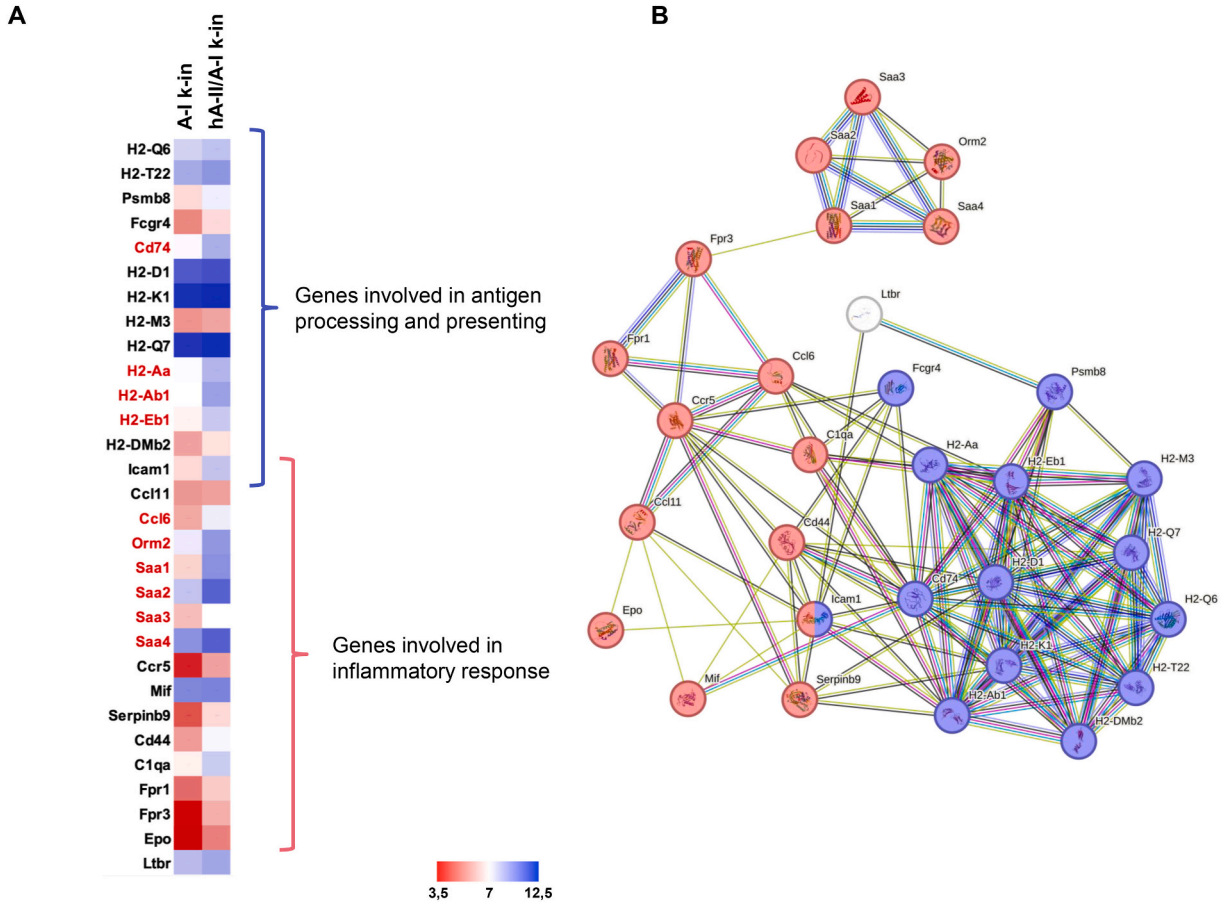

Fig. 7. Comparisons analyses of down-regulated DEGs in A-I versus hA-II/A-I k-in mice. (A) Heat map and list of genes involved in "antigen processing and presenting" and in "inflammatory response" biological functions (Gene Ontology). (B) Protein-protein association networks by STRING analyses of Cd74, histocompatibility antigens, Ccl6, Orm2, Saa1,2,3,4-related genes. Nodes are coloured by pathway membership (blue, antigen processing and presenting; red, inflammatory response) and edges are coloured by meaning of interactions. The log2 colour scale abundance for gene expression, and the fixed saturation limits were indicated. Please refer to the text for meaning of the all abbreviations used in the figure.

used to enrich trial design by pre-stratifying patients into higher and lower mortality risk groups [214,230]. In addition, by applying state-of-the-art methodologies, namely multiple functional evaluations in conjunction with proteomic, lipidomic, and glycomic analyses, for profiling structure-function relationships across HDL, it could be possible to achieve the best personalized diagnosis and eventually therapy [298].

All the preclinical and clinical studies published strengthened the concept that, rHDL supplementation may represent a potential therapeutic tool for patients with sepsis. Moreover, apoA-I_M and apoA-II showing superior anti-inflammatory and immunomodulatory activity compared to apoA-I, suggest the possibility of producing and testing a new formulation of small dense discoidal-rHDL, containing these two apolipoproteins and selected phospholipids and/or cholesteryl ester [185]. Eventually, resulting in a safer and less expensive end product.

However, oncoming tailored experimental and clinical studies should be planned to validate these promising results, aiming at including HDL therapy in the SOC protocol, for the treatment of infection disease, particularly in at-risk patients.

CRediT authorship contribution statement

Cinzia Parolini: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Data curation, Conceptualization.

Funding statement

This work was supported by MUR Progetto Eccellenza.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No new datasets have been created for the purpose of this review article.

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