Pulmonary Collectins, Arginases and Inducible NOS Regulate Nitric Oxide-Mediated Antibacterial Defense and Macrophage Polarization

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Abstract: Nitric oxide (NO) is important for combating bacterial infections in the lungs. Levels of NO in the lungs are regulated by L-arginine, arginases (ARG) and NO synthases (NOS). Expression levels of ARG and inducible NOS (iNOS) vary among different types of macrophages (M0, M1, M2). Several events including infection, inflammation and tissue repair/resolution polarize macrophages (M0) into either M1 or M2 types. In general, M1 and M2 macrophages express high levels of iNOS and ARG, respectively. Classically activated M1 macrophages that are related to killing intracellular pathogens release T_H1 type cytokines (e.g., IFNγ, TNFα, IL-1β, IL-12) whereas the alternatively activated M2 macrophages that are involved in humoral immune response release T_H2 type cytokines (e.g., IL-4, IL-10). Based on the activating cytokines, M2 macrophages are further subdivided into M2a, M2b or M2c. Macrophage activation and polarization are also regulated by other soluble proteins such as the innate immune pattern-recognition collectins (collagenous lectins), surfactant protein (SP)-A and SP-D. These soluble defense molecules are known to recognize microbes, and agglutinate and/or form immune complexes to enhance pathogen clearance by macrophages. In the absence of SP-D, mouse alveolar macrophages show exaggerated M1-like phenotype. Certain microbial pathogens also modulate lung environment or macrophages to evade the nitric oxide-mediated immune response. In summary, interplay among microbes, cytokines, ARG, NOS and collectins regulate alveolar macrophage types and NO production in the lungs. The balance among these molecules appears to help eliminate microbial pathogens form the lungs with minimal inflammation.

Keywords: Collectins, surfactant proteins SP-A, SP-D, arginases, NOS, macrophage polarization, nitric oxide.

INTRODUCTION

L-arginine is a cationic amino acid and its metabolism plays an important role in anti-microbial activity. It is transported into cells by the cationic amino acid transporter (CAT), and becomes converted to L-ornithine and urea by arginase (ARG). L-ornithine is a substrate for ornithine decarboxylase (ODC) for the production of polyamines, and for ornithine aminotransferase (OAT) for the production of L-proline. Polyamines are important for cell growth and differentiation, while L-proline is important for the synthesis of collagen. L-arginine is also consumed by nitric oxide synthase (NOS) that produces nitric oxide (NO). The relative expression of ARG and the inducible form of NOS (iNOS) is dependent on the presence of pathogens and the host innate immune response to those pathogens. In this review the role of arginase during host immune response during bacterial infection will be critically evaluated. In addition, the regulation of inflammatory responses by innate immune surfactant proteins, SP-A and SP-D, in response to bacterial pathogens will be discussed.

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COMPETITION FOR L-ARGININE DURING BACTERIAL KILLING

There are two isoforms of ARG: type I arginase (ARG1) and type II arginase (ARG2). ARG1 is a cytosolic enzyme and is primarily expressed in the liver, whereas ARG2 is a mitochondrial enzyme and is mainly expressed in extrahepatic tissues [1]. In the lungs, both isoforms are expressed in bronchial epithelial cells, fibroblasts and alveolar macrophages. L-arginine is also catabolized by nitric oxide synthase. NOS converts L-arginine into NO and citrulline. Subsequently, NO produces reactive intermediates such as peroxynitrite ($ONOO^-$) and nitrogen dioxide (NO_2^-), collectively known as reactive nitrogen species that are important mediators of bacterial killing by the host immune cells [2]. There are three isoforms of NOS: neuronal NOS (nNOS or NOS1), endothelial NOS (eNOS or NOS3), and inducible NOS (iNOS or NOS2). nNOS and eNOS are regarded as the constitutive NOS, and are primarily involved in the regulation of airway and vascular smooth muscle tone. iNOS, on the other hand, is constitutively expressed at low levels, but becomes upregulated in activated cells during infection [3]. Both ARG and NOS compete for their common substrate L-arginine and regulate immune responses to bacterial infection.

ROLE OF ARGINASE DURING BACTERIAL INFECTION

The cytokines expressed in the presence of pathogens tightly regulate the expression of ARG and NOS. T_H2

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cytokines such as IL-4, IL-10, IL-13, transforming growth factor (TGF)-β, and granulocyte monocyte-colony stimulating factor (GM-CSF) have been shown to induce the expression of ARG I [3]. In response to these T_H2 cytokines, transcription factors such as CCAAT-enhancer-binding proteins (C/EBPs) and signal transducer and activator of transcription (STAT) 6 are activated [4, 5]. It has been shown that both C/EBP-β and STAT6 are required for IL-4 mediated upregulation of ARG activity [6]. During bacterial infection, the balance between ARG and NOS activities are critical. Because ARG can compete with NOS for L-arginine, its activity can limit the production of NO that is important for bacterial killing [7]. Intracellular microorganisms take advantage of this competition between ARG and NOS, and limit the host NO production (Table **1**). Some bacterial pathogens express their own ARG and starve the host cell of L-arginine for the production of NO [7, 8]. Furthermore, NO produced by macrophage iNOS has been shown to be critical for *H. pylori* killing [9]. Other intracellular organisms have developed different strategies to reduce host L-arginine availability, where they directly sequester host L-arginine via increased arginine transporters once inside the host cell [10-13]. Furthermore, other bacterial species have been shown to induce T_H2 response in the host cell, which results in increased host ARG activity [14-18].

ROLE OF NITRIC OXIDE SYNTHASE DURING BACTERIAL INFECTION

T_H1 cytokines such as interferon γ (IFNγ), interleukin (IL)-1, tumour necrosis factor (TNF) have been shown to induce the expression of iNOS [19]. As such, iNOS is upregulated with the presence of bacterial antigens that stimulate classical activation of macrophages through the innate immune receptors. The requirement for NO in anti-bacterial response by the macrophages, however, has been controversial. In an infection model with *Burkholderia pseudomallei* and *B. cepacia* mice lacking iNOS did not show increased susceptibility for infection with these pathogens [20, 21]. On the other hand, INF-γ induced NO production from mouse macrophage cell line has been shown to enhance *B. pseudomallei* killing [22], and that mouse primary macrophages lacking iNOS exhibited poor anti-*Burkholderia* activity [23]. It has also been shown that *Bacillus anthracis* evade host defense mechanism through utilization of ARG to limit NO production, and that NO mediated killing is important in *B. anthracis* infection [24, 25]. In the lungs, it has been shown that NO is required for alveolar macrophage defense against *Klebsiella pneumoniae* infection [26] and *Chlamydophila pneumoniae* [27].

While the control of expression of NOS and ARG by T_H1 and T_H2 cytokines, respectively, are well established, this view may be too simplistic. LPS, which has been known as classic inducer of T_H1 response has been shown to upregulate both iNOS and ARG [28]. Furthermore, IFN-γ can also induce the expression of ARG. Therefore, the relative expression and control of ARG and NOS may be dependent on the activation status of the macrophage cells. The roles for ARG and NOS in macrophage activation are discussed later. The exact role or relevance of NO mediated bacterial killing in human macrophage also remains elusive. In response to IFN-γ and LPS, cationic amino acid transporter belonging to system y+, CAT2B is also upregulated, and is required for iNOS mediated NO production [29, 30]. Furthermore, it was recently shown that CAT2 deficient mice were more susceptible to infection by *Toxoplasma gondii*, a T_H1 inducing pathogen due to defective NO production [31]. In human alveolar macrophages, however, CAT2B expression is minimal, and instead, L-arginine transport is mainly accompanied by system y+L transporter, SLC7A7, and may limit NO production [32]. On the other hand, CAT2B is active, and plays a significant role in rodent alveolar macrophage [33]. Furthermore, stimuli that induce iNOS activation (IFN-γ and LPS) do not elicit the same response in human macrophage cells [34].

MACROPHAGE POLARIZATION

Macrophages show phenotypic heterogeneity depending on their microenvironment, and are thought to display polarized activation [35] (Fig. **1**). While classically activated macrophages (M1) exhibit T_H1 mediated antimicrobial response, alternatively activated macrophages (M2) show T_H2 associated effector response related to tissue repair [36, 37], immune modulation and resolution of inflammatory response [38]. As such, induction of iNOS and ARG-1 are

Table 1. Strategies Used by Bacteria to Reduce Host NO Production

Pathogen	Strategy	Cell Type Studied	Ref
Helicobacter pylori	Bacterial ARG expression (*rockF*)	Mϕ (RAW264.7)	[7, 8]
Listeria monocytogenes	Sequestration of host L-Arginine	Mϕ (J774)	[10]
Giardia lamblia		intestinal epithelial cells	[11-13]
Mycobacterium bovis (BCG)	Host ARG-1 upregulation	Mϕ (AM, J774)	[16, 17]
Toxoplasma gondii		Mϕ (AM, Peritoneal/ Bone marrow derived)	[15, 17]
Mycobacterium tuberculosis		Mϕ (AM)	[14, 17]
Salmonela enterica	Host ARG-2 upregulation	Mϕ (RAW264.7)	[18]

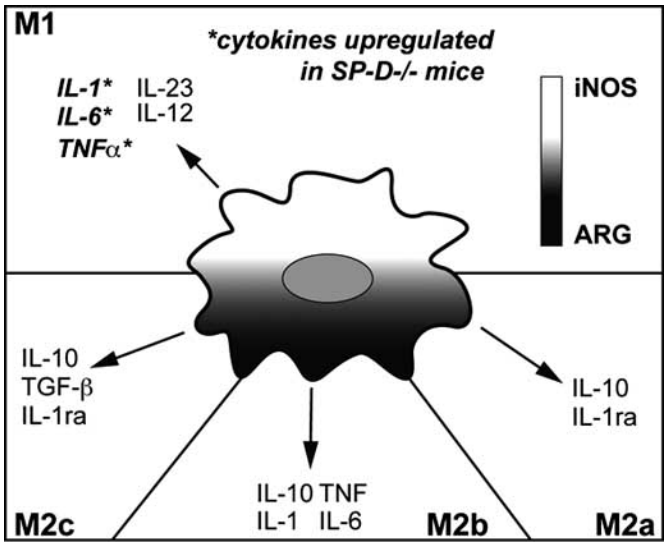

Fig. (1). Macrophage polarization.

Macrophages activation is polarized into classical activation, or M1 and alternative activation, or M2 phenotypes. M2 phenotype is further subdivided into M2a, M2b, and M2c according to the cytokines they produce [35]. Macrophages from mice deficient in SP-D express exaggerated amount of IL-1, IL-6 and TNFα, suggesting SP-D may have a role in suppressing M1 polarization.

thought to be the defining characteristics for macrophage polarization into M1 and M2 phenotype, respectively [37]. M2 macrophages are further divided into M2a, M2b, and M2c: M2a phenotype can be induced by IL-4 and IL-13; M2b phenotype is induced by TLR and IL1 receptor agonists (IL-1ra); M2c is induced by IL-10 and glucocorticoid hormones [35]. Therefore, it is thought that M1 phenotype marks the acute phase of antimicrobial response, while M2 phenotype is associated with chronic infection [35]. For example, chronic Q fever is caused by *Coxiella burnetii*, an intracellular bacterium that is capable of surviving within macrophages by interfering with the microbicidal activity of macrophages. Infection by *C. burnetii* causes mixed M1/M2 phenotype, but is predominantly M2 including the induction of TGF-beta1, IL-1 receptor antagonist (IL-1ra), CCL18, the mannose receptor, and arginase-1 [39]. This skew towards M2 polarization is thought to be responsible for *C. burnetii* persistence [39].

SP-A-AND SP-D-MEDIATED BACTERIAL CLEARANCE

Pulmonary Collectins

In the airways, the inflammatory response is tightly regulated by soluble innate immune proteins, SP-A and SP-D (Fig. **2**), and can influence cytokine secretion that affects ARG and NOS activity. The effects of SP-A and SP-D on inflammatory responses and bacterial infection in the lungs are discussed below. SP-A and SP-D are soluble pattern recognition receptors or proteins (PRR) that recognize pathogen associated molecular pattern (PAMP), which can recognize specific non-native molecular patterns [40, 41]. SP-A and SP-D are known as "ante-antibodies" [42, 43], because they predate antibodies and large quantities of them are present at lung mucosa, comprising >90% (w/w) of surfactant proteins [40]. These proteins are secreted by nasal epithelium [44], upper airway non-ciliated cells [45], and alveolar epithelial type II cells [46]. Multimeric assemblies of collectins enable them to recognize repeating molecular patterns present on various microbes (i.e., lipopolysaccharide and peptidoglycan) and glycoproteins present on allergens with high avidity [47]. Unlike antibodies, such as IgG, collectins pre-assemble their ligand-binding domains as multiples of trimeric subunits [47, 48].

SP-A and SP-D belong to the collectin family, and contain a collagenous region and a lectin or carbohydrate recognition domain (CRD). The basic unit of a collectin consists of a short cystine-rich interchain-disulfide bond forming N-terminal segment, a long fibrillar collagen-like region, a trimerizing amphipathic α-helical coiled-coil hydrophobic neck domain and a globular CRD [49-52]. Native SP-A and SP-D appear as bouquet of "tulip flowers" (6 trimers) and "X" (4 trimers) or "asterisk-like" structures (>10 trimers), respectively [53]. SP-A forms supraquaternary structures as uni- and multi- dimensional fibers [54], and interacts well with carbohydrate ligands such as mannose [55]. The globular domains of collectins recognize carbohydrate, whereas the rest of the molecule is thought to be primarily involved in structural organization and interactions with receptors and other molecules [50, 53]. This carbohydrate binding ability of collectins allows for the recognition of carbohydrate molecules on glycoproteins present on the surfaces of bacteria, viruses, and fungi, and thus, act as antimicrobial defense molecules.

MICROBICIDAL ACTIVITY OF THE PULMONARY COLLECTINS

As the major protein present in the airways, SP-A and SP-D play a significant role in the innate immune response to bacterial infection. Through its CRD, SP-A and SP-D are able to recognize and bind a diverse array of bacterial pathogens such as *Pseudomonas aeruginosa*, and *Escherichia coli* by binding to their lipopolysaccharides

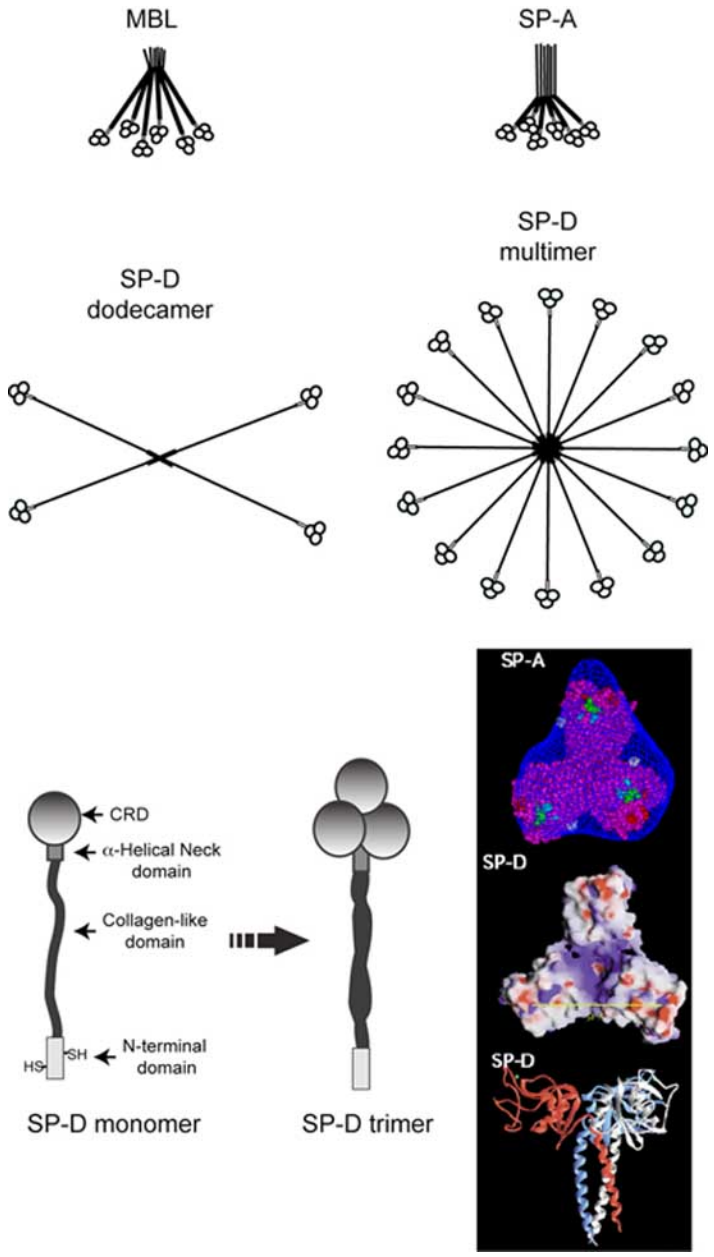

Fig. (2). Collectin molecules.

Surfactant protein (SP) -A and SP-D are referred to as pulmonary collectins (collagenous lectin), and are capable of binding to carbohydrate molecules present on various bacterial species. Both collectins have a basic functional unit made of a trimer, which can then assemble into higher oligomers (See references [100] and [51] for detailed review of collectin structure and function).

(LPS) [56], as well as *Streptococcus pneumoniae* and *Staphylococcus aureus* [57] through their lipoteicoic acid and peptidoglycan [58]. It has been shown that SP-A and SP-D directly enhance the uptake of bacteria by the alveolar macrophage and enhance their clearance [59]. Furthermore, studies using knock out mice for SP-A and SP-D have shown that these mice are susceptible for infection by the bacterial pathogens and have reduced pulmonary clearance [60, 61]. SP-A and SP-D also have direct microbicidal activity upon binding to the invading pathogen. SP-A and SP-D can inhibit the bacterial growth of gram-negative bacteria by increasing their membrane permeability [62-64].

REGULATION OF INFLAMMATORY RESPONSE BY THE COLLECTINS

SP-A deficient mice infected with *Mycoplasma pulmonis* not only had increased bacterial load, but also had increased NO production in the lungs, suggesting a role for SP-A in the suppression of NO production [65]. Mice deficient in SP-D also has increased NO content and upregulation of iNOS,

which was associated with decreased bacterial clearance [66, 67]. Collectin mediated control of NO production also seems to have regulatory effect on SP-D function. It was recently shown that SP-D becomes S-nitrosylated by NO, and that the S-nitrosylation of SP-D (SNO SP-D) results in disruption of dodecameric structure into individual trimers *in vitro* [68]. In this study, the authors suggested that the SNO-SP-D is responsible for the pro-inflammatory function of SP-D via CD91 mediated signaling [68]. The presence of SNO-SP-D *in vivo* during *Pneumocystis* lung infection has also been documented by this group [69]. It was also recently shown that SP-D treated with $ONOO^-$ becomes nitrated, and this nitration of SP-D results in non-reducible cross-linking between SP-D monomers and the loss of agglutinating activity of SP-D [70]. These studies demonstrate that SP-D not only participates in the induction of pro- and anti-inflammatory response, but its action may be regulated by the post-translational modifications.

Aside from its antimicrobial activity, a growing body of literature suggests a crucial role for innate immune lung collectins, SP-A and SP-D, in the regulation of inflammatory response [71]. Gene knockout studies show that SP-D regulates multiple functions in the lungs. Neutrophils and macrophages accumulate in the lungs of SP-D deficient mice [72-74]. Most of these macropahges are apoptotic [73], laden with lipid vesicles, and eventually become foamy [74, 75]. These macrophages secrete matrix metalloproteases (MMPs), cleave surface molecules including CD14 [76] and cause damage to the lung parenchyma and destroy alveoli [77]. Furthermore, SP-D binds to, and enhances the clearance of DNA in the lungs and reduces the generation of autoantibody against DNA [78]. This is particularly of interest for diseases such as cystic fibrosis characterized by increased DNA in the airway, lupus, as well as for neutrophil extracellular traps (NETs) [79]. SP-D deficient mice do not show signs of inflammation in the lungs at birth [74, 77]. However, at around the age of 8 weeks, these mice develop airway destruction, associated with pulmonary infiltration of foamy macrophage and monocytic cells [74]. In addition, there is a high level of superoxide production and increased NF-κB activity [80]. A truncated form of recombinant SP-D (n/CRD) reduces macrophage activation and release of pro-inflammatory cytokine. The n/CRD consists of a short collagenous region, neck, and the CRD region and it can also reduce alteration of lung parancyma in SP-D deficient mice [81, 82]. Conditional replacement of SP-D transgene, $(tetO)_7$-rSP-D, in SP-D deficient mice restores lung abnormalities [83]. Furthermore, SP-D has been shown to reduce pulmonary inflammation caused by endotoxins such as LPS and LTA in mice [84] and prevent endotoxin induced shock in newborn preterm lambs [85].

Although many studies have described putative receptors for SP-A and SP-D, a clear picture on the receptor and receptor-mediated signaling is yet to be elucidated. It has been suggested that SP-A (and SP-D) have both pro- and anti-inflammatory roles [86] and some mechanistic insight has been proposed for the control of inflammatory response mediated by the surfactant proteins. When pathogens or foreign particles (i.e. allergens) come in to the lung, SP-A binds these pathogens/allergens and interacts with the CD91/calreticulin receptor complex [86-88]. SP-A was shown to bind signal regulatory protein (SIRP) α through its CRD, and induce SHP-1 mediated inhibition of p38 MAPK pathway [86]. On the other hand, SP-A was suggested to bind to calreticulin/CD91 [88], and was shown to induce a pro-inflammatory response via MAPK pathway and NFκB signaling [86]. SP-D has also been shown to bind certain other proteins or putative receptors present in the lungs, including CD14 [89] and, toll like receptor (TLR) 4 [90]. SP-A has also been found to suppress lipopolysaccharide (LPS) induced TNF-α release by alveolar macrophages [91]. SP-D can also directly down regulates LPS-induced pro-inflammatory response by binding to TLR4 and MD2 [90, 92]. A recent report also suggests a role for SP-D in the modulation of alveolar macrophage polarization. The authors found that the alveolar macrophages from SP-D deficient mice expressed higher levels of M1 markers [93]. These studies suggest a role for SP-A and SP-D in preventing the induction of M1, or classically activated macrophages. Precise role(s) for the collectins in the macrophage polarization, however, is not yet determined. It is possible that the collectin molecules regulate macrophage polarization via ARG. Although some studies suggest that SP-A and SP-D modulate NO production, the role of SP-A and SP-D on ARG activity has not been described.

Many studies involving the role for SP-D in regulation of inflammatory response by the macrophages thus far has used both primary macrophages as well as cell lines, which may have skewed some of the interpretations. Most cell lines used have been peritoneal macrophage cell lines, and there has been many reports describing differences in the immune responses between alveolar and peritoneal macrophages. It has been long known that alveolar macrophages differentiate in response to GM-CSF, while peritoneal macrophages differentiate in response to M-CSF [94]. GM-CSF induces alveolar macrophage differentiation via induction of PU.1 [95, 96]. There is also differences in the expression of surface receptors between peritoneal and alveolar macrophages [97], whose expression have been shown to be mediated by both SP-A [98] and SP-D [99]. Furthermore, functional difference has also been described where alveolar macrophages are better able to macropinocytose small molecules [97]. Therefore, caution must be made in making conclusions regarding the role of the collectins on inflammatory responses by the alveolar macrophage.

CONCLUSION

L-arginine metabolism plays an important role during an inflammatory response, and a correct balance between iNOS and ARG is critical for proper antimicrobial response. Many bacterial species have evolved ways to thwart host arginine availability for NO production. Furthermore, the balance between iNOS and ARG also are characteristic of macrophage activation status, where M1 phenotype predominated by the induction of iNOS expression, and M2 phenotype predominantly expresses ARG. Innate immune proteins SP-A and SP-D also are thought to play a role in regulation of inflammatory response by macrophage cells. In particular, alveolar macrophages from mice deficient in SP-D show exaggerated upregulation of proinflammatory cytokines that are reminiscent of M1 phenotype. Therefore, these innate immune collectins seem to maintain the alveolar macrophages in a non-polarized phenotype.

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REFERENCES

[1] Maarsingh, H.; Pera, T.; Meurs, H. Arginase and pulmonary diseases. Naunyn. Schmiedebergs Arch. *Pharmacol*., **2008**, *378*, 171-184.

[2] Fang, F. C. Antimicrobial reactive oxygen and nitrogen species: concepts and controversies. *Nat. Rev*., **2004**, *2*, 820-832.

[3] Mori, M.; Gotoh, T. Arginine metabolic enzymes, nitric oxide and infection. *J. Nutr*., **2004**, *134*, 2820S-2825S; discussion 53S.

[4] Hebenstreit, D.; Wirnsberger, G.; Horejs-Hoeck, J.; Duschl, A. Signaling mechanisms, interaction partners, and target genes of STAT6. *Cytokine Growth Factor Rev*., **2006**, *17*, 173-188.

[5] Hou, J.; Schindler, U.; Henzel, W. J.; Ho, T. C.; Brasseur, M.; McKnight, S. L. An interleukin-4-induced transcription factor: IL-4 Stat. *Science*, **1994**, *265*, 1701-1706.

[6] Gray, M. J.; Poljakovic, M.; Kepka-Lenhart, D.; Morris, S. M., Jr. Induction of arginase I transcription by IL-4 requires a composite DNA response element for STAT6 and C/EBPbeta. *Gene*, **2005**, *353*, 98-106.

[7] Chaturvedi, R.; Asim, M.; Lewis, N. D.; Algood, H. M.; Cover, T. L.; Kim, P. Y.; Wilson, K. T. L-arginine availability regulates inducible nitric oxide synthase-dependent host defense against *Helicobacter pylori*. *Infect. Immun*., **2007**, *75*, 4305-4315.

[8] Gobert, A. P.; McGee, D. J.; Akhtar, M.; Mendz, G. L.; Newton, J. C.; Cheng, Y.; Mobley, H. L.; Wilson, K. T. Helicobacter pylori arginase inhibits nitric oxide production by eukaryotic cells: a strategy for bacterial survival. *Proc. Natl. Acad. Sci. U. S. A*., **2001**, *98*, 13844-13849.

[9] Bussiere, F. I.; Chaturvedi, R.; Cheng, Y.; Gobert, A. P.; Asim, M.; Blumberg, D. R.; Xu, H.; Kim, P. Y.; Hacker, A.; Casero, R. A., Jr.; Wilson, K. T. Spermine causes loss of innate immune response to *Helicobacter pylori* by inhibition of inducible nitric-oxide synthase translation. *J. Biol. Chem*., **2005**, *280*, 2409-2412.

[10] Klarsfeld, A. D.; Goossens, P. L.; Cossart, P. Five Listeria monocytogenes genes preferentially expressed in infected mammalian cells: plcA, purH, purD, pyrE and an arginine ABC transporter gene, arp. *J. Mol. Microbiol*., **1994**, *13*, 585-597.

[11] Eckmann, L.; Laurent, F.; Langford, T. D.; Hetsko, M. L.; Smith, J. R.; Kagnoff, M. F.; Gillin, F. D. Nitric oxide production by human intestinal epithelial cells and competition for arginine as potential determinants of host defense against the lumen-dwelling pathogen Giardia lamblia. *J. Immunol*., **2000**, *164*, 1478-1487.

[12] Touz, M. C.; Ropolo, A. S.; Rivero, M. R.; Vranych, C. V.; Conrad, J. T.; Svard, S. G.; Nash, T. E. Arginine deiminase has multiple regulatory roles in the biology of Giardia lamblia. *J. Cell Sci.*, **2008**, *121*, 2930-2938.

[13] Ringqvist, E.; Palm, J. E.; Skarin, H.; Hehl, A. B.; Weiland, M.; Davids, B. J.; Reiner, D. S.; Griffiths, W. J.; Eckmann, L.; Gillin, F. D.; Svard, S. G. Release of metabolic enzymes by Giardia in response to interaction with intestinal epithelial cells. *Mol. Biochem. Parasitol*., **2008**, *159*, 85-91.

[14] Schreiber, T.; Ehlers, S.; Heitmann, L.; Rausch, A.; Mages, J.; Murray, P. J.; Lang, R.; Holscher, C. Autocrine IL-10 induces hallmarks of alternative activation in macrophages and suppresses antituberculosis effector mechanisms without compromising T cell immunity. *J. Immunol*., **2009**, *183*, 1301-1312.

[15] Rutschman, R.; Lang, R.; Hesse, M.; Ihle, J. N.; Wynn, T. A.; Murray, P. J. Cutting edge: Stat6-dependent substrate depletion regulates nitric oxide production. *J. Immunol*., **2001**, *166*, 2173-2177.

[16] Peteroy-Kelly, M.; Venketaraman, V.; Connell, N. D. Effects of Mycobacterium bovis BCG infection on regulation of L-arginine uptake and synthesis of reactive nitrogen intermediates in J774.1 murine macrophages. *Infect. Immun*., **2001**, *69*, 5823-5831.

[17] El Kasmi, K. C.; Qualls, J. E.; Pesce, J. T.; Smith, A. M.; Thompson, R. W.; Henao-Tamayo, M.; Basaraba, R. J.; Konig, T.; Schleicher, U.; Koo, M. S.; Kaplan, G.; Fitzgerald, K. A.; Tuomanen, E. I.; Orme, I. M.; Kanneganti, T. D.; Bogdan, C.; Wynn, T. A.; Murray, P. J. Toll-like receptor-induced arginase 1 in macrophages thwarts effective immunity against intracellular pathogens. *Nat. Immunol*., **2008**, *9*, 1399-1406.

[18] Lahiri, A.; Das, P.; Chakravortty, D. Arginase modulates Salmonella induced nitric oxide production in RAW264.7 macrophages and is required for Salmonella pathogenesis in mice model of infection. *Microbes. Infect*., **2008**, *10*, 1166-1174.

[19] Bosca, L.; Zeini, M.; Traves, P. G.; Hortelano, S. Nitric oxide and cell viability in inflammatory cells: a role for NO in macrophage function and fate. *Toxicology*, **2005**, *208*, 249-258.

[20] Breitbach, K.; Klocke, S.; Tschernig, T.; van Rooijen, N.; Baumann, U.; Steinmetz, I. Role of inducible nitric oxide synthase and NADPH oxidase in early control of *Burkholderia pseudomallei* infection in mice. *Infect. Immun*., **2006**, *74*, 6300-6309.

[21] Segal, B. H.; Ding, L.; Holland, S. M. Phagocyte NADPH oxidase, but not inducible nitric oxide synthase, is essential for early control of Burkholderia cepacia and chromobacterium violaceum infection in mice. *Infect. Immun*., **2003**, *71*, 205-210.

[22] Utaisincharoen, P.; Anuntagool, N.; Arjcharoen, S.; Limposuwan, K.; Chaisuriya, P.; Sirisinha, S. Induction of iNOS expression and antimicrobial activity by interferon (IFN)-beta is distinct from IFN-gamma in Burkholderia pseudomallei-infected mouse macrophages. *Clin. Exp. Immunol*., **2004**, *136*, 277-283.

[23] Jones-Carson, J.; Laughlin, J.; Hamad, M. A.; Stewart, A. L.; Voskuil, M. I.; Vazquez-Torres, A. Inactivation of [Fe-S] metalloproteins mediates nitric oxide-dependent killing of Burkholderia mallei. *PLoS ONE*, **2008**, *3*, e1976.

[24] Raines, K. W.; Kang, T. J.; Hibbs, S.; Cao, G. L.; Weaver, J.; Tsai, P.; Baillie, L.; Cross, A. S.; Rosen, G. M. Importance of nitric oxide synthase in the control of infection by *Bacillus anthracis*. *Infect. Immun*., **2006**, *74*, 2268-2276.

[25] Weaver, J.; Kang, T. J.; Raines, K. W.; Cao, G. L.; Hibbs, S.; Tsai, P.; Baillie, L.; Rosen, G. M.; Cross, A. S. Protective role of Bacillus anthracis exosporium in macrophage-mediated killing by nitric oxide. *Infect. Immun*., **2007**, *75*, 3894-3901.

[26] Tsai, W. C.; Strieter, R. M.; Zisman, D. A.; Wilkowski, J. M.; Bucknell, K. A.; Chen, G. H.; Standiford, T. J. Nitric oxide is required for effective innate immunity against Klebsiella pneumoniae. *Infect. Immun*., **1997**, *65*, 1870-1875.

[27] Shimada, K.; Chen, S.; Dempsey, P. W.; Sorrentino, R.; Alsabeh, R.; Slepenkin, A. V.; Peterson, E.; Doherty, T. M.; Underhill, D.; Crother, T. R.; Arditi, M. The NOD/RIP2 pathway is essential for host defenses against Chlamydophila pneumoniae lung infection. *PLoS Pathog*, **2009**, *5*, e1000379.

[28] Peranzoni, E.; Marigo, I.; Dolcetti, L.; Ugel, S.; Sonda, N.; Taschin, E.; Mantelli, B.; Bronte, V.; Zanovello, P. Role of arginine metabolism in immunity and immunopathology. *Immunobiology*, **2007**, *212*, 795-812.

[29] Yeramian, A.; Martin, L.; Arpa, L.; Bertran, J.; Soler, C.; McLeod, C.; Modolell, M.; Palacin, M.; Lloberas, J.; Celada, A. Macrophages require distinct arginine catabolism and transport systems for proliferation and for activation. *Eur. J. Immunol*., **2006**, *36*, 1516-1526.

[30] Nicholson, B.; Manner, C. K.; Kleeman, J.; MacLeod, C. L. Sustained nitric oxide production in macrophages requires the arginine transporter CAT2. *J. Biol. Chem*., **2001**, *276*, 15881-15885.

[31] Thompson, R. W.; Pesce, J. T.; Ramalingam, T.; Wilson, M. S.; White, S.; Cheever, A. W.; Ricklefs, S. M.; Porcella, S. F.; Li, L.; Ellies, L. G.; Wynn, T. A. Cationic amino acid transporter-2 regulates immunity by modulating arginase activity. *PLoS Pathog*, **2008**, *4*, e1000023.

[32] Rotoli, B. M.; Dall'asta, V.; Barilli, A.; D'Ippolito, R.; Tipa, A.; Olivieri, D.; Gazzola, G. C.; Bussolati, O. Alveolar macrophages from normal subjects lack the NOS-related system y+ for arginine transport. Am. J. Respir. *Cell Mol. Biol*., **2007**, *37*, 105-112.

[33] Rothenberg, M. E.; Doepker, M. P.; Lewkowich, I. P.; Chiaramonte, M. G.; Stringer, K. F.; Finkelman, F. D.; MacLeod, C. L.; Ellies, L. G.; Zimmermann, N. Cationic amino acid transporter 2 regulates inflammatory homeostasis in the lung. *Proc. Natl. Acad. Sci. U. S. A*., **2006**, *103*, 14895-1900.

[34] Thomassen, M. J.; Kavuru, M. S. Human alveolar macrophages and monocytes as a source and target for nitric oxide. *Int. Immunopharmacol*, **2001**, *1*, 1479-1490.

[35] Benoit, M.; Desnues, B.; Mege, J. L. Macrophage polarization in bacterial infections. *J. Immunol*., **2008**, *181*, 3733-3739.

[36] Edwards, J. P.; Zhang, X.; Frauwirth, K. A.; Mosser, D. M. Biochemical and functional characterization of three activated macrophage populations. *J. Leukoc. Biol*., **2006**, *80*, 1298-1307.

[37] Munder, M.; Eichmann, K.; Modolell, M. Alternative metabolic states in murine macrophages reflected by the nitric oxide synthase/arginase balance: competitive regulation by CD4+ T cells correlates with Th1/Th2 phenotype. *J. Immunol*., **1998**, *160*, 5347-5354.

[38] Gordon, S. Alternative activation of macrophages. *Nat. Rev. Immunol*., **2003**, *3*, 23-35.

[39] Benoit, M.; Barbarat, B.; Bernard, A.; Olive, D.; Mege, J. L. Coxiella burnetii, the agent of Q fever, stimulates an atypical M2 activation program in human macrophages. *Eur. J. Immunol*., **2008**, *38*, 1065-70.

[40] Palaniyar, N.; Nadesalingam, J.; Reid, K. B. M. Receptors and ligands for collectins surfactant proteins A and D. In: *Lung Surfactant Function and Disorder*, Nag, K., Ed. Taylor & Frances Group: Florida, USA, **2005**, pp. 87-110.

[41] King, R. J.; Clements, J. A. Surface active materials from dog lung. II. Composition and physiological correlations. *Am. J. Physiol*., **1972**, *223*, 715-26.

[42] Takahashi, K.; Ip, W. E.; Michelow, I. C.; Ezekowitz, R. A. The mannose-binding lectin: a prototypic pattern recognition molecule. *Curr. Opin. Immunol*., **2006**, *18*, 16-23.

[43] Alan, R.; Ezekowitz, B. Ante-antibody immunity. *Curr. Biol*., **1991**, *1*, 60-62.

[44] Kim, J. K.; Kim, S. S.; Rha, K. W.; Kim, C. H.; Cho, J. H.; Lee, C. H.; Lee, J. G.; Yoon, J. H. Expression and localization of surfactant proteins in human nasal epithelium. *Am. J. Physiol. Lung Cell Mol. Physiol*., **2007**, *292*, L879-L884.

[45] Crouch, E.; Parghi, D.; Kuan, S. F.; Persson, A. Surfactant protein D: subcellular localization in nonciliated bronchiolar epithelial cells. *Am. J. Physiol*., **1992**, *263*, L60-L66.

[46] Persson, A.; Chang, D.; Rust, K.; Moxley, M.; Longmore, W.; Crouch, E. Purification and biochemical characterization of CP4 (SP-D), a collagenous surfactant-associated protein. *Biochemistry (Mosc)*., **1989**, *28*, 6361-6367.

[47] Wright, J. R. Immunoregulatory functions of surfactant proteins. *Nat. Rev. Immunol*., **2005**, *5*, 58-68.

[48] Palaniyar, N.; Nadesalingam, J.; Reid, K. B. Innate immune collectins bind nucleic acids and enhance DNA clearance *in vitro*. *Ann. N. Y. Acad. Sci*., **2003**, *1010*, 467-470.

[49] Head, J. F.; Mealy, T. R.; McCormack, F. X.; Seaton, B. A. Crystal structure of trimeric carbohydrate recognition and neck domains of surfactant protein *A. J. Biol. Chem*., **2003**, *278*, 43254-43260.

[50] Hakansson, K.; Lim, N. K.; Hoppe, H. J.; Reid, K. B. Crystal structure of the trimeric alpha-helical coiled-coil and the three lectin domains of human lung surfactant protein D. *Structure Fold. Des*., **1999**, *7*, 255-264.

[51] Hakansson, K.; Reid, K. B. Collectin structure: a review. *Protein Sci*., **2000**, *9*, 1607-1617.

[52] Shrive, A. K.; Tharia, H. A.; Strong, P.; Kishore, U.; Burns, I.; Rizkallah, P. J.; Reid, K. B.; Greenhough, T. J. High-resolution structural insights into ligand binding and immune cell recognition by human lung surfactant protein D. *J. Mol. Biol*., **2003**, *331*, 509-523.

[53] Palaniyar, N.; Ikegami, M.; Korfhagen, T.; Whitsett, J.; McCormack, F. X. Domains of surfactant protein A that affect protein oligomerization, lipid structure and surface tension. *Comp. Biochem. Physiol. A. Mol. Integr. Physiol*., **2001**, *129*, 109-127.

[54] Palaniyar, N.; Ridsdale, R. A.; Hearn, S. A.; Heng, Y. M.; Ottensmeyer, F. P.; Possmayer, F.; Harauz, G. Filaments of surfactant protein A specifically interact with corrugated surfaces of phospholipid membranes. Am. J. Physiol., **1999**, *276*, L631-L641.

[55] Nadesalingam, J.; Bernal, A. L.; Dodds, A. W.; Willis, A. C.; Mahoney, D. J.; Day, A. J.; Reid, K. B.; Palaniyar, N. Identification and characterization of a novel interaction between pulmonary surfactant protein D and decorin. *J. Biol. Chem*., **2003**, *278*, 25678-25687.

[56] Wang, L.; Brauner, J. W.; Mao, G.; Crouch, E.; Seaton, B.; Head, J.; Smith, K.; Flach, C. R.; Mendelsohn, R. Interaction of recombinant surfactant protein D with lipopolysaccharide: conformation and orientation of bound protein by IRRAS and simulations. *Biochemistry (Mosc).*, **2008**, *47*, 8103-8113.

[57] McNeely, T. B.; Coonrod, J. D. Comparison of the opsonic activity of human surfactant protein A for Staphylococcus aureus and Streptococcus pneumoniae with rabbit and human macrophages. *J. Infect. Dis*., **1993**, *167*, 91-97.

[58] Van de Wetering, J. K.; van Eijk, M.; van Golde, L. M.; Hartung, T.; van Strijp, J. A.; Batenburg, J. J. Characteristics of surfactant protein A and D binding to lipoteichoic acid and peptidoglycan, 2 major cell wall components of gram-positive bacteria. *J. Infect. Dis*., **2001**, *184*, 1143-1151.

[59] Giannoni, E.; Sawa, T.; Allen, L.; Wiener-Kronish, J.; Hawgood, S. Surfactant proteins A and D enhance pulmonary clearance of Pseudomonas aeruginosa. *Am. J. Respir. Cell Mol. Biol*., **2006**, *34*, 704-710.

[60] LeVine, A. M.; Kurak, K. E.; Bruno, M. D.; Stark, J. M.; Whitsett, J. A.; Korfhagen, T. R. Surfactant protein-A-deficient mice are susceptible to Pseudomonas aeruginosa infection. *Am. J. Respir. Cell Mol. Biol*., **1998**, *19*, 700-708.

[61] LeVine, A. M.; Whitsett, J. A.; Gwozdz, J. A.; Richardson, T. R.; Fisher, J. H.; Burhans, M. S.; Korfhagen, T. R. Distinct effects of surfactant protein A or D deficiency during bacterial infection on the lung. *J. Immunol*., **2000**, 165, 3934-3940.

[62] Wu, H.; Kuzmenko, A.; Wan, S.; Schaffer, L.; Weiss, A.; Fisher, J. H.; Kim, K. S.; McCormack, F. X. Surfactant proteins A and D inhibit the growth of Gram-negative bacteria by increasing membrane permeability. *J. Clin. Invest*., **2003**, *111*, 1589-1602.

[63] Kuzmenko, A. I.; Wu, H.; McCormack, F. X. Pulmonary collectins selectively permeabilize model bacterial membranes containing rough lipopolysaccharide. *Biochemistry (Mosc)*. **2006**, *45*, 2679-2685.

[64] Canadas, O.; Garcia-Verdugo, I.; Keough, K. M.; Casals, C. SP-A permeabilizes lipopolysaccharide membranes by forming protein aggregates that extract lipids from the membrane. *Biophys. J*., **2008**, *95*, 3287-94.

[65] Hickman-Davis, J. M.; Gibbs-Erwin, J.; Lindsey, J. R.; Matalon, S. Role of surfactant protein-A in nitric oxide production and mycoplasma killing in congenic C57BL/6 mice. *Am. J. Respir. Cell Mol. Biol*., **2004**, *30*, 319-325.

[66] Atochina, E. N.; Gow, A. J.; Beck, J. M.; Haczku, A.; Inch, A.; Kadire, H.; Tomer, Y.; Davis, C.; Preston, A. M.; Poulain, F.; Hawgood, S.; Beers, M. F. Delayed clearance of pneumocystis carinii infection, increased inflammation, and altered nitric oxide metabolism in lungs of surfactant protein-D knockout mice. *J. Infect. Dis*., **2004**, *189*, 1528-1539.

[67] Atochina, E. N.; Beers, M. F.; Hawgood, S.; Poulain, F.; Davis, C.; Fusaro, T.; Gow, A. J. Surfactant protein-D, a mediator of innate lung immunity, alters the products of nitric oxide metabolism. *Am. J. Respir. Cell Mol. Biol*., **2004**, *30*, 271-9.

[68] Guo, C. J.; Atochina-Vasserman, E. N.; Abramova, E.; Foley, J. P.; Zaman, A.; Crouch, E.; Beers, M. F.; Savani, R. C.; Gow, A. J. S-nitrosylation of surfactant protein-D controls inflammatory function. *PLoS Biol*., **2008**, *6*, e266.

[69] Atochina-Vasserman, E. N.; Gow, A. J.; Abramova, H.; Guo, C. J.; Tomer, Y.; Preston, A. M.; Beck, J. M.; Beers, M. F. Immune reconstitution during Pneumocystis lung infection: disruption of surfactant component expression and function by S-nitrosylation. *J. Immunol*., **2009**, *182*, 2277-2287.

[70] Matalon, S.; Shrestha, K.; Kirk, M.; Waldheuser, S.; McDonald, B.; Smith, K.; Gao, Z.; Belaaouaj, A.; Crouch, E. C. Modification of surfactant protein D by reactive oxygen-nitrogen intermediates is accompanied by loss of aggregating activity, *in vitro* and *in vivo*. *FASEB J*., **2009**. *23*, 1415-1430.

[71] Haczku, A. Protective role of the lung collectins surfactant protein A and surfactant protein D in airway inflammation. *J. Allergy Clin. Immunol*., **2008**, *122*, 861-79; quiz 80-1.

[72] Brandt, E. B.; Mingler, M. K.; Stevenson, M. D.; Wang, N.; Khurana Hershey, G. K.; Whitsett, J. A.; Rothenberg, M. E. Surfactant protein D alters allergic lung responses in mice and human subjects. *J. Allergy Clin. Immunol*., **2008**, *121*, 1140-47 e2.

[73] Clark, H.; Palaniyar, N.; Strong, P.; Edmondson, J.; Hawgood, S.; Reid, K. B. Surfactant protein D reduces alveolar macrophage apoptosis *in vivo*. *J. Immunol*., **2002**, *169*, 2892-2899.

[74] Botas, C.; Poulain, F.; Akiyama, J.; Brown, C.; Allen, L.; Goerke, J.; Clements, J.; Carlson, E.; Gillespie, A. M.; Epstein, C.; Hawgood, S. Altered surfactant homeostasis and alveolar type II cell morphology in mice lacking surfactant protein D. *Proc. Natl. Acad. Sci. USA*, **1998**, *95*, 11869-11874.

[75] Korfhagen, T. R.; Sheftelyevich, V.; Burhans, M. S.; Bruno, M. D.; Ross, G. F.; Wert, S. E.; Stahlman, M. T.; Jobe, A. H.; Ikegami, M.; Whitsett, J. A.; Fisher, J. H. Surfactant protein-D regulates surfactant phospholipid homeostasis *in vivo*. *J. Biol. Chem*., **1998**, *273*, 28438-28443.

[76] Senft, A. P.; Korfhagen, T. R.; Whitsett, J. A.; Shapiro, S. D.; LeVine, A. M. Surfactant protein-D regulates soluble CD14 through matrix metalloproteinase-12. *J. Immunol*., **2005**, *174*, 4953-4959.

[77] Wert, S. E.; Yoshida, M.; LeVine, A. M.; Ikegami, M.; Jones, T.; Ross, G. F.; Fisher, J. H.; Korfhagen, T. R.; Whitsett, J. A. Increased metalloproteinase activity, oxidant production, and emphysema in surfactant protein D gene-inactivated mice. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 5972-7.

[78] Palaniyar, N.; Clark, H.; Nadesalingam, J.; Shih, M. J.; Hawgood, S.; Reid, K. B. Innate immune collectin surfactant protein D enhances the clearance of DNA by macrophages and minimizes anti-DNA antibody generation. *J. Immunol*., **2005**, *174*, 7352-7358.

[79] Brinkmann, V.; Reichard, U.; Goosmann, C.; Fauler, B.; Uhlemann, Y.; Weiss, D. S.; Weinrauch, Y.; Zychlinsky, A. Neutrophil extracellular traps kill bacteria. *Science*, **2004**, *303*, 1532-1535.

[80] Yoshida, M.; Korfhagen, T. R.; Whitsett, J. A. Surfactant protein D regulates NF-kappa B and matrix metalloproteinase production in alveolar macrophages via oxidant-sensitive pathways. *J. Immunol*., **2001**, *166*, 7514-7519.

[81] Knudsen, L.; Ochs, M.; Mackay, R.; Townsend, P.; Deb, R.; Muhlfeld, C.; Richter, J.; Gilbert, F.; Hawgood, S.; Reid, K.; Clark, H. Truncated recombinant human SP-D attenuates emphysema and type II cell changes in SP-D deficient mice. *Respir. Res*., **2007**, *8*, 70.

[82] Clark, H.; Palaniyar, N.; Hawgood, S.; Reid, K. B. A recombinant fragment of human surfactant protein D reduces alveolar macrophage apoptosis and pro-inflammatory cytokines in mice developing pulmonary emphysema. *Ann. N. Y. Acad. Sci*., **2003**, *1010*, 113-116.

[83] Zhang, L.; Ikegami, M.; Dey, C. R.; Korfhagen, T. R.; Whitsett, J. A. Reversibility of pulmonary abnormalities by conditional replacement of surfactant protein D (SP-D) *in vivo*. *J. Biol. Chem*. **2002**, *277*, 38709-38713.

[84] Ikegami, M.; Scoville, E. A.; Grant, S.; Korfhagen, T.; Brondyk, W.; Scheule, R. K.; Whitsett, J. A. Surfactant protein-D and surfactant inhibit endotoxin-induced pulmonary inflammation. *Chest*, **2007**, *132*, 1447-1454.

[85] Ikegami, M.; Carter, K.; Bishop, K.; Yadav, A.; Masterjohn, E.; Brondyk, W.; Scheule, R. K.; Whitsett, J. A. Intratracheal recombinant surfactant protein d prevents endotoxin shock in the newborn preterm lamb. *Am. J. Respir. Crit. Care Med*., **2006**, *173*, 1342-1347.

[86] Gardai, S. J.; Xiao, Y. Q.; Dickinson, M.; Nick, J. A.; Voelker, D. R.; Greene, K. E.; Henson, P. M. By binding SIRPalpha or calreticulin/CD91, lung collectins act as dual function surveillance molecules to suppress or enhance inflammation. *Cell*, **2003**, *115*, 13-23.

[87] Ogden, C. A.; deCathelineau, A.; Hoffmann, P. R.; Bratton, D.; Ghebrehiwet, B.; Fadok, V. A.; Henson, P. M. C1q and mannose binding lectin engagement of cell surface calreticulin and CD91 initiates macropinocytosis and uptake of apoptotic cells. *J. Exp. Med*., **2001**, *194*, 781-795.

[88] Vandivier, R. W.; Ogden, C. A.; Fadok, V. A.; Hoffmann, P. R.; Brown, K. K.; Botto, M.; Walport, M. J.; Fisher, J. H.; Henson, P. M.; Greene, K. E. Role of surfactant proteins A, D, and C1q in the clearance of apoptotic cells *in vivo* and *in vitro*: calreticulin and CD91 as a common collectin receptor complex. *J. Immunol*., **2002**, *169*, 3978-3986.

[89] Sano, H.; Chiba, H.; Iwaki, D.; Sohma, H.; Voelker, D. R.; Kuroki, Y. Surfactant proteins A and D bind CD14 by different mechanisms. *J. Biol. Chem*., **2000**, *275*, 22442-22451.

[90] Ohya, M.; Nishitani, C.; Sano, H.; Yamada, C.; Mitsuzawa, H.; Shimizu, T.; Saito, T.; Smith, K.; Crouch, E.; Kuroki, Y. Human pulmonary surfactant protein D binds the extracellular domains of Toll-like receptors 2 and 4 through the carbohydrate recognition domain by a mechanism different from its binding to phosphatidylinositol and lipopolysaccharide. *Biochemistry (Mosc)*, **2006**, *45*, 8657-8664.

[91] McIntosh, J. C.; Mervin-Blake, S.; Conner, E.; Wright, J. R. Surfactant protein A protects growing cells and reduces TNF-alpha activity from LPS-stimulated macrophages. *Am. J. Physiol*., **1996**, *271*, L310-L319.

[92] Yamazoe, M.; Nishitani, C.; Takahashi, M.; Katoh, T.; Ariki, S.; Shimizu, T.; Mitsuzawa, H.; Sawada, K.; Voelker, D. R.; Takahashi, H.; Kuroki, Y. Pulmonary surfactant protein D inhibits lipopolysaccharide (LPS)-induced inflammatory cell responses by altering LPS binding to its receptors. *J. Biol. Chem*., **2008**, *283*, 35878-35888.

[93] Jain, D.; Tomer, Y.; Malur, M. S.; Thomassen, M. J.; Beers, M. F. SP-D Modulates Alveolar Macrophage Polarization and Activation. *Am. J. Respir. Crit. Care Med*., **2009**, *179*, A6270.

[94] Hamilton, J. A. Colony-stimulating factors in inflammation and autoimmunity. *Nat. Rev. Immunol*., **2008**, *8*, 533-44.

[95] Shibata, Y.; Berclaz, P. Y.; Chroneos, Z. C.; Yoshida, M.; Whitsett, J. A.; Trapnell, B. C. GM-CSF regulates alveolar macrophage differentiation and innate immunity in the lung through PU.1. *Immunity*, **2001**, *15*, 557-67.

[96] Bonfield, T. L.; Raychaudhuri, B.; Malur, A.; Abraham, S.; Trapnell, B. C.; Kavuru, M. S.; Thomassen, M. J. PU.1 regulation of human alveolar macrophage differentiation requires granulocyte-macrophage colony-stimulating factor. *Am. J. Physiol. Lung Cell Mol., Physiol*., **2003**, *285*, L1132-L1136.

[97] Guth, A. M.; Janssen, W. J.; Bosio, C. M.; Crouch, E. C.; Henson, P. M.; Dow, S. W. Lung Environment Determines Unique Phenotype of Alveolar Macrophages. *Am. J. Physiol. Lung Cell Mol. Physiol*., **2009**. *296*, 936-946.

[98] Gil, M.; McCormack, F. X.; Levine, A. M. Surfactant Protein A Modulates Cell Surface Expression of CR3 on Alveolar Macrophages and Enhances CR3-mediated Phagocytosis. *J. Biol. Chem*., **2009**, *284*, 7495-7504.

[99] Senft, A. P.; Korfhagen, T. R.; Whitsett, J. A.; LeVine, A. M. Surfactant protein D regulates the cell surface expression of alveolar macrophage beta(2)-integrins. *Am. J. Physiol. Lung Cell Mol. Physiol*., **2007**, *292*, L469-L475.

[100] Palaniyar, N.; Sorensen, G.; Holmskov, U. Immunoregulatory Roles of Lung Surfactant Protein A and D. In *Animal Lectin: A functional view*, Vasta, G., Ahmed, I., Eds. CRC Press: USA, **2008**; pp. 331-342.

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