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REVIEW

Pulmonary Surfactant and Bacterial Lipopolysaccharide: The Interaction and its Functional Consequences

M. KOLOMAZNIK[1,2], Z. NOVA[1,2], A. CALKOVSKA[1,2]

[1]Department of Physiology, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin, Slovakia, [2]Biomedical Center Martin, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin, Slovakia

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Summary

The respiratory system is constantly exposed to pathogens which enter the lungs by inhalation or *via* blood stream. Lipopolysaccharide (LPS), also named endotoxin, can reach the airspaces as the major component of the outer membrane of Gram-negative bacteria, and lead to local inflammation and systemic toxicity. LPS affects alveolar type II (ATII) cells and pulmonary surfactant and although surfactant molecule has the effective protective mechanisms, excessive amount of LPS interacts with surfactant film and leads to its inactivation. From immunological point of view, surfactant specific proteins (SPs) SP-A and SP-D are best characterized, however, there is increasing evidence on the involvement of SP-B and SP-C and certain phospholipids in immune reactions. In animal models, the instillation of LPS to the respiratory system induces acute lung injury (ALI). It is of clinical importance that endotoxin-induced lung injury can be favorably influenced by intratracheal instillation of exogenous surfactant. The beneficial effect of this treatment was confirmed for both natural porcine and synthetic surfactants. It is believed that the surfactant preparations have anti-inflammatory properties through regulating cytokine production by inflammatory cells. The mechanism by which LPS interferes with ATII cells and surfactant layer, and its consequences are discussed below.

Key words

Lipopolysaccharide • Pulmonary surfactant • Inhibition • Alveolar type II cells • Lung injury

Corresponding author

A. Calkovska, Department of Physiology and Biomedical Center Martin, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Mala Hora 4C, 036 01 Martin, Slovakia. E-mail: calkovska@jfmed.uniba.sk

Introduction

Pulmonary surfactant is a lipid-protein complex which reduces surface tension at the air/liquid interface, thereby prevents lung collapse. It is produced by the alveolar type II (ATII) cells and stored in the form of lamellar bodies (LB). After exocytosis LB are arranged into the tubular myelin that disperses into the thin film (Echaide *et al.* 2017).

About 80 % of the alveolar surfactant is phospholipids, which are at least 50 different species (Curstedt *et al.* 2013). Of these, phosphatidylcholine (PC) is about 70-80 % and dipalmitoylphosphatidylcholine (DPPC) constitutes the most important surface active component. Approximately 10 % of surfactant are neutral lipids, particularly cholesterol. Around 8-10 % of surfactant molecules form specific proteins. Hydrophilic proteins SP-A and SP-D are important for local host defense (Chroneos *et al.* 2010). Hydrophobic proteins SP-B and SP-C facilitate rapid adsorption of phospholipids at the air/liquid interface and stabilize the surfactant film during the respiratory cycle (Curstedt and Johansson 2010).

Many factors which interfere with alveolar environment are of clinical significance. The most important endogenous factors are plasma proteins entering the alveoli at increased permeability of

alveolar-capillary membrane and leading to acute respiratory distress syndrome (ARDS) (Mokra and Kosutova 2015). Oxygen treatment (Anseth *et al.* 2005, Zaher *et al.* 2007) and artificial pulmonary ventilation (de Prost and Dreyfuss 2012) are the most important exogenous factors that may impair ATII cells and pulmonary surfactant. Pulmonary surfactant can be also inactivated by meconium (Mokra and Mokry 2011), pro-inflammatory substances (de Beaufort *et al.* 2003), proteolytic enzymes or phospholipases (Holm *et al.* 1991) and bacteria (Mifsud *et al.* 2004). Complexing of lipopolysaccharide (LPS) with surfactant may contribute to the pathophysiological changes observed in some types of pneumonia (Brogden *et al.* 1986, DeLucca *et al.* 1988). Lipopolysaccharide, also termed endotoxin, is an integral part of the outer membrane of Gram-negative bacteria such as *Escherichia coli* and *Salmonella enterica*. It is composed of a hydrophilic polysaccharide (O-antigen), a core oligosaccharide and the endotoxin lipid A, a highly toxic part (Nikaido 2003). LPS possess proinflammatory activities and plays an important role in the pathogenesis of Gram-negative bacteria infection. Based on the morphology of the colonies, bacteria are identified as smooth strains expressing LPS with core oligosaccharide and O-antigen (S-LPS) or a rough strains which lack the O-antigen and can either express a complete or a truncated core oligosaccharide (Re-LPS) (Zhang *et al.* 2013). The mechanisms by which LPS interferes with ATII cells and the surfactant layer, and the consequences of this interactions are discussed below.

Lipopolysaccharide vs. phospholipid membranes interaction

Usually a simple model membranes are used to study interactions of phospholipids with various substances (Uhríková *et al.* 2004, Uhríková *et al.* 2012) including lipopolysaccharide (Cañadas *et al.* 2008, Cañadas *et al.* 2011). It was shown that Re-LPS, the minimal LPS form required for bacterial growth, interacts with DPPC films and consequently, DPPC monolayers fluidize and the surface properties change (García-Verdugo *et al.* 2007). Cañadas *et al.* (2011) evaluated the effect of the whole LPS molecule on the lung surfactant-like films composed of either DPPC or DPPC/palmitoyloleoylphosphatidylglycerol (POPG)/ palmitic acid (PA) (28:9:5.6, w/w/w). As a result, already low amount of smooth LPS fluidized DPPC monolayers and prevented it to reach low surface tension during area compression, mimicking exhalation.

Because native or animal-derived pulmonary surfactant is much more complex when it comes to phospholipid content, we studied the effect of LPS on modified porcine surfactant Curosurf® (Chiesi Farmaceutici, Parma, Italy) which is well characterized lipid-protein mixture used to treat neonatal respiratory distress syndrome. *In vitro* experiments were based on dynamic system of pulsating bubble surfactometer mimicking respiratory cycle, and optical microscopy and small- and wide-angle X-ray diffraction. Already 1 % LPS (w/w to surfactant phospholipids) prevented surfactant to reach low surface tension during area compression. LPS bound to the lipid bilayer of Curosurf® and disturbed its lamellar structure. Structural disarrangement induced by LPS was possible to restore by polymyxin B (Kolomaznik *et al.* unpublished observations). Polymyxin B is a cyclic amphipathic antibiotic which can mimic functional properties of surfactant protein B (Zaltash *et al.* 2000) and was previously shown to increase resistance of pulmonary surfactant against plasma proteins (Calkovska *et al.* 2005) and meconium (Stichtenoth *et al.* 2006).

What mechanism applies in LPS-induced surfactant inactivation? Competitive inhibition/adsorption when plasma proteins "compete" with surfactant molecules and display them from alveolar surface, is not applicable. In LPS/surfactant membrane model fluidization of surfactant film was suggested. The interaction of smooth LPS with synthetic lipid monolayers significantly fluidized these films, promoting early collapse and preventing the achievement of low surface tension. LPS exerts these fluidizing effects by acting as a „spacer“ between the lipid molecules and interfering with lipid packing upon compression (Cañadas *et al.* 2011). This mechanism has been described also in relation with lipids, mainly cholesterol (Hiansen *et al.* 2015).

Lipopolysaccharide vs. surfactant proteins interaction

From an immunological point of view, the interaction of LPS with surfactant proteins is most important. ***SP-A and SP-D*** belong to collectins and they play an important role in the innate host defense by binding and clearing invading microbes from the lungs (Holmskov *et al.* 2003). SP-A and SP-D also influence surfactant homeostasis by regulating the surfactant

function and metabolism. In addition to binding and opsonizing pathogens, SP-A and SP-D bind to the surfaces of host defense cells, promoting or inhibiting immune cell activity through multiple cellular pathways (Kingma and Whitsett 2006). They affect the secretion of proinflammatory cytokines and products of oxidative damage (Borron *et al.* 2000), and phagocytosis of apoptotic cells (Janssen *et al.* 2008).

The structure of SP-A and SP-D is optimized for their function, the ability to recognize and bind carbohydrates on the surface of pathogens. They interact with a variety of cells including macrophages, neutrophils, eosinophils, and lymphocytes (Crouch and Wright 2001). This interaction is mediated *via* the receptor specific for lung collectin, a signal regulatory protein alpha (SIRPα), and *via* non-specific binding receptor for collectin, such as calreticulin/CD91 complex (Gardai *et al.* 2003). Membrane molecules involved in some responses to LPS, such as CD14 (Sano *et al.* 2000) or the extracellular domain of toll-like receptor 2 (TLR2) (Murakami *et al.* 2002) are also included. They affect the removal of LPS by alveolar macrophages (van Rozendaal *et al.* 1999) and remove LPS from the surfactant membrane vesicles (Kuzmenko *et al.* 2006).

SP-A and SP-D interact with different phenotypes of LPS (Crouch and Wright 2001). SP-A probably binds to a rough type LPS in calcium-dependent manner. It binds specifically to LPS lipid A, but not to the entire LPS molecule (van Iwaarden *et al.* 1994, Sano *et al.* 2000). SP-D binds to LPS through a CRD domain, especially to rough LPS by recognizing LPS inner core L-*glycero*-D-*manno*-heptose (Hep) (Wang *et al.* 2008).

Interaction of collectins with LPS suggests that they could modulate cell activation and signaling pathways after LPS challenge. SP-A reduces release of TNF-α from LPS-stimulated alveolar macrophages in rats and humans (Arias-Diaz *et al.* 2000, Gardai *et al.* 2003). *In vivo* experiments demonstrated that SP-A knock-out mice produce significantly more TNF-α than wild-type mice following intratracheal LPS administration (Borron *et al.* 2000). In contrast, SP-D moderately increases the production of TNF-α in alveolar macrophages stimulated by LPS (Bufler *et al.* 2003).

LPS increases the expression of SP-A receptors in macrophages (Chroneos and Shepherd 1995) and increases the production of SP-A and SP-D by ATII cells (McIntosh *et al.* 1996). This complex mechanism involved in the modulation of SP-A and SP-D responses to LPS is not fully understood.

The binding of SP-A and SP-D on the membrane of Gram-negative bacteria increases the permeability of the bacterial membrane. The membrane destabilization is mediated through the interaction of the collectin C-terminal domain with the membrane of LPS and explains the antimicrobial effects of these proteins (Wu *et al.* 2003). This effect was studied more in particular by Cañadas *et al.* (2008) by interaction of SP-A with rough lipopolysaccharide (Re-LPS) membranes. Permeabilization of Re-LPS membranes by SP-A is related to the extraction of LPS molecules from the membrane and creation of protein aggregates containing LPS. In addition, given that SP-A is able to bind to the lipid A moiety of LPS, and this protein is associated with the surfactant monolayer, these authors also investigated whether SP-A can minimize S-LPS effects on lung surfactant-like monolayers. SP-A was suggested to act as an LPS scavenger (Cañadas *et al.* 2011). Recently, this concept was proven by showing that SP-A/LPS interaction induces conformational changes in LPS aggregates leading to biologically less active structures (Keese *et al.* 2014).

SP-B and SP-C are extremely hydrophobic surfactant proteins. They stabilize surfactant film on the surface of the alveoli and small airways and as recently evidenced, they also have immunomodulatory properties.

Reduced expression of SP-B initiates an inflammatory response (Ikegami *et al.* 2005) and lowers the capacity of the lungs to handle LPS-induces inflammation (Epaud *et al.* 2003). The situation is similar in SP-C knock-out mice, which are susceptible to bacterial and viral infections and develop an intense inflammatory reaction (Glasser *et al.* 2009) related to the ability of SP-C to bind LPS (Garcia-Verdugo *et al.* 2009).

Detailed analysis of synthetic SP-C analogue revealed that N-terminal domain binds to the lipid A of LPS, whereas C-terminal domain of SP-C may contribute to the optimal protein conformation (Augusto *et al.* 2002). Chaby and co-workers (2005) found that CD14 binds to SP-C at place recognizing LPS. Interaction with SP-C modulates CD14 conformation, allowing for more efficient binding of LPS (Augusto *et al.* 2003). This is reminiscent to the ability of SP-A to enhance the binding of Re-LPS to CD14 (Sano *et al.* 2000). An inflammatory response is modulated by exogenous surfactant preparations containing SP-B and SP-C, and also by protein-free lipid mixtures, DPPC (Gille *et al.* 2007), phosphatidylglycerol (Numata *et al.* 2010) or some minor surfactant phospholipids (Kuronuma *et al.* 2009). From

clinical point of view, it is important that also new generation synthetic surfactants containing SP-B and SP-C analogues and synthetic phospholipids possesses anti-inflammatory features. In this respect surfactant preparation CHF5633 significantly suppressed TNF-α mRNA expression in LPS-stimulated adult monocytes, indicating its potential anti-inflammatory effects (Glaser *et al.* 2016, Glaser *et al.* 2017).

Systemic effects of LPS on lung surfactant

In living body bacterial LPS stimulates innate immunity and initiates biochemical and cellular responses leading to the local inflammation and systemic toxicity. Upon systemic intravenous or intraperitoneal administration LPS leads to hypothermia or more often to mono-, bi- or polyphasic increase in body temperature and inflammation. The intensity of response depends on the LPS serotype, the dose, the way of administration and the ambient temperature (Rudaya *et al.* 2005, Wanner *et al.* 2013). An increase in the body temperature modifies breathing pattern and contributes to respiratory instability in thermal stress (Voss *et al.* 2004). The rats with LPS-induced fever develop rapid shallow breathing with high respiratory rate and reduced tidal volume, typical for thermal tachypnea that was attributed to altered neural respiratory control (Zila *et al.* 2012). It was not known if experimentally evoked fever contributes to surfactant inactivation, and if yes, whether it is related to the body temperature, inflammation or changes in breathing pattern. Therefore, we aimed to prove the hypothesis that the changes in breathing pattern during LPS-induced fever might be related to changes in surfactant specific proteins. Indeed, experimental fever evoked the changes in all four surfactant specific proteins. Changes in proteins related to local immune mechanisms (SP-A, SP-D) are probably resulting from the systemic inflammatory response due to LPS administration. Changes in proteins related to surface activity (SP-B and SP-C) might reflect the effort of the body to stabilize the lungs during alterations of breathing pattern in thermal challenge (Kolomaznik *et al.* 2014).

At intraperitoneal administration ATII cells are not directly challenged by LPS. Therefore, stimulation of surfactant proteins release by ATII cells is probably mediated through substances which initiate signaling cascade for inflammatory mediator expression including tumor necrosis factor α (TNF-α), interleukins (IL)-1β and IL-6, inducible nitric oxide synthase and cyclooxygenase 2, and nuclear factor (NF)-κB (Rossol *et al.* 2011, Soares *et al.* 2012). Moreover, surfactant secretion may be influenced also by some hormones released in fever (Cameron *et al.* 2010).

Direct effect of LPS in the alveolar compartment

LPS and alveolar type II cells

The respiratory system is constantly exposed to toxic substances and pathogens from air or *via* blood stream, which can damage alveolar epithelium and lead to severe respiratory disorders. The alveolar epithelium serves as a barrier between internal and external environment and thus has a critical function in the first line defense. The alveolar epithelium consists of two morphologically different cell types – alveolar type I (ATI) cells and alveolar type II (ATII) cells. The ATII cells comprise up to 5 % of the alveolar epithelial surface area (Wong and Johnson 2013). They are responsible for reparation of alveolar epithelium upon injury and for the production of pulmonary surfactant. They also contribute to lung host defense by the secretion of antimicrobial factors (Fehrenbach 2001, Wong and Johnson 2013). In this context ATII cells have been extensively studied. ATI cells also contain toll-like receptor 4 (TLR4), a receptor for LPS and have been shown to produce the pro-inflammatory cytokines in response to LPS (Wong and Johnson 2013), but because of the close relation to pulmonary surfactant only ATII/LPS interaction is discussed below.

The LPS administration causes rapid changes in the composition of the surfactant pool and the resident cell population (Garcia-Verdugo *et al.* 2008, Wu *et al.* 2011). The response of ATII cells to microbial infection and its possible mechanisms have been studied in a variety of models, including primary cell cultures and continuous cell lines, such as human lung carcinoma type II epithelium-like A549 cells. The exposure of ATII cells to LPS modulates the levels of SPs. SP-A expression at protein and mRNA levels increased in A549 cells when they were challenged by LPS, but LPS did not affect SP-D synthesis (Chuang *et al.* 2009, Wu *et al.* 2011). This is consistent with increased SP-A gene expression in lung cells of mice exposed to inhaled LPS (George *et al.* 2003). In contrast to increased SP-A expression, expression of SP-B was reduced in ATII cells stimulated with LPS (Wang WN *et al.* 2016), consistently with experiments using an animal model of ALI resulting from

LPS exposure (Ingenito *et al.* 2001, Wang WN *et al.* 2016). It was suggested that also the amount of protein could be lower after LPS treatment. Furthermore, LPS affected expression and membrane function of SP-B by reducing interaction and stability between SP-B and lipids (Wang WN *et al.* 2016). Similarly, SP-C expression was abnormally decreased in rat ATII cells exposed to LPS (Lin *et al.* 2017).

ATII cells express functional LPS receptors like TLR2 and TLR4 (Droemann *et al.* 2003, Armstrong *et al.* 2004, MacRedmond *et al.* 2005, Wu *et al.* 2011). TLR-dependent pathway possibly explains LPS-caused pulmonary inflammation and subsequent changes in SPs expression in ATII cells. LPS specifically activates TLRs leading to activation of the NF-κB signal transduction pathway. As a result, pro-inflammatory cytokines and chemokines such as IL-1β, IL-6, IL-8, TNF-α and Type 1 interferons (IFN) are secreted (Slevogt *et al.* 2008, Chuang *et al.* 2009, Wu *et al.* 2011, von Schéele *et al.* 2014, Wang X *et al.* 2016).

Exposure of both, ATII cells and A549 cells to LPS reduced cell viability and induced apoptosis, typical by the formation of apoptotic bodies, cell shrinkage, DNA fragmentation, and chromatin condensation, in concentration- and time-dependent manners (Chuang *et al.* 2011, Lin *et al.* 2017). Similarly, ATII cells in animal models of LPS-induced ALI showed a significant increase in apoptosis (Kitamura *et al.* 2001). It has been reported that intratracheal instillation of a high dose of LPS in mice directly caused the death of bronchial epithelial cells (Vernooy *et al.* 2001). Moreover, mechanical ventilation as a standard therapeutic approach in the management of the ALI, may induce apoptosis of ATII cells by mechanical stretching mediated by the intrinsic mitochondrial pathway (Kuhn *et al.* 2017).

Together with apoptosis, excessive autophagic activity of ATII cells is another main cause of ALI. This type of programmed cell death is characterized by the formation of autophagosomes, degradation of cytoplasmic contents, and little chromatin condensation (Tang *et al.* 2008). Recently, Lin *et al.* (2016) found different time courses of autophagy and apoptosis in the lungs of the rats with LPS-induced ALI. At early stages (1 h and 2 h) of ALI, the mode of lung cell death started with autophagy and reached a peak at 2 h. As ALI process progressed, apoptosis was gradually increased in the lung tissue and reached its maximal level at later stages (6 h), while autophagy was time-dependently decreased. It suggests that these two types of lung cell death might play distinct roles at different stages of LPS-induced ALI.

One of the major factors involved in LPS-induced death of alveolar epithelial cells could be an augmentation of intracellular reactive oxygen species (ROS) including increased levels of cellular nitric oxide (NO). ROS are important apoptotic factors that can cause oxidative stress and subsequent cell death (Chuang *et al.* 2011). As a ROS, NO has been implicated in the pathophysiology of ARDS in animals and humans (Kucukgul and Erdogan 2017). Previous studies showed that exposure of different cell types to LPS causes NO overproduction, subsequent cellular oxidative stress and eventually leads to cell death (Chen *et al.* 2005a, Chen *et al.* 2005b, Waak *et al.* 2009, Lee *et al.* 2010). In accordance with these studies, levels of intracellular ROS and NO were considerably increased also in A549 cells after LPS administration. Thus, LPS can directly damage alveolar epithelial cells *via* ROS-triggered apoptotic mechanism (Chuang *et al.* 2011).

The possibilities to control programmed epithelial cell death in ALI is now thoroughly investigated. Recombinant amphiregulin, a member of the epidermal growth factor family, suppressed epithelial cell apoptosis in LPS-induced lung injury in mice by inhibiting caspase-8 activity. It seems that amphiregulin signaling may be a therapeutic target for LPS-induced lung injury treatment through its prevention of epithelial cell apoptosis (Ogata-Suetsugu *et al.* 2017). Excessive autophagic activity of ATII cells in LPS-induced ALI might be suppressed by miR-34a *via* targeting autophagy-related gene FoxO3 (Song *et al.* 2017).

LPS and lung surfactant in the aveoli

Although the surfactant molecule contains effective protection mechanisms, under certain circumstances pulmonary surfactant may be damaged by excessive amounts of LPS. As mentioned above, *in vivo* LPS is a potent activator of innate immune responses and *via* TLR2 and TLR4 on the bronchial epithelium, alveolar epithelium including ATII cells and macrophages it plays crucial role in LPS-induced lung injury *in vivo* (Saito *et al.* 2005). It triggers NF-κB-mediated production pro-inflammatory cytokines (Aul *et al.* 2012) and intratracheal administration of LPS in sufficient dose induces inflammation and tissue damage resembling ALI and ARDS (Jansson *et al.* 2004, Blumenthal *et al.* 2006). High dose LPS induces IL-1β and TNF production leading to inflammation. Neutrophil influx into the

alveoli further worsens the lung damage by increasing pulmonary permeability, edema formation and cell death (McDonald and Usachencko 1999). Edema formation occurs 2 h after LPS administration and is dose-dependent (Jansson *et al.* 2004). All these changes can be mimicked by intratracheal administration of LPS in different animal species. Technical aspects, advantages and disadvantages of modelling of LPS-induced lung injury are reviewed e.g. in Matute-Bello *et al.* (2008).

Literature data regarding the appropriate dosage of LPS differ. In a number of studies the LPS was intratracheally administered in a wide range of 5-5,000 μg/kg of body weight (Sato *et al.* 2002, Jansson *et al.* 2004, Liu *et al.* 2013). In our pilot experiments, lung injury was induced by 100, 500 and 1,000 μg/kg in artificially ventilated rats. The animals survived 5 h ventilation with lung injury characterized with inflammation, oxidative damage lung edema, and ineffective gas exchange at 500 μg/kg of LPS. The inflammation was present not only locally, but also at the systemic level, as evidenced by the redistribution of inflammatory cells in the peripheral blood and bronchoalveolar lavage fluid (Kolomaznik *et al.* unpublished observations).

Endotoxin-induced lung injury can be favorably influenced by intratracheal instillation of exogenous surfactant. The positive effect of such treatment has been confirmed for clinically used modified porcine surfactant Curosurf® when it significantly reduced mortality in spontaneously-breathing rats with LPS-induced lung injury (van Helden *et al.* 1998). In a similar mouse model the positive effect of a synthetic surfactant based on KL4-protein was verified after 24 h (Kinniry *et al.* 2006) and the effect of natural porcine vs. synthetic surfactant after 72 h after LPS administration was tested in rats (Mittal and Sanyal 2011). Surfactant clearly has anti-inflammatory properties, regulates the production of cytokines by inflammatory cells, but the exact mechanism of this effect is not fully understood.

Conclusions

Lipopolysaccharide interferes with all major components of pulmonary surfactant. It occurs even directly by interaction with surfactant specific proteins and incorporation into the phospholipid layers, or indirectly through alveolar type II cells. LPS-induced changes of surfactant system and their reversal can be studied *in vitro* and in different animal models. As LPS-induced lung injury is serious clinical issue, it is important to search for effective animal models to study antibiotics transfer, to develop new generation synthetic surfactants with anti-inflammatory properties and to continue in testing the exogenous surfactant preparations as drug carriers into the LPS-challenged respiratory system.

Conflict of Interest

There is no conflict of interest.

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References

ANSETH JW, GOFFIN AJ, FULLER GG, GHIO AJ, KAO PN, UPADHYAY D: Lung surfactant gelation induced by epithelial cells exposed to air pollution or oxidative stress. *Am J Respir Cell Mol Biol* **33**: 161-168, 2005.

ARIAS-DIAZ J, GARCIA-VERDUGO I, CASALS C, SANCHEZ-RICO N, VARA E, BALIBREA JL: Effect of surfactant protein A (SP-A) on the production of cytokines by human pulmonary macrophages. *Shock* **14**: 300-306, 2000.

ARMSTRONG L, MEDFORD AR, UPPINGTON KM, ROBERTSON J, WITHERDEN IR, TETLEY TD, MILLAR AB: Expression of functional toll-like receptor-2 and -4 on alveolar epithelial cells. *Am J Respir Cell Mol Biol* **31**: 241-245, 2004.

AUGUSTO LA, LI J, SYNGUELAKIS M, JOHANSSON J, CHABY R: Structural basis for interactions between lung surfactant protein C and bacterial lipopolysaccharide: *J Biol Chem* **277**: 23484-23492, 2002.

AUGUSTO LA, SYNGUELAKIS M, JOHANSSON J, PEDRON T, GIRARD R, CHABY R: Interaction of pulmonary surfactant protein C with CD14 and lipopolysaccharide. *Infect Immun* **71**: 61-67, 2003.

AUL R, ARMSTRONG J, DUVOIX A, LOMAS D, HAYES B, MILLER BE, JAGGER C, SINGH D: Inhaled LPS challenges in smokers: a study of pulmonary and systemic effects. *Br J Clin Pharmacol* **74**: 1023-1032, 2012.

BLUMENTHAL S, BORGEAT A, PASCH T, REYES L, BOOY C, LAMBERT M, SCHIMMER RC, BECK-SCHIMMER B: Ropivacaine decreases inflammation in experimental endotoxin-induced lung injury. *Anesthesiology* **104**: 961-969, 2006.

BORRON P, MCINTOSH JC, KORFHAGEN TR, WHITSETT JA, TAYLOR J, WRIGHT JR: Surfactant-associated protein A inhibits LPS-induced cytokine and nitric oxide production in vivo. *Am J Physiol Lung Cell Mol Physiol* **278**: L840-L847, 2000.

BROGDEN KA, CUTLIP RC, LEHMKUHL HD: Complexing of bacterial lipopolysaccharide with lung surfactant. *Infect Immun* **52**: 644-649, 1986.

BUFLER P, SCHMIDT B, SCHIKOR D, BAUERNFEIND A, CROUCH EC, GRIESE M: Surfactant protein A and D differently regulate the immune response to nonmucoid Pseudomonas aeruginosa and its lipopolysaccharide. *Am J Respir Cell Mol Biol* **28**: 249-256, 2003.

CALKOVSKA A, SOME M, LINDERHOLM B, JOHANSSON J, CURSTEDT T, ROBERTSON B: Biophysical and physiological properties of porcine surfactant enriched with polymyxin B. *Biol Neonate* **88**: 101-108, 2005.

CAMERON A, HENLEY D, CARRELL R, ZHOU A, CLARKE A, LIGHTMAN S: Temperature-responsive release of cortisol from its binding globulin: a protein thermocouple. *J Clin Endocrinol Metab* **95**: 4689-4695, 2010.

CAÑADAS O, GARCÍA-VERDUGO I, KEOUGH KM, CASALS C: SP-A permeabilizes lipopolysaccharide membranes by forming protein aggregates that extract lipids from the membrane. *Biophys J* **95**: 3287-3294, 2008.

CAÑADAS O, KEOUGH KM, CASALS C: Bacterial lipopolysaccharide promotes destabilization of lung surfactant-like films. *Biophys J* **100**: 108-116, 2011.

CHABY R, GARCIA-VERDUGO I, ESPINASSOUS Q, AUGUSTO LA: Interactions between LPS and lung surfactant proteins. *J Endotoxin Res* **11**: 181-185, 2005.

CHEN RM, CHEN TL, CHIU WT, CHANG CC. Molecular mechanism of nitric oxide-induced osteoblast apoptosis. *J Orthop Res* **23**: 462-468, 2005a.

CHEN RM, CHEN TL, LIN YL, CHEN TG, TAI YT: Ketamine reduces nitric oxide biosynthesis in human umbilical vein endothelial cells by down-regulating endothelial nitric oxide synthase expression and intracellular calcium levels. *Crit Care Med* **33**: 1044-1049, 2005b.

CHRONEOS Z, SHEPHERD VL: Differential regulation of the mannose and SP-A receptors on macrophages. *Am J Physiol* **269**: L721-L726, 1995.

CHRONEOS ZC, SEVER-CHRONEOS Z, SHEPHERD VL: Pulmonary surfactant: an immunological perspective. *Cell Physiol Biochem* **25**: 13-26, 2010.

CHUANG CY, CHEN TL, CHEN RM: Molecular mechanisms of lipopolysaccharide-caused induction of surfactant protein-A gene expression in human alveolar epithelial A549 cells. *Toxicol Lett* **191**: 132-139, 2009.

CHUANG CY, CHEN TL, CHERNG YG, TAI YT, CHEN TG, CHEN RM: Lipopolysaccharide induces apoptotic insults to human alveolar epithelial A549 cells through reactive oxygen species-mediated activation of an intrinsic mitochondrion-dependent pathway. *Arch Toxicol* **85**: 209-218, 2011.

CROUCH E, WRIGHT JR: Surfactant proteins a and d and pulmonary host defense. *Annu Rev Physiol* **63**: 521-554, 2001.

CURSTEDT T, JOHANSSON J: Different effects of surfactant proteins B and C - implications for development of synthetic surfactants. *Neonatology* **97**: 367-372, 2010.

CURSTEDT T, CALKOVSKA A, JOHANSSON J: New generation synthetic surfactants. *Neonatology* **103**: 327-330, 2013.

DE BEAUFORT AJ, BAKKER AC, VAN TOL MJ, POORTHIUS BJ, SCHRAMA AJ, BERGER HM: Meconium is a source of pro-inflammatory substances and can induce cytokine production in cultured A549 epithelial cells. *Pediatr Res* **54**: 491-495, 2003.

DE PROST N, DREYFUSS D: How to prevent ventilator-induced lung injury? *Minerva Anestesiol* **78**: 1054-1066, 2012.

DELUCCA AJ 2ND, BROGDEN KA, ENGEN R: Enterobacter agglomerans lipopolysaccharide-induced changes in pulmonary surfactant as a factor in the pathogenesis of byssinosis. *J Clin Microbiol* **26**: 778-880, 1988.

DROEMANN D, GOLDMANN T, BRANSCHEID D, CLARK R, DALHOFF K, ZABEL P, VOLLMER E: Toll-like receptor 2 is expressed by alveolar epithelial cells type II and macrophages in the human lung. *Histochem Cell Biol* **119**: 103-108, 2003.

ECHAIDE M, AUTILIO C, ARROYO R, PEREZ-GIL J: Restoring pulmonary surfactant membranes and films at the respiratory surface. *Biochim Biophys Acta* **1859**: 1725-1739, 2017.

EPAUD R, IKEGAMI M, WHITSETT JA, JOBE AH, WEAVER TE, AKINBI HT: Surfactant protein B inhibits endotoxin-induced lung inflammation. *Am J Respir Cell Mol Biol* **28**: 373-378, 2003.

FEHRENBACH H: Alveolar epithelial type II cell: defender of the alveolus revisited. *Respir Res* **2**: 33-46, 2001.

GARCÍA-VERDUGO I, CAÑADAS O, TANEVA SG, KEOUGH KM, CASALS C: Surfactant protein A forms extensive lattice-like structures on 1,2-dipalmitoylphosphatidylcholine/rough-lipopolysaccharide-mixed monolayers. *Biophys J* **93**: 3529-3540, 2007.

GARCIA-VERDUGO I, RAVASIO A, DE PACO EG, SYNGUELAKIS M, IVANOVA N, KANELLOPOULOS J, HALLER T: Long-term exposure to LPS enhances the rate of stimulated exocytosis and surfactant secretion in alveolar type II cells and upregulates P2Y2 receptor expression. *Am J Physiol Lung Cell Mol Physiol* **295**: L708-L717, 2008.

GARCIA-VERDUGO I, GARCIA DE PACO E, ESPINASSOUS Q, GONZALEZ-HORTA A, SYNGUELAKIS M, KANELLOPOULOS J, RIVAS L, CHABY R, PEREZ-GIL J: Synthetic peptides representing the N-terminal segment of surfactant protein C modulate LPS-stimulated TNF-alpha production by macrophages. *Innate Immun* **15**: 53-62, 2009.

GARDAI SJ, XIAO YQ, DICKINSON M, NICK JA, VOELKER DR, GREENE KE, HENSON PM: By binding SIRPalpha or calreticulin/CD91, lung collectins act as dual function surveillance molecules to suppress or enhance inflammation. *Cell* **115**: 13-23, 2003.

GEORGE CL, WHITE ML, O'NEILL ME, THORNE PS, SCHWARTZ DA, SNYDER JM: Altered surfactant protein A gene expression and protein metabolism associated with repeat exposure to inhaled endotoxin. *Am J Physiol Lung Cell Mol Physiol* **285**: L1337-L1344, 2003.

GILLE C, SPRING B, BERNHARD W, GEBHARD C, BASILE D, LAUBER K, POETS CF, ORLIKOWSKY TW: Differential effect of surfactant and its saturated phosphatidylcholines on human blood macrophages. *J Lipid Res* **48**: 307-317, 2007.

GLASER K, FEHRHOLZ M, CURSTEDT T, KUNZMANN S, SPEER CP: Effects of the new generation synthetic reconstituted surfactant CHF5633 on pro- and anti-inflammatory cytokine expression in native and LPS-stimulated adult CD14+ monocytes. *PLoS One* **11**: e0146898, 2016.

GLASER K, FEHRHOLZ M , HENRICH B, CLAUS H, PAPSDORF M, SPEER CP: Anti-inflammatory effects of the new generation synthetic surfactant CHF5633 on Ureaplasma-induced cytokine responses in human monocytes. *Expert Rev Anti Infect Ther* **15**: 181-189, 2017.

GLASSER SW, WITT TL, SENFT AP, BAATZ JE, FOLGER D, MAXFIELD MD, AKINBI HT, NEWTON DA, PROWS DR, KORFHAGEN TR: Surfactant protein C-deficient mice are susceptible to respiratory syncytial virus infection. *Am J Physiol Lung Cell Mol Physiol* **297**: L64-L72, 2009.

HIANSEN JQ, KEATING E, ASPROS A, YAO LJ, BOSMA KJ, YAMASHITA CM, LEWIS JF, VELDHUIZEN RA: Cholesterol-mediated surfactant dysfunction is mitigated by surfactant protein A. *Biochim Biophys Acta* **1848**: 813-820, 2015.

HOLM BA, KEICHER L, LIU M, SOKOLOWSKI J, ENHORNING G: Inhibition of pulmonary surfactant function by phospholipases. *J Appl Physiol* **71**: 317-321, 1991.

HOLMSKOV U, THIEL S, JENSENIUS JC: Collections and ficolins: humoral lectins of the innate immune defense. *Annu Rev Immunol* **21**: 547-578, 2003.

IKEGAMI M, WHITSETT JA, MARTIS PC, WEAVER TE: Reversibility of lung inflammation caused by SP-B deficiency. *Am J Physiol Lung Cell Mol Physiol* **289**: L962-L970, 2005.

INGENITO EP, MORA R, CULLIVAN M, MARZAN Y, HALEY K, MARK L, SONNA LA: Decreased surfactant protein-B expression and surfactant dysfunction in a murine model of acute lung injury. *Am J Respir Cell Mol Biol* **25**: 35-44, 2001.

JANSSEN WJ, MCPHILLIPS KA, DICKINSON MG, LINDERMAN DJ, MORIMOTO K, XIAO YQ, OLDHAM KM, VANDIVIER RW, HENSON PM, GARDAI SJ: Surfactant proteins A and D suppress alveolar macrophage phagocytosis via interaction with SIRP alpha. *Am J Respir Crit Care Med* **178**: 158-167, 2008.

JANSSON AH, ERIKSSON C, WANG X: Lung inflammatory responses and hyperinflation induced by an intratracheal exposure to lipopolysaccharide in rats. *Lung* **182**: 163-171, 2004.

KEESE SP, BRANDENBURG K, ROESSLE M, SCHROMM AB: Pulmonary surfactant protein A-induced changes in the molecular conformation of bacterial deep-rough LPS lead to reduced activity on human macrophages. *Innate Immun* **20**: 787-798, 2014.

KINGMA PS, WHITSETT JA: In defense of the lung: surfactant protein A and surfactant protein D. *Curr Opin Pharmacol* **6**: 277-283, 2006.

KINNIRY P, PICK J, STEPHENS S, JAIN D, SOLOMIDES CC, NIVEN R, SEGAL R, CHRISTOFIDOU-SOLOMIDOU M: KL4-surfactant prevents hyperoxic and LPS-induced lung injury in mice. *Pediatr Pulmonol* **41**: 916-928, 2006.

KITAMURA Y, HASHIMOTO S, MIZUTA N, KOBAYASHI A, KOOGUCHI K, FUJIWARA I, NAKAJIMA H: Fas/FasL-dependent apoptosis of alveolar cells after lipopolysaccharide-induced lung injury in mice. *Am J Respir Crit Care Med* **163**: 762-769, 2001.

KOLOMAZNIK M, ZILA I, KOPINCOVA J, MOKRA D, CALKOVSKA A: Changes in lung surfactant proteins in rats with lipopolysaccharide-induced fever. *Physiol Res* **63** (Suppl 4): S619-S628, 2014.

KUCUKGUL A, ERDOGAN S: Low concentration of oleic acid exacerbates LPS-induced cell death and inflammation in human alveolar epithelial cells. *Exp Lung Res* **43**: 1-7, 2017.

KUHN H, NIEUWENHUIJSEN H, KARTHE B, WIRTZ H: Stretch-induced apoptosis in rat alveolar epithelial cells is mediated by the intrinsic mitochondrial pathway. *Exp Lung Res* **43**: 49-56, 2017.

KURONUMA K, MITSUZAWA H, TAKEDA K, NISHITANI C, CHAN ED, KUROKI Y, NAKAMURA M, VOELKER DR: Anionic pulmonary surfactant phospholipids inhibit inflammatory responses from alveolar macrophages and U937 cells by binding the lipopolysaccharide-interacting proteins CD14 and MD-2. *J Biol Chem* **284**: 25488-25500, 2009.

KUZMENKO AI, WU H, MCCORMACK FX: Pulmonary collectins selectively permeabilize model bacterial membranes containing rough lipopolysaccharide. *Biochemistry* **45**: 2679-2685, 2006.

LEE CJ, TAI YT, LIN YL, CHEN RM: Molecular mechanisms of propofol-involved suppression of no biosynthesis and inducible iNOS gene expression in LPS-stimulated macrophage-like raw 264.7 cells. *Shock* **33**: 93-100, 2010.

LIN J, TIAN J, WANG L, WU W, LI H, WANG X, ZENG X, ZHANG W: Apoptosis and surfactant protein-C expression inhibition induced by lipopolysaccharide in AEC II cell may associate with NF-κB pathway. *J Toxicol Sci* **42**: 53-61, 2017.

LIN L, ZHANG L, YU L, HAN L, JI W, SHEN H, HU Z: Time-dependent changes of autophagy and apoptosis in lipopolysaccharide-induced rat acute lung injury. *Iran J Basic Med Sci* **19**: 632-637, 2016.

LIU F, LI W, PAULUHN J, TRÜBEL H, WANG C: Lipopolysaccharide-induced acute lung injury in rats: comparative assessment of intratracheal instillation and aerosol inhalation. *Toxicology* **304**: 158-166, 2013.

MACREDMOND R, GREENE C, TAGGART CC, MCELVANEY N, O'NEILL S: Respiratory epithelial cells require Toll-like receptor 4 for induction of human beta-defensin 2 by lipopolysaccharide. *Respir Res* **6**: 116, 2005.

MATUTE-BELLO G, FREVERT CW, MARTIN TR: Animal models of acute lung injury. *Am J Physiol Lung Cell Mol Physiol* **295**: L379-L399, 2008.

MCDONALD RJ, USACHENCKO J: Neutrophils injure bronchial epithelium after ozone exposure. *Inflammation* **23**: 63-73, 1999.

MCINTOSH JC, SWYERS AH, FISHER JH, WRIGHT JR: Surfactant proteins A and D increase in response to intratracheal lipopolysaccharide. *Am J Respir Cell Mol Biol* **15**: 509-519, 1996.

MIFSUD AJ, EFSTRATIOU A, CHARLETT A, MCCARTNEY AC, HEALTH PROTECTION AGENCY GROUP B STREPTOCOCCUS WORKING GROUP: Early-onset neonatal group B streptococcal infection in London: 1990-1999. *BJOG* **111**: 1006-1011, 2004.

MITTAL N, SANYAL SN: In vivo effect of surfactant on inflammatory cytokines during endotoxin-induced lung injury in rodents. *J Immunotoxicol* **8**: 274-283, 2011.

MOKRA D, MOKRY J: Glucocorticoids in the treatment of neonatal meconium aspiration syndrome. *Eur J Pediatr* **170**: 1495-1505, 2011.

MOKRA D, KOSUTOVA P: Biomarkers in acute lung injury. *Respir Physiol Neurobiol* **209**: 52-58, 2015.

MURAKAMI S, IWAKI D, MITSUZAWA H, SANO H, TAKAHASHI H, VOELKER DR, AKINO T, KUROKI Y: Surfactant protein A inhibits peptidoglycan-induced tumor necrosis factor-alpha secretion in U937 cells and alveolar macrophages by direct interaction with toll-like receptor 2. *J Biol Chem* **277**: 6830-6837, 2002.

NIKAIDO H: Molecular basis of bacterial outer membrane permeability revisited. *Microbiol Mol Biol Rev* **67**: 593-656, 2003.

NUMATA M, CHU HW, DAKHAMA A, VOELKER DR: Pulmonary surfactant phosphatidylglycerol inhibits respiratory syncytial virus-induced inflammation and infection. *Proc Natl Acad Sci USA* **107**: 320-325, 2010.

OGATA-SUETSUGU S, YANAGIHARA T, HAMADA N, IKEDA-HARADA C, YOKOYAMA T, SUZUKI K, KAWAGUCHI T, MAEYAMA T, KUWANO K, NAKANISHI Y: Amphiregulin suppresses epithelial cell apoptosis in lipopolysaccharide-induced lung injury in mice. *Biochem Biophys Res Commun* **484**: 422-428, 2017.

ROSSOL M, HEINE H, MEUSCH U, QUANDT D, KLEIN C, SWEET MJ, HAUSCHILDT S: LPS-induced cytokine production in human monocytes and macrophages. *Crit Rev Immunol* **31**: 379-446, 2011.

RUDAYA AY, STEINER AA, ROBBINS JR, DRAGIC AS, ROMANOVSKY AA: Thermoregulatory responses to lipopolysaccharide in the mouse: dependence on the dose and ambient temperature. *Am J Physiol* **289**: 1244-1252, 2005.

SAITO T, YAMAMOTO T, KAZAWA T, GEJYO H, NAITO M: Expression of toll-like receptor 2 and 4 in lipopolysaccharide-induced lung injury in mouse. *Cell Tissue Res* **321**: 75-88, 2005.

SANO H, CHIBA H, IWAKI D, SOHMA H, VOELKER DR, KUROKI Y: Surfactant proteins A and D bind CD14 by different mechanisms. *J Biol Chem* **275**: 22442-22451, 2000.

SATO K, KADIISKA MB, GHIO AJ, CORBETT J, FANN YC, HOLLAND SM, THURMAN RG, MASON RP: In vivo lipid-derived free radical formation by NADPH oxidase in acute lung injury induced by lipopolysaccharide: a model for ARDS. *FASEB J* **16**: 1713-1720, 2002.

SLEVOGT H, ZABEL S, OPITZ B, HOCKE A, EITEL J, N'GUESSAN PD, LUCKA L, RIESBECK K, ZIMMERMANN W, ZWEIGNER J, TEMMESFELD-WOLLBRUECK B, SUTTORP N, SINGER BB: CEACAM1 inhibits Toll-like receptor 2-triggered antibacterial responses of human pulmonary epithelial cells. *Nat Immunol* **9**: 1270-1278, 2008.

SOARES DM, FIGUEIREDO MJ, MARTINS JM, MACHADO RR, SORGI C, FACIOLLI LH, ALVES-FILHO JC, CUNHA FQ, SOUZA GE: A crucial role for IL-6 in the CNS of rats during fever induced by the injection of live E. coli. *Med Microbiol Immunol* **201**: 47-60, 2012.

SONG L, ZHOU F, CHENG L, HU M, HE Y, ZHANG B, LIAO D, XU Z: MicroRNA-34a suppresses autophagy in alveolar type II epithelial cells in acute lung injury by inhibiting FoxO3 expression. *Inflammation* **40**: 927-936, 2017.

STICHTENOTH G, JUNG P, WALTER G, JOHANSSON J, ROBERTSON B, CURSTEDT T, HERTING E: Polymyxin B/pulmonary surfactant mixtures have increased resistance to inactivation by meconium and reduce growth of gram-negative bacteria in vitro. *Pediatr Res* **59**: 407-411, 2006.

TANG PS, MURA M, SETH R, LIU M: Acute lung injury and cell death: how many ways can cells die? *Am J Physiol* **294**: L632-L641, 2008.

UHRÍKOVÁ D, RAPP G, YARADAIKIN S, GORDELIY V, BALGAVÝ P: Influence of local anesthetics on the phosphatidylcholine model membrane: small-angle synchrotron X-ray diffraction and neutron scattering study. *Biophys Chem* **109**: 361-373, 2004.

UHRÍKOVÁ D, PULLMANNOVÁ P, SABÍKOVÁ A, DEVÍNSKY F, FUNARI SS: The microstructure of DNA-egg yolk phosphatidylcholine-gemini surfactants complexes: effect of the spacer length. *Drug Metabol Drug Interact* **27**: 47-54, 2012.

VAN HELDEN HP, KUIJPERS WC, LANGERWERF PE, LANGEN RC, HAAGSMAN HP, BRUIJNZEEL PL: Efficacy of Curosurf in a rat model of acute respiratory distress syndrome. *Eur Respir J* **12**: 533-539, 1998.

VAN IWAARDEN JF, PIKAAR JC, STORM J, BROUWER E, VERHOEF J, OOSTING RS, VAN GOLDE LM, VAN STRIJP JA: Binding of surfactant protein A to the lipid A moiety of bacterial lipopolysaccharides. *Biochem J* **303**: 407-411, 1994.

VAN ROZENDAAL BA, VAN DE LEST CH, VAN EIJK M, VAN GOLDE LM, VOORHOUT WF, VAN HELDEN HP, HAAGSMAN HP: Aerosolized endotoxin is immediately bound by pulmonary surfactant protein D in vivo. *Biochim Biophys Acta* **1454**: 261-269, 1999.

VERNOOY JH, DENTENER MA, VAN SUYLEN RJ, BUURMAN WA, WOUTERS EF: Intratracheal instillation of lipopolysaccharide in mice induces apoptosis in bronchial epithelial cells: no role for tumor necrosis factor-alpha and infiltrating neutrophils. *Am J Respir Cell Mol Biol* **24**: 569-576, 2001.

VON SCHÉELE I, LARSSON K, PALMBERG L: Interactions between alveolar epithelial cells and neutrophils under pro-inflammatory conditions. *Eur Clin Respir J* **1**: doi: 10.3402/ecrj.v1.24545, 2014.

VOSS LJ, BOLTON DP, GALLAND BC, TAYLOR BJ: Endotoxin effects on markers of autonomic nervous system function in the piglet: implications for SIDS. *Biol Neonate* **86**: 39-47, 2004.

WAAK J, WEBER SS, WALDENMAIER A, GÖRNER K, ALUNNI-FABBRONI M, SCHELL H, VOGT-WEISENHORN D, PHAM TT, REUMERS V, BAEKELANDT V, WURST W, KAHLE PJ: Regulation of astrocyte inflammatory responses by the Parkinson's disease-associated gene DJ-1. *FASEB J* **23**: 2478-2489, 2009.

WANG H, HEAD J, KOSMA P, BRADE H, MÜLLER-LOENNIES S, SHEIKH S, MCDONALD B, SMITH K, CAFARELLA T, SEATON B, CROUCH E: Recognition of heptoses and the inner core of bacterial lipopolysaccharides by surfactant protein d. *Biochemistry* **47**: 710-720, 2008.

WANG WN, ZHOU JH, WANG P, ZHANG XJ. The localization of SP-B and influences of lipopolysaccharide on it. *Eur Rev Med Pharmacol Sci* **20**: 2338-2345, 2016.

WANG X, LIU C, WANG G: Propofol protects rats and human alveolar epithelial cells against lipopolysaccharide-induced acute lung injury via inhibiting HMGB1 expression. *Inflammation* **39**: 1004-1016, 2016.

WANNER SP, YOSHIDA K, KULCHITSKY VA, IVANOV AI, KANOSUE K, ROMANOVSKY AA: Lipopolysaccharide-induced neuronal activation in the paraventricular and dorsomedial hypothalamus depends on ambient temperature. *PLoS One* **8**: e75733, 2013.

WONG MH, JOHNSON MD: Differential response of primary alveolar type I and type II cells to LPS stimulation. *PloS One* **8**: e55545, 2013.

WU H, KUZMENKO A, WAN S, SCHAFFER L, WEISS A, FISHER JH, KIM KS, MCCORMACK FX: Surfactant proteins A and D inhibit the growth of Gram-negative bacteria by increasing membrane permeability. *J Clin Invest* **111**: 1589-1602, 2003.

WU TT, CHEN TL, LOON WS, TAI YT, CHERNG YG, CHEN RM: Lipopolysaccharide stimulates syntheses of toll-like receptor 2 and surfactant protein-A in human alveolar epithelial A549 cells through upregulating phosphorylation of MEK1 and ERK1/2 and sequential activation of NF-κB. *Cytokine* **55**: 40-47, 2011.

ZAHER TE, MILLER EJ, MORROW DM, JAVDAN M, MANTELL LL: Hyperoxia-induced signal transduction pathways in pulmonary epithelial cells. *Free Radic Biol Med* **42**: 897-908, 2007.

ZALTASH S, PALMBLAD M, CURSTEDT T, JOHANSSON J, PERSSON B: Pulmonary surfactant protein B: a structural model and a functional analogue. *Biochim Biophys Acta* **1466**: 179-186, 2000.

ZHANG G, MEREDITH TC, KAHNE D: On the essentiality of lipopolysaccharide to Gram-negative bacteria. *Curr Opin Microbiol* **16**: 779-785, 2013.

ZILA I, MOKRA D, JAVORKA M, JAVORKA K, CALKOVSKA A: Lipopolysaccharide-induced fever alters Hering-Breuer reflex in anesthetized rats. *J Therm Biol* **37**: 475-478, 2012.