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Review Article

ROLE OF ALVEOLAR MACROPHAGES IN THE INFLAMMATORY RESPONSE AFTER TRAUMA

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ABSTRACT—Acute lung injury (ALI) and its more severe form, acute respiratory distress syndrome (ARDS), can result from both direct and indirect pulmonary damage caused by trauma and shock. In the course of ALI/ARDS, mediators released from resident cells, such as alveolar macrophages, may act as chemoattractants for invading cells and stimulate local cells to build up a proinflammatory micromilieu. Depending on the trauma setting, the role of alveolar macrophages is differentially defined. This review focuses on alveolar macrophage function after blunt chest trauma, ischemia/reperfusion, hemorrhagic shock, and thermal burns.

KEYWORDS—Alveolar macrophages, trauma, inflammation, blunt chest trauma, ischemia/reperfusion, hemorrhagic shock, burn

ABBREVIATIONS—ALI — acute lung injury; AP-1 — activator protein 1; ARDS — acute respiratory distress syndrome; AT2 cells — alveolar epithelial type 2 cells; CCR2 — CC chemokine receptor type 2; CINC-1 — cytokine-induced neutrophil chemoattractant 1; COX — cyclooxygenase; cPLA2 — cytosolic phospholipase A2; Hck — tyrosine-protein kinase Hck; HMGB1 — high-mobility group protein B1; HS/R — hemorrhagic shock/resuscitation; IL — interleukin; iNKT — invariant natural killer T cells; I/R — ischemia/reperfusion; IRAK4 — interleukin-1 receptor-associated kinase 4; JNK — *c*-Jun *N*-terminal kinase; KC — keratinocyte-derived chemokine; LPS — lipopolysaccharide; MCP-1 — monocyte chemotactic protein-1; MIP-1α — macrophage inflammatory protein-1α; MIP-2 — macrophage inflammatory protein 2; MyD88 — myeloid differentiation primary response gene (88); NF-κB — nuclear factor kappa B; Nlrp3 — NOD-like receptor family, pyrin domain containing protein 3; NO — nitric oxide; PCA — procoagulant activity; ROS — reactive oxygen species; Src — proto-oncogene tyrosine-protein kinase Src; TLR — toll-like receptor; TNF — tumor necrosis factor

INTRODUCTION

Acute lung injury (ALI) and its more severe form acute respiratory distress syndrome (ARDS) are common sequelae after trauma and shock. Aside from lung infection (1) and sepsis (2), ALI/ARDS can result from both direct pulmonary damage (e.g., blunt chest trauma) (3) and indirect damage (e.g., after burn injury) (4). A common complication of ARDS is pneumonia based on nosocomial infections, especially in mechanically ventilated patients (5). Acute lung injury and ARDS are characterized by increased vascular permeability caused by dysfunction of the alveolar-capillary membrane. The resulting lung edema–induced impairment of blood gas exchange leads to decreased arterial oxygenation. Cytokines released from resident cells, such as alveolar macrophages or alveolar epithelial type 2 (AT2) cells, into the alveoli induce the migration of large numbers of activated inflammatory cells into the air space (6, 7). In turn, mediator release from the accumulated inflammatory cells further contributes to the tissue damage in ALI and ARDS.

Alveolar macrophages are phagocytes (greek: *phagein*, "to eat"; *kýtos*, "hollow vessel"), which are located in the alveolar compartment of the lungs. Under physiologic conditions, alveolar macrophages play a pivotal role in the protection of the lungs against inhaled particles like dust, bacteria, and viruses. However, under inflammatory conditions, alveolar macrophages generate and release a multitude of mediators, such as cytokines, chemokines, complement factors, alarmins, and arachidonic acid metabolites (8–12) (Table 1). These mediators may act as chemoattractants for invading cells (6) or stimulate local cells (epithelial cells or interstitial macrophages) to build up a proinflammatory micromilieu (13).

Experimentally, alveolar macrophages have been analyzed in different trauma models in mice, rats, or swine (10, 14–17). Technically, alveolar macrophages are relatively easy to obtain by bronchoalveolar lavage and can be used for various functional *ex vivo*/*in vitro* analyses. In some cases, alveolar macrophages were depleted before the experimental insult, and changes in the inflammatory response after trauma were analyzed. However, although general mediator release in bronchoalveolar lavage fluids has been extensively analyzed in the clinical setting of trauma (18–20), there are only a few data on the specific role of alveolar macrophages after trauma. An exception is the alveolar macrophage function after burn injury, which has been studied to some extent in humans (21–23).

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TABLE 1. **Proinflammatory and anti-inflammatory mediators released by alveolar macrophages after trauma**

Proinflammatory mediators	Anti-inflammatory mediators
IL-1β	IL-10
TNF-α	TGF-β
IL-6	NO
MCP-1	
MIP-2	
MIP-1α	
CINC-1/KC/IL-8	
sFasL	
HMGB1	
Complement factors	
Thromboxanes	
Leukotrienes	
ROS (O_2^-, H_2O_2, OH^-)	
NO	

HMGB1 indicates high-mobility group protein B1; ROS, reactive oxygen species; sFasL, soluble Fas ligand.

The role of alveolar macrophage function in the global inflammatory response is still not fully understood. Because of their location in the immediate vicinity of the lung capillaries, mediators released from alveolar macrophages (or from other stimulated lung cells) may be transported via the bloodstream to distant organs. At these sites, the lung-derived mediators may stimulate cells for cytokine release, thereby modifying the inflammatory balance. For example, the systemic inflammatory response after blunt chest trauma leads to impaired fracture healing by altering the recruitment of inflammatory cells to the fracture site (24). The cellular source of the causative mediators, however, has not been investigated yet.

Depending on the trauma setting, the role of alveolar macrophages is differentially defined. Therefore, this review focuses on alveolar macrophage function after blunt chest trauma, ischemia/reperfusion, hemorrhagic shock, and thermal burns.

ALVEOLAR MACROPHAGES DECISIVELY MODULATE THE PROINFLAMMATORY AND ANTI-INFLAMMATORY RESPONSE AFTER BLUNT CHEST TRAUMA

Lung contusion induced by blunt chest trauma is a common injury that can occur in an isolated manner but more often is observed in patients with multiple injuries (25). A frequent complication of lung contusion is ALI/ARDS (25).

Alveolar macrophages activated by blunt chest trauma release chemokines (monocyte chemotactic protein 1 [MCP-1], macrophage inflammatory protein 2 [MIP-2]) and proinflammatory (interleukin 1β [IL-1β], IL-6, tumor necrosis factor–α [TNF-α]) and anti-inflammatory (IL-10) cytokines. Monocyte chemotactic protein 1 and MIP–2 generated by alveolar macrophages stimulate the migration of monocytes (6) and neutrophils (7, 14, 26, 27) into the contused lung (Fig. 1). However, neutrophils rapidly undergo apoptosis and accumulated apoptotic neutrophils are phagocytosed by alveolar macrophages (14). Fas ligand, which is expressed by alveolar macrophages

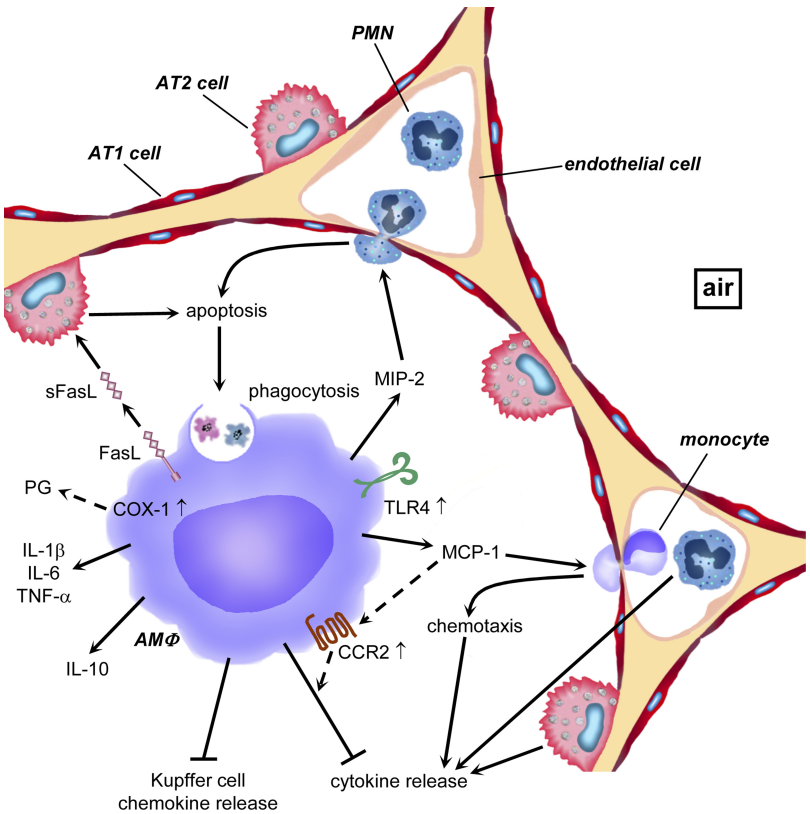

FIG. 1. **Role of alveolar macrophages after blunt chest trauma**. AMΦ indicates alveolar macrophage; AT1 cell, alveolar type 1 epithelial cell; AT2 cell, alveolar type 2 epithelial cell; CCR2, CC chemokine receptor 2; COX, cyclooxygenase; PG, prostaglandins; PMN, neutrophil; sFasL, soluble Fas ligand; TLR, toll-like receptor.

and released into the alveoli, induces apoptosis of alveolar epithelial type 2 cells (28–30), which are then also phagocytosed by alveolar macrophages (14). The binding of Fas ligand to Fas receptor on alveolar macrophages does not induce apoptosis but instead modifies the cytokine release (31). In the setting of additive *ex vivo* stimulation with soluble Fas ligand, IL-6 levels are enhanced whereas IL-10 levels are decreased, and MCP-1 expression remains unchanged (29).

Interestingly, 1 h after blunt chest trauma, alveolar macrophages from the contused lungs of swine show an increased expression of the constitutive isoform of the key enzyme in prostaglandin biosynthesis, cyclooxygenase 1 (COX-1), but not of the inducible isoform COX-2 (17). The significance of this phenomenon in the inflammation after blunt chest trauma is not clear, however, COX-1 inhibition during influenza A viral infection was detrimental to the host (32).

Toll-like receptor 4 (TLR4) expression on alveolar macrophages is significantly increased 48 h after blunt chest trauma in mice (33), priming them for the defense against gram-negative bacteria such as *Escherichia coli* or *Pseudomonas aeruginosa*. At this late time point after trauma, TNF-α and IL-6 concentrations in bronchoalveolar lavage fluids are not increased compared with those in control mice (33), possibly because cytokine concentrations have already returned to sham levels. Infection with *P. aeruginosa* causes a significant increase of TNF-α and IL-6 concentrations in bronchoalveolar lavage fluids of traumatized animals (33). This reaction shows that even at late time points, the alveolar macrophages are still in a "primed" state, although the primary inflammation after blunt chest trauma has already been resolved.

In the contused lung, alveolar macrophages exhibit not only a proinflammatory role (6) but also regulate cytokine release locally within the lungs as well as systemically (34). The binding of MCP-1 to its receptor CCR2 on alveolar macrophages may play a regulatory role as cytokine release in the lungs of $CCR2^{-/-}$ mice is significantly increased (35). The regulatory role of alveolar macrophages after blunt chest trauma has also been studied by our group (34). Using a nonlethal blast injury model of blunt chest trauma (36) and alveolar macrophage depletion indicated that alveolar macrophages ameliorate the local inflammatory response after lung contusion (34). This effect may be mediated by suppressing the cytokine release of AT2 cells and interstitial macrophages (34). Systemically, alveolar macrophages seem to suppress Kupffer cell chemokine release but are not involved in the splenic immunosuppression after blunt chest trauma (34, 37).

ALVEOLAR MACROPHAGES PLAY A CENTRAL ROLE IN ISCHEMIA/REPERFUSION INJURY IN LUNGS

Diminished blood flow during trauma or transplantation can lead to ischemia, which, together with the following restoration of blood flow (reperfusion), results in the clinical picture of ischemia/reperfusion injury (I/R). According to the temperature of the ischemic organ, I/R can be divided into warm

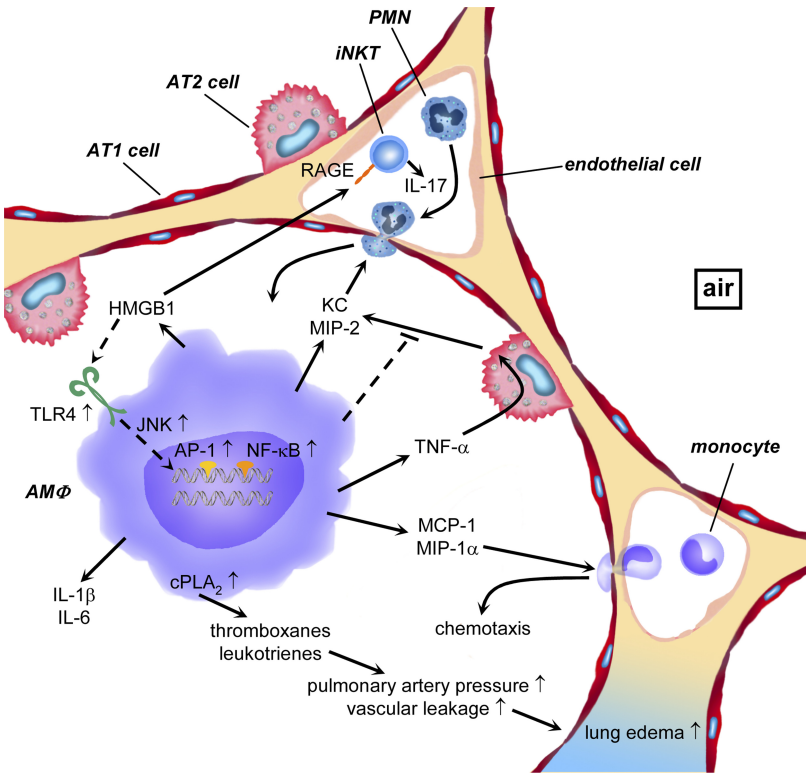

FIG. 2. **Role of alveolar macrophages after ischemia/reperfusion**. AMΦ indicates alveolar macrophage; AP1, activator protein 1; AT1 cell, alveolar type 1 epithelial cell; AT2 cell, alveolar type 2 epithelial cell; CCR2, CC chemokine receptor 2; COX, cyclooxygenase; $cPLA_2$, cytosolic phospholipase A2; HMGB1, high-mobility group protein B1; iNKT, invariant natural killer T cell; JNK, *c*-Jun *N*-terminal kinase; NF-κB, nuclear factor kappa B; PMN, neutrophil; RAGE, receptor for advanced glycation end products; sFasL, soluble Fas ligand; TLR, toll-like receptor.

Table 2. **Extrapulmonary I/R**

Authors	Model	Rat strain	AMΦ
LaNoue et al. (1998)	Gut I/R	Sprague Dawley	PGE_2, TxB_2, O_2-, PCA upregulated
Liu et al. (2001)	Liver I/R	Fischer	TNF-α, IL-1β upregulated
McGuire et al. (1996)	Liver I/R + endotoxemia	Fischer	AMΦ not activated
Moraes et al. (2008)	Gut I/R	Wistar	proinflammatory, not further specified
Silva et al. (2013)	Kidney I/R + OVA stimulation	Wistar	Phagocytosis and bacterial killing downregulated
Souza et al. (2000)	Gut I/R	Wistar	TNF-α, H_2O_2 upregulated

PCA indicates procoagulant activity.

and cold I/R. Examples of warm I/R lung injury are pulmonary sleeve resection during surgical treatment of lung cancer or cardiopulmonary bypass during heart surgery (38, 39). Cold I/R injury is the most common cause of respiratory failure after lung transplantation (40–42).

Intrapulmonary I/R

In terms of inflammation, however, temperature does not seem to be a major critical factor. Both warm and cold I/R lead to activation of alveolar macrophages with upregulation of gene expression via NF-κB and JNK/AP-1 (43) in the early phase of reperfusion (Fig. 2). Alveolar macrophages release a multitude of mediators, such as proinflammatory cytokines (IL-1β, IL-6, TNF-α), chemokines (keratinocyte-derived chemokine [KC], MIP-2, MCP-1, MIP-1α), alarmins (high-mobility group protein B1 [HMGB1]), and arachidonic acid metabolites (8–12, 44). Through the release of TNF-α, AT2 cells are stimulated to release neutrophil chemoattractants such as KC and MIP-2 (13). Along the chemokine gradient, neutrophils and monocytes migrate into the lungs.

Cytosolic phospholipase A_2 ($cPLA_2$) activity in alveolar macrophages is increased by I/R. The resulting release of thromboxane contributes to increased pulmonary artery pressure, which, together with leukotriene-induced vascular leakage and neutrophil infiltration, exacerbates lung edema (9).

Opposite results regarding alveolar macrophage function in two models of warm *ex vivo* I/R with preceding alveolar macrophage depletion (10, 45) may be well attributed to different fluid reperfusion protocols. Although alveolar macrophages seem to exhibit a proinflammatory profile when Krebs-Henseleit buffer was used (10), they present a rather suppressive functional profile in the model using diluted whole blood (45).

A new role of alveolar macrophages in the initiation of I/R injury has been described in a recent publication: the binding of alveolar macrophage-derived HMGB1 to the receptor for advanced glycation end products (RAGE) on invariant natural killer T cells (iNKT) results in the release of the

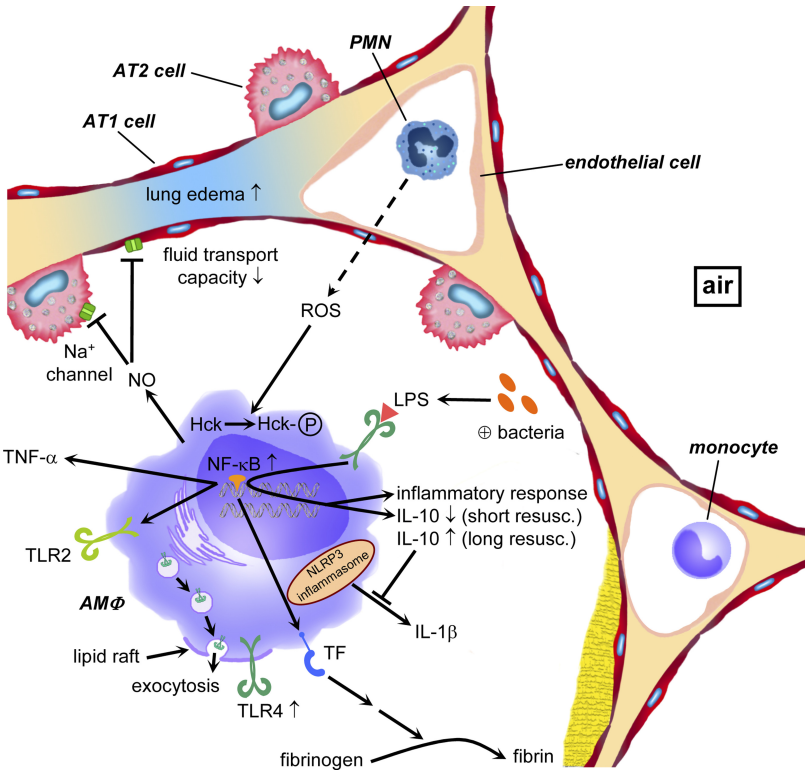

Fig. 3. **Role of alveolar macrophages after hemorrhagic shock**. AMΦ indicates alveolar macrophage; AT1 cell, alveolar type 1 epithelial cell; AT2 cell, alveolar type 2 epithelial cell; CCR2, CC chemokine receptor 2; COX, cyclooxygenase; Hck, tyrosine-protein kinase Hck; LPS, lipopolysaccharide; NF-κB, nuclear factor kappa B; NO, nitric oxide; PMN, neutrophil; ROS, reactive oxygen species; sFasL, soluble Fas ligand; TF, tissue factor; TLR, toll-like receptor; ⊕, exposure to.

neutrophil-chemoattractant IL-17 and subsequent neutrophil infiltration (46). Furthermore, toll-like receptor 4 (TLR4) on alveolar macrophages plays an important role in I/R-induced inflammation, as a TLR4 knockout leads to reduced cytokine expression and an inability to recruit neutrophils into the lung (12). Considering the fact that HMGB1 binds specifically to TLR4 (47), it may activate alveolar macrophages (48) in an autocrine or paracrine manner.

Extrapulmonary I/R

The majority of the studies focused on the alveolar macrophage function after pulmonary I/R, however, alveolar macrophages are also influenced by extrapulmonary I/R, for example, in the gut, kidneys, or liver (Table 2). Three studies on I/R in the gut and liver (49–51) showed activation of alveolar macrophages, with the release of TNF-α, IL-1β, and arachidonic acid metabolites (prostaglandin E_2, thromboxane A_2), which seems to be comparable to the alveolar macrophage reaction to pulmonary I/R. In addition, production of reactive oxygen species (O_2^-, H_2O_2) by alveolar macrophages has been described (50, 51). The proinflammatory activity of alveolar macrophages after gut I/R mediates the development of ALI, as depletion of alveolar macrophages leads to decreased lung permeability and blocks the occurrence of ALI (52).

However, a combination of hepatic I/R and endotoxemia did not activate alveolar macrophages, as determined by unchanged superoxide formation of alveolar macrophages (53). Interestingly, kidney I/R led to reduced phagocytic and microbicidal capacity of alveolar macrophages in ovalbumin-immunized rats (54).

HEMORRHAGIC SHOCK/RESUSCITATION INDUCES MULTIPLE CHANGES IN ALVEOLAR MACROPHAGES

Hemorrhage with a significant loss of intravascular blood volume and consequential hypovolemia, tachycardia, and reduced blood pressure is known as hemorrhagic shock (HS). During severe hypovolemia, decreases in blood flow in all organs leads to reduced delivery of oxygen and nutrients to the tissues and subsequent cellular hypoxia. Hypoxia in turn stimulates the production and release of reactive oxygen species (ROS). Fluid resuscitation can cause further injury because of the release of increasing amounts of ROS (e.g., by activated neutrophils) (55).

Surprisingly, despite hypoxic conditions in the lung tissue (comparable to I/R injury), alveolar macrophages are not fully activated early (up to 3 h) after HS/resuscitation (HS/R), as reflected by unaltered cytokine concentrations and neutrophil cell counts in the bronchoalveolar lavage fluids (56, 57). However, oxidative stress during HS/R primes alveolar macrophages, resulting in an enhanced inflammatory response to lipopolysaccharide (LPS) (Fig. 3). As a consequence, minor lung infections may result in the development of posthemorrhage global lung inflammation, a common cause of morbidity after HS/R. The sensitization of alveolar macrophages to LPS is caused by redistribution of TLR4 from the Golgi apparatus or from endosomes to lipid rafts in the plasma membrane and its colocalization with the adaptor protein MyD88 in a common signaling complex (58). In addition, the Src family kinase Hck, which plays an important role in LPS-induced cytokine

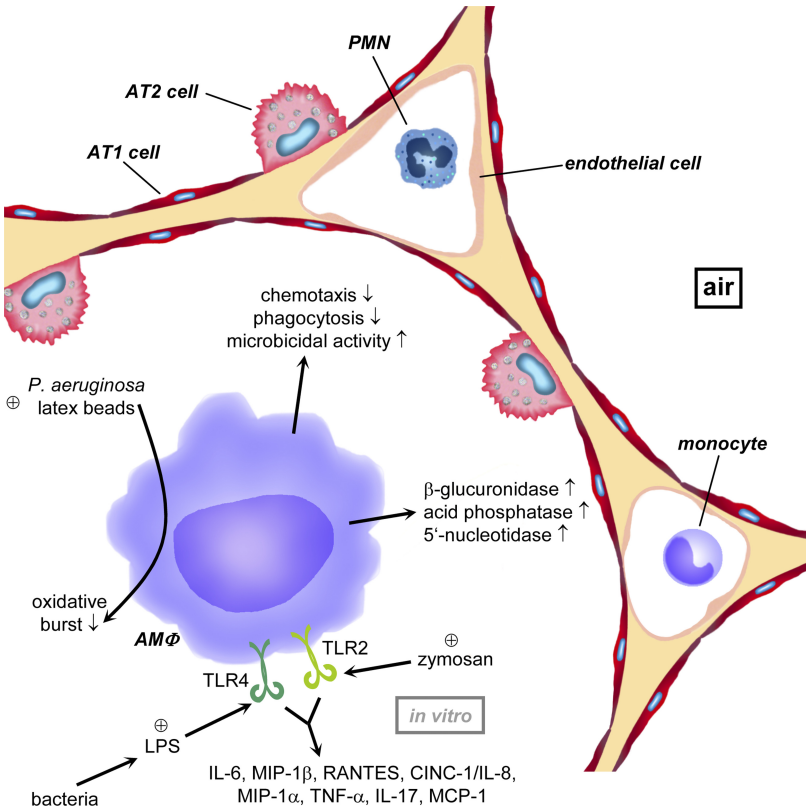

FIG. 4. **Role of alveolar macrophages after thermal burns**. AMΦ indicates alveolar macrophage; AT1 cell, alveolar type 1 epithelial cell; AT2 cell, alveolar type 2 epithelial cell; CCR2, CC chemokine receptor 2; COX, cyclooxygenase; LPS, lipopolysaccharide; PMN, neutrophil; sFasL, soluble Fas ligand; TLR, toll-like receptor; ⊕, exposure to.

production, is phosphorylated and activated in an oxidant-dependent manner (59).

Hemorrhagic shock/resuscitation in general does not seem to result in mediator release from unstimulated alveolar macrophages. However, alveolar macrophages are capable of releasing NO (60, 61) and TNF-α (60) in a 24-h culture when isolated 4.5 to 6 h after hemorrhage and short resuscitation time of 30 min or less.

On stimulation with LPS, alveolar macrophages show a MyD88-dependent increase of IRAK4 activity (55) as well as the translocation of the transcription factor NF-κB from the cytoplasm to the nucleus (62, 63). Nuclear factor-κB activation leads to the production and release of proinflammatory mediators such as TNF-α (56, 57, 64) and CINC-1 (15, 62, 65). Contrasting results regarding the release of the anti-inflammatory cytokine IL-10 may be caused by the duration of the resuscitation time. When resuscitation lasts 20 min, LPS-induced IL-10 release is noticeably reduced (15, 66), whereas after a prolonged resuscitation time of 2 h, LPS-induced IL-10 release is enhanced (56). In turn, IL-10 suppresses generation of proinflammatory IL-1β via negative-feedback regulation of the Nlrp3 inflammasome (66).

The increased expression of tissue factor in alveolar macrophages after HS/R leads to increased procoagulant activity (PCA), that is, the activation of the extrinsic pathway of coagulation (57), which is associated with pulmonary fibrin deposition, a pathologic feature of acute lung injury.

The increased NO release from LPS-stimulated alveolar macrophages into the alveoli (61) results in the inhibition of a Na^+ channel, with a subsequent decrease in the fluid transport capacity of the alveolar epithelium, and consequently the development of pulmonary edema (67).

Regarding TLR4 expression, which is normally suppressed by LPS, HS/R stabilizes TLR4 gene transcription and protein levels (68). Through TLR4 signaling, the expression of the peptidoglycan receptor TLR2 is upregulated (63, 69), "priming" the alveolar macrophages for infections with gram-positive bacteria.

THERMAL BURN INJURY PRIMES ALVEOLAR MACROPHAGES FOR AN EXCESSIVE INFLAMMATORY RESPONSE

Thermal burns can be caused by a variety of factors including fire, hot liquids, steam, or hot objects. Respiratory complications (pneumonia, ARDS, pulmonary embolism) are major causes of death after burn injury (70, 71). The role of alveolar macrophages in the development of ALI/ARDS in burn-injured patients has not been fully understood.

In the initial hyperinflammatory phase after burn, macrophages, monocytes, and neutrophils are activated by toxic metabolites. Clinically and experimentally, the inflammatory response of alveolar macrophages after burn injury is somehow delayed until 3 to 5 days after injury (Fig. 4). Although IL-6 concentrations in lung tissue (72) and bronchoalveolar lavage fluids (22) are increased on days 3 and 4 after burn, respectively, there is no corresponding IL-6 expression in alveolar macrophages (72). Nonstimulated alveolar macrophages release barely any inflammatory mediators in the first 7 days after thermal injury (16). In contrast, on stimulation with the TLR4 agonist LPS, alveolar macrophages release CINC-1/IL-8 early (day 1) after burn injury, whereas TNF-α concentrations and bioactivity as well as IL-6 concentrations are increased on days 3 and 4 (22, 73). Thus, alveolar macrophages may contribute to significantly elevated levels of IL-6 and TNF-α in lung tissue on days 3 and 4 of an *in vivo* model of burn and *P. aeruginosa* infection (74). Interestingly, 7 days after burn injury, LPS-stimulated alveolar macrophages release increased concentrations of IL-6, MIP-1β, and RANTES but not TNF-α, KC (CINC-1), MCP-1, or MIP-1α (16). However, stimulation with the TLR2 agonist zymosan leads not only to the release of IL-6 but also to generation of TNF-α, IL-17, MIP-1β, and MCP-1 (16). Reaction of alveolar macrophages to both TLR4 and TLR2 agonists points to a priming for an excessive inflammatory response to gram-positive and gram-negative bacteria, which makes burn patients more susceptible to pulmonary complications in the later phases after burn injury. Especially if burn injury occurs in combination with inhalation injury, alveolar macrophages are primed for an increased inflammatory response to LPS and cytokine release is increased already early after injury (22).

The functional response of alveolar macrophages (chemotaxis, phagocytotic activity, respiratory burst, and microbicidal activity) is also significantly influenced by burn injury. Although overall microbicidal activity is enhanced in alveolar macrophages after burn injury, the phagocytotic activity is significantly depressed (75). The respiratory burst after phagocytosis of *P. aeruginosa* or latex beads is suppressed, even after stimulation with phorbol myristate acetate (PMA) (76). Under these conditions, alveolar macrophages are incapable of locally clearing a secondary infection with *P. aeruginosa*, resulting in the spread of the infection to the periphery and development of systemic inflammatory response and sepsis (77). Chemotaxis to zymosan-activated serum as well as random migration of alveolar macrophages is significantly impaired after burn injury (78). An exception from this is the unaltered migration of alveolar macrophages from burn-injured smokers toward casein- and zymosan-activated serum (23). The defective chemotaxis is accompanied by increases in RNA, protein, the lysosomal enzymes beta-glucuronidase and acid phosphatase, as well as the ectoenzyme membrane marker 5′-nucleotidase (78).

Smoke inhalation in addition to burn injury induces a significant hypersensitivity of alveolar macrophages to LPS with an increased release of IL-1RA, IL-6, IL-8, IL-10, G-CSF, IFN-γ, RANTES, TNF-α, and VEGF on day 1 after injury (21, 22). There is also increased random migration as well as increased target-specific migration of alveolar macrophages toward casein, zymosan-activated serum, and *N*-formylmethionyl-leucyl-phenylalanine (fMLP) (23).

CONCLUSIONS

Depending on the initial damage, the role of alveolar macrophages may be proinflammatory and anti-inflammatory and their inflammatory response may be immediate (blunt chest trauma, ischemia/reperfusion) or delayed (hemorrhagic shock, burn). "Priming" of alveolar macrophages for defense against

pathogens in the delayed inflammatory response is an important step in the development of ALI or ARDS. Besides own generation and release of inflammatory mediators, alveolar macrophages also significantly regulate the inflammatory response after trauma and shock.

At present, there is a lack of data on the systemic extrapulmonary consequence of alveolar macrophage activation after trauma, except for a suppressive effect on Kupffer cells after blunt chest trauma. Therefore, studies addressing systemic effects of alveolar macrophages in lung injury are needed. It is noteworthy that there are also no direct comparative studies on signal transduction pathways in alveolar macrophages after various traumas. Nevertheless, it is likely that generation of reactive oxygen species in the lung and TLR4 expression, as well as the release of inflammatory cytokines by alveolar macrophages, are similar between the different trauma settings. However, despite some similarities, such as increased TLR4 expression, a "one-fits-all" model of alveolar macrophage function after trauma and shock is neither feasible nor realistic. Moreover, the complex response after a combination of blunt chest trauma with hemorrhagic shock, ischemia/reperfusion, or burn injury has so far not been investigated. Further experimental and clinical studies on alveolar macrophage function after trauma are needed, especially with regard to preexisting conditions, such as nicotine-induced chronic obstructive pulmonary disease or asthma.

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