Neutrophils in Innate Immunity

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ABSTRACT

Neutrophils are an important component of innate immunity in the lungs. During bacterial pneumonia, neutrophils are recruited from the capillaries of the pulmonary circulation in the gas-exchanging regions of the lungs. This process requires the coordinated activation of many cells within the lungs, including neutrophils and capillary endothelial cells. Cellular activation during innate immune responses is mediated in part by tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1–initiated signaling through their receptors, activation of nuclear factor kappa B (NF-κB) and downstream gene transcription, endothelial cell signaling initiated by neutrophil adherence to intercellular adhesion molecule (ICAM)-1, and binding of leukocyte adhesion molecules to cellular and matrix ligands. These events are essential to effective host defense during pneumonia.

KEYWORDS: Neutrophils, pneumonia, cytokines, adhesion molecules, host defense

Objectives: Upon completion of this article, the reader should be able to: (1) summarize the roles of the cytokines tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1 and the transcription nuclear factor-kappa B (NF-κB) in innate immunity; and (2) describe neutrophil adhesion pathways and signaling induced by ligation of intercellular adhesion molecule (ICAM)-1.
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Neutrophils are a critical arm of innate immunity in the lungs. Neutrophil recruitment in response to inflammatory stimuli within the lungs is regulated through complex parallel and sequential events. This review focuses primarily on neutrophil recruitment within the distal gas-exchanging regions of the lungs, where emigration occurs primarily through the pulmonary circulation rather than through the bronchial vessels. Most neutrophil emigration in the pulmonary circulation takes place in the capillaries rather than in the postcapillary venules of the systemic circulation. In response to many stimuli, initial events include the production of the cytokines, tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1α and IL-1β). Activation of the transcription factor nuclear factor-kappa B (NF-κB) is also often an early event in host defense, and TNF-α and IL-1 are important regulators of NF-κB activation. One of the genes regulated by NF-κB is intercellular adhesion molecule (ICAM)-1, an adhesion molecule that serves as the major endothelial cell receptor for CD11/CD18. When CD11/CD18 and ICAM-1 bind, intracellular signaling is induced in both cell types. CD11/CD18 is not always required for neutrophil emigration, and innate immune responses to organisms that induce common community-acquired pneumonias may result in neutrophil emigration through CD11/CD18-independent pathways.

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This review examines these four aspects of neutrophil recruitment during innate immune responses, TNF-α and IL-1–initiated signaling through their receptors, activation of NF-κB and downstream gene transcription, endothelial cell signaling initiated by neutrophil adherence to ICAM-1, and adhesion pathways mediating neutrophil emigration.

TNF-α AND IL-1

Neutrophil recruitment requires the coordinated expression of genes for adhesion molecules and chemokines. During pneumonia, gene transcription is likely induced initially in cells in the air spaces whose pattern-recognition receptors, such as Toll-like receptors,[1] bind conserved microbial structures, such as lipopolysaccharide (LPS) or unmethylated CpG deoxyribonucleic acid (DNA). This initial wave of gene transcription also results in the expression of the early-response cytokines, TNF-α and IL-1. These cytokines induce the expression of adhesion molecules and chemokines in cells that have not been directly activated by microbe-derived ligands.[2,3] In this way, proinflammatory signals originally elicited by microbes in the alveolar air spaces may be communicated to other cells in the lungs and to cells in extrapulmonary tissues.

TNF-α is elaborated as a membrane protein and released from the cell surface by TNF-α cleaving enzyme.[4] Two different receptors signal in response to TNF-α: TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2).[5] Soluble TNF-α signals primarily through TNFR1, whereas TNFR2 responds preferentially to membrane-bound TNF-α.[6,7] Both receptors activate NF-κB transcription factors and induce gene transcription.

IL-1α and IL-1β are also initially elaborated as cytosolic proteins that are released to the extracellular milieu subsequent to proteolytic processing by calpain, for IL-1α, or caspase-1, for IL-1β.[8] The type I IL-1 receptor (IL1RI) binds to both IL-1α and IL-1β, functioning as a signaling receptor that activates NF-κB and induces gene expression.[9] In contrast, the type II IL-1 receptor (IL1RII) does not contain an intracellular signaling domain. By functioning as a decoy receptor, IL1RII decreases signaling from IL-1α and IL-1β.[9] Thus signaling from IL-1α and IL-1β is mediated exclusively by IL1RI.

TNF-α, IL-1α, and IL-1β are expressed during pneumonia in the lungs of experimental animals and patients.[10–17] To test the hypothesis that TNF-α and/or IL-1α and β are essential to innate immune responses during pneumonia, the response to *Escherichia coli* within the lungs was compared in mice deficient in one or more of the receptors for these cytokines. Compared with WT (wild type) mice, TNF receptor–deficient mice lacking both TNFR1 and TNFR2 show no decrease in NF-κB translocation, neutrophil emigration, or edema accumulation during *E. coli* pneumonia, suggesting that TNF receptors are not required for a full response to this organism when studied using mutant mice.[18] These mice do show an increase in the number of *E. coli* remaining in the lung at this early time point of 6 hours, suggesting that TNF-α may facilitate the clearance of this organism. Similarly, mice deficient in IL1R1 have no defect in neutrophil emigration or edema accumulation during *E. coli* pneumonia.[19]

Thus signaling through either TNF receptors or IL1R1 is not independently essential to these innate immune responses when examined using mutant mice. However, TNF-α and IL-1 induce overlapping signaling pathways and the expression of overlapping sets of genes,[20] suggesting that responses to *E. coli* in the lungs may require signaling from either TNF-α or IL-1. In fact, mice deficient in both TNFR1 and IL1R1 have a defect in innate immunity to *E. coli*. Neutrophil emigration and edema accumulation are only half of that observed in the lungs of WT mice during *E. coli* pneumonia.[19] These studies suggest that TNFR1 and IL1RI have essential but overlapping roles in mediating innate immunity in the lungs. Furthermore, these data indicate that pathways exist for neutrophil emigration and edema accumulation independent of these two receptors. TNF-α signaling though TNFR2 is unlikely to contribute to these responses because TNFR1/IL1R1–deficient mice given the soluble chimeric molecule TNFR: ImmunoglobulinG to antagonize TNF-α have no greater or additional defects.[21] More likely, a portion of neutrophil emigration and edema accumulation elicited by *E. coli* in the lungs may occur through pathways that do not require these cytokines.

The mechanisms by which TNF-α and IL-1 contribute to maximal neutrophil recruitment remain speculative. Concentrations of the neutrophil chemokine KC are significantly decreased in bronchoalveolar lavage fluids from TNFR1/IL1R1 deficient mice.[19] Because KC is required for neutrophil emigration elicited by gram-negative bacterial stimuli in the lungs,[22] an essential role for TNF-α and IL-1 receptors in amplifying chemokine expression may have contributed to this defect in emigration. In addition, although NF-κB translocation is not detectably decreased in the lungs, the nuclear translocation of NF-κB in the liver is significantly reduced during *E. coli* pneumonia in TNFR1/IL1R1 mice compared with WT.[19] These data demonstrate that signaling to extrapulmonary tissues during *E. coli* pneumonia requires these receptors. NF-κB mediates the expression of hepatocyte-derived acute phase proteins facilitating neutrophil recruitment and activation, including serum amyloid A and complement C3.[23–25] In this way, these cytokine receptors may be critical to systemic responses that influence local inflammation.

These studies indicate that TNF-α and IL-1 share functions contributing to neutrophil emigration and the accumulation of extravascular plasma during *E. coli* pneumonia. Because neutrophils and plasma proteins are essential to combating bacterial infections, inhibiting these innate immune responses could compromise host defenses. However, given that pneumonia is an important risk factor for acute lung injury and the acute respiratory distress syndrome, decreasing the inflammatory response to microbes in the lungs may be protective for some patients. These studies suggest that the combined inhibition of signaling from TNF-α and IL-1 may be more effective than inhibition of TNF-α or IL-1 alone in limiting inflammation and injury during respiratory infection.

NF-κ B

All three signaling receptors for TNF-α and IL-1, as well as the Toll-like receptors, which recognize conserved microbial structures, activate NF-κB transcription factors.[26] NF-κB complexes include homo- or heterodimers of NF-κB proteins (RelA, RelB, c-Rel, p50, and p52). NF-κB complexes are maintained in the cytoplasm of most cells by their interactions with inhibitor IκB proteins, preventing their nuclear import and mediating their nuclear export. Upon appropriate receptor stimulation, signaling pathways activate IκB kinases (IKK), which phosphorylate IκB proteins, resulting in their ubiquitination and proteasomal degradation. NF-κB proteins contain nuclear localization sequences, and NF-κB complexes accumulate in the nucleus after liberation from IκB proteins. NF-κB complexes bind specific nucleic acid sequences (κB sites) in the DNA and recruit multiprotein complexes that modify histones, remodel chromatin, and direct the expression of nearby genes.[27] Activation of NF-κB is sufficient to induce gene expression mediating neutrophil recruitment because adenoviral expression of constitutively active IKK in lung cells in vivo in the absence of other events associated with inflammation causes expression of the chemokines KC and MIP-2 and the accumulation of neutrophils.[28]

NF-κB is activated during experimental lung infections and in patients with lung injury and modulates innate immune responses. For example, *E. coli* and *E. coli* LPS in rodent lungs induce the rapid nuclear accumulation of the NF-κB complexes RelA/p50 and p50/p50.[17,18,29] NF-κB complexes accumulate in the alveolar macrophages of patients with the acute respiratory distress syndrome.[30,31] In particular, NF-κB RelA is essential to induction of ICAM-1, IL-8, KC, and MIP-2 by LPS or cytokines in vitro,[2,32,33] and ICAM-1,[34] KC,[22] and MIP-2[35] are required for neutrophil recruitment elicited by LPS in rodent lungs. Studies in vivo have been hampered because the targeted deletion of the gene for RelA results in embryonic lethality.[36] The additional genetic deficiency of TNFR1 rescues RelA-deficient mice through the embryonic period,[37] presumably due to essential roles for RelA in the expression of genes protective against TNFR1-induced cytotoxicity. However, mice deficient in both TNFR1 and RelA (TNFR1/RelA mutants) die within several weeks of birth.[37] The TNFR1/RelA mutants, in contrast to either the WT or TNFR1-deficient mice, demonstrate widespread evidence of infection, including pneumonia and bacteremia, and the life spans of TNFR1/RelA mice are prolonged by antibiotic treatment, indicating that RelA is required for effective host defenses and prevention of lethal bacterial infections.[37]

To determine whether RelA is essential to gene expression and neutrophil emigration in the lungs, *E. coli* LPS was delivered intranasally to TNFR1/RelA mutant mice at 3 to 5 days of age. The increase in expression of molecules mediating neutrophil emigration, including ICAM-1, KC, and MIP-2, is significantly less in the lungs of TNFR1/RelA mice compared with WT or TNFR1-deficient mice.[37] Furthermore, neutrophil emigration is compromised in TNFR1/RelA mutant mice compared with WT or TNFR1- deficient mice.[37] Thus, RelA mediates the LPS-induced expression of chemokines and adhesion molecules required for neutrophil emigration in the lungs.

The cells in which RelA-induced gene expression is particularly important for neutrophil emigration have not been conclusively identified. Reconstitution of lethally irradiated WT mice with RelA-deficient hematopoietic stem cells results in WT mice with RelA-deficient leukocytes, including alveolar macrophages and circulating neutrophils.[37] Compared with WT mice with WT leukocytes, neutrophil emigration elicited by LPS in the lungs is not decreased in the lungs of WT mice with leukocytes deficient in RelA, TNFR1, or both.[37] Comparing these results with the studies of mice deficient in TNFR1 and RelA in all cells suggests that gene induction by RelA in nonhematopoietic cells, such as epithelial and endothelial cells of the lung, is critical to neutrophil recruitment.

In resting cells, RelA-containing NF-κB complexes are typically bound to inhibitor proteins of the IκB family, including IκB-α, IκB-β, and IκB-ε.[26] Immunoprecipitation of RelA from mouse lungs co-precipitates all three of these IκB proteins.[29] The immunoprecipitation of each of the IκB proteins co-precipitates RelA but fails to co-precipitate the other IκB proteins.[29] Thus each of these IκB proteins forms discrete complexes with RelA in mouse lungs. After intratracheal instillation of LPS, IκB-α and IκB-β protein levels decrease in the lungs.[29] In contrast, IκB-ε levels increase,[29] indicating distinct mechanisms for regulation of this IκB protein. These data suggest that the nuclear translocation of RelA complexes results from

the LPS-induced degradation of IκB-α and IκB-β. Studies to determine the functions of these IκB have demonstrated that IκB-β deficiency did not affect the nuclear accumulation of NF-κB complexes, neutrophil recruitment to alveolar air spaces, or pulmonary edema,[29] suggesting IκB-β proteins do not possess unique properties essential to NF-κB translocation or to acute inflammation induced by *E. coli* LPS in the lungs. Studies examining IκB-α are not yet feasible because deficiency of this molecule results in uncontrolled inflammation and perinatal lethality.[38]

IκB proteins are only one mechanism by which cells inhibit RelA. Other endogenous means for inhibiting gene induction by RelA include p50/p50 homodimers,[39–41] steroid hormones,[42,43] cyclopentenone prostaglandins,[44] histone deacetylases,[45,46] and Twist transcription factors.[47] Mimicking these inhibitory pathways with pharmacological agents may be candidate approaches for patients with excessive lung inflammation. Furthermore, host variation in these molecular pathways, resulting from genetic polymorphisms and previous or current environmental stresses, may predispose subpopulations to acute lung injury during infection. The role of RelA in mediating the LPS-induced expression of proinflammatory genes and amplifying neutrophil recruitment suggests that limiting RelA activity may be important to protecting the lungs from injury.

ICAM-1–DEPENDENT SIGNALING INTO PULMONARY MICROVASCULAR ENDOTHELIAL CELLS DURING NEUTROPHIL ADHESION

ICAM-1 is an adhesion molecule expressed by endothelial and other cells. In many pulmonary inflammatory responses, such as those induced by *E. coli* LPS or TNF-α, ICAM-1 expression is increased on the luminal surface of pulmonary capillary endothelium.[48,49] Its expression is regulated by NF-κB.[2,37] The interaction between neutrophil β2 integrins and endothelial cell (EC) ICAM-1 often mediates the adhesion of neutrophils to pulmonary capillary ECs, a process that is usually a prerequisite for subsequent neutrophil migration across the endothelium and into the alveolar space during pulmonary inflammation.[50] Blockade of ICAM-1 expression in the lungs by antisense oligonucleotides or treatment with anti–ICAM-1 antibodies largely prevents neutrophil sequestration and emigration into the alveolar space induced by many inflammatory stimuli,[51–53] demonstrating an indispensable role for ICAM-1 in these responses.

Recent studies using cultured ECs have provided evidence that ICAM-1, in addition to its role as an adhesion molecule for leukocytes, functions as a signaling molecule when ligated by leukocytes, antibodies, or fibrinogen.[54–59] These studies led to the hypothesis that ICAM-1–induced signaling cascades and downstream events in pulmonary capillary ECs may play important roles in modulating neutrophil migration along or across ECs. Support for this concept is provided by studies of Sans and colleagues,[60] who demonstrated that in a reconstituted cell line, expression of ICAM-1 without its cytoplasmic domain required for signaling prevents neutrophil transmigration without inhibiting neutrophil adhesion. Using cultured human and rat pulmonary microvascular ECs, we have recently shown that ICAM-1 ligation induces a cascade of signaling events into ECs, resulting in cytoskeletal changes of ECs.[61–64] Inhibition of signaling events in ECs prevents neutrophil migration toward EC borders, the preferred site of neutrophil emigration across pulmonary capillary ECs in vivo.[65,66] ICAM-1–initiated signaling cascades are the focus of the remainder of this section.

Cultured human pulmonary microvascular ECs express little ICAM-1 on their surface. However, in response to stimulation by TNF-α for 8 or 24 hours, the expression of ICAM-1 is induced on the surface of these ECs,[61,67] correlating with in vivo studies. This increase in ICAM-1 expression is accompanied by increased adhesion of isolated human neutrophils.[61] Stimulation of ECs by TNF-α for 24 hours also results in changes in the F-actin cytoskeleton that include the disassembly of the peripheral F-actin cytoskeleton and increases in the F-actin stress fibers.[63] Neutrophil adherence to TNF-α–treated ECs for 2 to 10 minutes induces thickening of F-actin bundles and formation of F-actin clusters in ECs.[63] Quantification of F-actin staining in ECs demonstrates an increase in both the mean staining intensity and the percentage of the EC area occupied by F-actin.[63] In addition, the apparent stiffness of ECs increases in response to neutrophil adherence for 2 to 15 minutes, as evaluated by magnetic twisting cytometry.[63] Addition of neutrophils to ECs that are not pretreated with TNF-α does not alter the actin cytoskeleton or the apparent stiffness of ECs. This increase in the apparent stiffness of ECs is not prevented by inhibitors of myosin light chain kinase but is inhibited by pretreatment with cytochalasin D, which induces F-actin depolymerization,[68] or jasplakinolide, which binds F-actin and stabilizes F-actin by preventing F-actin depolymerization.[69] These results suggest that the stiffening response results from changes in the F-actin cytoskeleton in ECs initiated by neutrophil adherence. Together, these studies indicate that neutrophil adherence to TNF-α–pretreated pulmonary microvascular ECs induces changes in the F-actin cytoskeleton of ECs.

These cytoskeletal changes induced by neutrophils are inhibited by pretreatment with an anti–ICAM-1 antibody and are mimicked by crosslinking ICAM-1 with antibodies, as evaluated by magnetic twisting cytometry and by visualizing F-actin distribution.[61] These

ICAM-1–induced changes in the F-actin cytoskeleton do not occur when only the primary antibody is bound but rather require the addition of a secondary antibody, suggesting that cross-linking ICAM-1 (i.e., bringing more ICAM-1 molecules closer together) is necessary for transducing signaling events into ECs.

Ongoing studies are beginning to delineate the signaling pathways initiated by ICAM-1 that result in these changes in the F-actin cytoskeleton following neutrophil adherence. Cross-linking ICAM-1 with antibodies induces redistribution of ICAM-1 into aggregates on the surface of human pulmonary microvascular ECs.[61,64] In cultured human umbilical vein ECs, clustering of ICAM-1 and its association with actin-binding proteins such as ezrin (a membrane cytoskeletal linker), α-actinin, and vinculin in response to ligation of ICAM-1 by antibodies or adherence of leukocytes have been observed.[54,70] These changes in ICAM-1 require phosphoinositides and Rho, and are thought to play important roles in mediating firm adhesion of leukocytes.[54,70] The role of ezrin, phosphotidylinositols, and Rho in ICAM-1–initiated signaling within human pulmonary microvascular ECs remains to be determined.

Downstream signaling events following ICAM-1 ligation and clustering on pulmonary microvascular ECs are depicted in Fig. 1. They include activation of xanthine oxidase and generation of reactive oxygen species (ROS) by this enzyme in ECs.[61,64] Production of ROS in turn leads to activation of p38 mitogen-activated protein kinase (MAPK) and subsequent phosphorylation of heat shock protein 27 (hsp27), an actin-binding protein that may modulate F-actin polymerization upon phosphorylation.[62,64,71] Pretreatment of ECs with SB203580, an inhibitor of p38 MAPK, prevents the changes in the F-actin cytoskeleton in ECs induced by neutrophils or cross-linking ICAM-1, indicating that p38 MAPK is required for the cytoskeletal changes initiated by ICAM-1 ligation.[62]

These studies led to the hypothesis that during neutrophil adherence to TNF-α–treated pulmonary microvascular ECs, ICAM-1–initiated signaling events and cytoskeletal changes may modulate neutrophil migration along ECs to reach EC borders. Our studies demonstrate that there is a time-dependent increase in the percentage of neutrophils present at EC borders after addition of neutrophils to TNF-α–treated ECs, indicating that neutrophils migrate toward EC borders.[63] Pretreatment of ECs with an inhibitor of p38 attenuates neutrophil migration toward EC borders.[62] These data suggest that activation of p38 and phosphorylation of its downstream substrates in ECs play important roles in mediating neutrophil migration toward EC borders, where neutrophil transmigration occurs.

Neutrophil emigration occurs within the microvasculature, primarily from the pulmonary capillaries during inflammation in the lung parenchyma.[50]

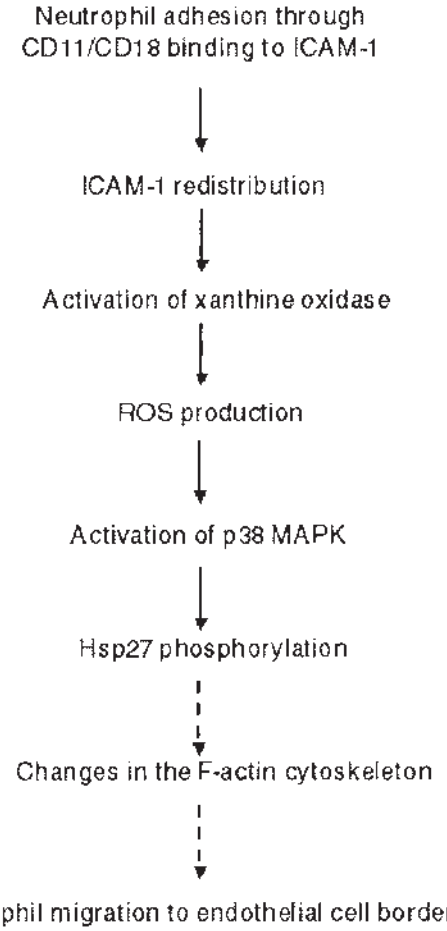

Figure 1 Ligation of intercellular adhesion molecule (ICAM)-1 initiates signaling pathways into pulmonary microvascular endothelial cells (ECs) during neutrophil adherence, resulting in cytoskeletal changes. ICAM-1–initiated signaling pathways result in activation of p38 mitogen-activated protein kinase (MAPK) and subsequent phosphorylation of hsp27. Phosphorylation of hsp27 is postulated to mediate the actin cytoskeletal changes.

Endothelial cells of the pulmonary vasculature may have specialized responses to neutrophil adhesion. For example, comparison of cultured pulmonary arterial ECs (PAECs) and pulmonary microvascular ECs (PMECs) isolated from rats show that adherence of rat neutrophils induces an increase in F-actin staining and the stiffening response of TNF-α–pretreated rat PMECs, but not rat PAECs.[64] This difference between ECs isolated from these two sites is not due to differences in the expression of ICAM-1 following TNF-α treatment or in ICAM-1 clustering in response to cross-linking antibodies. However, ICAM-1–dependent activation of p38 MAPK occurs in TNF-α–pretreated PMECs, but not PAECs. This activation of p38 in PMECs is prevented by allopurinol, an inhibitor of xanthine oxidase (see Fig. 1). Measurement of xanthine oxidase activity reveals that this enzyme's activity in PMECs is increased by neutrophil adhesion. In contrast, PAECs demonstrate a much higher basal level of activity of this oxidase, and no detectable increase is induced by neutrophil adherence.

Taken together, these data suggest that differences between rat PMECs and PAECs in their cytoskeletal responses to neutrophil adherence are due to differences in ICAM-1–initiated signaling pathways. The difference in signaling seems to lie between ICAM-1 clustering (which occurs in both cell types) and p38 activation, perhaps in the activation of xanthine oxidase.

Whether these ICAM-1–initiated signaling events and actin cytoskeletal changes in ECs during neutrophil adherence are required for neutrophil emigration into the alveolar space during inflammatory processes in vivo remains to be determined. Dynamic changes in actin cytoskeletal organization do occur and appear essential for neutrophil emigration during inflammatory responses in vivo. For instance, intratracheal instillation of phalloidin, which prevents F-actin rearrangement in lung capillary ECs and epithelial cells, inhibits neutrophil emigration into the alveolar spaces by 83% in response to *Streptococcus pneumoniae*.[72] In addition, phalloidin instillation attenuates neutrophil emigration and edema formation in acid aspiration lung injury.[73] These studies suggest that changes in the cytoskeleton in ECs and epithelial cells are required for neutrophil emigration during acute pulmonary inflammation. Generation of genetically altered animal models such as animals expressing a truncated form of ICAM-1 without its cytoplasmic domain required for signaling will help elucidate the physiological significance of ICAM-1–initiated signaling events in mediating neutrophil emigration in lung inflammation in vivo.

NEUTROPHIL EMIGRATION

Although adhesion mediated by CD11/CD18 and ICAM-1 ligation is required for neutrophil emigration in response to some stimuli (including *E. coli*, *E. coli* endotoxin, *Pseudomonas aeruginosa*, IL-1, IgG immune complexes), the CD11/CD18 adhesion complex is not required in response to others (including *S. pneumoniae*, *Staphylococcus aureus*, Group B *Streptococcus,* C5a, KC, hyperoxia[50]). The selection of CD11/CD18–dependent or –independent pathways appears to be determined by which cytokines are produced very early in host defense toward these stimuli.[50] Although TNF-α and IL-1 appear important in initiating CD11/CD18–mediated adhesion, other cytokines such as interferon gamma (IFN-γ) appear important in regulating the CD11/CD18–independent pathway.[74] CD11/CD18–independent adhesion is not mediated by members of the selectin family, VLA-4 (very late antigen-4), or PECAM-1 (platelet–endothelial cell adhesion molecule-1).[50,75,76] Presently, the molecules that mediate adhesion when CD11/CD18 is not required are not known, and whether neutrophil–endothelial cell adhesion molecules in the traditional sense are needed is also not clear.

Following adhesion and transendothelial migration, neutrophils pass through slitlike holes in the endothelial basal lamina into the connective tissue matrix within the thick side of the capillary loop.[65,66] The cellular processes of fibroblasts within this matrix extend from these holes to similar holes within the basal lamina of alveolar epithelial cells.[65,66] Neutrophils are often in contact with these fibroblasts as they crawl toward the alveolar spaces, suggesting that they use these cells as a track. Neutrophils prefer to pass between Type I and Type II cells, rather than between Type I/Type I borders.[65,66] CD44, the receptor for hyaluronic acid and other connective tissue molecules, and β1 integrins appear important in neutrophil emigration toward some stimuli.[77,78] The molecular signals regulating neutrophil transit following transendothelial cell migration are only beginning to be elucidated.

SUMMARY

Host defense and innate immunity are complex processes that often require recruitment of neutrophils. Production of TNF-α and IL-1, activation of NF-κB, and subsequent gene expression are important steps in neutrophil recruitment early in the response to many stimuli. Neutrophil–endothelial cell interactions through CD11/CD18-mediated adhesion to ICAM-1 are also often but not always critical and depend upon the stimulus. Both the adhesive function of these molecules and the signaling cascades that are initiated within both cell types may be important in modulating neutrophil recruitment and their subsequent ability to combat infection. Our understanding is incomplete at this time, and our ability to modulate innate immunity therapeutically will be greatly enhanced by a clearer understanding of the multiple pathways through which the host responds to stimuli within the lungs.

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