Airways Inflammation and COPD*

Epithelial-Neutrophil Interactions

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Neutrophils are recognized as major cellular mediators of inflammation. They contain specific and highly regulated mechanisms for controlling the expression of adhesion molecules that allow for their tethering and migration into inflammatory sites. These adhesion molecules not only are activated by exogenous pollutants but are regulated by endothelial and epithelial cell signals. Lipid mediators, such as platelet-activating factor, reactive oxygen and nitrogen species, and cytokines from airway epithelial cells, further control neutrophil functions such as infiltration and activation resulting in an increase in respiratory burst activity and release of granule enzymes, such as elastase. Furthermore, virus and bacteria products affect inflammation by increasing secondary epithelial mediators. However, once the endogenous or exogenous agents are expelled, neutrophil populations are programmed to die and are cleared by macrophage phagocytosis.

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Abbreviations: AP = activation protein; E-selectin = endothelial selectin; GM-CSF = granulocyte/macrophage colony-stimulating factor; ICAM = intercellular adhesion molecule; IFN-β = interferon-beta; IL-1β = interleukin-1beta; LFA = lymphocyte function-associated antigen; LPS = lipopolysaccharide; L-selectin = leukocyte selectin; LT = leukotriene; Mac = macrophage antigen; NF-κB = nuclear factor κB; PAF = platelet-activating factor; P-selectin = platelet selectin; PSGL = platelet selectin glycoprotein ligand; RNS = reactive nitrogen species; TNF = tumor necrosis factor; VCAM = vascular cell adhesion molecule

Inflammation is a localized protective response in vascularized tissues induced by microbial infection and/or cell and tissue injury, and in the airways the neutrophil is widely accepted to be a central effector cell in this pathogenic process. Under normal conditions, the role of the neutrophil is to kill and eliminate endogenous and exogenous stimuli such as airborne pollutants, allergens, and microbes by employing phagocytosis, a respiratory burst, and the release of cytotoxic mediators and proteases. However, these defense mechanisms are dependent solely on the ability of the inflammatory cells to adhere to and migrate through a normally tight microvascular endothelial barrier.

In the present review, we examine the mechanisms of neutrophil migration into the airways by their utilization of adhesion molecules, the inflammatory products expelled from these cells (especially elastase), the role of viral and bacterial products in exacerbating airway inflammation, and how this inflammatory response is coordinated by the epithelium. Finally, the role of apoptosis in clearing neutrophil populations from injured airways will be discussed.

Adhesion Molecules

Leukocyte migration from the circulation into tissues is widely acknowledged to occur by a sequential activation of adhesive proteins and their ligands on leukocytes and endothelial cells. Monocytes, lymphocytes, and neutrophils all migrate using similar sequential mechanisms, although they differ in their responses to chemotactic and inflammatory signals, as well as in the qualitative and quantitative expression of adhesion molecules. Under normal conditions, circulating neutrophils roll along the blood vessel walls. Once an appropriate stimulus is present, however, rolling neutrophils adhere firmly to endothelial cells and are primed to migrate from the bloodstream to the site of injury.

The initial attachment of neutrophils and their movement along vessel walls are due to a reversible binding to transmembrane glycoproteins (ie, the selectins) on neutrophils and endothelial cells. These molecules contain an extracellular NH²-terminal, a calcium-dependent lectin region, an epidermal growth factor-like domain, and a short, intracellular COOH terminus. The following three selectins have been identified and are named for the principal cell types in which they occur: leukocyte selectin (L-selectin); endothelial selectin (E-selectin); and platelet selectin (P-selectin).

L-selectin is expressed solely on leukocytes, and the binding of neutrophils to postcapillary venules can be blocked by antibodies directed against L-selectin. Although expressed constitutively, neutrophils do not express L-selectin uniformly. Neutrophils that are newly released from bone marrow contain higher levels of L-selectin than older, circulating neutrophils. Although L-selectin is shed routinely from the neutrophil surface under normal conditions during rolling along vessel walls, the status of the neutrophil also seems to correlate with the level of L-selectin expressed. Comparative analyses of lymphocytes that had not migrated (type-I) and transmigrated lymphocytes (type-II) showed that L-selectin expression is significantly lower on the latter. Similarly, decreased expression levels of L-selectin have been detected on neutrophils following their migration from the bloodstream to a site of inflammation, demonstrating that L-selectin is down-regulated following neutrophil transendothelial migration. Although mediators such as lipopolysaccharide (LPS) and tumor necrosis factor (TNF)-α have been shown to cause autodigestion of L-selectin, an L-selectin sheddase that is thought to be most important in vivo.

Spertini and colleagues identified an inducible ligand for neutrophil L-selectin in endothelial monolayers, a
sialomucin oligosaccharide located on glycosylation-dependent cell adhesion molecule-1, and mucosal addressin cell adhesion molecule-1 in Peyer patches. However, the binding of L-selectin to these ligands is reversible and is not neutrophil-specific, because they also exhibit similar affinities for selectins expressed on platelets, lymphocytes, and monocytes.

P-selectin and E-selectin also have been shown to participate in neutrophil-endothelial cell adhesion. Unlike L-selectin, which is expressed constitutively, these molecules require appropriate inflammatory stimuli for expression. For instance, P-selectin is stored intracellularly in Weibel-Palade bodies of endothelial cells and in α-granules of platelets but is mobilized to the cell surface within minutes of the exposure of the endothelium to inflammatory mediators, including histamine, thrombin, and oxidants. Once on the endothelial cell surface, P-selectin is available to interact with neutrophil P-selectin glycoprotein ligand (PSGL)-1, a disulfide-bonded homodimer expressed on rolling neutrophils that is capable of binding two P-selectin ligands simultaneously. Compared to L-selectin binding, which is rapid and short-lived, P-selectin binding causes slower rolling velocities and the eventual tethering of neutrophils to vessel surfaces. As with L-selectin binding, however, the P-selectin/PSGL-1 interaction is brief and reversible unless downstream adhesive events are invoked.

In contrast to P-selectin, E-selectin is not stored but, rather, is stimulated by cytokines and requires de novo messenger RNA and protein synthesis. It is inducible by various interleukins (ILs), TNF-α, LPS, and endotoxins, with peak expression and activity in vitro occurring 4 to 6 h after the exposure of endothelial cells to inflammatory cytokines. E-selectin mediates the adhesion of CD4 T cells and monocytes, and can support the tethering and rolling of neutrophils in a fashion similar to P-selectin. It has been postulated that E-selectin is responsible for maintaining neutrophil rolling after P-selectin has been down-regulated.

The next step of transendothelial neutrophil migration is their firm adhesion to vessel walls. The signal necessary to initiate this stable neutrophil-endothelial cell interaction has been postulated to be either a receptor-mediated event in response to inflammatory cytokines or an event propagated from signals from activated selectins. As mentioned previously, in the presence of appropriate stimuli, L-selectin is shed from circulating neutrophils. Similarly, P-selectin binding is accompanied by a rapid redistribution of PSGL-1 to uropods on activated neutrophils. Cytoplasmic domains of bound and activated L-selectin and PSGL-1 have been linked to signal transduction pathways. It is possible, therefore, that the selectins may function to promote the transition to firm adhesion in neutrophils by activating the integrin expression pathway.

The integrins, a group of heterodimeric transmembrane glycoproteins that are expressed on neutrophils and other hematopoietic cells, coordinate cell-cell and cell-extracellular matrix adhesions. All integrins are composed of a single α-subunit (CD11) and a single β-subunit (CD18), which together form an extracellular ligand-binding site. Cytoplasmic tails of integrins contain phosphorylation sites and provide linkages to cytoskeletal proteins involved in signal transduction. There are 16 α-subunits and 8 β-subunits that give rise to a variety of integrins. Only macrophage antigen (Mac)-1 (ie, αMβ2 and CD11b/CD18), however, and lymphocyte-associated function antigen (LFA)-1 (ie, αLβ2 and CD11a/CD18) mediate neutrophil binding to the endothelium. Since only low levels of LFA-1 are expressed on neutrophils, and since this is unaltered by cell activation, most research has focused on Mac-1-dependent responses. In neutrophils, preformed Mac-1 is stored in the specific and gelatines granules, as well as in secretory vesicles, but it is rapidly mobilized to the cell surface in response to bacterial peptide formyl-methionyl-leucyl-phenylalanine or to weaker stimuli that mobilize only the secretory vesicles. Inflammatory stimuli also can promote the transcription and translation of Mac-1 genes, thus prolonging integrin involvement during inflammation. The ligand-binding site on membrane Mac-1 lies within an extracellular region of the α-subunit called the “inserted domain” that is inaccessible to potential ligands unless integrins are activated by intracellular or extracellular signals.

An important endothelial ligand for Mac-1 is intercellular adhesion molecule (ICAM)-1, which belongs to the Ig superfamily, a third family of adhesion molecules. ICAM-1 exhibits low constitutive expression on endothelial cell membranes but is markedly induced by exposure to inflammatory cytokines. LFA-1 also can bind to ICAM-1, but it has a higher affinity to the related protein ICAM-2, a ligand to which Mac-1 binds with less affinity. Other members of the Ig gene superfamily have been shown to be involved in leukocyte adhesion. The vascular cell adhesion molecule (VCAM)-1 was found to bind to very late antigen-4 on activated human and rat neutrophils, and VCAM-1/very late antigen-4 interaction can mediate the adhesion of neutrophils to the endothelium in vitro. Similarly, the platelet-endothelial cell adhesion molecule-1, a noninducible molecule that is constitutively and uniformly expressed on all endothelial cells, is thought to be involved in leukocyte adhesion and/or migration through vessel walls.

**Epithelial Signals**

Deleterious environmental stimuli such as airborne pollutants, allergens and microbes cause the airway epithelium to alter defense mechanisms such as the secretion of mucus, the production of oxygen and nitrogen species, the efficiency of ciliary beating, the transport of ions for fluid absorption and secretion, and the influx of inflammatory cells. The epithelium is also a target for factors released by infiltrating inflammatory cells and serves as a major effector of inflammation. On encountering such agents, the epithelium produces mediators, such as interferon-γ and TNF-α, that provoke epithelial cells to produce secondary mediators including lipid mediators, reactive oxygen species (ROS), reactive nitrogen species (RNS), and cytokines. These secondary mediators can further affect pathophysiologic alterations such as hypersecretion of mucus and increased inflammation.
LIPID MEDIATORS

Lipid mediators, including prostaglandins, leukotrienes (LTs), hydroxyeicosatetraenoic acids, and platelet-activating factor (PAF), are produced both by infiltrating inflammatory cells and by airway epithelial cells in response to various stimuli. These lipid mediators produced by the epithelium can act in an autocrine or paracrine manner to stimulate airway epithelial cells to produce other mediators. For example, PAF, which is a potent inflammatory mediator that is produced by a wide variety of cells,51 stimulates the further production of eicosanoids, including LTs and hydroxyeicosatetraenoic acids.50 These mediators are chemotactic for neutrophils, eosinophils, and macrophages, they activate eosinophils and macrophages, and they alter vascular and epithelial permeability.52 In addition, a number of inflammatory cells exhibit increased expression of IL-6, TNF-α, and interferon-γ when treated with PAF, LTB4, or prostaglandin E2.53

ROS AND RNS

Reactive species such as superoxide anion radicals (ie, O2•−), hydroxyl radicals (ie, OH•), hydrogen peroxide (ie, H2O2), nitric oxide, and peroxyxinitrite (ie, ONOO−) alter several cell functions. Although the release of oxidants from macrophages, eosinophils, and neutrophils is well-documented, only as recently as 1998 was the production of these species by airway epithelial cells examined.54 For example, bronchial and tracheal epithelial cells have been shown to release H2O2 in response to inflammatory stimuli.55

ROS and RNS are potent effectors of intracellular signaling in many cell types including airway epithelial cells. Following exposure to superoxide, H2O2, or ozone, O2•− can stimulate epithelial mucus secretion.56,57 Data from our laboratory also implicate OH• as an intracellular signaling molecule for ICAM-1 expression in primary cultures of normal human bronchial epithelial cells and in an epithelial cell line.58 Similarly, nitric oxide up-regulates ciliary beat frequency in bovine bronchial epithelial cells58 and stimulates mucus secretion from guinea-pig tracheal epithelial cells.59−61

In addition to roles in intracellular signaling, ROS and RNS from inflammatory and epithelial cells can directly injure the airway endothelium, amplifying inflammatory cell influx. Also, these reactive species can alter the expression and activation of oxidant-regulated transcription factors such as nuclear factor-κB (NF-κB) and activation protein (AP)-1,62 which are involved in regulating the expression of many proinflammatory cytokines, such as IL-6 and IL-8.

CYTOKINES

Cytokines are pluripotent protein mediators of inflammation63 that are produced and secreted by a wide variety of cell types, including neutrophils,64 monocytes, macrophages, endothelial cells, and epithelial cells.65−67 The supernatants of cultured airway epithelial cells contain detectable amounts of cytokines such as IL-1, IL-6, IL-8, granulocyte-macrophage colony stimulating factor (GM-CSF) and granulocyte colony stimulating factor.49 On epithelial cell stimulation, the expression of these molecules is increased in order to direct inflammatory cells to the site of an injury. The processes of this up-regulation are complex but may be due to the release of IL-1 and TNF-α, which are known to increase the expression and release of these secondary cytokines.

TNF-α, which was originally identified as a product of activated macrophages, is also produced by endothelial cells, mast cells, leukocytes, and the airways epithelium.52,68 TNF-α has multiple biological effects such as causing the enhanced expression of ICAM-1 and VCAM-1 on the pulmonary endothelium and airway epithelium and the enhanced expression of E-selectin and LFA-1 on eosinophils and neutrophils.69 Furthermore, in airway epithelial cells, TNF-α has been shown to alter cell migration and permeability and to stimulate the secretion of GM-CSF, IL-6, and IL-8.52,70

IL-8 is produced by alveolar macrophages, lymphocytes, and epithelial cells; it was the first chemokine shown to be produced by neutrophils and has been studied extensively.71 It is well-documented that cytokines and growth factors (eg, TNF-α, IL-1, and GM-CSF), chemoattractants (formyl-methionyl-leucyl-phenylalanine, PAF, and LTB4), proteolytic enzymes, various bacteria, fungi, protozoa, and viruses possess the capacity to trigger the secretion of substantial amounts of IL-8 by neutrophils.72 Although this molecule is also chemotactic for eosinophils, basophils, and T-lymphocyte subsets,73 its main actions are in neutrophil recruitment and activation, causing a release of granule enzymes, an increase in respiratory burst activity, the up-regulation of adhesion molecules, and the increased adherence of neutrophils to unstimulated endothelial cells.64,71,74

IL-8 AND COPD

Several studies have suggested that the overexpression of IL-8 is central to pathophysiologic changes in the airways and to the severity of airflow obstruction that may ultimately lead to diseases such as COPD, asthma, and cystic fibrosis. For example, neutrophils, and not eosinophils, have been implicated in the creation of the symptoms of acute exacerbations of asthma.75−78 Likewise, in induced sputum samples from COPD patients, significant increases in the concentrations of IL-8, TNF-α, and neutrophils are found compared with concentrations found in samples from unaffected smoking and nonsmoking control subjects.77 The percentages of neutrophils in the patients with COPD were significantly correlated with the degree of airflow limitation. Similarly, chronic bronchitis patients with moderate-to-severe airflow obstruction had a higher percentage of neutrophils in BAL fluid than did those patients with no airflow obstruction or only mild airflow obstruction.79 Airway neutrophilia correlated not only with airflow obstruction but also with sputum production and smoking history.79,80

Chronic exposure to pollutants and tobacco smoke has major effects on the airway epithelium.80 An increase in the percentage of neutrophils has been identified in sputum samples from smokers who developed airflow...
obstruction over a 15-year period. Furthermore, the annual decline in lung function was related to the proportion of neutrophils, again suggesting a causal relationship. Neutrophils isolated from these patients expressed higher levels of Mac-1, which is involved in cellular migration and is correlated with airflow obstruction, suggesting that a greater degree of cellular activation was associated with the airway disease.

The induction of stress responses in epithelial cells causes stimulation of the ras/MAPK pathway leading to the induction of DNA synthesis, as well as the activation of transcription factors NF-κB and AP-1. Stimuli known to activate the NF-κB complex include TNF-α, TNF-β, IL-1, LPS, phorbol esters, ultraviolet light, ROS, and a number of viruses. ICAM-1, IL-1β, and TNF-α activate both AP-1 and NF-κB in lung tissues. GM-CSF, IL-6, IL-1, VCAM-1, and E-selectin all contain NF-κB or NF-κB-like sites in their 5′ flanking regions. Furthermore, binding sites for AP-1 have been found in promoters of ICAM-1, E-selectin, VCAM-1, and tissue factors. These transcription factors are involved in the increased expression of many cytokines and mediators.

**Viral and Bacterial Effects on Airway Inflammation**

Airway epithelial cells serve as a barrier to invading allergens, and they produce enzymes and mediators that maintain normal airway homeostasis. They are also, however, the principal host cells for respiratory viruses, which can cause varying degrees of damage on infection. Respiratory viruses such as rhinovirus, respiratory syncytial virus, and influenza rapidly stimulate epithelial cells to secrete a wide range of proinflammatory mediators, including IL-6, IL-8, IL-11, and GM-CSF. Early activation of epithelial cells and other resident airway cells stimulates changes in endothelial cell physiology such as increased ICAM-1 expression and increased vascular permeability, leading to edema, obstruction, and increased responsiveness and secretions. It is most likely, therefore, that the increase in adhesion molecule expression plus the increase in virus-induced cytokines results in the increased binding of neutrophils and eosinophils to epithelial cells that leads to the infiltration of inflammatory cells. Neutrophils have been shown to be the primary cell type that is recruited to the airways during the acute stages of viral respiratory infections. This is likely in response to chemotactic factors, such as IL-8 and LTB₄, that are released during the initial stages of the viral infection.

Although respiratory viruses damage the airways, bacterial products, particularly LPSs from Gram-negative bacteria, also induce inflammation that is mediated through IL-8. LPS-activated macrophages that secrete TNF-α cause an up-regulation in IL-8 expression through NF-κB-dependent and AP-1-dependent pathways. However, IL-8 production in bacterial infections is not LPS-dependent. A Gram-positive Staphylococcus aureus, which lacks LPSs, enterotoxin A, capsular polysaccharides, and lipoteichoic acid, also induces IL-8 expression.

In contrast, *Shigella flexneri* uses a unique method of bacteria-induced apoptosis as a trigger for inflammation. Thus, shortly after undergoing phagocytosis by tissue macrophages, the bacteria escape from the phagolysosome and release bacterial invasion plasmid antigen B into the cytosol, where it interacts with the cysteine protease IL-1β-converting enzyme which, once activated, causes macrophage death. Before dying, apoptotic macrophages release IL-1, which recruits neutrophils to the affected area.

**Neutrophil Inflammatory Response**

As neutrophils move to a site of inflammation or injury to remove invading particles such as bacteria and viral products, they degrade connective tissue, releasing peptides that may serve as chemoattractants. Similarly, the activation of the neutrophils results in the further release of the chemoattractants LTB₄ and IL-8, thereby self-perpetuating the inflammatory response. Finally, the elastase released by neutrophils can activate complement factor 5, resulting in the release of C5a, which is also a chemoattractant. On reaching the site of inflammation, the neutrophil proceeds to clear the airway of microbes via a combination of ROS products from the respiratory burst, the action of cytotoxic proteins, and bacterial degradation by granule proteases.

The granules of the neutrophil also contain proteins with cytotoxic potential, most of which are located within the azurophil granules. These include the defensins or human neutrophil peptides 1 to 4 (a family of cyclic single-chain peptides with molecular masses of about 4 kd), which are highly toxic to fungi, enveloped viruses, and bacteria. Three major serine proteases, elastase, cathespin G, and proteinase 3, also are contained in the azurophil granules. Neutrophil elastase and cathespin G are both bactericidal.

The mechanisms by which neutrophils degranulate are not completely understood. Investigators have shown that granule release is dependent either on protein kinase C or on cyclic guanosine 3′,5′-monophosphate-dependent kinase activation. In contrast, preliminary studies from our laboratory suggest that synergistic activation of both protein kinase C and cyclic guanosine 3′,5′-monophosphate-dependent kinase is necessary for the exocytosis of azurophil granules. The molecule that mediates this cross-talk is the myristoylated alanine-rich C kinase substrate protein. Preliminary data suggest that this mechanism is also involved in the release of specific granules of the neutrophil. This mechanism also has been determined to control mucin granule secretion in primary cultures of human bronchial epithelial cells, although it is unknown whether this is a ubiquitous mechanism for all granule exocytosis.

Once the granules have released their products at the site of inflammation, they can cause major effects on the airways. Neutrophil elastase has been hypothesized to signal epithelial cells to release IL-8 in order to recruit more inflammatory cells to the site of injury, although a 1998 preliminary report on bronchial epithelial cells indicated that this may not be the case in vivo. However,
in experimental animal models, mucus gland hyperplasia,\textsuperscript{121} as well as inflammation and airways damage, is seen within a short period after the addition of neutrophil elastase.\textsuperscript{122}

Studies in vitro have demonstrated that the addition of neutrophil elastase to mucus glands results in excessive mucus secretion,\textsuperscript{123} epithelial damage, and a significant slowing of the beat frequency of the ciliated epithelium.\textsuperscript{124}

Furthermore, neutrophil elastase also has been shown to damage IgGs\textsuperscript{125} and an important opsonophagocytic receptor, C3bi, resulting in the further impairment of critical lung defenses.\textsuperscript{126} The impairment of such important host defense mechanisms can result in bacterial colonization even in patients that are in a stable clinical state,\textsuperscript{127} thereby driving further neutrophil recruitment.

The recruitment of neutrophils to the airway would be expected to lead to an increase in microbial phagocytosis and killing, and, if sufficient, will result in the sterilization of the airway with subsequent reductions in the number of proinflammatory cytokines released by bacterial products. In addition, the neutrophils become less activated, resulting in a reduction in the release of chemoattractants and neutrophil elastase. The inactivation of neutrophil elastase would be facilitated further by the development of inflammation. Thus, neutrophil elastase causes increased protein leakage between epithelial cells,\textsuperscript{129} and this, together with the acute-phase response, will result in the leakage of large quantities of α1-antitrypsin from the circulation into the airways. The net effect will be to increase the ability of the airway secretions to inhibit neutrophil elastase, thereby negating both its potentially harmful effects as well as the beneficial ones that should no longer be needed as microbes are cleared.

Under normal conditions, the release of neutrophil elastase in the airways is inhibited by a secretory leukocyte proteinase inhibitor, but research has shown that active neutrophil elastase reduces epithelial cell release of this inhibitor.\textsuperscript{129} Although this process may be detrimental, it is possible that it also plays an important role in host defense because neutrophil elastase, as noted earlier, is bactericidal\textsuperscript{111} and perhaps, more importantly, elastase causes mucus release from glands\textsuperscript{123} to entrap the bacteria, leading to their removal by mucociliary clearance or expectoration.

**APOPTOSIS**

Aging neutrophils undergo spontaneous apoptosis or programmed cell death in the absence of cytokines or other proinflammatory agents prior to their removal by macrophages.\textsuperscript{130} This phagocytic removal of intact, apoptotic neutrophils prevents them from releasing their cytotoxic content into the extracellular space, as would occur if the cells died by necrosis. In patients with acute inflammation, neutrophil accumulation within tissues can be extremely high because of the targeted influx from the circulation and because their constitutive apoptotic pathway is delayed by the action of local inflammatory mediators.\textsuperscript{131} Recently, it was determined that the binding of fibronectin causes a delay in apoptotic events.\textsuperscript{132} Thus, the potential for inflammatory neutrophils to cause tissue damage via the release of toxic ROS and granule enzymes is very high. Death by apoptosis\textsuperscript{133} and safe removal by phagocytic cells thus helps to limit tissue damage during the resolution of inflammation.

Apoptic neutrophils lose their ability to move by chemotaxis, to generate a respiratory burst, or to degranulate phagocytize, or change shape.\textsuperscript{134} This loss of function results from the disablement of the activation pathways of the neutrophils and from the decreased expression of surface receptors aids in this shutdown in activity by preventing them from efficiently binding with extracellular ligands. These inactive neutrophils, which have altered surface epitopes, then undergo phagocytosis.\textsuperscript{135}

The role of TNF-α in neutrophil apoptosis has been controversial.\textsuperscript{136–138} Recently, however, it was shown\textsuperscript{139} that the pretreatment of neutrophils with TNF-α caused a significant increase in apoptosis when cells were subsequently treated with various agonists. These results suggest that TNF-α primes the neutrophils to die as a result of further triggers.

**CONCLUSION**

In conclusion, it is important to understand the molecules and pathways involved in regulating and controlling neutrophil inflammation. Unfortunately, the current treatments for inflammation only control the influx of neutrophils to the site of injury. However, by better understanding all the mechanisms employed by the neutrophil, pharmacologic agents that will better control this universal and sometimes debilitating condition can be developed.

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