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# Nature and Consequences of the Systemic Inflammatory Response Induced by Lung Inflammation

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Additional information is available at the end of the chapter

## 1. Introduction

Lung inflammation is the basis for the majority of acute and chronic lung conditions. Acute lung injury (ALI) caused by either communicable (such as infection) or non-communicable (such as acid aspiration) diseases are characterized by a rapidly induced inflammatory response in the lung. There are numerous causes for ALI, as the lung is exposed to external factors either via the airways (infectious agents and environmental pollutants) or via the blood stream (sepsis, endotoxin, fat) and, when severe, can lead to acute respiratory distress syndrome (ARDS), a spectrum of lung diseases characterized by a severe inflammatory process in the lung parenchyma causing diffuse alveolar damage and respiratory failure [1, 2]. This acute inflammatory response in the lung is strongly associated with a systemic inflammatory response that may lead to multiple organ dysfunction and is associated with high mortality [3]. Similarly, chronic inflammatory lung conditions such as chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis and interstitial lung diseases, especially those associated with collagen vascular disease, have in recent years also been shown to be accompanied by a systemic inflammatory response, albeit different in nature [4-14]. In addition, the systemic response induced by chronic lung inflammation is also associated with downstream adverse effects on different organ systems. This chapter will focus on defining the nature and features of this systemic response as a consequence of lung inflammation and will focus predominantly on chronic inflammatory lung conditions.

## 2. Lung conditions associated with a systemic inflammatory response

Numerous lung conditions, especially inflammatory lung conditions, are known to be associated with a systemic inflammatory response. Although the associations and consequen-

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ces of the systemic response in acute lung injury and inflammation have been well established [1, 2, 15], the associations in chronic inflammatory lung conditions are less well known. This chapter will discuss the current knowledge surrounding inflammatory lung conditions and their associations with a systemic response.

## 2.1. Acute lung inflammation

The most recognized causes of acute lung inflammation are those induced either by infection or by direct or indirect ALI: for example, infections beginning in the lungs frequently transition into systemic events with hemodynamic effects (shock) and remote organ dysfunction such as acute kidney injury, which, when severe, may lead to death. Traditionally, the transition of infection from a localized event to one that is systemic in scope has been termed sepsis and is characterized by fever, tachycardia, tachypnea and a constellation of other signs and symptoms indicating that the pathogen and the humoral events that accompany the infectious process, are now systemically distributed. Furthermore, a number of publications suggest that clinical events such as severe tissue injury and ischemia-reperfusion injury may also activate the systemic response of the host in a similar manner to sepsis [16, 17]. The recognition of this common pathophysiologic phenotype of the sepsis syndrome led to the term ''systemic inflammatory response syndrome'' or SIRS, characterized by global activation of the inflammatory cascade, with an increase in circulating proinflammatory mediators leading to adverse downstream effects on numerous organ systems (so called multi-organ dysfunction). As mentioned, SIRS is an inflammatory response resulting from either local or systemic inflammatory events which may be initiated by either infectious or non-infectious insults [18, 19].

The local acute inflammatory response in the lung is complex and involves activation of the innate immune response via binding of microbial products or cell injury-associated endogenous molecules (danger-associated molecular patterns [DAMPs]) to pattern recognition receptors such as the toll-like receptors on the lung epithelium and alveolar macrophages [20]. Complex autocrine and paracrine inter-relationships exist between cytokines and other proinflammatory mediators such as endothelial adhesion molecules that both initiate and amplify the inflammatory response. This is augmented further by the margination and migration of polymorphonuclear neutrophils (PMNs) and other humoral responses, both dependent or independent of the cells, such as lipid mediators, proteases, oxidants, growth factors (such as transforming growth factors [TGFs]), nitric oxide and neuropeptides [21]. Increased permeability of microvascular barriers results in extravascular accumulation of protein-rich edema fluid in airspaces, a cardinal feature of acute inflammation and a central pathophysiologic mechanism in ALI/ARDS.

The local inflammatory insult in the lung may exceed the efficiency of the inflammatory response to effectively contain it, resulting in inflammatory elements of either bacterial cell products and toxins or cellular alarmins, pathogen-associated molecular patterns (PAMPs) and other inflammatory elements of the local response to gain systemic access in sufficient quantity to activate the systemic inflammatory response.

The magnitude of the insult is not the sole determining factor for host failure to contain the inflammatory response: in some instances, defects in the hosts' responses may contribute

significantly. Host defects may be attributed to prior corticosteroid treatment, protein-calorie malnutrition or even genetic make-up, for example. The systemic response is characterized by activation of the coagulation cascade, complement proteins and the acute phase response.

Activation of cellular elements of blood such as platelets, granulocytes and mast cells cause degranulation and release of potent proinflammatory contents systemically, resulting in the systemic unleashing of otherwise beneficial local effects, leading to significant adverse effects on multiple extra-pulmonary organs.

## 2.2. Chronic lung inflammation

Since the 1970's and 1980's, the importance and consequences of the systemic response following acute lung inflammation have been recognized and well described, however, the systemic inflammatory response in chronic inflammatory lung conditions has only been recognized within the last ten years. The consequences and significance of this "lower grade" systemic response has only recently been more clearly defined. The chronic systemic inflam-matory response in the lung is characterized by mobilization and activation of inflammatory cells into the circulation, the production of acute phase proteins and an increase in circulating inflammatory mediators. Of all the chronic inflammatory lung conditions, the systemic responses and consequences have been best characterized in COPD.

An integral component of the systemic inflammatory response is the stimulation of the hematopoietic system, specifically the bone marrow, which results in the release of leukocytes and platelets into the circulation. Large population-based studies have shown that the magnitude of the leukocytic response is a predictor of total mortality, independent of smoking [22-24].

Chronic cigarette smoking increases circulating leukocyte numbers [25, 26], including imma-ture neutrophils, and results in high levels of myeloperoxidase and $\alpha_1$-antitrypsin, the latter a natural inhibitor of serine proteases and responsible for alveolar wall damage [27, 28], suggesting that the systemic response feeds back to the lung and perpetuates the lung inflammatory response.

The acute phase response is an early and key part of the systemic component of the innate immune response and C-reactive protein (CRP) is a robust marker of this response. Subjects with severe airflow obstruction are more likely to have elevated CRP-levels and, in addition, high CRP levels have been related directly to severity of COPD and the associated systemic inflammation, independent of cigarette smoking and coronary artery disease [29-32].

Local anti-inflammatory therapy (inhaled corticosteroids) reduces circulating CRP whereas withdrawal of inhaled corticosteroids results in a significant increase in CRP levels [33], suggesting that lung inflammation drives the CRP levels in the blood of subjects with COPD. Moreover, CRP levels increase further during COPD exacerbations when lung inflammation flares up [33]. The increased circulating levels of CRP in COPD are associated with other mediators such as IL-6, which is the predominant cytokine regulator of CRP production by hepatocytes.

Lastly, subjects with COPD have higher levels of several circulating proinflammatory medi‐ators such as tumor necrosis factor (TNF)-$\alpha$ and its receptors (TNFR-55 and -75), which are associated with leukocyte activation and the concomitant weight loss in these subjects [34-39]. Levels of the proinflammatory mediators IL-6 and IL-8 have also been shown to increase systemically during acute exacerbations of COPD [40, 41] suggesting that exacerbation of lung inflammation fuels the systemic response.

Chronic obstructive pulmonary disease is predominantly caused when the lung is exposed to noxious particulate matter and gases from cigarette smoke. Lung inflammation induced by inhalation of other air pollutants such as particulate matter or $PM_{10}$, nitric dioxide or ozone also causes a low grade inflammatory response in the lung. Experimental animal models exposed to ambient air pollutants [42, 43] and studies in humans [44, 45] have both shown that the inflammatory response in the lung induced by air pollutants is also associated with systemic inflammation, suggesting that the systemic response is not specific for cigarette smoke exposure (Figure 1).
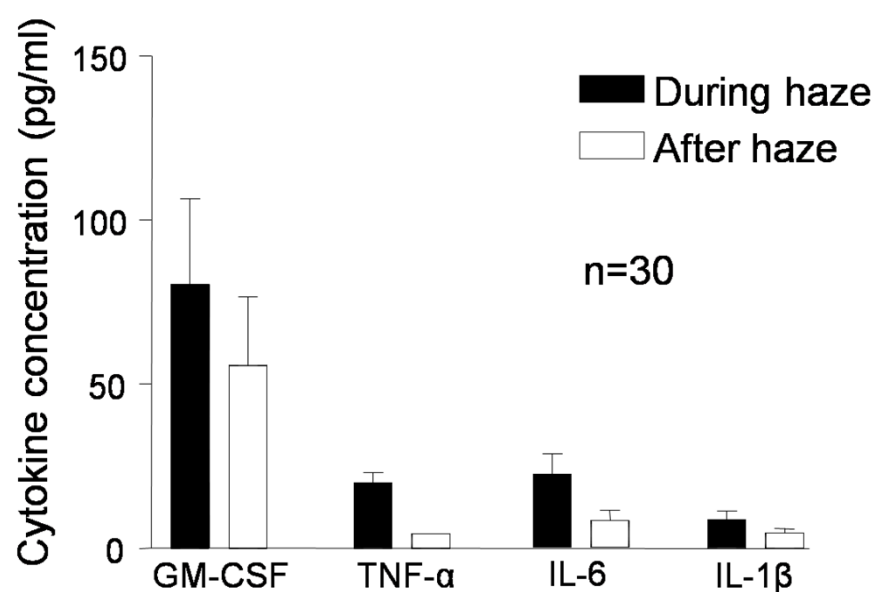


**Figure 1.** Cytokines in the blood of subject during the Southeast Asia forest fires of 1997. The black bars represent the concentrations of cytokines in the serum during the haze period and the white bars after the haze cleared. Cytokine levels were higher during haze compared with after haze. Values are mean ± SEM of all samples with values within the detection limit of the assay (n = 30 per group).

Similar to lung inflammation caused by inhalation exposure, the systemic response has also been well documented in other inflammatory lung conditions such as asthma [4-7], suppura‐tive lung conditions such as bronchiectasis [8, 9], interstitial lung disease (ILD), in particular, ILD associated with collagen vascular diseases such as lupus erythematosus, rheumatoid arthritis and scleroderma [10-14]. As stated previously, these chronic inflammatory lung conditions are associated with increased levels of acute phase proteins such as CRP, stimula‐tion of the bone marrow with altered circulating leukocyte and platelets and increased circulating proinflammatory mediators. Extensive studies have been undertaken to identify potential biomarkers capable of predicting disease severity and prognosis, implying that the

systemic response to lung inflammation is an integral part of the disease and has important implications for disease pathogenesis and prognosis.

## 3. Lung cells contribute to the systemic inflammatory response induced by lung inflammation

The cells lining the airways are mainly epithelial cells but also include alveolar macrophages and both cell types are exposed to the external environment. They are the first responders in the lung when the lung is exposed to external factors such as cigarette smoke, air pollutants or infectious agents. These cells are critically important in the processing and neutralization of inhaled environmental contaminants which include airborne particulate matter (PM), cigarette smoke, bacteria and viruses, shown in Figure 2. Alveolar macrophages are one of the most potent producers of inflammatory mediators in the lung. It is known that human alveolar macrophages exposed to $PM_{10}$ (EHC-93) [46] are able to phagocytose these particles *in vivo* [43] and *in vitro* [45] and produce, in a dose-dependent manner, an array of mediators such as IL-1$\beta$, IL-6 and TNF-$\alpha$ that are part of the innate immune response. To test the contribution of the mediators produced by alveolar macrophages to the systemic response, supernatants from alveolar macrophages, incubated *ex vivo* with urban PM, were instilled into the lungs of rabbits. The supernatants produced a systemic bone-marrow stimulation response similar to that produced by direct deposition of urban PM into the rabbit lung [42, 43]. Analysis of the supernatants showed that the proinflammatory mediators IL-1$\beta$ and IL-6, the chemokine macrophage inflammatory protein (MIP)-1$\alpha$ and granulocyte macrophage colony-stimulating factor (GM-CSF) are elevated when macrophages are incubated with urban PM [45]. Studies showing a strong relationship between the quantity of particles phagocytosed by macrophages in lung tissue and the magnitude of the systemic response, after urban PM exposure (Figure 3), support the notion that the production of inflammatory mediators by alveolar macrophages is important and suggests that alveolar macrophages are significant contributors to the innate component of the systemic response following an inflammatory stimulus in the lung

Similar experiments using bronchial epithelial cells showed that, when exposed to urban PM, cells produce excess GM-CSF, IL-1$\beta$, IL-6, TNF-$\alpha$, IL-8 and leukemia inhibitory factor (LIF) in a dose-dependent manner [47-49]. Some overlap was evident when comparing mediators produced by alveolar macrophages with those produced by bronchial epithelial cells after exposure to similar doses of urban PM, however, some distinct differences in the type and the magnitude of cytokine production was observed (Figure 4). The relative contributions of macrophages and epithelial cells in the production of mediators responsible for the systemic inflammatory response need to be determined. Alveolar macrophages are professional phagocytes and the magnitude of their cytokine production is significantly higher than bronchial epithelial cells, after the same level of exposure (Figure 4). These studies suggest that alveolar macrophages are key effector cells, responsible, at least, for generating the systemic inflammatory response associated with exposure to air pollution. However, although the macrophages are more potent producers of proinflammatory mediators expressed per cell basis, the airspace epithelial cells out-number the alveolar macrophages approximately ten
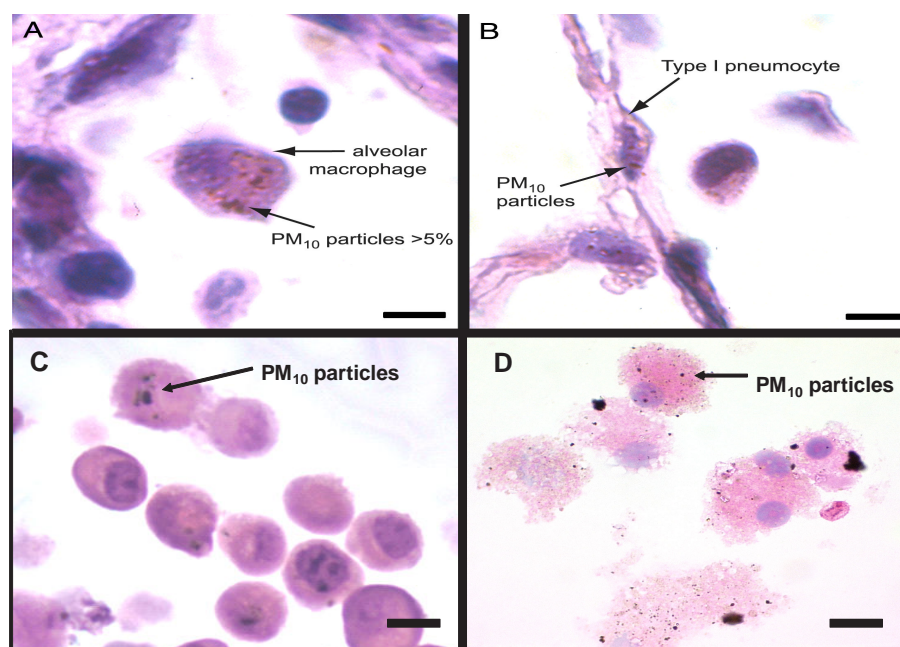
**Figure 2.** Photomicrographs of ambient particles phagocytosed by alveolar macrophages (A and D) and bronchial epithelial cells (B and C). **A and B:** Ambient particles (EHC-93] in alveolar macrophages (A) and both type I and type II epithelial cells (B) in rabbits exposed to 5 mg EHC-93 twice a week for 4 wks. **C:** Particles in primary cultures of human bronchial epithelial cells exposed to EHC-93 [100 µg/ml) for 24h. **D:** Particles in alveolar macrophages exposed to EHC-93 [100 µg/ml) for 24 h. The bar represents 10 µm [162].
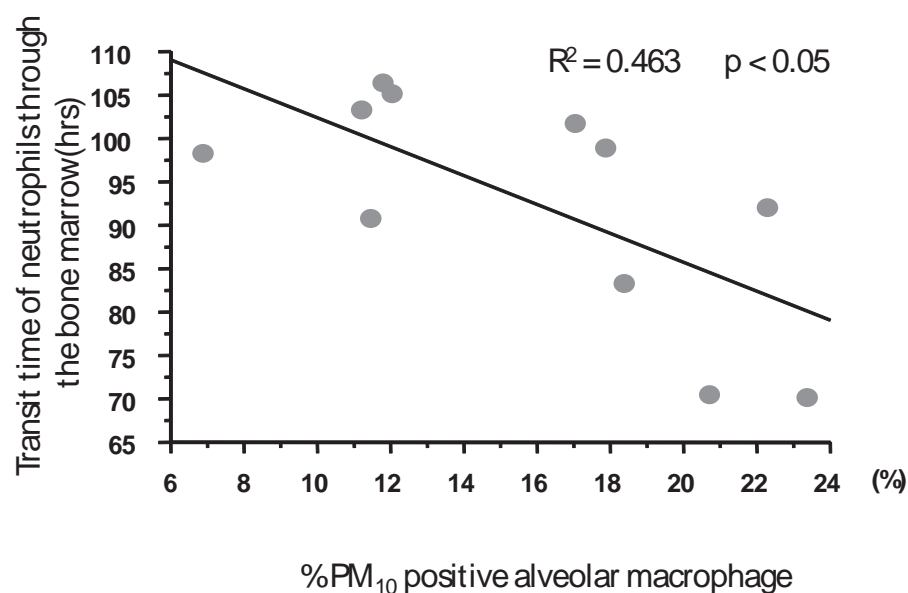


**Figure 3.** Relationship between the fraction of alveolar macrophages (AMs) that phagocytosed $PM_{10}$ particles and the transit time of PMNs though the bone marrow. Rabbits were exposed to 5 mg $PM_{10}$ (EHC-93) twice a week for 4 weeks, and AMs with particles in their cytoplasm were enumerated using quantitative histological methods. Dividing PMNs in the marrow were labeled with 5-bromo-2-deoxyuridine and the transit time of PMNs through the bone marrow was measured. Faster transit times of PMNs through the marrow were associated with an increased percentage of AMs with phagocytosed particles ($R^2 = 0.46$, $p < 0.05$) [162].

times. Furthermore, the interaction between macrophages and epithelial cells has a synergistic effect on the production and release of mediators involved in the systemic inflammatory response [50], therefore alveolar macrophages and airspace epithelial cells both play central roles in the activation of the innate immune response and the production of inflammatory mediators involved in the systemic response to lung inflammation.
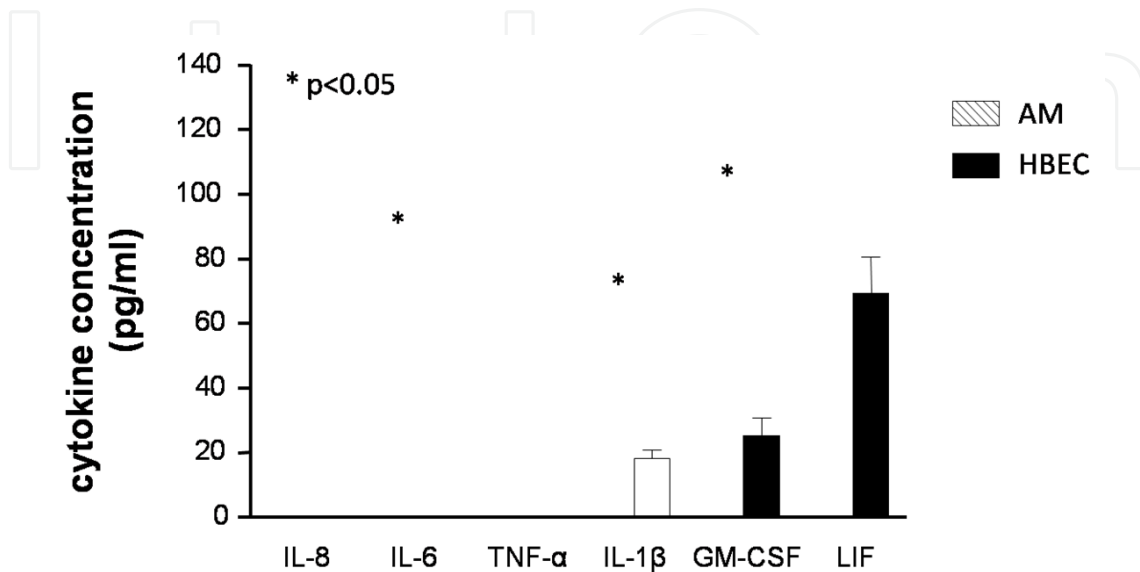


**Figure 4.** Cytokines produced by human AMs and bronchial epithelial cells (HBECs) when exposed to 100 µg/mL of $PM_{10}$ (EHC-93) for 24 h. Differences between two groups were compared by Mann–Whitney U test. Alveolar macrophages produced significantly more IL-6, IL-1β and GM-CSF than bronchial epithelial cells when exposed to the same amount of $PM_{10}$ [162].

The roles of other lung cells such as connective tissue cells (fibroblast, smooth muscle cells), immune cells (lymphocytes and dendritic cells) and vascular cells (endothelium) in the systemic response to lung inflammation are less clear. Several studies have documented increased levels of endothelial specific markers (soluble P, E and L-selectin, intercellular adhesion molecule [ICAM]-1, vascular cell adhesion molecule [VCAM]-1 and endothelin-1) present in the circulation during lung inflammation [51-53] but whether these mediators come directly from the lung or are released secondary to the initial circulating proinflammatory mediators such as IL-1β and TNF-α, is unclear. Mediators released from connective tissue cells and immune cells of the adaptive immune responses tend to be more localized in cellular niches with less of a systemic consequence.

## 4. Mediators of the systemic inflammatory response induced by lung inflammation

Lung inflammation has been associated with an array of different circulating cellular or non-cellular mediators that may differ significantly depending on the type and the character of the inflammatory response in the lung.

**4.1. Cellular components of the systemic response to lung inflammation**

Increased circulating leukocyte counts, specifically granulocyte counts, have been used for decades as biomarkers of local inflammatory or infectious processes, including lung inflammation. Large population-based studies showing leukocytosis as a predictor of total mortality, independent of other risk factors such as cigarette smoking, underline the importance of increases in circulating leukocytes [23, 54, 55]. Therefore, an integral component of the systemic response to lung inflammation is the stimulation of the hematopoietic system, specifically the bone marrow, which results in an increase in circulating leukocytes. In humans, leukocyte increases caused by bone marrow stimulation can be identified and quantified by an increase in circulating immature granulocytes (band cells and metamyelocytes) [42], in contrast to increases in leukocyte counts induced by exercise or other cathecholamine stress that results largely in demargination of existing intravascular leukocytes [56]. When associated with lung inflammation, an increase in circulating band cells signifies that signals from the lung have activated and stimulated the bone marrow to release immature leukocytes. In humans both acute lung inflammation such as pneumonia [57] and chronic lung inflammation such as exposure to cigarette smoke or other air pollutants [44] have been shown to increase circulating band cells counts, implicating a systemic response that stimulates the bone marrow. In contrast, two separate studies of healthy subjects residing in regions with low particulate air pollution (such as the South Pole) for prolonged periods, showed that the circulating white blood cell (WBC) count fell below the normal range shortly after the subjects entered this pristine environment, remained low for the entire period that they were in this environment, and then returned to normal levels when they returned to the either the US [58] or Japan [59]. The Japanese study also showed that the fall in circulating leukocytes was associated with a fall in the number of circulating band cells, indicating a reduction in bone marrow output [59]. These studies suggest that the reductions in circulating WBC and band cell counts are the result of a reduction in bone marrow stimulation initiated by signals generated in the lung. To more accurately quantify the bone marrow response to lung inflammation, one group has developed a method to label precursor cells in the marrow with the thymidine analogue 5'bromo-2-deoxyuridine (BrdU) [60-62], allowing accurate identification of newly released leukocytes from the bone marrow and simplifying functional studies. Using this method they demonstrated that acute lung inflammation caused by a focal infection [61], as well as chronic lung inflammation induced by either cigarette smoke or urban air pollutants [27, 42, 63, 64], stimulate the bone marrow and accelerates the transit times of granulocytes and monocytes through the marrow, releasing them into the circulating pool of leukocytes. The ability to follow these labeled cells in the circulation allowed study of cell behavior and functional capability whereby this group was able to show preferential sequestration of younger PMNs in the gravity independent lung regions of animals exposed to cigarette smoke [63] and less efficient migration into inflammatory sites, compared to more mature cells [65, 66]. *In vitro* studies support these findings, showing that younger PMNs released from the bone marrow are less deformable and less chemotactic than mature PMNs already in the circulation [67].

Collectively, these studies have established that the circulating blood contains granulocytes such as neutrophils of varying ages and functional capabilities and that lung inflammation-

induced bone marrow stimulation increases the population of younger PMN with a greater potential to damage tissue (Figure 5). This knowledge may be relevant to the pathogenesis of acute lung inflammation-induced adverse organ dysfunction in conditions such as sepsis, or the systemic adverse effects associated with chronic inflammatory lung conditions such as COPD. The immature leukocytes also tend to preferentially sequester in lung capillaries [65, 67] where they may further damage the lung and fuel lung inflammation, causing a vicious cycle of lung inflammation leading to systemic inflammation that feeds back, resulting in further lung inflammation (Figure 5). It is possible that the bone marrow stimulation associated with both acute and chronic inflammatory lung conditions contributes to the development of acute lung injury such as in ARDS as well as chronic lung injury promoting centrilobular emphysema in susceptible subjects.
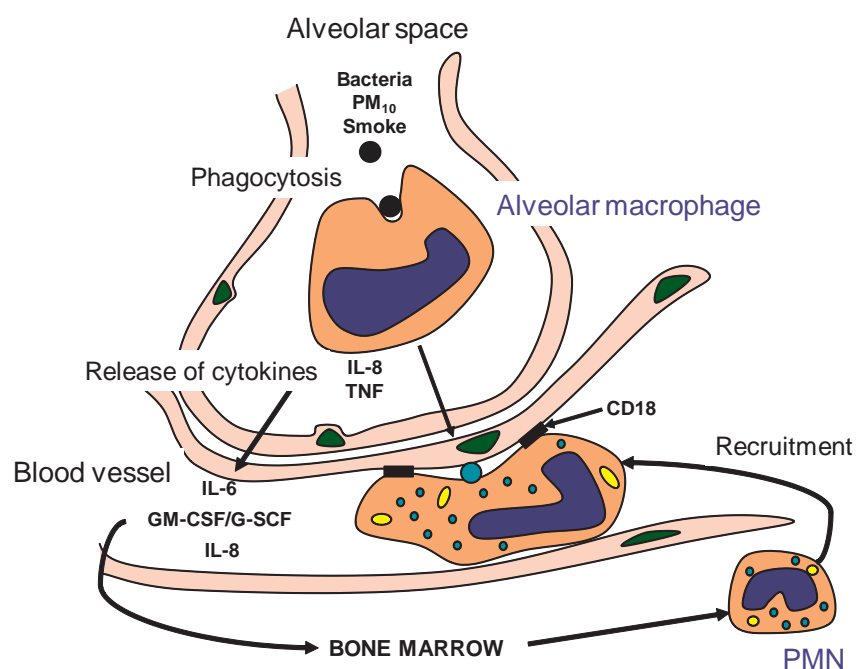


**Figure 5.** Lung injury induced by immature PMNs. Alveolar macrophages and epithelial cells phagocytose bacteria, particulate matter or cigarette smoke and induce cytokine production. These cytokines spill over into the circulation and stimulate the bone marrow to recruit leukocytes. The newly recruited immature PMNs tend to preferentially sequester in lung capillaries where they may be activated and degranulate, further damaging the lung. Lung damage leads to excess cytokine production which further fuels the systemic inflammation.

## 4.2. Non-cellular components of systemic response to lung inflammation

Common to nearly all inflammatory lung conditions are the production and release of mediators of the innate immune response. These circulating mediators, specifically the "acute response" cytokines IL-1$\beta$, IL-6 and TNF-$\alpha$, activate the acute-phase response [68], by stimulating the liver to produce acute phase proteins, such as fibrinogen, that increases blood coagulability, which is a major risk factor for acute cardiovascular events in susceptible individuals [69]. Another acute-phase protein, CRP, is strongly associated with

inflammation in general but, in epidemiological studies, has also been correlated with the extent of atherosclerosis and heart disease [29, 70]. C-reactive protein has become the hallmark biomarker indicative of the extent and severity of cardiovascular disease [71-73] as well as many other systemic inflammatory conditions, for example auto-immune collagen vascular diseases such as rheumatoid arthritis and lupus erythematosus. The acute response is a specific, well-orchestrated sequence of events, characterized by an early release of the "alarm" cytokines IL-1$\beta$ and TNF-$\alpha$, followed by a second wave of cytokines (IL-8, IL-6, monocyte chemotactic protein [MCP]-1 and MIP-1$\alpha$ ) and growth factors such as GM-CSF and G-CSF. The second wave of cytokines produced in the lung is of particular importance in inducing the systemic inflammatory response. Granulocyte macrophage colony-stimulating factor is a hematopoietic growth factor that stimulates granulocyte and monocyte differentiation and release from the bone marrow, activates circulating leuko-cytes such as neutrophils and prolongs leukocyte survival in the circulation and tissues [74]. In addition, GM-CSF has also recently been identified as an important granulocyte deganulation factor that may enhance tissue damage induced by granulocytes [75]. One of the "acute response" cytokines that induces cytokine production by many cells is IL-1$\beta$, which is known to stimulate hematopoiesis, activate endothelial cells, induce the acute-phase response and is pyrogenic [76]. Similarly, IL-6 stimulates hepatocytes to produce acute phase proteins, including CRP, fibrinogen and antiproteases [77], stimulates hemato-poiesis, specifically the production of platelets and has a broad stimulating effect on B- and T-cells. In addition, IL-6 activates the bone marrow, accelerates the transit time of granulo-cytes through the bone marrow promotes their release into the circulation and increases their sequestration in microvascular beds [78]. All the acute-phase response cytokines are proinflammatory in nature and suppress the production of anti-inflammatory cytokines such as IL-10, in fact, low circulating levels of this cytokine have been associated with a poor outcome in sepsis [79, 80]. Collectively, the acute response cytokines have the ability to elicit a systemic inflammatory response in response to lung inflammation that is characterized by an increase in circulating leukocytes, platelets and pro-inflammatory and prothrombotic mediators. In addition, cytokines also have the ability to activate circulat-ing leukocytes and platelets, as well as vascular endothelium, to promote leukocyte–endothelial adhesion and migration into tissues.

Part of the lung injury or initial stress insult in the lung is the formation and release of microparticles (MP), which are small vesicles (0.1–1 mm in diameter) containing cell membrane, that are released by a variety of cells types following either activation or an insult such as oxidative stress [81]. Platelets, endothelial cells, leukocytes, erythrocytes and tumor cells are cell types prone to MP shedding. Microparticles are composed of cell membranes, with receptors, enclosing cytosolic components, including enzymes, transcrip-tion factors, mRNA and microRNA, all derived from the parent cell. Microparticles contain signaling elements that may activate receptors on target cells and may also bind to target cells and transfer part of their contents [82]. Moreover, because MPs circulate, they not only act on their local environment but also on sites far from their origin, thereby serving as a cell-to-cell communication network. Microparticles are known to affect inflammation, coagulation, endothelial function, cell survival, and intercellular communication [81].

Moreover, they have been documented at sites of inflammation [83, 84] and increased numbers of circulating MPs have been reported in systemic diseases such as autoimmune collagen vascular disorders, atherosclerosis, hypercoagulability states, disseminating malignancies and infection, among others [85, 86]. Circulating endothelial MPs are associated with activated, damaged or stressed endothelial cells and are biomarkers of vascular injury. Microparticles may also remotely induce endothelial dysfunction by altering the intracellular production of vasorelaxing molecules such as nitric oxide and contributing to the recruitment of leukocytes at the remote site [81, 87, 88]. Recently, MPs have been shown to increase during inflammatory lung conditions such as COPD [89] and increase further during acute COPD exacerbations [90]. Furthermore, subjects with autoimmune collagen vascular disorders with lung involvement have increased levels of circulating endothelial MPs [91], suggesting that MPs are not just useful biomarkers of lung inflammation, but may play a critically important role in the pathogenesis of the downstream adverse effects that lung inflammation appears to have on distant organs.

## 5. Mechanisms of lung inflammation-induced systemic inflammation

Several mechanisms have been postulated to explain the association of lung inflammation with the systemic inflammatory response (Figure 6). The hypothesis with the most supporting experimental evidence postulates that inflammatory mediators generated in lung tissue translocate into the circulation. As the lung receives substantial cardiac output, it is reasonable to suppose that small molecules may translocate from lung tissue to the blood stream, following a natural gradient, a process that may be augmented by increases in capillary permeability which often accompanies the lung inflammatory process. It has been suggested that a gradient of the acute proinflammatory mediator, elastase, and its natural inhibitor, $\alpha$1-anti-trypsin, forms across the lung during acute neutrophilic lung inflammation [92] and "spills over" into the systemic circulation. Recent studies from another group has confirmed these findings in experimental models of acute (lipopolysaccharides [LPS]-induced) and chronic (air pollution-induced) lung inflammation [93, 94], supporting the hypothesis that the lung *per se* contribute directly to the systemic inflammatory response associated with lung inflammation.

There is also some evidence indicating that triggers of lung inflammation, such as ultrafine particulate matter, LPS and other bacterial toxins, translocate from the airspaces to the bloodstream [84, 95-97], either directly contributing to the systemic response or stimulating circulating immune cells such as monocytes to produce proinflammatory mediators that contribute to the systemic response. Collectively, there is ample evidence that small molecules or particles have the ability to directly translocate from the lung into the blood stream, generating a systemic inflammatory response. This is a particularly important mechanism if vascular permeability is compromised during the lung inflammatory response because it will accelerate the systemic inflammatory response caused by lung inflammation.
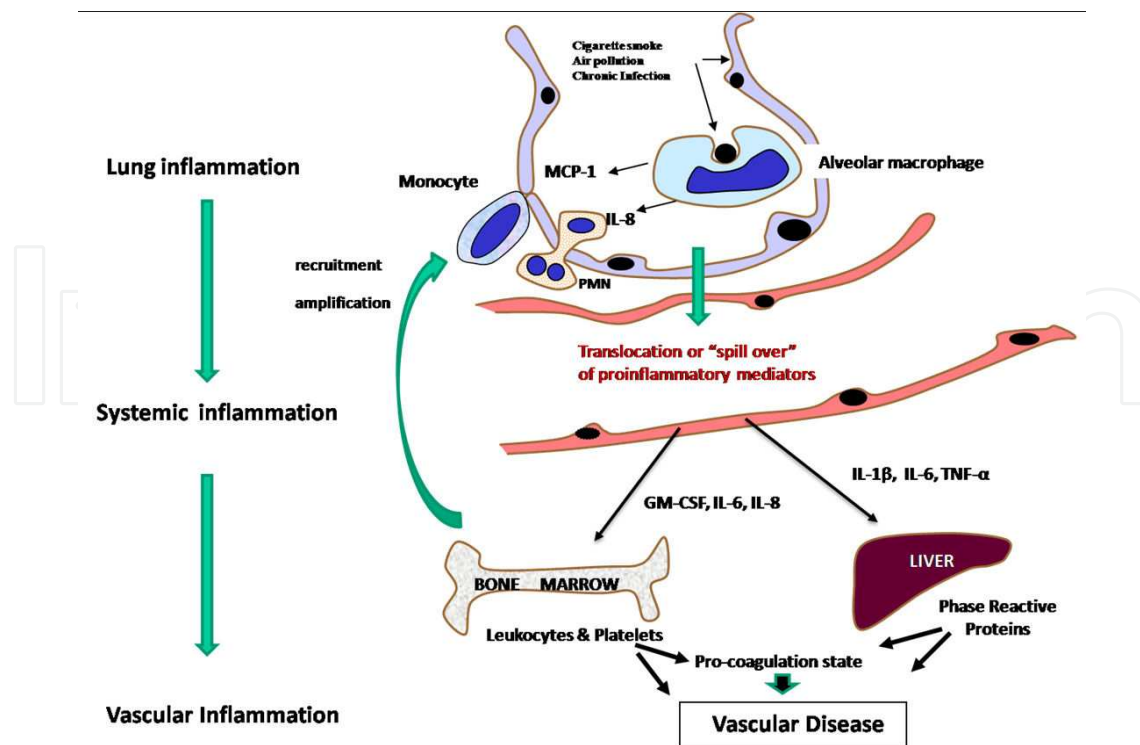
**Figure 6.** Impact of pulmonary inflammation on distant organ systems. Inflammatory mediators generated in the lung "spill over" into the circulation, activating the liver to release acute-phase proteins and the bone marrow to release leukocytes and platelets. Together, these circulating effector proteins and cells promote vascular disease and may precipitate acute vascular events. Systemic inflammation also enhances lung inflammation by promoting the recruitment of immune cells into lung tissues.

## 5.1. Feedback of downstream effects of the systemic response to acute lung inflammation

Bacterial or viral lung infections are common causes of acute lung inflammation that lead to ALI/ARDS [1]. During the past decade, novel and highly virulent respiratory viruses such as the Severe Acute Respiratory Syndrome Coronavirus (SARS CoV) and highly pathogenic strains of influenza viruses have emerged as important causes of excessive lung damage in infected humans. Acute lung injury and associated inflammation frequently have systemic manifestations, coined the "systemic inflammatory response syndrome (SIRS)". Many patients with refractory ALI/ARDS succumb to multiple organ failure (MOF) rather than respiratory failure, underlining the importance of the systemic response to lung injury. Many studies have been undertaken to investigate the cellular or molecular mechanisms of acute lung injury-induced systemic manifestations [1, 2, 15]. The deterioration from ALI/ARDS to MOF involves many steps, including the activation of multiple inflammatory pathways, increased expression of chemoattractants which results in endothelial changes and the release of proinflammatory cytokines such as IL-1$\beta$, IL-6 and TNF-$\alpha$, margination and migration of neutrophils as well as systemic activation of monocytes, all contributing to diffuse microvascular injury which is thought to lead to multi-organ injury and eventual failure [98]. Currently it is thought that the pivotal injury occurs to the vascular endothelium, leading to increased vascular permeability, which is then followed by translocation of inflammatory mediators and activated leukocytes into organ tissue resulting in organ inflammation and, finally, dysfunction. Organs particular

vulnerable to microvascular dysfunction are the kidney, liver, brain and the gastrointestinal system. Containing the lung inflammatory response is critically important in order to inhibit progression to a systemic inflammatory response fueled by the vicious cycle of increased cytokine production and cellular damage, underlining the importance of lung inflammation as the primary "driver" for the downstream multiple organ dysfunction.

## 5.2. Chronic lung inflammation and vascular dysfunction

Circulating cytokines produced in the lung activate the vascular endothelium and this activation is associated with increased expression of several adhesion proteins such as ICAM-1, VCAM-1 and E-selectin. Both soluble ICAM-1 and VCAM-1 are upregulated in circulating blood during chronic inflammation and are correlated with increased disease in coronary and carotid arteries in humans. Support of these observations comes from animal models that have shown instillation of atmospheric particles into the lungs of rabbits [99] and mice [100] results in development of atherosclerosis, followed by rapid progression of the atherosclerotic process over the surface of the aorta with concomitant destabilization of existing atherosclerotic plaques (Figure 7). Furthermore, particulate deposition in murine lungs is associated with upregulation of both ICAM-1 and VCAM-1 on the endothelium overlying the atherosclerotic plaques [101]. In addition, the number of particle-phagocytosing alveolar macrophages shows a strong positive association with the extent of atherosclerosis (Figure 8), as well as with markers of systemic inflammation such as CRP [102]. These studies demonstrate that lung inflammation stimulates alveolar macrophages, increases circulating markers of inflammation, increases endothelial activation and dysfunction and suggests a cause and effect relationship between lung inflammation and the development and progression of vascular diseases such as atherosclerosis.
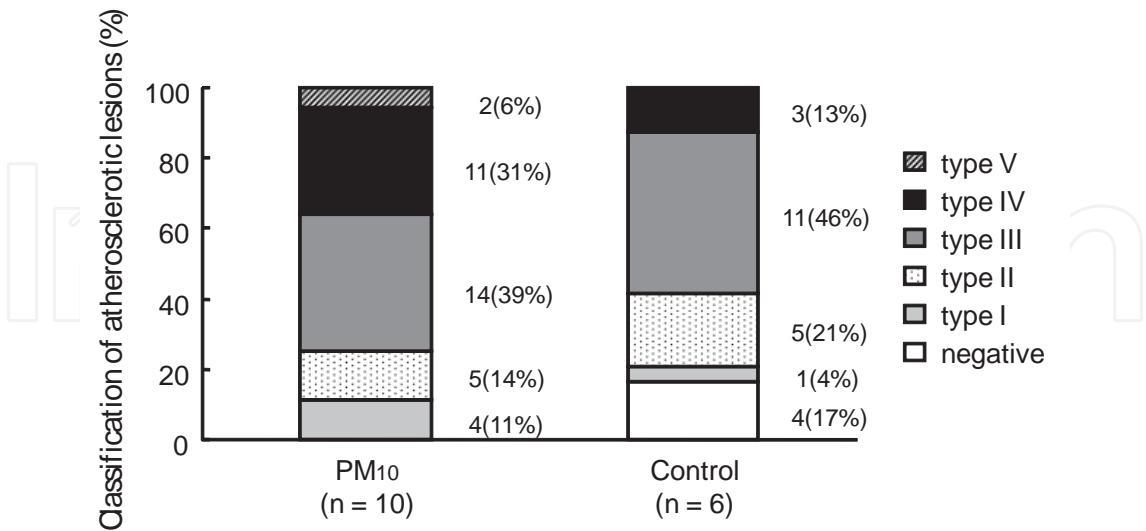


**Figure 7.** The severity of atherosclerotic lesions in the aorta. Results shown in rabbits exposed to $PM_{10}$ for four weeks (n = 10) or saline (controls; n = 6). The classification is based on the guidelines of the American Heart Association (AHA) [163, 164]. $PM_{10}$ exposure was associated with progression to more advanced phenotypes of atherosclerosis compared with the control group.

$$Y = 11.0 + 0.29\,X,\ r = 0.53,\ p < 0.05$$
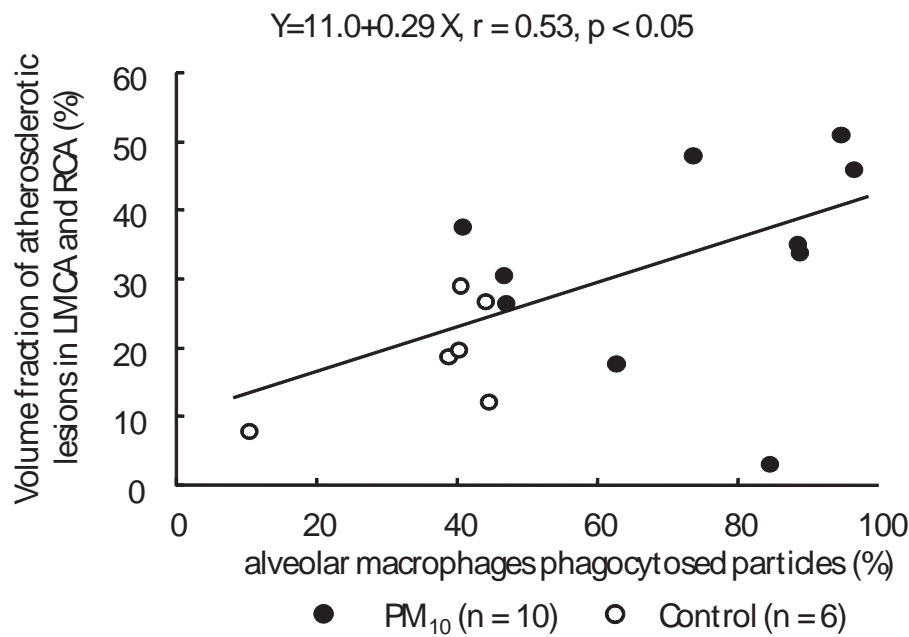
**Figure 8.** The correlation between the percentage of alveolar macrophages that phagocytosed particles in the lung and the vol/vol (volume fraction) of atherosclerotic lesions in the left main coronary artery (LMCA) and right coronary artery (RCA). Results shown in rabbits exposed to $PM_{10}$ for four weeks (solid circles; n = 10) or saline (controls; open circles; n = 6). The volume fraction (vol/vol) of atherosclerosis was determined by point counting the sections. The correlation between variables were examined by the Spearman rank correlation test (r = 0.53, p < 0.05) [99].

### 5.3. Systemic inflammation in COPD

Numerous studies have established that COPD is associated with a low-grade systemic inflammatory response, which has been implicated in the pathogenesis of the majority of the systemic effects associated with COPD, including muscle weakness, weight loss, cardiovascular disease, depression, diabetes and osteoporosis [103]. Patients with stable COPD have increased numbers of circulating leukocytes, increased levels of acute phase response proteins (CRP and fibrinogen) and increased cytokine levels (IL-6 and TNF-$\alpha$) [104] that increase further with acute exacerbations [105, 106].

Chronic obstructive pulmonary disease is a chronic inflammatory condition of the airways and lung parenchyma caused predominantly by the inhalation of toxic particles and noxious gasses, with cigarette smoking contributing to the bulk of the disease burden. There is a strong association between cardiovascular disease and COPD morbidity and mortality. Cardiovascular events are the predominant reason for hospitalizations (morbidity) and a leading cause of mortality in subjects with mild and moderate COPD [107]. Furthermore, epidemiological studies have shown that compromised lung function (FEV1) in subjects with COPD is associated with cardiovascular morbidity and mortality, even after controlling for smoking history [107], suggesting that the inflammatory response in the lung which causes the reduced lung function also impacts the vasculature. The mechanisms of COPD-induced cardiovascular disease are still unclear, however, animals models of cigarette exposure or exposure to ambient particulate matter suggest that the systemic response induced by these inhalation stimuli causes vascular dysfunction that may promote the development and progression of athero-

sclerotic vascular disease [99-102]. Activation of coronary vasculature by the systemic response to COPD lung inflammation also impacts other vascular beds such as the cerebral vascular bed. Circulating inflammatory mediators such as IL-1β, IL-6, TNF-$\alpha$, $\alpha$1-antichymotrypsin and TNFR1 are associated with cognitive decline, either through a direct neurotoxic effect or through cerebral atherosclerosis effects [108, 109]. Figure 9 highlights potential pathways of blood vessel activation due to systemic inflammation in COPD that results in endothelial dysfunction and destabilization of atherosclerotic plaques, possibly leading to vascular events such as acute coronary syndrome and stroke.
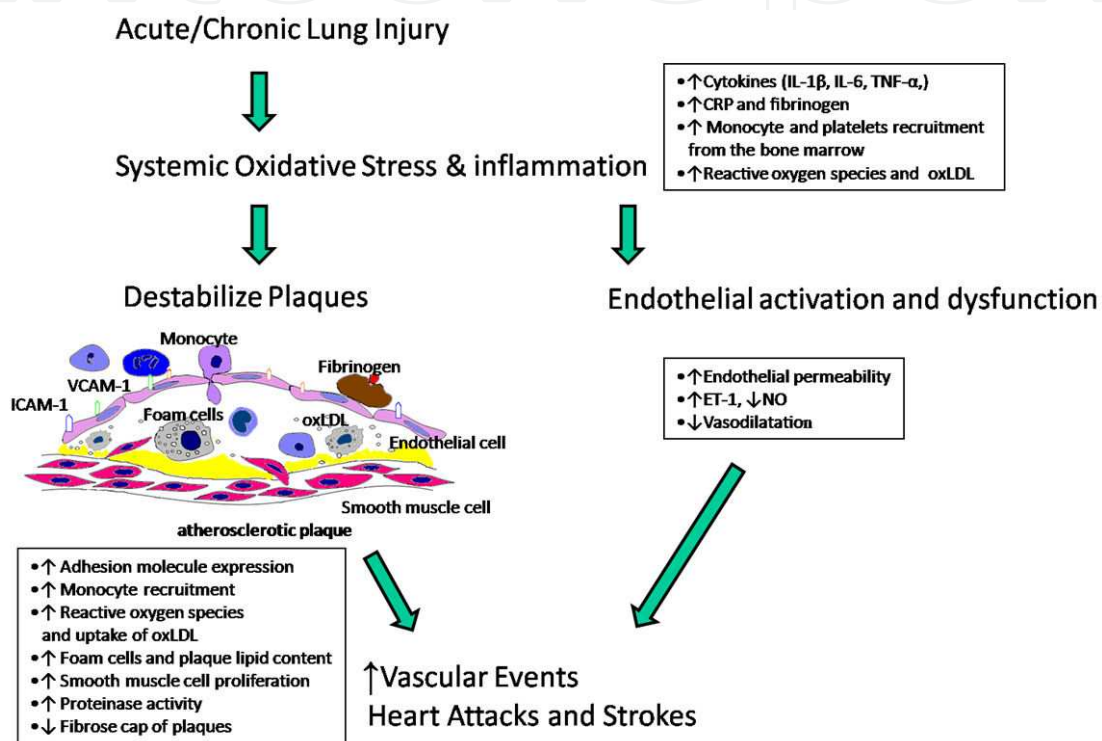


**Figure 9.** Impact of lung injury on blood vessels. Circulating mediators such as IL-6 induce the release of CRP and fibrinogen from the liver. In addition, IL-6 and GM-CSF stimulate the bone marrow to release leukocytes and platelets, while TNF-α and IL-1β activate vascular endothelial cells and upregulate endothelial ICAM-1 and VCAM-1, thereby promoting the recruitment of monocytes into blood vessel walls. Activation of endothelial cells also increases endothelial permeability, promotes uptake of oxidized low-density lipoproteins (oxLDL) into vessel walls, promotes the release of endothelin-1 (ET-1) and decreases availability of nitric oxide (NO). Together, these changes in blood vessel walls lead to endothelial dysfunction and promote vulnerability of atherosclerotic plaques to rupture, possibly leading to acute cardiac events or strokes.

Cachexia and muscle wasting are hallmarks of COPD, especially in subjects with severe disease and, currently, the mechanisms underlying these downstream effects of COPD are a topic of active investigation. In COPD subjects, skeletal muscle shows increased apoptosis, increased oxidative stress and increased inflammatory cell infiltration [110, 111], suggesting that inflammatory processes play a role in the physiologic changes seen in skeletal muscles of COPD subjects. Furthermore, the underlying inflammatory and oxidative processes in the lungs, in addition to the downstream proinflammatory systemic responses, shifts the hormo-

nal balance towards catabolism, reducing testosterone levels and increasing catecholamine synthesis, especially in the severe stages of the disease (FEV1<30%) [112]. It is reasonable to postulate that the systemic inflammatory response associated with COPD lung inflammation contributes to the skeletal muscle inflammation and concomitant muscle wasting seen in COPD.

Both diabetes mellitus type2 and osteoporosis are associated with COPD, especially in subjects with greater disease severity [113-115]. The mechanisms underlying the former two diseases are complex but a postulated mechanisms linking them with COPD is the presence of elevated circulating levels of proinflammatory mediators such as IL-1$\beta$, IL-6 and TNF-$\alpha$. Therefore it seems reasonable to postulate that the systemic response in COPD may either aggravate or enhance the development of osteoporosis and diabetes, to a certain extent.

### 5.4. Systemic inflammation in other inflammatory lung conditions

Asthma is predominantly an inflammatory condition of the airways, however a systemic inflammatory response has also been well documented, evidenced by an increase in circulating proinflammatory cytokines such as IL-6 and TNF-$\alpha$ that stimulate hepatic production of acute-phase proteins such as CRP, as well as an increase in immune cells such as neutrophils and eosinophils [4, 116]. Circulating TNF-$\alpha$ and IL-6 levels are further elevated during asthma exacerbation [117, 118]. Downstream consequences of this systemic response are less well studied and are insufficiently understood, therefore require further investigation. Similarly, interstitial lung disease and fibrosis are a large group of inflammatory lung conditions that include chronic hypersensitivity pneumonitis, sarcoidosis, drug-induced lung disease, lung disease associated with collagen vascular disease, idiopathic pulmonary fibrosis (IPF) and more. Many of these lung conditions are associated with increased circulating levels of pro-inflammatory mediators such as IL-1$\beta$, IL-6, TNF-$\alpha$, TGF-$\beta$ and platelet-derived growth factor (PDGF) [119, 120]. In conditions that exclusively involve the lung such as hypersensitivity pneumonitis and IPF, translocation of these mediators from the lung into the circulation may be responsible for the measured systemic response, however the effect of these mediators on other organ systems are unclear and require further study.

### 5.5. Effect of the systemic inflammatory response on lung inflammation

It is well known that non-pulmonary disorders (for example sepsis, trauma, massive transfusion, drug overdose, pancreatitis) cause lung injury and inflammation. "Crosstalk" between lungs and distal organs is an emerging, interesting and clinically relevant field [121, 122]. A complex network of cytokines, as well as proinflammatory chemokines such as CXCL1, from distant organs can initiate and amplify the lung injury [123, 124]. Many of the mediators involved in the systemic response have the ability to both damage lungs directly and stimulate the bone marrow to release leukocytes into the circulation. In addition, leukocytes that may have been sequestered in the lung could be released, potentially causing additional lung injury [125, 126]. These newly released leukocytes, specifically granulocytes such as neutrophils, have been shown to be preferentially sequestered in the pulmonary capillary bed where, if activated, they may contribute to further lung injury and damage [65, 66].

Patients afflicted with lung injury more commonly than not encounter more than 'one-hit' modulating the immunological response to injury by increasing duration and amplitude of the inflammatory response [127]. In animal models, the traditional "single-hit" model is no longer considered a good approximation of human ALI/ARDS, whereas a "two-hit" model has been shown to increase the inflammatory response in the lung [127-130]. This "priming" phenomenon may be pivotal in subjects with chronic lung inflammation, such as COPD, where the systemic inflammatory response induced by the chronic lung inflammation may feed-back, aggravating the lung inflammatory response. This vicious cycle of inflammation promoting further inflammation may be the reason why subjects with COPD still have active lung inflammation many years after they have stopped smoking [131]. This phenomenon is also seen in patients with asthma, where, even years after cessation of exposure, patients with Western red cedar-initiated asthma have persistent airflow obstruction [132]. In this study, higher impairment was associated with serum IFN-$\gamma$ (Figure 10), which supports the hypothesis of a vicious cycle of inflammation with crosstalk between the lung and systemic inflammatory responses.
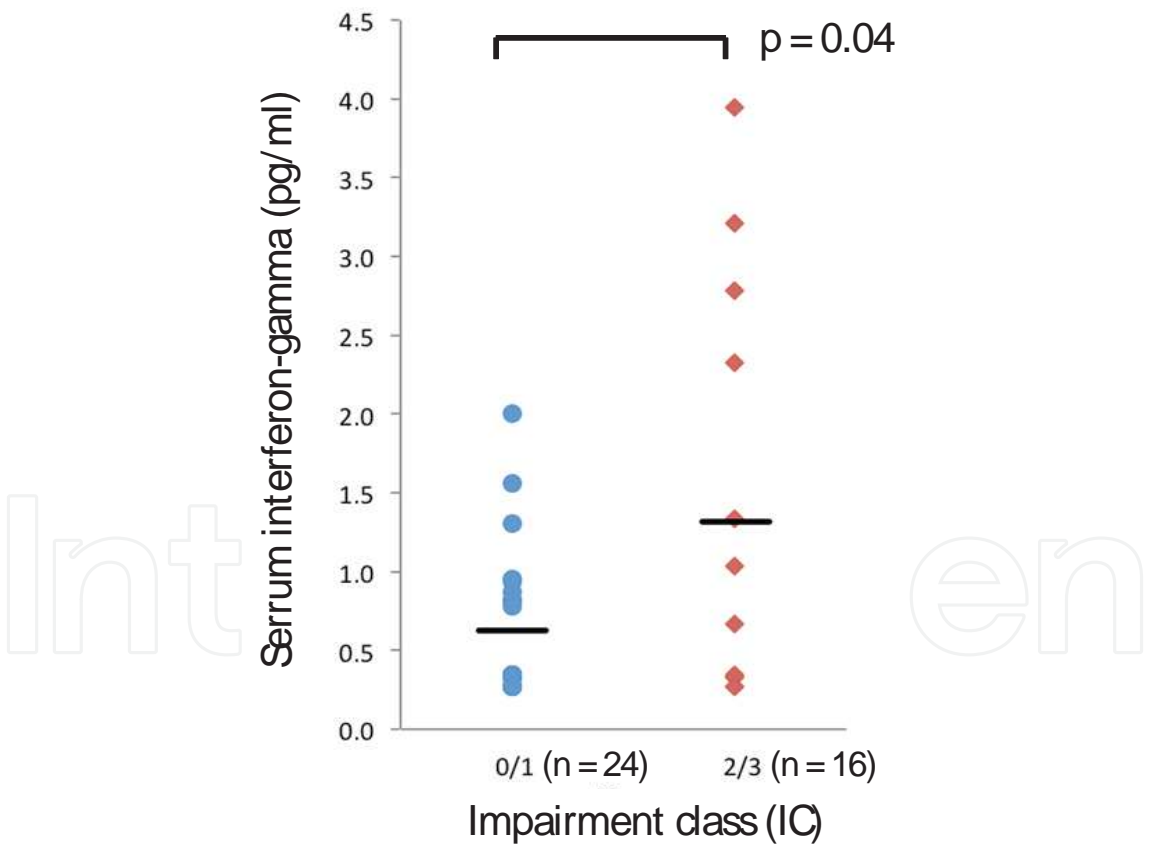


**Figure 10.** Serum interferon-gamma, stratified by higher (2/3) versus lower (0/1) respiratory impairment (IC = impairment class). The blood samples were collected from 40 non-smoking male at a mean interval of 25 years from cedar asthma diagnosis and 17 years from last cedar exposure. The respiratory impairment class was defined by ATS guidelines [165]. Asthma-related respiratory impairment was associated with higher interferon-gamma levels in serum (average 1.32 pg/ml for IC2/3 versus average 0.62 pg/ml for IC0/1; p = 0.04) [132].

## 6. Therapeutic alterations of lung inflammation-induced systemic responses

The mediators of systemic responses to lung inflammation are clinically useful tools with which to grade the severity of lung inflammation or to use as biomarkers for following the progression of the disease. Neutralization of these mediators using effector molecules termed "immunoresolvents" may prove useful in attenuating the downstream consequences of the systemic inflammatory response. Potential advantages of immunoresolvents lie in the possibilities of both attenuating leukocyte activation and decreasing recruitment into tissues, thereby reducing organ damage. However, in a study with more than 10,000 patients with sepsis, anti-inflammatory agents designed to inhibit specific host mediators, for example anti-TNF antibodies and IL-1 receptor antagonists, failed to show benefit, despite promising preclinical testing [133]. Similarly, another multicenter, randomized, double-blind study in patients with moderate to severe COPD showed that infliximab (anti-TNF-$\alpha$ monoclonal antibody) had no therapeutic benefit in reducing acute exacerbation of COPD [134]. Although many proinflammatory neutralizing therapies have the potential to be useful, they also evoke some unwanted effects, for example, TNF-specific antibody therapy reduces TNF-$\alpha$ concentrations but is also associated with increased susceptibility to infections and malignancies [134]. Clearly, immunosuppression is a critical drawback to some treatments and new therapeutics targeting resolution of inflammation would be required to circumvent this side effect.

The anti-inflammatory cytokine IL-10 balances the proinflammatory response and serves to limit and terminate the cascade of proinflammatory cytokines. Research shows that treatment with IL-10 reduces neutrophil and leukocyte recruitment and decreases proinflammatory cytokine-production in lung inflammation [135-138], underlining the importance of balancing the acute inflammatory response and suggesting that treatment using a combination of different therapeutic agents to alter outcome in the systemic inflammatory milieu may be more successful.

Recently several classes of pro-resolving mediators have been identified, including resolvins, protectins and maresins [139]. These specialized lipid mediators are derived via enzymatic processing from dietary omega-3 polyunsaturated fatty acids and have anti-inflammatory activity in lung inflammation [140, 141].

Originally designed to lower cholesterol, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase class of drugs, also called "statins", are recognized as anti-inflammatory agents [142]. Experimental observations suggest that these agents have pleiotropic anti-inflammatory properties *in vitro* including the inhibition of isoprenoid synthesis, which leads to the inhibition of small proinflammatory signaling GTPases such as Rho, Rac and Cdc42 [143, 144]. Animal studies have demonstrated that statins attenuate lung injury in ischemia-reperfusion, peritonitis and aerosolized LPS models [145-147]. In addition, statins downregulate the $PM_{10}$-induced overactive bone marrow by attenuating systemic inflammatory responses such as the recruitment and activation of alveolar macrophages and polymorphonuclear leukocytes, as well as reducing local proinflammatory cytokine production and promoting the clearance of $PM_{10}$ particles from lung tissues to regional lymph nodes [148, 149].

Several observational studies suggest that statins may represent a useful therapeutic adjunctive modality for ALI/ARDS: a benefit of prior statin use was found in patients with pneumonia [150-152]. Similarly, other studies showed a reduction in the frequency of COPD exacerbations, hospitalization, and mortality after statin therapy, which may be a result of a direct effect on lung inflammation, an impact on the systemic consequences of COPD, or both [153-161]. These studies indicate that statins are effective in decreasing lung and systemic inflammation in humans *in vivo*.

## 7. Conclusion

A systemic response is a hallmark of both acute and chronic lung inflammatory conditions. The nature and magnitude of this systemic response differs depending on the nature and magnitude of the inflammatory response in the lung. Mediators generated in the lung as part of the lung inflammatory response, translocate to the systemic circulation, contributing to the systemic response. This systemic response has significant downstream adverse consequences on distant organs suggesting it is as an important therapeutic target. Therapeutic tools to modify and alter the systemic response induced by lung conditions, are still lacking and need further study.

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## References

[1]  Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med. 2000 May 4;342(18):1334-49.

[2]  Matthay MA, Zimmerman GA. Acute lung injury and the acute respiratory distress syndrome: four decades of inquiry into pathogenesis and rational management. Am J Respir Cell Mol Biol. 2005 Oct;33(4):319-27.

[3]  Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, et al. Incidence and outcomes of acute lung injury. N Engl J Med. 2005 Oct 20;353(16):1685-93.

[4]  Girdhar A, Kumar V, Singh A, Menon B, Vijayan VK. Systemic inflammation and its response to treatment in patients with asthma. Respir Care. 2011 Jun;56(6):800-5.

[5]  Jousilahti P, Salomaa V, Hakala K, Rasi V, Vahtera E, Palosuo T. The association of sensitive systemic inflammation markers with bronchial asthma. Ann Allergy Asthma Immunol. 2002 Oct;89(4):381-5.

[6]  Olafsdottir IS, Gislason T, Thjodleifsson B, Olafsson I, Gislason D, Jogi R, et al. C reactive protein levels are increased in non-allergic but not allergic asthma: a multicentre epidemiological study. Thorax. 2005 Jun;60(6):451-4.

[7]  Takemura M, Matsumoto H, Niimi A, Ueda T, Matsuoka H, Yamaguchi M, et al. High sensitivity C-reactive protein in asthma. Eur Respir J. 2006 May;27(5):908-12.

[8]  Wilson CB, Jones PW, O'Leary CJ, Hansell DM, Dowling RB, Cole PJ, et al. Systemic markers of inflammation in stable bronchiectasis. Eur Respir J. 1998 Oct;12(4):820-4.

[9]  Martinez-Garcia MA, Perpina-Tordera M, Roman-Sanchez P, Soler-Cataluna JJ, Carratala A, Yago M, et al. [The association between bronchiectasis, systemic inflammation, and tumor necrosis factor alpha]. Arch Bronconeumol. 2008 Jan;44(1):8-14.

[10]  Weinrib L, Sharma OP, Quismorio FP, Jr. A long-term study of interstitial lung disease in systemic lupus erythematosus. Semin Arthritis Rheum. 1990 Aug;20(1):48-56.

[11]  Hamblin MJ, Horton MR. Rheumatoid arthritis-associated interstitial lung disease: diagnostic dilemma. Pulm Med. 2011;2011:872120.

[12]  Fischer A, du Bois R. Interstitial lung disease in connective tissue disorders. Lancet. 2012 Aug 18;380(9842):689-98.

[13]  Solomon JJ, Olson AL, Fischer A, Bull T, Brown KK, Raghu G. Scleroderma lung disease. Eur Respir Rev. 2013 Mar 1;22(127):6-19.

[14]  Castelino FV, Varga J. Interstitial lung disease in connective tissue diseases: evolving concepts of pathogenesis and management. Arthritis Res Ther. 2010;12(4):213.

[15]  Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. J Clin Invest. 2012 Aug 1;122(8):2731-40.

[16]  Fry DE. Sepsis syndrome. Am Surg. 2000 Feb;66(2):126-32.

[17]  Klune JR, Tsung A. Molecular biology of liver ischemia/reperfusion injury: established mechanisms and recent advancements. Surg Clin North Am. 2010 Aug;90(4):665-77.

[18] American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med. 1992 Jun;20(6):864-74.

[19] Goris RJ, te Boekhorst TP, Nuytinck JK, Gimbrere JS. Multiple-organ failure. Generalized autodestructive inflammation? Arch Surg. 1985 Oct;120(10):1109-15.

[20] Opitz B, van Laak V, Eitel J, Suttorp N. Innate immune recognition in infectious and noninfectious diseases of the lung. Am J Respir Crit Care Med. 2010 Jun 15;181(12): 1294-309.

[21] Windsor AC, Walsh CJ, Mullen PG, Cook DJ, Fisher BJ, Blocher CR, et al. Tumor necrosis factor-alpha blockade prevents neutrophil CD18 receptor upregulation and attenuates acute lung injury in porcine sepsis without inhibition of neutrophil oxygen radical generation. J Clin Invest. 1993 Apr;91(4):1459-68.

[22] Friedman GD, Klatsky AL, Siegelaub AB. The leukocyte count as a predictor of myocardial infarction. N Engl J Med. 1974 Jun 6;290(23):1275-8.

[23] Grimm RH, Jr., Neaton JD, Ludwig W. Prognostic importance of the white blood cell count for coronary, cancer, and all-cause mortality. JAMA. 1985 Oct 11;254(14): 1932-7.

[24] Weiss ST, Segal MR, Sparrow D, Wager C. Relation of FEV1 and peripheral blood leukocyte count to total mortality. The Normative Aging Study. Am J Epidemiol. 1995 Sep 1;142(5):493-8; discussion 9-503.

[25] Corre F, Lellouch J, Schwartz D. Smoking and leucocyte-counts. Results of an epidemiological survey. Lancet. 1971 Sep 18;2(7725):632-4.

[26] Chan-Yeung M, Abboud R, Buncio AD, Vedal S. Peripheral leucocyte count and longitudinal decline in lung function. Thorax. 1988 Jun;43(6):462-6.

[27] van Eeden SF, Hogg JC. The response of human bone marrow to chronic cigarette smoking. Eur Respir J. 2000 May;15(5):915-21.

[28] Terashima T, Wiggs B, English D, Hogg JC, van Eeden SF. The effect of cigarette smoking on the bone marrow. Am J Respir Crit Care Med. 1997 Mar;155(3):1021-6.

[29] Torres JL, Ridker PM. Clinical use of high sensitivity C-reactive protein for the prediction of adverse cardiovascular events. Curr Opin Cardiol. 2003 Nov;18(6):471-8.

[30] Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. Circulation. 2003 Mar 25;107(11):1514-9.

[31] Shaaban R, Kony S, Driss F, Leynaert B, Soussan D, Pin I, et al. Change in C-reactive protein levels and FEV1 decline: a longitudinal population-based study. Respir Med. 2006 Dec;100(12):2112-20.

[32] Pinto-Plata VM, Mullerova H, Toso JF, Feudjo-Tepie M, Soriano JB, Vessey RS, et al. C-reactive protein in patients with COPD, control smokers and non-smokers. Thorax. 2006 Jan;61(1):23-8.

[33] Sin DD, Lacy P, York E, Man SF. Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2004 Oct 1;170(7):760-5.

[34] Chung KF. Cytokines in chronic obstructive pulmonary disease. Eur Respir J Suppl. 2001 Dec;34:50s-9s.

[35] Eid AA, Ionescu AA, Nixon LS, Lewis-Jenkins V, Matthews SB, Griffiths TL, et al. Inflammatory response and body composition in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001 Oct 15;164(8 Pt 1):1414-8.

[36] Di Francia M, Barbier D, Mege JL, Orehek J. Tumor necrosis factor-alpha levels and weight loss in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1994 Nov;150(5 Pt 1):1453-5.

[37] Gustafsson A, Asman B, Bergstrom K. Cigarette smoking as an aggravating factor in inflammatory tissue-destructive diseases. Increase in tumor necrosis Factor-alpha priming of peripheral neutrophils measured as generation of oxygen radicals. Int J Clin Lab Res. 2000;30(4):187-90.

[38] Noguera A, Batle S, Miralles C, Iglesias J, Busquets X, MacNee W, et al. Enhanced neutrophil response in chronic obstructive pulmonary disease. Thorax. 2001 Jun; 56(6):432-7.

[39] de Godoy I, Donahoe M, Calhoun WJ, Mancino J, Rogers RM. Elevated TNF-alpha production by peripheral blood monocytes of weight-losing COPD patients. Am J Respir Crit Care Med. 1996 Feb;153(2):633-7.

[40] Schols AM, Buurman WA, Staal van den Brekel AJ, Dentener MA, Wouters EF. Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. Thorax. 1996 Aug;51(8):819-24.

[41] Dentener MA, Creutzberg EC, Schols AM, Mantovani A, van't Veer C, Buurman WA, et al. Systemic anti-inflammatory mediators in COPD: increase in soluble interleukin 1 receptor II during treatment of exacerbations. Thorax. 2001 Sep;56(9):721-6.

[42] Terashima T, Wiggs B, English D, Hogg JC, van Eeden SF. Phagocytosis of small carbon particles (PM10) by alveolar macrophages stimulates the release of polymorphonuclear leukocytes from bone marrow. Am J Respir Crit Care Med. 1997 Apr;155(4): 1441-7.

[43] Mukae H, Vincent R, Quinlan K, English D, Hards J, Hogg JC, et al. The effect of repeated exposure to particulate air pollution (PM10) on the bone marrow. Am J Respir Crit Care Med. 2001 Jan;163(1):201-9.

[44] Tan WC, Qiu D, Liam BL, Ng TP, Lee SH, van Eeden SF, et al. The human bone marrow response to acute air pollution caused by forest fires. Am J Respir Crit Care Med. 2000 Apr;161(4 Pt 1):1213-7.

[45] van Eeden SF, Tan WC, Suwa T, Mukae H, Terashima T, Fujii T, et al. Cytokines involved in the systemic inflammatory response induced by exposure to particulate matter air pollutants (PM(10)). Am J Respir Crit Care Med. 2001 Sep 1;164(5):826-30.

[46] Vincent R, Bjarnason SG, Adamson IY, Hedgecock C, Kumarathasan P, Guenette J, et al. Acute pulmonary toxicity of urban particulate matter and ozone. Am J Pathol. 1997 Dec;151(6):1563-70.

[47] Fujii T, Hayashi S, Hogg JC, Vincent R, Van Eeden SF. Particulate matter induces cytokine expression in human bronchial epithelial cells. Am J Respir Cell Mol Biol. 2001 Sep;25(3):265-71.

[48] Boland S, Baeza-Squiban A, Fournier T, Houcine O, Gendron MC, Chevrier M, et al. Diesel exhaust particles are taken up by human airway epithelial cells in vitro and alter cytokine production. Am J Physiol. 1999 Apr;276(4 Pt 1):L604-13.

[49] Hashimoto S, Gon Y, Matsumoto K, Takeshita I, Maruoka S, Horie T. Inhalant corticosteroids inhibit hyperosmolarity-induced, and cooling and rewarming-induced interleukin-8 and RANTES production by human bronchial epithelial cells. Am J Respir Crit Care Med. 2000 Sep;162(3 Pt 1):1075-80.

[50] Fujii T, Hayashi S, Hogg JC, Mukae H, Suwa T, Goto Y, et al. Interaction of alveolar macrophages and airway epithelial cells following exposure to particulate matter produces mediators that stimulate the bone marrow. Am J Respir Cell Mol Biol. 2002 Jul;27(1):34-41.

[51] Al Lawati N, Mulgrew A, Cheema R, vanEeden S, Butt A, Fleetham J, et al. Pro-atherogenic cytokine profile of patients with suspected obstructive sleep apnea. Sleep Breath. 2009 Nov;13(4):391-5.

[52] Bruno A, Alessi M, Soresi S, Bonanno A, Riccobono L, Montalbano AM, et al. Increased leptin/leptin receptor pathway affects systemic and airway inflammation in COPD former smokers. J Inflamm Res. 2011;4:51-9.

[53] Bijanzadeh M, Ramachandra NB, Mahesh PA, Savitha MR, Vijayakumar GS, Kumar P, et al. Soluble intercellular adhesion molecule-1 and E-selectin in patients with asthma exacerbation. Lung. 2009 Sep-Oct;187(5):315-20.

[54] Friedman J, Goldberg H, Horvath TB, Meares RA. The effect of tobacco smoking on evoked potentials. Clin Exp Pharmacol Physiol. 1974 May-Jun;1(3):249-58.

[55] Friedman J, Horvath T, Meares R. Tobacco smoking and a 'stimulus barrier'. Nature. 1974 Mar 29;248(447):455-6.

[56] van Eeden SF, Granton J, Hards JM, Moore B, Hogg JC. Expression of the cell adhesion molecules on leukocytes that demarginate during acute maximal exercise. J Appl Physiol. 1999 Mar;86(3):970-6.

[57] Terashima T, Amakawa K, Matsumaru A, van Eeden S, Hogg JC, Yamaguchi K. BAL induces an increase in peripheral blood neutrophils and cytokine levels in healthy volunteers and patients with pneumonia. Chest. 2001 Jun;119(6):1724-9.

[58] Muchmore HG, Blackburn AB, Shurley JT, Pierce CM, McKown BA. Neutropenia in healthy men at the South Polar Plateau. Arch Intern Med. 1970 Apr;125(4):646-8.

[59] Sakai M, Sato Y, Sato S, Ihara S, Onizuka M, Sakakibara Y, et al. Effect of relocating to areas of reduced atmospheric particulate matter levels on the human circulating leukocyte count. J Appl Physiol. 2004 Nov;97(5):1774-80.

[60] Bicknell S, van Eeden S, Hayashi S, Hards J, English D, Hogg JC. A non-radioisotopic method for tracing neutrophils in vivo using 5'-bromo-2'-deoxyuridine. Am J Respir Cell Mol Biol. 1994 Jan;10(1):16-23.

[61] Terashima T, Wiggs B, English D, Hogg JC, van Eeden SF. Polymorphonuclear leukocyte transit times in bone marrow during streptococcal pneumonia. Am J Physiol. 1996 Oct;271(4 Pt 1):L587-92.

[62] Goto Y, Hogg JC, Suwa T, Quinlan KB, van Eeden SF. A novel method to quantify the turnover and release of monocytes from the bone marrow using the thymidine analog 5'-bromo-2'-deoxyuridine. Am J Physiol Cell Physiol. 2003 Aug;285(2):C253-9.

[63] Terashima T, Klut ME, English D, Hards J, Hogg JC, van Eeden SF. Cigarette smoking causes sequestration of polymorphonuclear leukocytes released from the bone marrow in lung microvessels. Am J Respir Cell Mol Biol. 1999 Jan;20(1):171-7.

[64] Goto Y, Hogg JC, Shih CH, Ishii H, Vincent R, van Eeden SF. Exposure to ambient particles accelerates monocyte release from bone marrow in atherosclerotic rabbits. Am J Physiol Lung Cell Mol Physiol. 2004 Jul;287(1):L79-85.

[65] Lawrence E, Van Eeden S, English D, Hogg JC. Polymorphonuclear leukocyte (PMN) migration in streptococcal pneumonia: comparison of older PMN with those recently released from the marrow. Am J Respir Cell Mol Biol. 1996 Mar;14(3):217-24.

[66] van Eeden SF, Kitagawa Y, Sato Y, Hogg JC. Polymorphonuclear leukocytes released from the bone marrow and acute lung injury. Chest. 1999 Jul;116(1 Suppl):43S-6S.

[67] van Eeden SF, Lawrence E, Sato Y, Kitagawa Y, Hogg JC. Neutrophils released from the bone marrow by granulocyte colony-stimulating factor sequester in lung microvessels but are slow to migrate. Eur Respir J. 2000 Jun;15(6):1079-86.

[68] Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med. 1999 Feb 11;340(6):448-54.

[69] Heinrich J, Assmann G. Fibrinogen and cardiovascular risk. J Cardiovasc Risk. 1995 Jun;2(3):197-205.

[70] Haverkate F, Thompson SG, Pyke SD, Gallimore JR, Pepys MB. Production of C-reactive protein and risk of coronary events in stable and unstable angina. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. Lancet. 1997 Feb 15;349(9050):462-6.

[71] Tracy RP, Lemaitre RN, Psaty BM, Ives DG, Evans RW, Cushman M, et al. Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and the Rural Health Promotion Project. Arterioscler Thromb Vasc Biol. 1997 Jun;17(6):1121-7.

[72] Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med. 1997 Apr 3;336(14):973-9.

[73] Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. Circulation. 1998 Aug 25;98(8):731-3.

[74] Mire-Sluis A, Thorpe R. Quality considerations for recombinant DNA-derived biological therapeutic products: a control perspective on cytokines. BioDrugs. 1999 Jun; 11(6):367-76.

[75] Topham MK, Carveth HJ, McIntyre TM, Prescott SM, Zimmerman GA. Human endothelial cells regulate polymorphonuclear leukocyte degranulation. FASEB J. 1998 Jun;12(9):733-46.

[76] Mire-Sluis AR. Analytical characterisation of cytokines and growth factors. Dev Biol Stand. 1999;97:3-9.

[77] Mackiewicz A, Laciak M, Gorny A, Baumann H. Leukemia inhibitory factor, interferon gamma and dexamethasone regulate N-glycosylation of alpha 1-protease inhibitor in human hepatoma cells. Eur J Cell Biol. 1993 Apr;60(2):331-6.

[78] Suwa T, Hogg JC, Klut ME, Hards J, van Eeden SF. Interleukin-6 changes deformability of neutrophils and induces their sequestration in the lung. Am J Respir Crit Care Med. 2001 Mar;163(4):970-6.

[79] Schaaf BM, Boehmke F, Esnaashari H, Seitzer U, Kothe H, Maass M, et al. Pneumococcal septic shock is associated with the interleukin-10-1082 gene promoter polymorphism. Am J Respir Crit Care Med. 2003 Aug 15;168(4):476-80.

[80] Shu Q, Fang X, Chen Q, Stuber F. IL-10 polymorphism is associated with increased incidence of severe sepsis. Chin Med J (Engl). 2003 Nov;116(11):1756-9.

[81] Rautou PE, Vion AC, Amabile N, Chironi G, Simon A, Tedgui A, et al. Microparticles, vascular function, and atherothrombosis. Circ Res. 2011 Aug 19;109(5):593-606.

[82] Mause SF, Weber C. Microparticles: protagonists of a novel communication network for intercellular information exchange. Circ Res. 2010 Oct 29;107(9):1047-57.

[83] Choi HS, Ashitate Y, Lee JH, Kim SH, Matsui A, Insin N, et al. Rapid translocation of nanoparticles from the lung airspaces to the body. Nat Biotechnol. 2010 Dec;28(12): 1300-3.

[84] Oberdorster G, Sharp Z, Atudorei V, Elder A, Gelein R, Lunts A, et al. Extrapulmonary translocation of ultrafine carbon particles following whole-body inhalation exposure of rats. J Toxicol Environ Health A. 2002 Oct 25;65(20):1531-43.

[85] Morel O, Jesel L, Freyssinet JM, Toti F. Cellular mechanisms underlying the formation of circulating microparticles. Arterioscler Thromb Vasc Biol. 2011 Jan;31(1):15-26.

[86] Amabile N, Rautou PE, Tedgui A, Boulanger CM. Microparticles: key protagonists in cardiovascular disorders. Semin Thromb Hemost. 2010 Nov;36(8):907-16.

[87] Boulanger CM, Amabile N, Tedgui A. Circulating microparticles: a potential prognostic marker for atherosclerotic vascular disease. Hypertension. 2006 Aug;48(2): 180-6.

[88] Boulanger CM, Scoazec A, Ebrahimian T, Henry P, Mathieu E, Tedgui A, et al. Circulating microparticles from patients with myocardial infarction cause endothelial dysfunction. Circulation. 2001 Nov 27;104(22):2649-52.

[89] Thomashow MA, Shimbo D, Parikh MA, Hoffman EA, Vogel-Claussen J, Hueper K, et al. Endothelial microparticles in mild chronic obstructive pulmonary disease and emphysema. The Multi-Ethnic Study of Atherosclerosis Chronic Obstructive Pulmonary Disease study. Am J Respir Crit Care Med. 2013 Jul 1;188(1):60-8.

[90] Takahashi T, Kobayashi S, Fujino N, Suzuki T, Ota C, He M, et al. Increased circulating endothelial microparticles in COPD patients: a potential biomarker for COPD exacerbation susceptibility. Thorax. 2012 Dec;67(12):1067-74.

[91] Guiducci S, Distler JH, Jungel A, Huscher D, Huber LC, Michel BA, et al. The relationship between plasma microparticles and disease manifestations in patients with systemic sclerosis. Arthritis Rheum. 2008 Sep;58(9):2845-53.

[92] van Eeden SF, de Beer P. Community-acquired pneumonia: evidence of functional inactivation of alpha 1 proteinase inhibitor. Crit Care Med. 1990 Nov;18(11):1204-9.

[93] Tamagawa E, Suda K, Wei Y, Xing L, Mui T, Li Y, et al. Endotoxin-induced translocation of interleukin-6 from lungs to the systemic circulation. Innate Immun. 2009 Aug; 15(4):251-8.

[94] Kido T, Tamagawa E, Bai N, Suda K, Yang HH, Li Y, et al. Particulate matter induces translocation of IL-6 from the lung to the systemic circulation. Am J Respir Cell Mol Biol. 2011 Feb;44(2):197-204.

[95]   Godleski JJ, Verrier RL, Koutrakis P, Catalano P, Coull B, Reinisch U, et al. Mechanisms of morbidity and mortality from exposure to ambient air particles. Res Rep Health Eff Inst. 2000 Feb(91):5-88; discussion 9-103.

[96]   Nemmar A, Hoet PH, Vanquickenborne B, Dinsdale D, Thomeer M, Hoylaerts MF, et al. Passage of inhaled particles into the blood circulation in humans. Circulation. 2002 Jan 29;105(4):411-4.

[97]   Peters A, Veronesi B, Calderon-Garciduenas L, Gehr P, Chen LC, Geiser M, et al. Translocation and potential neurological effects of fine and ultrafine particles a critical update. Part Fibre Toxicol. 2006;3:13.

[98]   Fry DE. Sepsis, systemic inflammatory response, and multiple organ dysfunction: the mystery continues. Am Surg. 2012 Jan;78(1):1-8.

[99]   Suwa T, Hogg JC, Quinlan KB, Ohgami A, Vincent R, van Eeden SF. Particulate air pollution induces progression of atherosclerosis. J Am Coll Cardiol. 2002 Mar 20;39(6):935-42.

[100]  Sun Q, Wang A, Jin X, Natanzon A, Duquaine D, Brook RD, et al. Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. JAMA. 2005 Dec 21;294(23):3003-10.

[101]  Yatera K, Hsieh J, Hogg JC, Tranfield E, Suzuki H, Shih CH, et al. Particulate matter air pollution exposure promotes recruitment of monocytes into atherosclerotic plaques. Am J Physiol Heart Circ Physiol. 2008 Feb;294(2):H944-53.

[102]  Tamagawa E, Bai N, Morimoto K, Gray C, Mui T, Yatera K, et al. Particulate matter exposure induces persistent lung inflammation and endothelial dysfunction. Am J Physiol Lung Cell Mol Physiol. 2008 Jul;295(1):L79-85.

[103]  van Eeden SF, Sin DD. Chronic obstructive pulmonary disease: a chronic systemic inflammatory disease. Respiration. 2008;75(2):224-38.

[104]  Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax. 2004 Jul;59(7):574-80.

[105]  Wedzicha JA, Seemungal TA, MacCallum PK, Paul EA, Donaldson GC, Bhowmik A, et al. Acute exacerbations of chronic obstructive pulmonary disease are accompanied by elevations of plasma fibrinogen and serum IL-6 levels. Thromb Haemost. 2000 Aug;84(2):210-5.

[106]  Karadag F, Karul AB, Cildag O, Yilmaz M, Ozcan H. Biomarkers of systemic inflammation in stable and exacerbation phases of COPD. Lung. 2008 Nov-Dec;186(6):403-9.

[107]  Sin DD, Wu L, Man SF. The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature. Chest. 2005 Jun;127(6):1952-9.

[108] Engelhart MJ, Geerlings MI, Meijer J, Kiliaan A, Ruitenberg A, van Swieten JC, et al. Inflammatory proteins in plasma and the risk of dementia: the rotterdam study. Arch Neurol. 2004 May;61(5):668-72.

[109] Borson S, Scanlan J, Friedman S, Zuhr E, Fields J, Aylward E, et al. Modeling the impact of COPD on the brain. Int J Chron Obstruct Pulmon Dis. 2008;3(3):429-34.

[110] Agusti A, Morla M, Sauleda J, Saus C, Busquets X. NF-kappaB activation and iNOS upregulation in skeletal muscle of patients with COPD and low body weight. Thorax. 2004 Jun;59(6):483-7.

[111] Agusti AG, Sauleda J, Miralles C, Gomez C, Togores B, Sala E, et al. Skeletal muscle apoptosis and weight loss in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2002 Aug 15;166(4):485-9.

[112] Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998 Jun;157(6 Pt 1):1791-7.

[113] Agusti AG. Systemic effects of chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2005;2(4):367-70; discussion 71-2.

[114] Biskobing DM. COPD and osteoporosis. Chest. 2002 Feb;121(2):609-20.

[115] Rana JS, Mittleman MA, Sheikh J, Hu FB, Manson JE, Colditz GA, et al. Chronic obstructive pulmonary disease, asthma, and risk of type 2 diabetes in women. Diabetes Care. 2004 Oct;27(10):2478-84.

[116] Fahy JV. Eosinophilic and neutrophilic inflammation in asthma: insights from clinical studies. Proc Am Thorac Soc. 2009 May 1;6(3):256-9.

[117] Warwick G, Thomas PS, Yates DH. Non-invasive biomarkers in exacerbations of obstructive lung disease. Respirology. 2013 Jul;18(5):874-84.

[118] Kato M, Yamada Y, Maruyama K, Hayashi Y. Serum eosinophil cationic protein and 27 cytokines/chemokines in acute exacerbation of childhood asthma. Int Arch Allergy Immunol. 2010;152 Suppl 1:62-6.

[119] Martinet Y, Rom WN, Grotendorst GR, Martin GR, Crystal RG. Exaggerated spontaneous release of platelet-derived growth factor by alveolar macrophages from patients with idiopathic pulmonary fibrosis. N Engl J Med. 1987 Jul 23;317(4):202-9.

[120] Wynn TA. Integrating mechanisms of pulmonary fibrosis. J Exp Med. 2011 Jul 4;208(7):1339-50.

[121] Doi K, Ishizu T, Fujita T, Noiri E. Lung injury following acute kidney injury: kidney-lung crosstalk. Clin Exp Nephrol. 2011 Aug;15(4):464-70.

[122] Quilez ME, Lopez-Aguilar J, Blanch L. Organ crosstalk during acute lung injury, acute respiratory distress syndrome, and mechanical ventilation. Curr Opin Crit Care. 2012 Feb;18(1):23-8.

[123] Ahuja N, Andres-Hernando A, Altmann C, Bhargava R, Bacalja J, Webb RG, et al. Circulating IL-6 mediates lung injury via CXCL1 production after acute kidney injury in mice. Am J Physiol Renal Physiol. 2012 Sep 15;303(6):F864-72.

[124] Zhang H, Neuhofer P, Song L, Rabe B, Lesina M, Kurkowski MU, et al. IL-6 transsignaling promotes pancreatitis-associated lung injury and lethality. J Clin Invest. 2013 Mar 1;123(3):1019-31.

[125] Klut ME, Doerschuk CM, Van Eeden SF, Burns AR, Hogg JC. Activation of neutrophils within pulmonary microvessels of rabbits exposed to cigarette smoke. Am J Respir Cell Mol Biol. 1993 Jul;9(1):82-9.

[126] Klut ME, van Eeden SF, Whalen BA, Verburgt LM, English D, Hogg JC. Neutrophil activation and lung injury associated with chronic endotoxemia in rabbits. Exp Lung Res. 1996 Jul-Aug;22(4):449-65.

[127] Lang JD, Hickman-Davis JM. One-hit, two-hit... is there really any benefit? Clin Exp Immunol. 2005 Aug;141(2):211-4.

[128] Lee JS, Su X, Rackley C, Matthay MA, Gupta N. Priming with endotoxin increases acute lung injury in mice by enhancing the severity of lung endothelial injury. Anat Rec (Hoboken). 2011 Jan;294(1):165-72.

[129] Sato Y, van Eeden SF, English D, Hogg JC. Bacteremic pneumococcal pneumonia: bone marrow release and pulmonary sequestration of neutrophils. Crit Care Med. 1998 Mar;26(3):501-9.

[130] Sato Y, Van Eeden SF, English D, Hogg JC. Pulmonary sequestration of polymorphonuclear leukocytes released from bone marrow in bacteremic infection. Am J Physiol. 1998 Aug;275(2 Pt 1):L255-61.

[131] Hogg JC. Why does airway inflammation persist after the smoking stops? Thorax. 2006 Feb;61(2):96-7.

[132] Carlsten C, Dybuncio A, Pui MM, Chan-Yeung M. Respiratory impairment and systemic inflammation in cedar asthmatics removed from exposure. PLoS One. 2013;8(2):e57166.

[133] Eichacker PQ, Parent C, Kalil A, Esposito C, Cui X, Banks SM, et al. Risk and the efficacy of antiinflammatory agents: retrospective and confirmatory studies of sepsis. Am J Respir Crit Care Med. 2002 Nov 1;166(9):1197-205.

[134] Rennard SI, Fogarty C, Kelsen S, Long W, Ramsdell J, Allison J, et al. The safety and efficacy of infliximab in moderate to severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2007 May 1;175(9):926-34.

[135] Buff SM, Yu H, McCall JN, Caldwell SM, Ferkol TW, Flotte TR, et al. IL-10 delivery by AAV5 vector attenuates inflammation in mice with Pseudomonas pneumonia. Gene Ther. 2010 May;17(5):567-76.

[136] Sawa T, Corry DB, Gropper MA, Ohara M, Kurahashi K, Wiener-Kronish JP. IL-10 improves lung injury and survival in Pseudomonas aeruginosa pneumonia. J Immunol. 1997 Sep 15;159(6):2858-66.

[137] Zuany-Amorim C, Haile S, Leduc D, Dumarey C, Huerre M, Vargaftig BB, et al. Interleukin-10 inhibits antigen-induced cellular recruitment into the airways of sensitized mice. J Clin Invest. 1995 Jun;95(6):2644-51.

[138] Dokka S, Malanga CJ, Shi X, Chen F, Castranova V, Rojanasakul Y. Inhibition of endotoxin-induced lung inflammation by interleukin-10 gene transfer in mice. Am J Physiol Lung Cell Mol Physiol. 2000 Nov;279(5):L872-7.

[139] Serhan CN. Novel lipid mediators and resolution mechanisms in acute inflammation: to resolve or not? Am J Pathol. 2010 Oct;177(4):1576-91.

[140] Hsiao HM, Sapinoro RE, Thatcher TH, Croasdell A, Levy EP, Fulton RA, et al. A novel anti-inflammatory and pro-resolving role for resolvin D1 in acute cigarette smoke-induced lung inflammation. PLoS One. 2013;8(3):e58258.

[141] Shahar E, Folsom AR, Melnick SL, Tockman MS, Comstock GW, Gennaro V, et al. Dietary n-3 polyunsaturated fatty acids and smoking-related chronic obstructive pulmonary disease. Atherosclerosis Risk in Communities Study Investigators. N Engl J Med. 1994 Jul 28;331(4):228-33.

[142] Jain MK, Ridker PM. Anti-inflammatory effects of statins: clinical evidence and basic mechanisms. Nat Rev Drug Discov. 2005 Dec;4(12):977-87.

[143] Zhou Q, Liao JK. Pleiotropic effects of statins. - Basic research and clinical perspectives. Circ J. 2010 May;74(5):818-26.

[144] Laufs U, Liao JK. Isoprenoid metabolism and the pleiotropic effects of statins. Curr Atheroscler Rep. 2003 Sep;5(5):372-8.

[145] Naidu BV, Woolley SM, Farivar AS, Thomas R, Fraga C, Mulligan MS. Simvastatin ameliorates injury in an experimental model of lung ischemia-reperfusion. J Thorac Cardiovasc Surg. 2003 Aug;126(2):482-9.

[146] Fischetti F, Carretta R, Borotto G, Durigutto P, Bulla R, Meroni PL, et al. Fluvastatin treatment inhibits leucocyte adhesion and extravasation in models of complement-mediated acute inflammation. Clin Exp Immunol. 2004 Feb;135(2):186-93.

[147] Jacobson JR, Barnard JW, Grigoryev DN, Ma SF, Tuder RM, Garcia JG. Simvastatin attenuates vascular leak and inflammation in murine inflammatory lung injury. Am J Physiol Lung Cell Mol Physiol. 2005 Jun;288(6):L1026-32.

[148] Miyata R, Bai N, Vincent R, Sin DD, Van Eeden SF. Novel properties of statins: suppression of the systemic and bone marrow responses induced by exposure to ambi-

ent particulate matter (PM(10)) air pollution. Am J Physiol Lung Cell Mol Physiol. 2012 Sep 15;303(6):L492-9.

[149] Miyata R, Bai N, Vincent R, Sin DD, Van Eeden SF. Statins reduce ambient particulate matter-induced lung inflammation by promoting the clearance of particulate matter, < 10 mum from lung tissues. Chest. 2013 Feb 1;143(2):452-60.

[150] Chalmers JD, Singanayagam A, Murray MP, Hill AT. Prior statin use is associated with improved outcomes in community-acquired pneumonia. Am J Med. 2008 Nov; 121(11):1002-7 e1.

[151] Mortensen EM, Restrepo MI, Anzueto A, Pugh J. The effect of prior statin use on 30-day mortality for patients hospitalized with community-acquired pneumonia. Respir Res. 2005;6:82.

[152] Thomsen RW, Riis A, Kornum JB, Christensen S, Johnsen SP, Sorensen HT. Preadmission use of statins and outcomes after hospitalization with pneumonia: population-based cohort study of 29,900 patients. Arch Intern Med. 2008 Oct 27;168(19): 2081-7.

[153] Blamoun AI, Batty GN, DeBari VA, Rashid AO, Sheikh M, Khan MA. Statins may reduce episodes of exacerbation and the requirement for intubation in patients with COPD: evidence from a retrospective cohort study. Int J Clin Pract. 2008 Sep;62(9): 1373-8.

[154] Frost FJ, Petersen H, Tollestrup K, Skipper B. Influenza and COPD mortality protection as pleiotropic, dose-dependent effects of statins. Chest. 2007 Apr;131(4):1006-12.

[155] Ishida W, Kajiwara T, Ishii M, Fujiwara F, Taneichi H, Takebe N, et al. Decrease in mortality rate of chronic obstructive pulmonary disease (COPD) with statin use: a population-based analysis in Japan. Tohoku J Exp Med. 2007 Jul;212(3):265-73.

[156] Keddissi JI, Younis WG, Chbeir EA, Daher NN, Dernaika TA, Kinasewitz GT. The use of statins and lung function in current and former smokers. Chest. 2007 Dec; 132(6):1764-71.

[157] Lee TM, Lin MS, Chang NC. Usefulness of C-reactive protein and interleukin-6 as predictors of outcomes in patients with chronic obstructive pulmonary disease receiving pravastatin. Am J Cardiol. 2008 Feb 15;101(4):530-5.

[158] Mancini GB, Etminan M, Zhang B, Levesque LE, FitzGerald JM, Brophy JM. Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. J Am Coll Cardiol. 2006 Jun 20;47(12):2554-60.

[159] Soyseth V, Brekke PH, Smith P, Omland T. Statin use is associated with reduced mortality in COPD. Eur Respir J. 2007 Feb;29(2):279-83.

[160] Melbye H, Halvorsen DS, Hartz I, Medbo A, Brox J, Eggen AE, et al. Bronchial airflow limitation, smoking, body mass index, and statin use are strongly associated

with the C-reactive protein level in the elderly. The Tromso Study 2001. Respir Med. 2007 Dec;101(12):2541-9.

[161]  van Gestel YR, Hoeks SE, Sin DD, Simsek C, Welten GM, Schouten O, et al. Effect of statin therapy on mortality in patients with peripheral arterial disease and comparison of those with versus without associated chronic obstructive pulmonary disease. Am J Cardiol. 2008 Jul 15;102(2):192-6.

[162]  van Eeden SF, Hogg JC. Systemic inflammatory response induced by particulate matter air pollution: the importance of bone-marrow stimulation. J Toxicol Environ Health A. 2002 Oct 25;65(20):1597-613.

[163]  Stary HC, Chandler AB, Dinsmore RE, Fuster V, Glagov S, Insull W, Jr., et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation. 1995 Sep 1;92(5):1355-74.

[164]  Stary HC, Chandler AB, Glagov S, Guyton JR, Insull W, Jr., Rosenfeld ME, et al. A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation. 1994 May;89(5):2462-78.

[165]  Guidelines for the evaluation of impairment/disability in patients with asthma. American Thoracic Society. Medical Section of the American Lung Association. Am Rev Respir Dis. 1993 Apr;147(4):1056-61.