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Review

Cigarette smoking and innate immunity

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Abstract. Cigarette smoking is a worldwide epidemic and the most prevalent cause of many diseases leading to increased morbidity and mortality globally. The impact of smoking on pathogenesis of cancer is being extensively studied however cigarette smoke as an immunosuppressant is less well recognized. Here we review the immunosuppressive effects of cigarette smoke and the mechanisms by which smoking affects host innate immunity including structural and functional changes in the respiratory ciliary epithelium, lung surfactant protein, and immune cells such as alveolar macrophages, neutrophils, lymphocytes and natural killer (NK) cells. Thus smoking cessation should be emphasized not only for prevention of cancer and coronary artery disease but also for patients with recurrent infections and immunosuppressive states.

Introduction

Smoking is one of the most common addictions of modern times. It has been implicated as an etiological agent for various chronic diseases including variety of infections, cancers, heart diseases, and chronic lung diseases which put together are the leading causes of morbidity and mortality in today's society. Cigarette smoking is a well known risk factor leading to cancer of various organs, coronary artery disease, and respiratory illnesses such as chronic obstructive airways disease (COPD). The effects of smoking on innate immune function are less well studied however; accumulating data suggest that cigarette smoke compromises the immune system and increases susceptibility to infections [1–3]. In this manuscript we review the effects of cigarette smoke on innate immune function. The effects of cigarette smoke on the immune cells are summarized in figure 1.

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Epidemiology of smoking in US

Overall although smoking rates have declined over the years, more than one in five Americans smoke. In 2004, this included about 21 percent of adults and more than 22 percent of high school students. Consequently, smoking is the leading cause of premature death in the United States [4]. Each year, an estimated 438,000 Americans die as a result of smoking or exposure to second hand smoke, and for each person who dies from a smoking-related disease, about 20 more are living with a smoking-attributable illness. The estimated costs of smoking-related medical expenses and loss of productivity exceed $167 billion annually [4].

Contents of cigarette smoke

The smoke from a cigarette contains more than 45,000 chemicals, which have various toxic, mutagenic and carcinogenic effects. The content and concentration of chemical ingredients can vary widely in the different cigarette brands. Cigarette smoke generates various components both in the cellular and extracellular compartments, ranging from particulate matter to water solutes and gaseous extracts. The major components of smoke that lead to many of the deleterious effects include nicotine, tar, ammonia, carbon monooxide, carbon dioxide, formaldehyde, acrolein, acetone, benzopyrenes, hydroxyquinone, nitrogen oxides and cadmium [5]. Many of these agents are known to be carcinogenic and toxic to the cells [6] however; tar and nicotine have shown to be immunosuppressive by affecting the innate immune response of the host and increasing the susceptibility to infections. Cigarette smoke that contains high levels of tar and nictotine induce greater immunologic changes than cigarette smoke that contains lower levels of these compounds [7]

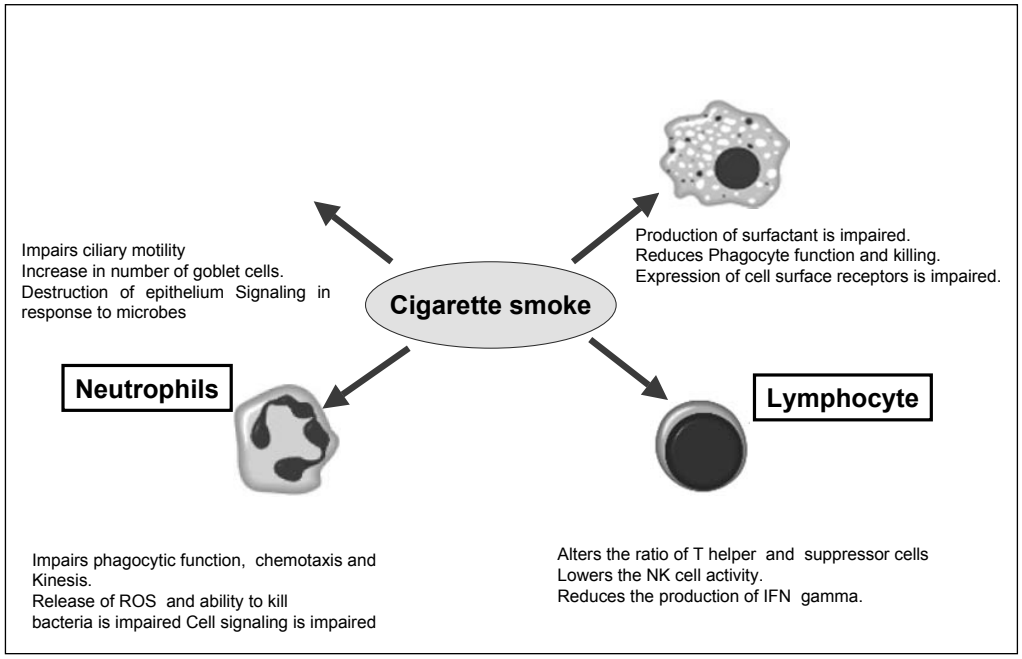

Fig. 1. Smoking affects the function of immune cells by a variety of mechanisms. The effects on epithelial, macrophage, neutrophils and lymphocytes are shown.

Chronic exposure to cigarette smoke causes T cell unresponsiveness [7]. Nicotine which is the major component impairs antigen mediated signal transduction in lymphocytes [8] and induces a state of T cell anergy [9]. This apparent T cell anergy may account for or contribute to the immunosuppressive and anti-inflammatory properties of cigarette smoke. Sopori et al demonstrated that nicotine inhibits the antibody forming cell responses through impairment of antigen mediated signalling in T cells by suppressing the intracellular calcium responses [10–11]. In a rat model Singh et al found that both acute and chronic exposure to nicotine causes immunosuppression by distinct mechanisms [12]. They treated rats acutely with nicotine for 1, 2, or 24 h by a single intraperitoneal injection or implanted with constant-release miniosmotic pumps containing nicotine for a 3-week period to cause a chronic exposure. In their study acute, but not chronic, nicotine administration increased the plasma corticosterone concentration. Moreover, adrenalectomy abrogated the acute but not chronic nicotine effects thus implying distinct mechanisms of action in the two settings.

Besides affecting the T cell responses nicotine modulates the production of inflammatory cytokines by alveolar macrophages [13]. In an *in vitro* study Matsunga et al showed that treatment of alveolar macrophages with nicotine after infection with *L. pneumophila* significantly enhanced the replication of bacteria in the macrophages and selectively down-regulated the production of IL-6, IL-12, and TNF-alpha, but not IL-10, induced by infection. They further showed that nicotine-induced suppression of antimicrobial activity and cytokine responses of alveolar macrophages was mediated by nicotinic acetylcholine receptors [14]. In epidemiological studies cigarette smoking was found to be an independent risk factor to the increased susceptibility to Legionella pneumonia [15–16].

The tar content of the smoke also alters the function of immune cells. Ouyang et al evaluated the effects of cigarette smoke extracts from cigarettes of different tar content on the *in vitro* production of IL-1beta, IL-2, IFN-gamma, and TNF-alpha. The inhibitory effect was demonstrated to be related to hydroxyquinone which is the phenolic compound [17]. McCue et al showed that phenolic extracts of the cigarette smoke which mainly contain hydroxyquinone and catechol, inhibit lymphocyte proliferation [18] which is immunosuppressive. Lee et al studied the effects of acrolein which is a component of the cigarette smoke on nasal epithelial cells *in vitro* [19]. They found that acrolein inhibits the expression of message and protein of IL-8 and human beta defensin-2 in *vitro* in the sinonasal epithelial cells. Thus all these studies indicate that various components of cigarette smoke can affect the immune response of different cell types.

Effects of smoking on ciliary epithelium

The mucociliary system forms the first line of defense against invading pathogens. The apical surface of the respiratory epithelium is covered with cilia which beat at 1000 beats per minute. The epithelium not only provides a physical barrier to the invading microbes but with its ciliary movement removes the particulate matter and participates in generating an inflammatory response to invading pathogens [20–22]. Cigarette smoke has deleterious effects on the ciliary epithelium which are mediated by a number of mechanisms.

There are typical histologic changes in the airways of cigarette smokers consisting of varying degrees of denudation of ciliary epithelium, an increase in the number of goblet cells, submucosal gland hypertrophy and squamous cell metaplasia [23–24]. Chronic exposure to cigarette smoke decreases ciliary beating and interferes with proper airway

clearance. A decrease in ciliary beat frequency has been found in the airways of hamsters exposed to cigarette smoke for a year. However, this effect appears to be species dependent as in rats exposed to cigarette smoke for a similar period demonstrated increased ciliary beat [25].

Delayed rate of bacterial clearance has been noted in smoke-exposed compared with sham-exposed mice. This is associated with increased inflammation characterized by greater numbers of neutrophils and mononuclear cells in the bronchoalveolar lavage. In a mouse model of *P.aeruginosa* lung infection Drannik et al showed that cigarette smoke impairs bacterial clearance leading to increased inflammation and morbidity related to epithelial damage and inflammation [26]. This suggests that cigarette smoke affects respiratory immune-inflammatory responses elicited by bacteria. The mechanism for the increased susceptibility to infection may also be related to a change in the CFTR (cystic fibrosis transmembrane conductance regulator expression gene). Cigarette smoke decreases the expression of CFTR gene, protein, and function *in vitro* in nasal respiratory epithelium of smokers [27]. CFTR may also be necessary for internalization of *P.aeruginosa* and this may be a mechanism by which this acquired deficiency may predispose to infection [28–29]. Whether cigarette smoke alters the expression of TLRs (Toll-like receptors) on epithelial cells which are critical to host response has not been studied. In human studies an increase in incidence of *Pneumococcal* infection has been reported in alcoholics in particular if they smoke which may be related to deficient bacterial clearance [30].

The inflammatory response generated by the epithelial cells is altered by smoking. *In vitro* cigarette smoke leads to an increased production of IL-8 from human bronchial epithelial cells [31]. This effect is mediated by activation of PKC (protein kinase C). In human and bovine bronchial epithelial cells Wyatt et al demonstrated that cigarette smoke extract (CSE) increases PKC activity *in vitro*. They further showed that CSE-stimulated PKC activation is required for C5a-mediated IL-8 release from human bronchial epithelial cells [32–34]. In a mouse model of *P.aeruginosa* addition of cigarette smoke enhanced the inflammatory response. After infection with *P.aeruginosa,* the levels of proinflammatory cytokines (tumor necrosis factor-alpha, interleukin-1beta, and interleukin-6) and chemokines (monocyte chemoattractant protein-1 [MCP-1] and macrophage inflammatory protein-2 [MIP-2]) as well as myeloperoxidase were significantly higher in mice that were treated with smoke compared to sham exposed animals [35]. In this study the proteolytic activity in lungs of smoke-exposed animals was much higher compared to the untreated control animals. Mio et al performed BAL in smokers and non-smokers and showed that IL-8 in BAL from smokers was higher than in BAL from nonsmokers [36]. These data suggests that cigarette smoke potentiates the inflammatory response generated by the epithelial cells both *in vitro* and *in vivo*.

Cigarette smoke has multiple effects on gene expression in the airway epithelial cells. Microarray studies of bronchial epithelial cells obtained from the airway of smokers and nonsmokers by bronchial brushing have indicated that cigarette smoke induces the expression of redox-regulating genes [37–38] and genes that are involved in the regulation of inflammation [39]. In a recent study Maunders et al found that in general there is a marked reduction in gene expression of smokers suggesting a shut down of many cellular processes. In addition there was a significant down regulation of many genes involved in the formation of tight junctions such as occludin, tight junction protein 1 (TJP1 or ZO1), and claudin-1 (CLDN1) [40]. Olivera et al investigated transepithelial electrical resistance (TER) in response to cigarette smoke *in vitro* and demonstrated that TER was decreased with an increase in albumin influx indicating a loss in barrier function to ions and macromolecules. They further showed that the smoke-induced loss of epithelial barrier function in human bronchial epithelium is a regulated process rather than a cytotoxic response. Thus cigarette smoke damages the epithelial junctions and makes it more permeable [41].

Effects of smoking on surfactant

Surfactant proteins play an important role in enhancing the surface properties of the lung and contribute to host-defense against microbes that are synthesized by alveolar epithelial type II cells. Two of the surfactant-associated proteins, SP-A and SP-D, have important host defense properties, while the remaining two, SP-B and SP-C, are hydrophobic and interact with phospholipids to optimize surface tension lowering function [42]. SP-A and SP-D bind to surface structures expressed by a wide variety of micro-organisms and have the capacity to modulate multiple leukocyte functions, including the enhanced internalization and killing of certain micro-organisms *in vitro* [42].

Exposure to cigarette smoke also affects the levels of surfactant which may additionally contribute to altered host immunity. In a rat model Subramaniam et al measured SP-B content in the bronchoalveolar lavage following chronic exposure to cigarette smoke and found that the levels of SB-P were significantly lower in smokers compared to non-smokers thus suggesting that cigarette smoke may have an inhibitory effect on surfactant secretory processes [43]. Similarly Honda et al performed BAL on healthy smokers and control subjects and measured the content of SP-A and SP-D in BAL fluids. They found that the levels of SP-A and SP-D were significantly decreased in smokers compared to the non-smokers. Thus decreased levels of surfactant in the lungs may be another mechanism by which cigarette smoke is immunosuppressive [44].

Effects of smoking on alveolar macrophages

The pulmonary alveolar macrophage is the resident mononuclear phagocyte in the lung which plays an important role in the afferent limb of the immune responses. Macrohages are responsible for the presentation of antigen to the immunocompetent cells. Like most mononuclear phagocytes the pulmonary alveolar macrophage is large cell (15–50 μm) even in the resting stage. The internal structure of the cell shows a large number of organelles and inclusions which contain a vast repertoire of enzymes which can be used to destroy organisms intracellularly. Alveolar macrophage is the key phagocytic cell in the normal lung. The number of alveolar macrophages is increased in the BAL of smokers [45] and

exposure to cigarette smoke also changes the macrophage phenotype [46]. The phagocytic function of macrophage is significantly reduced by cigarette smoke, [47–51] capacity of the macrophage to clear the inflammatory cells and debris from the lungs [47, 48, 52]. Besides the phenotypic changes human alveolar macrophage interact with cigarette smoke to modify the extracelluar matrix proteins which dramatically down regulates their ability to phagocytose apoptotic neutrophils [47].

In a mouse model Ortega et al showed that the ability of the macrophage both to attach to *C. albicans* and the capacity to ingest the yeast was significantly reduced in mice that were exposed to cigarette smoke [50] *In vitro* filtered gas phase of cigarette smoke or acrolein suppressed the phagocytic uptake and intracellular digestion of staphylococci by macrophages from mice [53] In another in *vitro* study using alveolar macrophages from healthy smokers and nonsmokers King et al demonstrated that the macrophages from smokers did not have the bactericidal or bacteriostatic properties that were seen in macrophages from healthy non-smokers [51]. The ability of the phagosomes and the lysosomes to fuse is defective in macrophage from smokers compared to non-smokers which impairs the capacity of macrophage to kill microbes [54]. Thus cigarette smoke-induced alterations in the ability of the macrophage to phagocytose and kill microbes and clear cell debris leading to depressed pulmonary host defense mechanisms.

Besides affecting the phagocytic and killing abilities of the macrophage cigarette smoke alters macrophage survival and gene profiling. In *in vitro* studies Aoshiba et al demonstrated that mouse, rat, and human alveolar macrophages and human blood monocyte-derived macrophages cultured with cigarette smoke extracts undergo apoptosis [55]. Alveolar macrophages also secrete many inflammatory mediators, oxidants, proteins and proteinases in response to cigarette smoke extract. Using affymetrix microarrays Heyguy et al showed that macrophages from smokers had an up regulation of 40 genes and down regulation of 35 genes compared to the non-smoking individuals [56] Most of these genes belonged to the functional categories of immune-inflammatory response, cell adhesion, extracellular matrix, proteolysis and antiproteolysis, lysosomal function, antioxidant-related function, signal transduction, and transcription factors. Expression of TLR2, TLR4 and CD14 on alveolar macrophage of smokers in response to their ligands is also significantly less compared to non-smokers [57]. In a recent study Noakes et al examined the cord blood monocyte immune responses of neonates of smoking and nonsmoking mothers. They showed that infants of smoking mothers had a significantly attenuated innate TLR-mediated response compared with infants of nonsmokers in monocytes [58]. Together these studies suggest that the inflammatory response generated by alveolar macrophage from smokers is significantly different than that of non-smokers which eventually alter the immune function of these cells.

Effects of smoking on polymorphonuclear neutrophils

Neutrophils are the primary inflammatory cells and contribute significantly to phagocytosis and clearing of microbes from the lungs. Exposure to cigarette smoke leads to an influx of macrophage and neutrophils in the airways. The function of neutrophils in smokers is deranged as compared to non-smoker which may further compromise host defenses [53, 59, 60]. *In vitro* treatment of neutrophils with cigarette smoke extract results in a dramatic suppression of neutrophil caspase-3-like activity leading to impaired phagocytosis [61].The filtered gas phase of cigarette smoke or acrolein suppresses the phagocytic uptake and intracellular digestion of staphylococci by neutrophils *in vitro* [53]. This effect is related to marked changes in the morphology of cytoplasmic membrane. Cigarette smoke also inhibits cellular adhesion, disturbs glycolysis and arachidonic metabolism; inhibits calcium and magnesium ATPase [53].

Neutrophil functions such as kinesis and chemotaxis, glycolytic activity and interaction with particles such as zymosan is also significantly affected by cigarette smoke. Exposure to smoke makes the neutrophils loose their ability to generate respiratory burst in the phagosome to toxic products [62]. When neutrophils from healthy non-smoking subjects are incubated with nicotine the ability of these cells to phagocytose is compromised. This is in part related to a decrease in the ability of the neutrophils to form actin filaments due to interference in the calcium signaling [63]. The Fc receptors which are involved in phagocytosis through interaction with complement are suppressed by cigarette smoke [64]. Together these effects make these cells less effective against bacteria and more noxious towards surrounding tissues thus compromising their ability to clear bacteria and other microbes.

Effects of cigarette smoking on alveolar lymphocytes and NK cells

Cigarette smoking alters the T cell responses, which has been associated with increased susceptibility to respiratory tract infections. Studies on bronchoalveolar lavage and biopsies from smokers with chronic bronchitis or COPD have revealed an increased number of CD8+ T-cells in the lungs of smokers as compared to non-smokers [65–67]. *In vitro* activation of T lymphocytes as assessed by surface markers and production of cytokines was significantly suppressed by cigarette smoke thus leading to altered immune response of the lymphocytes [68]. Ferson et al observed that lymphocytes from healthy smokers have a low natural killer-cell activity and the levels of immunoglobulins are significantly lower in smokers compared to non-smokers [69]. In a pilot study with 6 subjects three of whom were smokers and three non-smokers Buttner et al found that although the ratio of cytotoxic and helper T lymphocytes remained unchanged there was a significant difference in gene profiling between lymphocytes from smoking and non-smoking individuals. They did not evaluate the function of the lymphocytes but their data suggests that the ability of lymphocytes to respond to antigens and infectious agents may be significantly altered by cigarette smoking [70].

Smoking increased the frequency of CD3 (+) lymphocytes and decreased CD56 (+) cells at 14–20 weeks gestation which suggests that smoking affects several immune parameters leading to immunosuppression in pregnancy [71].

Avanzini et al examined the intracellular cytokine profile in adenoids and peripheral blood cells of children exposed to passive smoke. In their study children who were exposed to tobacco smoke had a significantly lower percentage of INFgamma producing CD4+ and CD8+ cells in adenoids. Moreover there was a significant correlation between the quantity of exposure and reduction in Th1 (CD4+INFgamma+ and CD8+INFgamma+) cells in adenoids. This reduction may be a contributing factor in the increased susceptibility of children exposed to passive smoking to respiratory tract infections [72]. T-cell activation, proliferation and expression of the cytotoxic proteins are significantly reduced by exposure to cigarette smoke [68]. Spleen cells from animals that are subjected to the heavy dose of cigarette smoke have a significant reduction in their natural killer cell-mediated lytic activity and a decreased response to concanavalin A [73]. Cigarette smoke impairs NK cell-dependent tumor immune surveillance which further suggests that the immune response to antigens is altered in these cells [74]. Thus it appears that cigarette smoke may alter the number and type of lymphocyte population in the lungs, activation and expression of cytokines. This in turn leads to functional defects in adaptive immune response by these cells predisposing to infections. However, the precise mechanism by which cigarette smoke alters the T cell responses is not well understood and needs further studies.

Effect of smoking on signaling events in inflammatory cells

Cells of both the innate and adaptive immune system activate several signaling pathways in response to bacterial infection. Cigarette smoke can inhibit the basal and stimulated cytokine production in cultured cell lines and primary cells. Many of the functional changes in cells of the innate immunity described above may be a result of altered signaling in these cells. Broncho-alveolar cells from smokers have a dysregulated activation of MAP kinases and NF-κB. Cells from smokers are more sensitive, and have a faster kinetic activation of NF-kappa B compared to cells from nonsmokers [75]. All three classes of MAP kinase-ERK, JNK, and p38-are simultaneously activated by LPS in cells from smokers and nonsmokers. However, the individual MAP kinases exhibit differential kinetics of activation. Activation of p38 is more rapid in cells from smokers, whereas the activation of ERK and JNK is similar in both groups [75]. In a recent study in which cultured macrophage cells were exposed to cigarette smoke there was a delay in production of key cytokines such as IL-1beta and IL-6 and reduced glutathione levels. This was associated with a reduction in NF-κB activation [76]. Chronic exposure of mice and rats to cigarette smoke or nicotine inhibits T cell responsiveness with decreased antibody response. This inhibition resulted from aberrant antigen- mediated signaling and depletion of calcium stores in animals that were exposed to nicotine [77]. Thus the effects of cigarette smoke on signaling may depend on the length of exposure of the cells and the concentration of nicotine or other constituents in the cigarette smoke. Altered signalling in the immune cells may be a mechanism by which the response of cells to bacteria is inhibited by cigarette smoke.

Summary and conclusions

Cigarette smoke has a major impact on health issues worldwide. Many of the healthcare consequences of cigarette smoking could be related to its ability to compromise the immune system, and a constant low level of infection that may be responsible for the pathogenesis of inflammatory disease induced by smoking. Genetics may be a contributory factor in the sensitivity to cigarette smoke; however a predisposition to infection could potentially interact with cigarette smoke to induce inflammatory changes associated with various diseases. Many related adverse effects of exposure to cigarettes may result from the ability of cigarette smoke extracts to interfere with the immune system although the mechanism by which cigarette smoke alters immunity is not completely understood. We have reviewed some of the experimental evidence that points towards smoke as an immunosuppressant for the function of immune cells including respiratory epithelial cells, macrophage, neutrophils and lymphocytes. Smoking also causes activation of resident cells and the recruitment of inflammatory cells into the lungs, which leads to release of pro-inflammatory cytokines, chemotactic factors, oxygen radicals and proteases which alter the function of immune cells. The role of cigarette smoke as an immunosuppressant should be recognized for otherwise healthy smokers, pregnant women and in patients who are immuncompromised. Smoking cessation should be emphasized not only for prevention of cancer, coronary artery disease, chronic bronchitis and emphysema but also because of the consequences of smoking on the innate immune function.

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