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ABSTRACT

Cigarette smoke (CS) causes considerable morbidity and mortality by inducing cancer, chronic lung and vascular diseases, and oral disease. Despite the well-recognized risks associated with smoking, the habit remains unacceptably prevalent. Several toxins present in CS have immunomodulatory effects. CS also contains trace amounts of microbial cell components, including bacterial lipopolysaccharide. These and other CS constituents induce chronic inflammation at mucosal surfaces and modify host responses to exogenous antigens. The effects of CS on immunity are far-reaching and complex; both pro-inflammatory and suppressive effects may be induced. The net effect of CS on immunity depends on many variables, including the dose and type of tobacco, the route and chronicity of exposure, and the presence of other factors at the time of immune cell stimulation, such as Toll receptor ligands or other inflammatory mediators. CS impairs innate defenses against pathogens, modulates antigen presentation, and promotes autoimmunity. CS also impairs immunity in the oral cavity and promotes gingival and periodontal disease and oral cancer. The recognition of specific mechanisms by which CS affects host immunity is an important step toward elucidating mechanisms of tobacco-induced disease and may identify novel therapeutic approaches for the management of diseases that afflict smokers.

Abbreviations: AP-1, activator protein-1; CD, cluster of differentiation; COPD, chronic obstructive pulmonary disease; HLA, human leukocyte antigen; IFN γ , interferon gamma; IL, interleukin; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; NF- κ B, nuclear factor kappa-B; RAGE, receptors for advanced glycation end-products; ROS, reactive oxidative species; ROR γ t, retinoic acid receptor-related orphan receptor transcription factor; STAT, signal transducer and activator of transcription; T-bet, T-box transcription factor; Th, T-helper; TLR, Toll-like receptors; TNF α , Tumor necrosis factor alpha; and TSLP, thymic stromal lymphopoietin.

KEY WORDS: tobacco, immunity, inflammation, autoimmunity, cigarette smoke, nicotine.

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Cigarette Smoking and Inflammation: Cellular and Molecular Mechanisms

INTRODUCTION

More than 400,000 people die each year in the United States alone as a result of past or current cigarette smoke (CS) use; adult smokers lose an average 13 to 15 yrs of life-expectancy because they smoke (Morris, 1995; CDC, 2002; Heidrich *et al.*, 2007). Despite widespread knowledge of the risks posed by CS, the worldwide prevalence of tobacco use is estimated to be in excess of one billion persons (Jha *et al.*, 2002; Proctor, 2004; Samet and Wipfli, 2010). CS is a complex mixture of thousands of chemicals generated upon the burning or heating of tobacco leaves. CS contains thousands of chemicals that have cytotoxic, mutagenic, carcinogenic, or antigenic properties (Fig. 1) (Bluhm *et al.*, 1971; Ding *et al.*, 2008). The passive or active inhalation of CS results in the rapid dissolution of toxins in oral/airway epithelial lining fluids and systemic uptake. Combustion is an important step that produces reactive oxidative substances (ROS) that are otherwise not present in the leaf or the ash (Huang *et al.*, 2005). The products of combustion can be divided into gaseous and particulate components (Bluhm *et al.*, 1971; Witschi, 2005). Most of the toxic CS components are present in the particulate phase (Witschi, 2005). CS has far-reaching effects on host immunity that range from alteration of innate immunity in the oral, nasal, and airway mucosa, to alterations in adaptive immunity at the systemic level. Many toxic effects induced by CS, particularly the induction of carcinogenesis, result from direct genetic or epigenetic effects resulting in altered gene functions (for example, cell cycle, DNA repair, and tumor suppressor genes). While recognizing that CS may induce cancer and other diseases by multiple mechanisms, the current review will focus on molecular and cellular mechanisms by which CS promotes immune dysfunction. The current review aims to synthesize a large body of literature regarding CS-induced immune dysfunction. This review takes into account the inherent difficulty in comparing research findings generated in different model systems of CS exposure. Some of the apparently contradictory findings outlined below may be partially explained by differences in the models of CS-extract generation (filtered or unfiltered CS, extraction in physiologic media, buffered media or organic extracts, solubilization of smoke material captured on a filter, acute or prolonged exposure, etc.) and *in vivo* CS exposure (nose cone exposure, whole-body exposure, and challenge of animals by intra-tracheal CS-extracts).

CIGARETTE SMOKE EXERTS INFLAMMATORY AND SUPPRESSIVE EFFECTS ON IMMUNE CELLS

Gaseous and particulate CS constituents first interface with the immune system at the mucosal surfaces lining the oral cavity, sinuses, and airways.

Thousands of ROS are produced in the burning cigarette and are not removed by cigarette butt filters (Huang *et al.*, 2005). ROS contained in the gaseous phase are often short-lived and affect primarily the upper airways. Those in the particulate phase, particularly the semiquinone radicals, have the ability to secondarily generate more free radicals (Huang *et al.*, 2005). ROS damage epithelial cells lining the airways by inducing peroxidation of lipids and other cell membrane constituents, activate oxidative-sensitive cellular pathways, and induce DNA damage (Valavanidis *et al.*, 2009). CS constituents (particularly ROS) activate epithelial cell intracellular signaling cascades that lead to inflammatory gene activation [*e.g.*, interleukin-8 or IL-8 and tumor necrosis factor- α (TNF α)] (Churg *et al.*, 2002; Chung, 2005). The secretion of these inflammatory mediators promotes chronic immune cell recruitment and inflammation.

Not all effects of CS on host immunity are stimulatory. T-cells may be induced to proliferate and secrete cytokines that mediate important biological functions. The ensuing adaptive T-cell inflammatory response may be categorized as T-helper (Th)1, Th2, and Th17-type inflammation (Zhou *et al.*, 2009). The designation of Th cells as Th1, 2, or 17 reflects the preferential activation of specific transcriptional T-cell factors and secretion of cytokines; for example, a preponderance of Th1 polarized T-cells produce interferon- γ (IFN γ) rather than interleukin-4 (IL-4), which is produced primarily by Th2 polarized cells (Zhou *et al.*, 2009). CS suppresses certain Th1 responses, while facilitating the generation of Th2 inflammation (Cozen *et al.*, 2004; Vassallo *et al.*, 2005; Nakamura *et al.*, 2008; de Heens *et al.*, 2009; Robays *et al.*, 2009). For example, acute exposure of dendritic cells to cigarette smoke extract suppresses their activation by bacterial lipopolysaccharide (LPS), resulting in reduced secretion of interleukin-12 (Th1 polarizing) and interleukin-23 (Th17 polarizing) cytokines (Vassallo *et al.*, 2005; Kroening *et al.*, 2008). Similarly, lung and systemic dendritic cells extracted from mice exposed to CS secrete less IL-12 and IL-23 when activated *ex vivo* with LPS (Kroening *et al.*, 2008). In an animal model of respiratory syncytial virus intranasal infection, mice exposed to CS showed an increase in lung eosinophils (a marker of Th2 inflammation), and reduced levels of Th1 cytokines, compared with air-exposed mice (Phaybouth *et al.*, 2006). In an animal model of ovalbumin-mediated asthma, Robays *et al.* showed that CS enhanced Th2 polarized eosinophilic airway inflammation (Robays *et al.*, 2009). In parallel to these findings, de Heens *et al.* observed that *in vitro* stimulation of peripheral blood T-cells of individual smokers produced greater amounts of interleukin-13 (Th2 cytokine) than that of control non-smokers (de Heens *et al.*, 2009). Whether CS promotes Th17 inflammation is not definitively established, although there is evidence suggesting that, in certain individuals, chronic CS exposure may promote adaptive Th17 immunity to self-antigen (Shan *et al.*, 2009). Analysis of the epidemiologic data showing increased prevalence of inflammatory diseases associated with Th17 inflammation in smokers also suggests that chronic CS exposure may promote Th17 polarized immunity (Heliovaara *et al.*, 1993; Zivadinov *et al.*, 2009). The mechanisms by which CS promotes preferential Th2 priming (and potentially Th17 inflammation) are not fully understood,

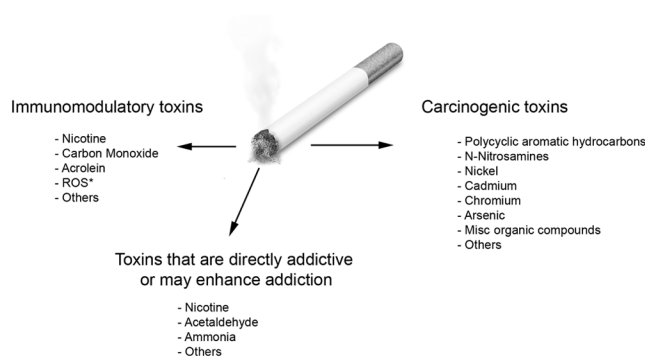


Figure 1. Cigarette smoke is a mixture of thousands of chemicals generated from the burning or heating of tobacco. The extraordinarily large collection of compounds present in cigarette smoke may be classified into broad groups, based on known target effects. Many carcinogenic toxins are now known to exist in cigarette smoke. Nicotine is the predominant addictive cigarette smoke constituent, although other chemicals contribute directly or indirectly to the addictive nature of CS (some by modifying nicotine effects). Nicotine, carbon monoxide, ROS, and acrolein are among the more important cigarette smoke toxins with immunomodulatory potential, although many more may exist. *ROS refers to reactive oxidant substances.

but may involve suppression of Th1 polarizing cytokine production (Vassallo *et al.*, 2005), altered antigen-presenting cell activation (Kroening *et al.*, 2008; Robays *et al.*, 2009), induction of Th2 polarizing factors from epithelial or other cells (Nakamura *et al.*, 2008; Smelter *et al.*, 2010), host genetic factors, and possibly direct effects on T-cells. While many studies describe CS-extract or CS as an adjuvant of adaptive Th2 immunity (Byron *et al.*, 1994; Vassallo *et al.*, 2005; Nakamura *et al.*, 2008; Van Hove *et al.*, 2008; de Heens *et al.*, 2009; Robays *et al.*, 2009; Smelter *et al.*, 2010), other studies implicate a role for CS as an inducer of Th1 immunity (Kang *et al.*, 2008; Huang *et al.*, 2010). These seemingly contradictory observations may be the result of differences in techniques used to prepare CS-extracts, different rodent models of CS exposure, and other co-factors.

CS is one of the most important modifiers of host responses to pathogens (Zambon *et al.*, 1996; Nuorti *et al.*, 2000). Outcomes and severity of pneumonia due to *Streptococcus pneumoniae* and influenza infection are substantially worse in smokers (Kark *et al.*, 1982; Nuorti *et al.*, 2000). Smokers are also more likely to develop both latent and active tuberculosis (Kolappan and Gopi, 2002). There are many potential mechanisms by which CS hinders immunity to infection, including the modulation of intracellular epithelial and immune cell signaling (Gualano *et al.*, 2008; Modestou *et al.*, 2010) and suppression of innate and adaptive immune cell activation (Modestou *et al.*, 2010).

CIGARETTE SMOKE ALTERS MUCOSAL IMMUNITY

The airway epithelium is a regulator of immune responses to a variety of insults, including CS. CS directly activates epithelial cells and induces chemokine and inflammatory mediator release (Fig. 2) (Mio *et al.*, 1997; Kode *et al.*, 2006; Pace *et al.*, 2008). Epithelial cells express Toll-like receptors (TLRs) that

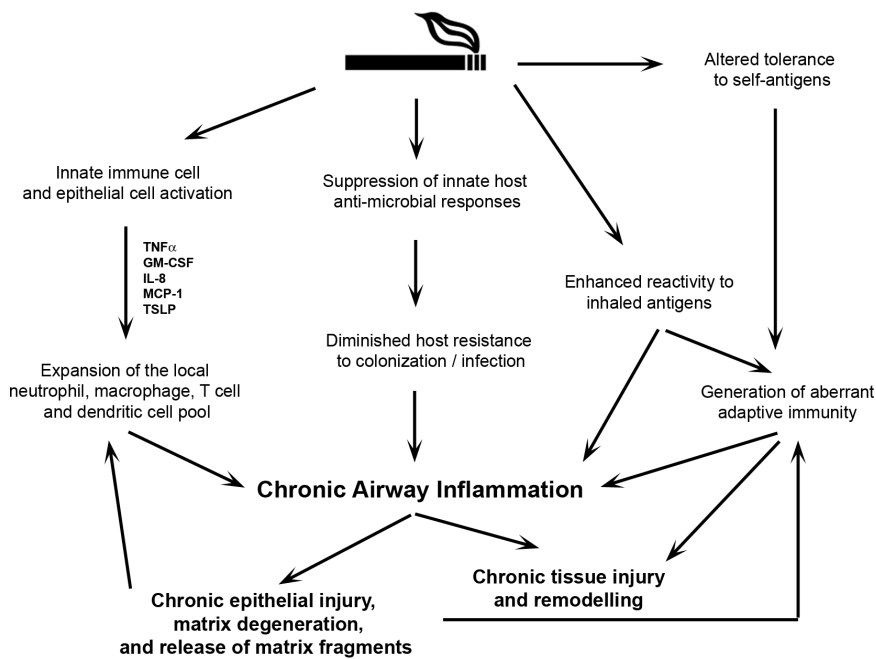


Figure 2. Cigarette smoke modulates inflammation and promotes chronic inflammation in the conducting airways by a variety of mechanisms. Direct activation of epithelial and immune cells in the oral and conducting airways induces the secretion of pro-inflammatory factors (some of which are listed in Fig. 1) that promote the recruitment and survival of other immune cells, including neutrophils, macrophages, T-cells, and dendritic cells. Simultaneously, CS impairs innate host defense mechanisms, subdues innate responses to pathogens, and alters adaptive immune responses to inhaled antigens. The net result of these effects is a state of chronic injury and inflammation of the airways. Repetitive injury coupled with abnormal tolerogenic responses to self-antigens and co-existent pathogen colonization may promote the development of auto-reactive immunity, which further perpetuates tissue injury and inflammation.

recognize pathogen-associated molecules (Pace *et al.*, 2008). For example, airway epithelial cells express TLR3, which binds double-stranded viral RNA (Yamin *et al.*, 2008). Epithelial cells stimulated with a combination of CS-extract and viral double-stranded RNA produce significantly higher levels of chemokines than when incubated with either stimulus independently (Yamin *et al.*, 2008). Despite this heightened cellular activation, epithelial-mediated innate immune responses to infectious pathogens are compromised by CS. CS-extracts suppress human beta-defensin-2 production (an endogenous secreted antimicrobial peptide) by gingival cells (van der Toorn *et al.*, 2007). In another study, current or former smoking was associated with significantly reduced beta-defensin-2 levels in pharyngeal fluid and sputum from patients with acute pneumonia (Herr *et al.*, 2009). CS also reduces mucosal ciliary motility, increases goblet cell numbers, and stimulates mucus hypersecretion (Chung, 2005). These effects result in persistent mucosal epithelial activation and diminished anti-microbial functions relevant to the clearance of infection, and may partially explain the higher likelihood of smokers to develop colonization and subsequent infection.

CS alters many cell-signaling pathways involved in cellular activation. CS constituents activate several cell-signaling pathways, including mitogen-activated protein kinases (MAPK), nuclear factor kappa-B (NF- κ B), signal transducer and activator

of transcription (STAT), and activatory protein-1 (AP-1), all of which are also involved in the regulation of inflammatory, cell cycle, and other genes (Iles *et al.*, 2005; Kroening *et al.*, 2008; Liu *et al.*, 2008; Smelter *et al.*, 2010). Among these, CS-induced activation of the NF- κ B and AP-1 transcription factors is critically involved in the regulation of inflammatory chemokine generation, altered corticosteroid resistance, altered responsiveness to acute pathogen challenge, and altered cell death regulation (Laan *et al.*, 2004; Walters *et al.*, 2005; Liu *et al.*, 2008; Modestou *et al.*, 2010). Liu *et al.* reported that CS-extract induces up-regulation of anti-apoptotic factors and activates NF- κ B, the latter response being essential to prevent CS-induced cell death (Liu *et al.*, 2008). Epithelial cells exposed to CS-extract also display significantly increased activity of the intracellular signaling molecule Ras, an effect that is at least partially dependent on the activation of receptors for advanced glycation end-products (RAGE) by CS-constituents (Reynolds *et al.*, 2010). Elevated Ras activity, a characteristic feature of epithelial-derived lung cancers (Bos, 1989), has been shown to be a key cellular checkpoint through which

CS-induced RAGE activation converges, culminating in downstream NF- κ B activation and inflammatory gene expression (Reynolds *et al.*, 2010). In addition to directly inducing NF- κ B activation in epithelial cells, CS constituents also may prevent homeostatic NF- κ B activation in stressed epithelial cells during pathogen challenge (Manzel *et al.*, 2011). Manzel *et al.* showed that, following an acute exposure to combined mainstream and sidestream CS, mice challenged with *H. influenzae* showed suppressed NF- κ B and downstream defense gene expression when compared with wild-type mice, indicating that CS constituents not only induce NF- κ B components directly, but can also modulate cellular inflammatory NF- κ B-dependent activation in the context of infection (Manzel *et al.*, 2011). ROS in CS also activate AP-1, which is important in the induction of monocyte and macrophage activation and IL-8 production (Walters *et al.*, 2005). The activation of AP-1 is also important in the development of corticosteroid-resistant inflammation (Walters *et al.*, 2005). Although CS itself induces AP-1 activation, in the setting of acute LPS challenge of cells previously treated with CS-extracts, activation of AP-1 in bronchial epithelial cells is blunted (Laan *et al.*, 2004). These findings support the notion that CS induces chronic inflammation in the airways while simultaneously modulating mucosal functions, resulting in diminished acute responsiveness to infectious challenge.

CS regulates the development of Th2 polarized allergic states by directly inducing pro-allergic factors. CS induces the production of thymic stromal lymphopoietin (TSLP) by epithelial (Nakamura *et al.*, 2008) and airway smooth-muscle cells (Smelter *et al.*, 2010). TSLP activates dendritic cells that promote Th2 polarization (Liu *et al.*, 2007). A survey of TSLP gene single-nucleotide polymorphisms revealed gene variants that are more susceptible to activation due to increased affinity for binding of the AP-1 transcription factor (Harada *et al.*, 2009). Furthermore, certain TSLP gene polymorphisms result in higher levels of TSLP production by bronchial epithelial cells in response to viral respiratory infections (Harada *et al.*, 2009). TSLP stimulation is a specific way by which CS may promote a permissive setting for allergic inflammation in the airways and may be an important mechanism by which CS promotes airway inflammation.

CS also directly modulates dendritic cell functions. Dendritic cells are potent antigen-presenting cells that lie beneath mucosal epithelial cells and serve to process and present antigen to lymphocytes (Mellman and Steinman, 2001). Because of their capacity to influence both innate and adaptive immunity, dendritic cells are of critical importance in the regulation of mucosal immunity (Mellman and Steinman, 2001). In myeloid dendritic cells activated by LPS or CD40 ligand, CS may either stimulate (augment production of secreted prostaglandin-E₂, IL-8, and IL-10) (Vassallo *et al.*, 2005, 2008) or suppress (IL-12 and IL-23) production of inflammatory mediators (Kroening *et al.*, 2008). Myeloid dendritic cells incubated with CS-extract also display diminished T-cell-stimulatory capacity (Vassallo *et al.*, 2005; Mortaz *et al.*, 2009a). These effects are mediated by different CS constituents and involve activation of diverse cellular signaling mediators (Kroening *et al.*, 2008; Vassallo *et al.*, 2008). For instance, some of the CS-induced inhibitory effects on dendritic cell functions are induced by ROS, while others are mediated by nicotine or other chemicals (Kroening *et al.*, 2008; Vassallo *et al.*, 2008). Robbins *et al.* showed that *in vivo* exposure of mice to CS diminishes lung dendritic cell activation and their capacity to induce antigen-specific T-cell proliferation in thoracic draining lymph nodes (Robbins *et al.*, 2008). Although dendritic cells exposed to CS display diminished T-cell-stimulatory capacity and suppressed Th1 polarizing function, their migratory capacity to draining lymph nodes is preserved and potentially even enhanced (Robbins *et al.*, 2008; Robays *et al.*, 2009). CS-extract also suppresses anti-viral cytokine generation from plasmacytoid dendritic cells activated by a TLR9 agonist (Mortaz *et al.*, 2009b). CS can thus affect dendritic cell functions both directly and indirectly.

In addition to dendritic cells, antigen-presenting cell functions are shared with macrophages and B-cells. Although increased numbers of macrophages are present in the airways and sinuses of smokers, these cells are functionally impaired (Green and Carolin, 1967; Hodge *et al.*, 2003; Kirkham *et al.*, 2004). Phagocytic function of alveolar macrophages is dampened by CS-induced oxidative stress (Green, 1968). CS impairs the phagocytic uptake of both bacteria and apoptotic cells, which may result in impaired healing of epithelial wounds and accumulation of apoptotic and inflammatory cellular debris

(Hodge *et al.*, 2003; Kirkham *et al.*, 2004). The effect of CS on macrophage secretion of TNF α is not fully defined (Kuschner *et al.*, 1996; Yang *et al.*, 2006). For example, one study showed enhanced constitutive and inducible TNF α secretion by alveolar macrophages obtained by lung lavage of rodents acutely exposed to CS (Pessina *et al.*, 1993), while another study reported a significant attenuation of inducible macrophage TNF α levels in a chronic model of CS exposure (Gaschler *et al.*, 2008).

CS induces qualitative and quantitative defects in circulating natural killer cells which are important in host anti-tumor and viral responses (Ginns *et al.*, 1985; Lu *et al.*, 2007). In smokers, natural killer cells produce significantly less IFN γ and TNF α upon activation, when compared with non-smokers (Mian *et al.*, 2008). CS-extract also reduces cytotoxic functions of natural killer cells (Mian *et al.*, 2008). Using a mouse model of metastatic melanoma, Lu *et al.* observed a substantial increase in lung metastases among mice exposed to CS compared with control mice, and posited that CS-impaired natural killer cell-dependent tumor immune surveillance is an important mechanism underlying the observed increased predisposition to lung metastases (Lu *et al.*, 2007).

CIGARETTE SMOKE AND AUTOIMMUNITY

It is increasingly appreciated that CS promotes certain autoimmune diseases like rheumatoid arthritis (Heliövaara *et al.*, 1993; Silman *et al.*, 1996; Hutchinson *et al.*, 2001). A recent meta-analysis identified a two-fold increased risk of developing seropositive rheumatoid arthritis for individuals who smoked for more than 20 yrs, and a three-fold increased risk for rheumatoid arthritis in male smokers (Sugiyama *et al.*, 2010). CS has also been associated with positivity for anti-citrullinated peptide antibodies, implying that smoking promotes the generation of auto-antibodies to citrullinated peptides (Klareskog *et al.*, 2006). Furthermore, it has been linked to extra-articular rheumatoid disease, including lung disease (Harel-Meir *et al.*, 2007). A major gene-environment interaction between rheumatoid arthritis susceptibility HLA-DR genes and CS was observed with a 21-fold increased relative risk of developing seropositive arthritis reported in European studies (Klareskog *et al.*, 2006).

Potential mechanisms by which CS promotes rheumatoid arthritis include the release of intracellular proteins from ROS-activated or injured cells, augmentation of auto-reactive B-cell function (Klareskog *et al.*, 2006), altered presentation of antigens by CS-impaired antigen-presenting cells (Vassallo *et al.*, 2005; Robays *et al.*, 2009), altered regulatory T-cell functions (Lee *et al.*, 2007), and T-cell activation by antigens found in CS. Using an animal model of collagen-induced arthritis, Chujo *et al.* showed that the addition of CS condensate into the antigen/adjuvant emulsion used to induce arthritis in mice resulted in exacerbation of arthritis (Chujo *et al.*, 2010). The same group also showed that nasal exposure of mice to CS condensate augmented the induction and development of joint changes in collagen-induced arthritis (Okamoto *et al.*, 2011). In contrast, another group reported a delay in the development of arthritis in mice exposed to CS (Lindblad *et al.*, 2009). The contrasting findings reported may reflect differences in methodologies used

to expose mice to CS and the animal models of arthritis. A recent study also suggested a role for nicotine in the development of autoimmune arthritis. Mice lacking the alpha7 nicotinic receptor (one of the key nicotinic receptors expressed by immune and non-immune cells) developed milder collagen-induced arthritis and less cartilage destruction, compared with wild-type controls (Westman *et al.*, 2010). Nicotine may differentially affect the severity of rodent autoimmune arthritis, since treatment of rodents with nicotine prior to immunization with antigen aggravated arthritis, while nicotine treatment following onset of arthritis resulted in amelioration of disease (Yu *et al.*, 2011).

Autoimmune mechanisms may also be relevant in the pathogenesis of chronic obstructive pulmonary disease (COPD), another prevalent CS-induced disease. Individuals with COPD have a state of persistent airway inflammation (Garcia-Garcia *et al.*, 1996; Saetta *et al.*, 1998; Demedts *et al.*, 2007). While the influx of inflammatory cells in the lung may be mediated by direct CS effects, the airway inflammation characteristic of COPD persists even following smoking cessation. The smoldering nature of this inflammation suggests that it is mediated by factors independent of direct CS toxicity, including adaptive immune responses to epithelial or other cellular antigens exposed following repeated injury of lung tissue (Fig. 2) (Churg *et al.*, 2002; Chung, 2005; Lee *et al.*, 2007; Cosio *et al.*, 2009; Shan *et al.*, 2009). In COPD patients, specific T-cell responses can be elicited from lung-derived elastin peptides (Lee *et al.*, 2007; Shan *et al.*, 2009). In addition, antibodies to elastin are increased in COPD patients as compared with control individuals, implying that COPD is associated with autoantibody generation (Lee *et al.*, 2007). COPD patients also have significantly fewer regulatory T-cells in the lungs, which has been interpreted as evidence for antigen-specific autoimmunity partially mediated by a failure of usual homeostatic regulatory T-cell function (Lee *et al.*, 2007). In another study, reduced levels of regulatory T-cell numbers were shown to be limited to small, but not large, airways (Isajevs *et al.*, 2009). In a seemingly contrasting report, Smyth *et al.* (2007) showed that both “healthy” smokers and smokers with COPD have increased numbers of regulatory T-cells in the lung lavage fluid when compared with non-smokers; however, these cells expressed low levels of CD27, implying an impairment in functional suppressive capacity. Whether CS itself is directly responsible for these observed immune abnormalities in COPD is not clear.

CIGARETTE SMOKING, IMMUNITY, AND ORAL DISEASE

CS and the chewing of tobacco products are the main modifiable risk factors for chronic periodontitis. Smokers have poorer periodontal health and respond suboptimally to periodontal treatment (MacFarlane *et al.*, 1992). Persistent inflammation and chronic infection are central in the pathogenesis of periodontitis (Delima *et al.*, 2002; Behl *et al.*, 2008; de Heens *et al.*, 2009). Smokers are susceptible to colonization by *Porphyromonas gingivalis* (*P. gingivalis*), a causative agent of periodontitis (Zambon *et al.*, 1996). CS exposure modifies the responses of gingival and immune cells to bacteria like *P. gingivalis* (Payne

et al., 1996; Bagaitkar *et al.*, 2009; Borch *et al.*, 2009). While some studies show suppressed *P. gingivalis*-mediated activation of immune cells following incubation with CS-extract or nicotine (Payne *et al.*, 1996; Borch *et al.*, 2009), others have shown skewing of immune cell activation to *P. gingivalis* following acute CS-extract exposure, resulting in more pronounced Th2 cytokine production (de Heens *et al.*, 2009). Acute CS exposure also induces the expression of certain bacterial genes potentially relevant to virulence (Bagaitkar *et al.*, 2009). CS promotes an environment permissive for colonization and infection with pathogens like *Escherichia coli*, *Staphylococcus aureus*, and the fungi *Candida albicans* and *Aspergillus fumigatus* (Kamma *et al.*, 1999).

There are several mechanisms by which CS-induced modulation of innate immune responses in the oral cavity facilitates colonization and chronic infection. Human gingival epithelial cells incubated with CS-extract produce substantially fewer anti-microbial peptides when activated with TLR ligands (Mahanonda *et al.*, 2009). CS also activates cells in the oral cavity in ways that facilitate chronic inflammation, even though many antimicrobial functions are suppressed or modulated (Mahanonda *et al.*, 2009). CS may also dysregulate innate immune responses in the oral cavity by modifying local TLR expression, distribution, and activation, thereby promoting an environment permissive for chronic inflammation (Beklen *et al.*, 2008; Pace *et al.*, 2008). Another potential mechanism by which CS promotes periodontal disease is through up-regulation of RAGE receptors on gingival cells (Katz *et al.*, 2005). Human gingival cells exposed to nornicotine (a nicotine metabolite) up-regulate RAGE expression (Katz *et al.*, 2005). RAGE has various ligands that primarily include endogenous molecules generated or released during cellular stress, including advanced glycation end-products (AGEs) (Sims *et al.*, 2010). It is plausible that CS-induced RAGE expression on epithelial cells promotes the pro-inflammatory effects of AGEs present in the environment (and also present in CS itself), thereby augmenting chronic inflammatory responses in the gingival tissue of smokers. A role for CS-induced RAGE expression and enhanced RAGE signaling in periodontitis is also supported by observations that blockade of RAGE in mice infected with *P. gingivalis* resulted in significant attenuation of inflammation and periodontal bone loss compared with control mice (Lalla *et al.*, 2000). Aberrant adaptive inflammation mediated by CS effects on CD4+ T-cells may potentially be relevant in the development of bone loss observed in severe periodontal disease (Teng *et al.*, 2000), and it is possible that persistently activated Th2-polarized T-cell inflammation may be involved in the development of more progressive periodontal lesions (Bartova *et al.*, 2000; de Heens *et al.*, 2009).

FINAL COMMENTS

CS causes diverse changes in immunity that lead to heightened constitutive inflammation, skewing of adaptive T-cell-mediated immunity, impaired responses to pathogens, and suppressed anti-tumor immune cell functions. When the exposure to CS is sustained, a chronic inflammatory process ensues that has the

potential to promote enhanced microbial colonization and infection, persistence of apoptotic material and abnormal processing of cellular debris, induction of autoimmunity to self-antigen, and architectural remodeling. The consequences of unchecked CS-induced inflammation and immune dysregulation continue to be an area of active research. While a potential solution to the tobacco disease epidemic may be attainable with widespread and effective smoking cessation methodologies, the unfortunate reality is that tobacco use is actually on the rise on a global level (Samet and Wipfli, 2010). Education regarding mechanisms by which smoking and second-hand CS promote disease remains a crucial component of tobacco control policy, and objective scientific data are critically needed to counteract deceptive marketing strategies by producers of tobacco. Understanding specific mechanisms by which tobacco impairs immunity may also provide important new therapeutic targets for the treatment of many diseases that afflict smokers.

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