Editorial Commentary

Smoking, immunity, and DNA damage

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Tobacco toxicology and teratogenic effects

The normal lung of non-smokers contains alveolar macrophages as guardian residents. However, when tobacco smoke enters the lungs it triggers a dramatic influx of macrophages and neutrophils in the bronchi and pulmonary epithelia. Smoking directly exposes the epithelial tissue to at least 60 powerful chemical carcinogens with the potential to cause DNA damage to larynx, bronchi, and lung epithelial cells. The most common compounds in tobacco smoke are nicotine, formaldehyde, ammonia, carbon monoxide, carbon dioxide, benzopyrenes, tar, acetone, hydroxyquinone, cadmium, and nitrogen oxides (1).

Tar and nicotine have immunosuppressive effects on the innate immune response and tobacco products containing high concentrations of tar and nicotine cause the greatest immunologic changes. For instance, cigarette smoke altogether suppresses or decreases neutrophils phagocytic activity and affects chemotaxis, kinesis, and cell signaling. It also inhibits the release of reactive oxygen species (ROS), thus compromising pathogen killing by neutrophils and other cells of the innate immunity (1).

In addition to the carcinogenic and epigenetic chemicals present in the smoke of cigarettes, cigars, pipes, etc., nicotine may also contribute to the genesis of lung cancer. The tobacco-related damage of the respiratory epithelia plus the suppressive role of nicotine on the programmed cell-death (apoptosis) mechanism may be an important factor for the survival of malignant cells and the formation of multiple epithelial lesions known as field-mutations. Apoptosis is the main protective cellular mechanism against proliferation of cells bearing irreversible DNA damage (2). Numerous field-mutations are found spread across the epithelia on the lungs of smokers and former smokers, each cell surrounded by an inflammatory response. Chronic inflammation is considered a major consequence of smoking that also leads to increased cell proliferation in the exposed pulmonary epithelia by enhancing progressive cell transformation and survival, which finally results in cancer cells (3). Eventually one of those field-mutations escapes from the inflammatory siege and starts promoting stroma formation, angiogenesis and rapid cell proliferation, resulting in epithelial tumor.

Nicotine is a toxic and highly addictive alkaloid with affinity to nicotinic acetylcholine receptors (nAChR), which are found on the surface of pulmonary epithelial cells as well as on mesotheliomas, SCLC, and NSCLC, showing a suppressive effect on the pro-apoptotic signaling pathways. Of course, nicotine is also rapidly absorbed from the lungs into the blood stream and reaches the cholinergic receptors on neurons of the reward centers in the CNS, causing strong addiction. It works also at the nicotinic receptors in the peripheral nervous system (4,5).

nAChR participate in the autocrine-proliferative network involved in the growth of cancer cells by upregulating growth factors, such as vascular endothelial growth factors (VEGF) that promotes angiogenesis, and fibroblastic growth factors (FGF) that promotes stromal tissue growth. Therefore, nicotine may play a pleiotropic role that includes cell proliferation and angiogenesis, besides down-regulating anti-inflammatory microRNAs in lung cells and stimulating the expression of inflammatory cytokines which contribute to tissue damage. These findings suggest that nicotine might play a direct role in the pathogenesis of human lung cancers and in the etiology of idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), and emphysema (6-10).

According to toxicology studies, nicotine is highly toxic and the lethal dose for adult humans is around 1.0 mg/kg or ~60 mg in a human with average body mass. Oral

ingestion of 4 to 8 mg of nicotine may cause vomiting, high blood pressure, dizziness, convulsions, and tachycardia—even leading to atrial fibrillation, depending on the body mass (11). The potential toxicity of nicotine in candies, chewing gums, and e-cigarettes should also not to be taken lightly, especially with children in the household. It suffices 1 g of nicotine to send a toddler to the emergency room (12).

Tobacco impact on immunity

As mentioned before, one of the first impacts on immunity caused by smoking is to trigger an inflammatory chronic response in the lungs, which increases over the years due to repeated exposure to smoke and the addition of new field-mutations across the pulmonary epithelia. Macrophages are considered the main players of chronic inflammation, which results in tissue destruction due to the increased release of high levels of pro-inflammatory cytokines and matrix metalloproteinases, as compared to non-smokers (13,14).

The augmented expression of adhesion molecules on activated macrophages enhances cell-to-cell interactions with T cells, which results in cytokine synthesis and release. Il-1 secreted by macrophages activates clonal proliferation of helper T lymphocytes (CD4+ Th). T helper cells secrete interleukin 2 (IL-2) that activates cytotoxic T lymphocyte effector T cells (CD8+ T cell). Alveolar macrophages are the main phagocytic cells in the lungs of non-smokers and those levels are increased in the bronchi-alveolar fluid (BAL) of smokers. Those macrophages also show altered phenotypes with the phagocytic activity significantly reduced, which decreases macrophages ability to eliminate inflammatory debris and apoptotic neutrophils from the lung (11).

Heguy *et al.* [2006] genotyped alveolar macrophages from smokers and non-smokers and found that 40 genes had increased expression whereas 35 others had decreased expression in smokers, when compared to non-smokers. Most of the altered genes played roles in the inflammatory response, cell adhesion, extracellular matrix, modulation of proteolysis, signal transduction, lysosomal function, antioxidant activity, and transcription factors (15).

Forsslund *et al.* [2014] investigated subpopulations of lymphocytes in 40 current smokers, 40 never smokers, and 40 former smokers, including patients with COPD (smokers and former smokers). They analyzed the BAL and the peripheral blood of all subjects and found that smokers (with or without COPD) had higher percentages of CD8+ T cells and natural killer (NK) T-like cells in the BAL than did never-smokers and ex-smokers with COPD. However, the percentages of CD4+ T cells were lower in smokers than in the nonsmoking subjects. In peripheral blood, the frequency of CD4+ T cells was increased in the two smoking groups (with and without COPD). Current smokers also had increased levels of activated naive and effector CD4+ T cells than nonsmokers, especially non-smoker patients with COPD. In male smokers with COPD, the percentage of CD8+ T cells in BAL fluid positively correlated with the daily number of smoked cigarettes (16).

NK cells (CD56+ CD3-) are also present in increased rates in the BAL fluid and peripheral blood of smokers, with and without COPD, while NK CD16+ levels are comparatively lower in the peripheral circulation of non-smokers without the disease (17,18). Other studies found that cigarette smoke have a suppressive activity on the expression of genes coding interferon gamma (IFN-γ) and tumor necrosis factor alfa (TNF-α) in human NKs CD56+ CD3-, in addition to reducing production of perforin, cytotoxicity, and cytolysis (19-21).

Cigarette smoke also contains high concentrations of ROS, and a recently published report showed that cigarette smoke extract (CSE) stimulates the synthesis of interleukin-17A (IL-17A) which, by its turn, induced the production of interleukine-8 (IL-8) via the receptors IL-17R on the surface of epithelial cells of the lungs and bronchi. IL-17 also activates pro-inflammatory signaling pathways by occupying receptors IL-17RA and IL-17RC on fibroblasts, endothelial and epithelial cells. IL-17 also recruits neutrophils to the respiratory tract by releasing IL-8 from the endothelial cells (22). Despite the amplification of inflammation, neutrophils exposed to tobacco smoke lose their ability to generate respiratory bursts and reduces phagocytosis, thus becoming less efficient in fighting pathogens in the respiratory tract (23,24).

The immune system always triggers, simultaneously, pro-inflammatory and anti-inflammatory responses, aiming at eliminating a pathogen (or a mutated protein) while preventing autoimmunity. Transforming growth factor beta (TGF-β) binds to receptors on the surface of cytotoxic T cells and transforms them into regulatory T cells (Tregs) which act by modulating the inflammatory process. Three subpopulations of Tregs were found in healthy smokers and patients with COPD: suppressive (rTregs) CD25++ CD45RA+; activated CD+++CD45RA- (aTregs), and pro-inflammatory CD25++CD45RA- (FrIII). FrIII secretes pro-inflammatory cytokines and when its population predominates over the other two, inflammation is enhanced

and the risk of autoimmunity increases (25). It was found that smoking impairs the immunosuppressive function of Tregs and causes imbalance between Treg subpopulations by reducing the number of rTregs and favoring autoimmunity in COPD patients, when compared with smokers without the disease. In contrast, rTreg levels are detected abnormally high in some healthy smokers, which predisposes to respiratory infections due to its immune suppressive effect. In COPD patients it was found that lower levels of rTregs and aTregs are accompanied by larger populations of FrIII cells which enhance cytokine secretion and the maintenance of inflammation (26).

Final thoughts

There is a vast literature on the impact of smoking on the immune system, which corroborates the mentioned studies; and new findings are underway. Carcinogens present in the smoke of tobacco products have an important role in altering the genome of immune cells, whether by implanting chemical adducts in the cellular DNA or by inducing irreversible genetic damage (27). Nicotine-releasing non-smoking surrogates are not at all innocuous and although some studies have been considering nicotine administration as a potential immune modulator for Parkinson, Alzheimer and Crohn's diseases, the matter remains highly controversial and requires deeper investigations (28).

All in all, tobacco smoking continues to be a huge public health challenge and a social and economic burden to nations, families, and individuals who precociously lose their health, productivity, and their lives under the yoke of nicotine addiction.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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