Original Article

Role of Immuno-Inflammatory Cells Modified by Smoking in Periodontitis

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Abstract

Periodontal disease is a chronic immuno-inflammatory disease resulting in the destruction of periodontal tissues. Oral biofilm with anaerobic microorganisms represents the main etiological factor for the occurrence of periodontal disease. However, the disease is influenced by several risk factors among which cigarette smoking is a major risk factor. The relationship between smoking and periodontal diseases has been studied broadly over the past 30 years. Cigarette smoke contains numerous toxic chemicals, which are known to have adverse effects on human cells and periodontal tissues. Chemicals found in cigarette smoke are also highly genotoxic and may lead to various forms of DNA damage. The initiation and progression of periodontal destruction result from the imbalance between the potentially pathogenic and intrinsic bacteria in dental plaque and the efficiency of the host's defense. Nicotine appears to disrupt the integrity and function of periodontal tissues. Smokers present with higher proportion of sites with deeper probing depths and clinical attachment loss compared with nonsmokers. Smoking results in cellular damage and also acts as an immunosuppressor. Many of the substances in cigarette smoke causes cytogenetic damage, immunomodulatory effects, carcinogenic or addictive activity. Smoking has been identified as an important long-term predictor for tooth loss in patients treated for periodontitis, and, also appears to cause a stronger inflammatory reaction with an increased release of tissue destructive substances. Therefore, this article is designed to elaborate the role of immuno-inflammatory cells modified by smoking in periodontitis.

Keywords: Smoking, Immune Cells, Periodontal Disease.

INTRODUCTION

Tobacco smoke is a complex mixture of thousands of different chemicals many of which have toxic and carcinogenic activity. The possibility that human diseases associated with cigarette smoke reflect the effects of tobacco smoke on the immune system. Since then, a large body of evidence tends to support this inference. The effects of cigarette smoke on the immune system may depend on the amount and duration of smoke exposure, ethnic background, genetic influence, and the gender of the smoker.1 The observation that exposure to smoke from high-tar high-nicotine cigarettes is more immunosuppressive than the smoke from low-tar low-nicotine cigarettes, this suggests that tar and nicotine may be important immuno-toxic components within cigarette smoke.2 Thus, effects of cigarette smoke on the immune system may reflect the cumulative effects of both immunosuppressive and immunostimulatory components of cigarette smoke. There is increasing evidence that chronic nicotine treatment leads to inhibition of the antibody response indicating that nicotine is a major immunosuppressive component in cigarette smoke. Growing evidence has indicated the positive association of cigarette smoking with abnormal responses of innate and adaptive immune. Thus this article discusses the immunomodulatory effects of smoking on immune-inflammatory cells.

Effects of Cigarette Smoking on Cells of Innate Immunity

Neutrophils

Smoking may influence the polymorphonuclear leukocytes (PMNs) by affecting the release of proteases such as elastase and collagenase. Elastase is one of the major proteases released by neutrophils. During inflammation elastase is release into the gingival tissue and increased levels are found in the gingival crevicular fluid (GCF). An increased release of elastase may contribute to the tissue destruction and development of periodontitis. The influence of smoking on elastase levels in periodontal disease conditions is controversial. Both increased, decreased, and similar levels of GCF elastase in smokers as compared to

non-smokers have been reported.3

The activity of the neutrophil proteases is mainly modulated by the serum protease inhibitors α-1-antitrypsin (α-1-AT) and α-2-macroglobulin (α-2-MG). An imbalance between protease and protease inhibitor is considered responsible for the development of emphysema in tobacco smokers. According to Gadek et al this imbalance is due to a decreased α-1-AT activity in smokers.4 It was found that the concentration of α-2-MG in plasma was increased in smokers compared to non-smokers.5 Lower levels of α-2-MG in plasma was reported in periodontitis patients in sites with tissue destruction compared to sites without tissue destruction.22 Smokers with periodontitis had suppressed levels of GCF α-2-MG and α-1-AT compared to nonsmokers, may be due to the less capillary permeability in smokers, since tobacco exerts vasoconstrictive effects on oral mucosal tissues.6

Macrophages

Macrophages play important role in inflammation and respond to exogenous pathogens via phagocytosis and digestion, and recruit/activate lymphocytes via their antigen-presenting ability.7M2 macrophage is regarded as a subset of anti-inflammatory cells that can attenuate inflammation8, whereas M1 macrophage is referred to as pro-inflammatory cells9. The bone marrow-derived mast cells exposed to cigarette smoke promoted the polarization of murine macrophages into M2 subset. Cigarette smoke has been shown to suppress phagocytic ability in macrophages in response to infection. Ko and others reported that both smoking and nicotine treatments could enhance the expression of pro-inflammatory chemokine IL-8 in macrophages of both humans and mice.10 The smoke-treated human macrophages and IL-8 produced by these macrophages facilitated inflammation, although studies on murine macrophages demonstrated that smoking remarkably suppressed the phagocytosis of macrophages and enhanced bacterial survival. Metcalfe et al found that cigarette smoke extract inhibited the responses of alveolar macrophages to TLR signaling and Haemophilus influenza stimulation.11 Regulatory mechanisms that control inflammatory mediators can also become dysfunctional when external stimulation of exposure to tobacco smoke, persists. Such chronic stimulation of macrophage-mediated immune responses may culminate in irreversible remodeling of resident tissues. The effects of nicotine on monocytes were not restricted to inhibition of the production of oxygen radicals, but it also interfered with secretion of the pro inflammatory cytokine, interleukin 1β (IL 1β).11 Several studies have shown nicotine to have both direct effect on the release of PGE2 and IL-1β by human monocytes treated with lipopolysaccharide and to inhibit the aerobic antimicrobial functions of mononuclear and PMNs leukocytes.

Dendritic Cells (DCS)

Dendritic cells are highly specialized antigen presenting cells (APCs) of the immune system. They are potent activators of naive T cells and are therefore regarded as important initiators of primary specific immune responses.12 T cells from smokers have shown a decreased ability to proliferate in response to T-cell mitogens.

Several cytokines such as IL- β, IL-10, IL-12 and TNF-α are produced by DCs in response to bacterial antigens. DCs exposed to nicotine produce lower levels of IL-1 β, IL-10, TNF- α and IL-12.13 The pro-inflammatory cytokines are down regulated, smokers exhibit reduced inflammation of the gingiva.

Natural Killer Cells (NK)

NK cells are a vital part of the innate immune system and play an essential role against microbial infections and tumour surveillance through rapidly secreting array of cytokines including IFN- ɣ and TNF- α. IFN- ɣ, provide innate resistance to a variety of intracellular pathogens prior to the development of adaptive immune responses.14-16 NK cells sense invading pathogens through a family of TLRs, which are capable of recognizing distinct molecular components in microbes. In NK cells, stimulation of TLR-3 leads to the production of IFN- ɣ and enhances cytotoxic activities. Cigarette smoke reduced NK cell cytotoxic ability, which was associated with reduced perforin expression by poly I:C-stimulated human NK cells. Importantly, cigarette smoke did not impact the cell viability but compromised NK cell function.17 In contrast, cigarette smoke likely inhibits IFN- ɣ secretion by interfering with cytokine signaling pathways required for IFN- ɣ production. More recently, it has been reported that nicotine inhibits the IL-18-enhanced production of IFN- ɣ by peripheral blood mononuclear cells.18

Effects of Cigarette Smoking on Cells of Adaptive Immunity

T lymphocytes

T lymphocytes (T cells) are a major subset of immune cells mediating adaptive immunity. In general, activation and differentiation of naive T cells upon antigen recognition generate effector T cells and, at a small frequency, memory and regulatory T cells. These cells exert their functions in response to specific antigens through their helper, effector, cytotoxic or regulatory capacities. Various studies have shown the profound impacts of cigarette smoking on T cells and their release of pro-inflammatory mediators.13

CD8+ T cells are also known as cytotoxic T lymphocytes (CTLs), which play an important role in host immune defence via

killing infected or damaged cells. Nicotine showed reduced levels of pulmonary Th2-related chemokines and cytokines, and inhibited eosinophil migration. Th17 cell is actively involved in worsening smoking-associated inflammation and autoimmune diseases, including COPD, Crohn's disease (CD), colitis, Rheumatoid Arthritis (RA) and psoriasis via suppression of IL-17 expression. Moreover, cigarette smoking may promote autoimmune diseases by enhancing Th1 polarization. Smoking also promotes Th2 mediated pulmonary inflammation and allergy in animal studies. Further investigations, especially in humans, are needed to provide mechanistic insight into the effects of cigarette smoke on Th1/Th2/Th17 responses and allergy or autoimmune diseases mediated by these T helper cells.

T helper cells

Forsslund et al analysed T cells in Broncho-alveolar lavage (BAL) fluid and peripheral blood from 40 nonsmokers, 40 smokers with normal pulmonary function and 38 COPD patients. They found that the percentage of CD8+ BAL cells of smoking groups was higher than that of non-smoking groups while the frequency of CD4+ T cells in both BAL and blood of smokers was lower than that of non-smokers 19. Zhang et el found that the homeostasis of circulating T helper cells was disrupted in chronic COPD patients compared with healthy nonsmokers.20 Second-hand smoke (SHS) also affected T cell components. Effects of smoking on Th1 cells causes increase in its cell percentage and alteration of interferon-ɣ; on Th2, it causes increase in Interleukins (IL) like – IL 4, IL 5, IL 13; on Th17, it causes increase in IL 6, IL 23, IL 17.13

B Cells

Recent investigations have focused on the mechanisms underlying smoking-induced changes in distribution and function of B cells. Epidemiologic studies showed that cigarette smoking resulted in higher prevalence of (class-switched) memory B cells in peripheral blood and memory IgG+ B cells in the lung and lowers regulatory B cell numbers.8,9 Moreover, analyses of Immunoglobulins (IG) levels in smokers demonstrated a decreased production of IgA, IgG, IgM and elevated level of circulating IgE.10-12

Regulatory T Cells (Treg)

Cigarette smoking impairs immunosuppressive function of Tregs by reducing the number of suppressive Tregs or increasing the prevalence of non-suppressive Tregs. The increased Treg numbers may occur in some smokers under circumstances, leading to worsened respiratory infections and periodontal disease conditions.13 Epidemiologic investigations have revealed that smoke exposure is associated with the imbalance of Tregs in COPD patients or smokers. Barceló et al. reported a significant downregulation of CD4+ CD25+ Treg cells in BAL fluid of patients with COPD compared with healthy smokers. Subsequent analyses by other groups demonstrated a similar tendency in circulating CD4+ and CD8 + Tregs of COPD patients.21 Furthermore, smoking or passive cigarette smoke exposure during gestation contributed to reduced Treg numbers in cord blood, resulting in a higher risk of neonatal atopic dermatitis and food allergy.22

Memory Lymphocytes

Memory T cells are a subset of T lymphocytes that have been previously challenged by foreign pathogens or antigens and can respond rapidly and vigorously upon reencounter with the same antigen. Similarly, memory B cells can quickly and effectively generate antibodies upon encounter with a previously-met antigen.52 Thus, both memory lymphocytes play important roles in human immune defences. Early studies showed that tobacco smoking apparently elevated memory T cells (CD3+ CD45RO+, CD4+ CD45RO+) and class-switched memory B cells in human peripheral blood.23-25

In mice, smoking also reduces memory T cells, especially cytotoxic T lymphocytes. These results indicate that cigarette smoking exerts dual influences on the generation of memory T cells, perhaps depending on an individual's genetic background and environment.13

Effects of Cigarette Smoking on Human Erythrocytes and Platelets

Cigarette smoke contains a considerable amount of oxygen free radicals such as superoxide anions, nitrogen radicals and hydroxyl radicals. In cigarette smoking, blood constituents like plasma, platelets, RBC and WBC are exposed to smoke. The blood cells contain strong antioxidant-defence system, consisting of proteins or enzymes and small molecules like vitamins C and E, to maintain the reducing environment of the body. Among these antioxidant enzymes, catalase, glutathione peroxidase and superoxide dismutase (SOD) directly inactivate free radicals and prevent free radical initiated reactions and plays a significant role in neutralizing the deleterious effects of H2O2. Red blood cells and platelets decreased antioxidant enzyme activities may lead to the accumulation of H2O2 and making them prone to damage by iron mediated formation of oxy-radicals.

In addition to the impairment of antioxidant status of a cell, cigarette smoking causes an imbalance in the intraplatelet redox state, which in turn becomes an important mechanism for the impaired platelet derived nitric oxide bioactivity in smokers.26 Accumulation of these reactive free radicals causes loss of cell membrane integrity. The ultimate result of smoking and neutrophil inflammation is an oxidant/antioxidant imbalance. The toxic products or free radicals present in cigarette smoke are

thought to activate inflammatory immune responses, which may play an important role in smoking-related oxidative tissue damage.

Padmavathi et al found increased lipid peroxidation and protein oxidation in erythrocyte and platelet membranes of smokers suggesting the susceptibility for oxidative damage by free radicals. However, polyunsaturated fatty acids within the membrane and iron-rich haemoglobin make red cells more susceptible to peroxidative damage.27 It has been reported that the carbon and oxygen centred radicals generated from nitric oxide in the gas phase of cigarette smoke initiate platelet and erythrocyte membrane lipid peroxidation, this process results in structural alterations and leading to impairment of the membrane related functions. In addition, proteins appear to be the most critical targets of oxidative insult within the cell because their oxidative modification severely impairs their catalytic functions. One possibility for increased carbonyl content in smokers is that cigarette smoke contains protein damaging radicals, such as hydroxyl, peroxyl, alkoxyl and these radicals oxidize proteins. Decrease in plasma vitamin C and GSH content in smokers, increased the susceptibility towards oxidative stress in these subjects. Under hypoxic conditions, kidney produces and secretes erythropoietin (EPO) to increase the production of red blood cells. Smoking may influence biomarkers of iron status through its inflammatory effect on metabolites. In continuous exposure to carbon monoxide by cigarette smoke may produce a degree of hypoxia that leads to increased haemoglobin concentrations as an adaptive response by up-regulating EPO.

Effects of Smoking on Cells of Allergic Reactions

Human Mast Cells

Mast cells are potent source of producing which has a regulatory role in angiogenesis and vascular function.28,29 In inflammatory conditions, mast cells are activated by cytokines and release pro-inflammatory mediators. The mechanism by which mast cell mediated angiogenesis has been attributed to synthetizing pro-angiogenic micro-molecules including heparin, histamine, basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF) and various cytokines such as TNF-α and IL-8.29-31 Mast cells have a unique biologic feature because of involvement in chronic inflammation and even tumor development. Mast cells synthesize and release cytokines, growth factors and angiogenic compounds. Chronic inflammation stimulates the proliferation of tissue mast cells population and recruitment of circulating precursors. After activation, mast cells produce pro-angiogenic mediators such as VEGF and promote angiogenesis in inflammatory conditions. As histamine is a main product of mast cells, these cells can regulate bone destruction. Mast cells have multifactorial role in tissue new angiogenesis by producing different metalloproteases. Mast cells stimulate the migration and proliferation of endothelial cells in angiogenesis progression. On a mutual action, VEGF directly or indirectly recruits mast cells to tissues. Smoking suppresses the number of mast cells production which may lead to decreased gingival bleeding, reduced number of new blood vessels formation and delayed wound healing. 32

Basophils

Cigarette smoking has been reported to result in both an increase and a decrease in the number of circulating basophils. The observed decrease in the number of circulating basophils detected in smokers shortly after cigarette smoking has been attributed to basophil degranulation. Samanek and Avaido, observed that cigarette smokers had higher histamine levels in blood compared to non-smokers.33 It has been speculated that repeated degranulation of basophils following chronic smoke inhalation may result in an increased number of basophils being released by the bone marrow. These data may suggest that basophil cells, like phagocytic leukocytes, have a non-cholinergic receptor that is sensitive to nicotinic agonists.34 Previous studies performed on capillary blood collected before and 10 min following completion of smoking one or two cigarettes have shown that cigarette smoking directly triggers basophil degranulation.

Discussion

Experimental studies on plaque-induced gingivitis in humans suggest that clinical signs of gingival inflammation are not so prominent in smokers due to suppression of immune response. A clinical study has shown that a single cigarette can reduce the peripheral blood velocity by 40% in one hour.35 The mechanism by which smoking may affect wound healing is unknown. One possible explanation is that the substances in tobacco and its smoke, particularly nicotine, cotinine, carbon monoxide, and hydrogen cyanide are cytotoxic to those cells that are involved in wound healing. The vasoconstrictive effects of nicotine increase platelet adhesiveness, increase the risk of microvascular occlusion and cause tissue ischemia. These phenomena can negatively influence periodontal wound healing and the repair and regenerative capacities of periodontal tissues in smoking patients. Other proposed mechanisms regarding the negative effect of smoking on periodontal tissues include decreased vascular flow; decreased IgG production and lymphocyte proliferation; altered neutrophilic function; amplified prevalence of periodontal pathogens; and negative local effects on growth factor and cytokine production.36,37 Smoking may impair the periodontal tissue defenses to the bacterial invasion induced by plaque. Exposure to tobacco smoke decreases, alters, and

impairs polymorphonuclear leukocytes, which play an essential role in periodontal defense. The compromised phagocytic functions of these cells—adhesion, ingestion, and motility—can worsen the periodontal pathology. Smokers exhibit discrete inflammatory signs even in the presence of extensive tissue destruction.

The negative effects of smoking on the humoral immune response have been extensively studied and have been considered as one of the main mechanisms for the increased occurrence of periodontitis in smokers.38,39 A recent study showed a decreased respiratory burst in neutrophils, indicating a decreased ability to kill bacteria by the production of reactive oxygen species, but increased degranulation, which contributes to an elevated release of tissue-degrading enzymes and consequently tissue destruction. 40

Grossi et al41 reported that smokers have less reduction in subgingival T. forsythia and P. gingivalis after non-surgical treatment compared with former and non-smokers, suggesting that smoking impairs periodontal healing. Smoking generally decreases serum IgG concentrations and decreases IgG2 antibody production in patients with early onset periodontitis. The proliferative response of T-cells to antigens is decreased by long term exposure to cigarette smoke. There is enough evidence, indicating that smoking affects the innate and immune host responses. Although smokers actually have significantly higher numbers of neutrophils, the first line of defense against bacterial infection, their function is impaired in peripheral circulation. Neutrophils have shown decreased chemotaxis, phagocytosis, and adherence in smokers. Integrin expression and protease inhibitor production is also affected. On the other hand, exposure of unstimulated neutrophils to smoke has been shown to elevate the oxidative burst, which could enhance tissue destruction through direct toxic effect. Antibody production is another protective host mechanism that is altered by smoking.

Proinflammatory cytokines ⁄ chemokines compared with controls. Among periodontitis patients, smokers had decreased amounts of several proinflammatory cytokines (interleukin-1a, interleukin-6 and interleukin-12 [p40]), chemokines (interleukin-8, monocyte chemotactic protein-1, macrophage inflammatory protein-1 and regulated upon activation, normal T-cell expressed, and secreted [RANTES]) and the T-cell regulators (interleukin-7 and interleukin-15). These findings seem to indicate that smoking may have an immunosuppressant effect contributing to an increased susceptibility to periodontitis.

Conclusion

Tobacco smoking seems to induce changes in innate and immune cells such as decreased leukocyte chemotaxis and decreased production of immunoglobulins, and impaired phagocytosis. It is also found that, smoking appears to cause a stronger inflammatory reaction with an increased release of tissue destructive substances (e.g. reactive oxygen species, collagenase, serine proteases and proinflammatory cytokines). An increased inflammatory response is in line with the overall hypothesis that periodontitis is a hyper inflammatory condition rather than a hypo-inflammatory condition. Compared with nonsmokers, smokers demonstrate satisfactory but slower and less complete healing after periodontal treatment. Nevertheless, the accelerated progression and greater severity of periodontal disease in smokers must not preclude aggressive treatment. Although the deleterious local and systemic effects of tobacco products on periodontal health are confirmed, further research is still warranted to enhance our understanding of this entire process.

Conflict of Interest

The authors have no proprietary, financial or other personal interest of any nature or kind in any product, service, and/or company that is presented in this article.

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Data availability

Datasets related to this article will be available upon request to the corresponding author

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REFERENCES

1. Tomar SL, Asma S. Smoking-attributable periodontitis in the United States: findings from NHANES III. Journal of periodontology. 2000 May;71(5):743-51.
2. Pindborg JJ. Tobacco and gingivitis. Journal of dental research. 1947 Jun;26(3):261-4.
3. Alavi AL, Palmer RM, Odell EW, Coward PY, Wilson RF. Elastase in gingival crevicular fluid from smokers and non-smokers with chronic inflammatory

periodontal disease. Oral Diseases. 1995 Sep;1(3):110-4.
4. Gadek JE, Fells GA, Crystal RG. Cigarette smoking induces functional antiprotease deficiency in the lower respiratory tract of humans. Science. 1979 Dec 14;206(4424):1315-6.
5. Tappia PS, Troughton KL, Langley-Evans SC, Grimble RF. Cigarette smoking influences cytokine production and antioxidant defences. Clinical Science (London, England: 1979). 1995 Apr 1;88(4):485-9.
6. Persson L, Bergström J, Ito H, Gustafsson A. Tobacco smoking and neutrophil activity in patients with periodontal disease. Journal of periodontology. 2001 Jan;72(1):90-5.
7. Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. Nature reviews immunology. 2008 Dec;8(12):958-69.
8. Li H, Yang T, Ning Q, Li F, Chen T, Yao Y, Sun Z. Cigarette smoke extract–treated mast cells promote alveolar macrophage infiltration and polarization in experimental chronic obstructive pulmonary disease. Inhalation Toxicology. 2015 Dec 6;27(14):822-31.
9. Mills C. M1 and M2 macrophages: oracles of health and disease. Critical Reviews™ in Immunology. 2012;32(6).
10. Ko HK, Lee HF, Lin AH, Liu MH, Liu CI, Lee TS, Kou YR. Regulation of cigarette smoke induction of IL-8 in macrophages by AMP-activated protein kinase signaling. Journal of cellular physiology. 2015 Aug;230(8):1781-93.
11. Metcalfe HJ, Lea S, Hughes D, Khalaf R, Abbott-Banner K, Singh D. Effects of cigarette smoke on Toll-like receptor (TLR) activation of chronic obstructive pulmonary disease (COPD) macrophages. Clinical & Experimental Immunology. 2014 Jun;176(3):461-72.
12. Nouri-Shirazi M, Guinet E. Evidence for the immunosuppressive role of nicotine on human dendritic cell functions. Immunology. 2003 Jul;109(3):365-73.
13. Qiu F, Liang CL, Liu H, Zeng YQ, Hou S, Huang S, Lai X, Dai Z. Impacts of cigarette smoking on immune responsiveness: up and down or upside down?. Oncotarget. 2017 Jan 3;8(1):268.
14. Bancroft GJ. The role of natural killer cells in innate resistance to infection. Current opinion in immunology. 1993 Aug 1;5(4):503-10.
15. Biron CA. Activation and function of natural killer cell responses during viral infections. Current opinion in immunology. 1997 Feb 1;9(1):24-34.
16. Cerwenka A, Lanier LL. Natural killer cells, viruses and cancer. Nature reviews immunology. 2001 Oct;1(1):41-9.
17. Mian MF, Lauzon NM, Stämpfli MR, Mossman KL, Ashkar AA. Impairment of human NK cell cytotoxic activity and cytokine release by cigarette smoke.
18. Strzelak A, Ratajczak A, Adamiec A, Feleszko W. Tobacco smoke induces and alters immune responses in the lung triggering inflammation, allergy, asthma and other lung diseases: a mechanistic review. International journal of environmental research and public health. 2018 May;15(5):1033.
19. Forsslund H, Mikko M, Karimi R, Grunewald J, Wheelock ÅM, Wahlström J, Sköld CM. Distribution of T-cell subsets in BAL fluid of patients with mild to moderate COPD depends on current smoking status and not airway obstruction. Chest. 2014 Apr 1;145(4):711-22.
20. Zhang MQ, Wan Y, Jin Y, Xin JB, Zhang JC, Xiong XZ, Chen L, Chen G. Cigarette smoking promotes inflammation in patients with COPD by affecting the polarization and survival of Th/Tregs through up-regulation of muscarinic receptor 3 and 5 expression. PloS one. 2014 Nov 6;9(11):e112350.
21. Barcelo B, Pons J, Ferrer JM, Sauleda J, Fuster A, Agusti AG. Phenotypic characterisation of T-lymphocytes in COPD: abnormal CD4+ CD25+ regulatory T-lymphocyte response to tobacco smoking. European Respiratory Journal. 2008 Mar 1;31(3):555-62.
22. Hinz D, Bauer M, Röder S, Olek S, Huehn J, Sack U, Borte M, Simon JC, Lehmann I, Herberth G, LINA Study Group. Cord blood T regs with stable FOXP3 expression are influenced by prenatal environment and associated with atopic dermatitis at the age of one year. Allergy. 2012 Mar;67(3):380-9.
23. Good-Jacobson KL, Tarlinton DM. Multiple routes to B-cell memory. International immunology. 2012 Jul 1;24(7):403-8.
24. Tanigawa T, Araki S, Nakata A, Kitamura F, Yasumoto M, Sakurai S, Kiuchi T. Increase in memory (CD4+ CD29+ and CD4+ CD45RO+) T and naive (CD4+ CD45RA+) T-cell subpopulations in smokers. Archives of Environmental Health: An International Journal. 1998 Nov 1;53(6):378-83.
25. Nakata A, Takahashi M, Irie M, Fujioka Y, Haratani T, Araki S. Relationship between cumulative effects of smoking and memory CD4+ T lymphocyte subpopulations. Addictive Behaviors. 2007 Jul 1;32(7):1526-31.
26. Takajo Y, Ikeda H, Haramaki N, Murohara T, Imaizumi T. Augmented oxidative stress of platelets in chronic smokers: mechanisms of impaired platelet-derived nitric oxide bioactivity and augmented platelet aggregability. Journal of the American College of Cardiology. 2001 Nov 1;38(5):1320-7.
27. Padmavathi P, Raghu PS, Reddy VD, Bulle S, Marthadu SB, Maturu P, Varadacharyulu NC. Chronic cigarette smoking-induced oxidative/nitrosative stress in human erythrocytes and platelets. Molecular & Cellular Toxicology. 2018 Jan;14(1):27-34.
28. Rodewald HR, Feyerabend TB. Widespread immunological functions of mast cells: fact or fiction?. Immunity. 2012 Jul 27;37(1):13-24.
29. Kennedy S, Wu J, Wadsworth RM, Lawrence CE, Maffia P. Mast cells and vascular diseases. Pharmacology & therapeutics. 2013 Apr 1;138(1):53-65.
30. Grutzkau A, Kruger-Krasagakes S, Baumeister H, Schwarz C, Kogel H, Welker P, Lippert U, Henz BM, Moller A. Synthesis, storage, and release of vascular endothelial growth factor/vascular permeability factor (VEGF/VPF) by human mast cells: implications for the biological significance of VEGF206. Molecular biology of the cell. 1998 Apr 1;9(4):875-84.
31. Möller A, Lippert U, Lessmann D, Kolde G, Hamann K, Welker P, Schadendorf D, Rosenbach T, Luger T, Czarnetzki BM. Human mast cells produce IL-8. The Journal of Immunology. 1993 Sep 15;151(6):3261-6.
32. Naderi NJ, Semyari H, Hemmati R. The effect of smoking on mast cells density and angiogenesis in chronic periodontitis. Iranian journal of pathology. 2017;12(4):384.
33. Samanek M, Aviado DM. Bronchopulmonary Effects of Tobacco and Related Substances: II. Bronchial Arterial Injections of Nicotine and Histamine. Archives of Environmental Health: An International Journal. 1965 Aug 1;11(2):152-9.
34. Davies BD, Hoss W, Lin JP, Lionetti F. Evidence for a noncholinergic nicotine receptor on human phagocytic leukocytes. Molecular and cellular biochemistry. 1982 Jan;44(1):23-31.
35. Chapple IL. Reactive oxygen species and antioxidants in inflammatory diseases. Journal of clinical periodontology. 1997 May;24(5):287-96.
36. Johnson GK, Hill M. Cigarette smoking and the periodontal patient. Journal of periodontology. 2004 Feb;75(2):196-209.
37. Solomon HA, Priore RL, Bross ID. Cigarette smoking and periodontal disease. The Journal of the American Dental Association. 1968 Nov 1;77(5):1081-4.
38. Moszczyński P, Żabiński Z, Moszczyński Jr P, Rutowski J, Słowiński S, Tabarowski Z. Immunological findings in cigarette smokers. Toxicology letters. 2001 Jan 3;118(3):121-7.
39. Gyllén P, Andersson BA, Qvarfordt I. Smokeless tobacco or nicotine replacement therapy has no effect on serum immunoglobulin levels. Respiratory medicine. 2004 Feb 1;98(2):108-14.
40. Hu J, Qian W, Yu Z, Xu T, Ju L, Hua Q, Wang Y, Ling JJ, Lv H. Increased neutrophil respiratory burst predicts the risk of coronary artery lesion in Kawasaki disease. Frontiers in Pediatrics. 2020 Jul 28;8:391.
41. Grossi SG, ZAMBON J, MACHTEI EE, SCHIFFERLE R, ANDREANA S, GENCO RJ, CUMMINS D, HARRAP G. Effects of smoking and smoking cessation on healing after mechanical periodontal therapy. The Journal of the American Dental Association. 1997 May 1;128(5):599-607.