Journal of Neuroimmunology 329 (2019) 24–34

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Review Article

Effects of cigarette smoke on immunity, neuroinflammation and multiple sclerosis

Mohammed Alrouji[a,b], Ali Manouchehrinia[c], Bruno Gran[a], Cris S. Constantinescu[a,*]

[a] Division of Clinical Neuroscience, Section of Clinical Neurology, University of Nottingham, Nottingham, United Kingdom
[b] School of Applied Medical Sciences, Shaqra University, Saudi Arabia
[c] Department of Clinical Neuroscience, Karolinska Institutet, Solna, Sweden

ARTICLE INFO

Keywords:
Smoking
Multiple sclerosis
Neuroinflammation
T cells
B cells

ABSTRACT

Cigarette smoking is the most prominent significant cause of death and morbidity. It is recognised as a risk factor for a number of immune mediated, inflammatory diseases including multiple sclerosis (MS). Here, we review the complex immunological effects of smoking on the immune system, which include enhancement of inflammatory responses with a parallel reduction of some immune defences, resulting in an increased susceptibility to infection and a persistent proinflammatory environment.

We discuss the effect of smoking on the susceptibility, clinical course, disability, and mortality in MS, the likely benefits of smoking cessation, and the specific immunological effects of smoking in MS.

In conclusion, smoking is an important environmental risk factor for MS occurrence and outcome, and it acts in significant part through immunological mechanisms.

1. Introduction

Multiple Sclerosis (MS) is a chronic inflammatory demyelinating disease with progressive neurodegeneration of the central nervous system (CNS) in which autoreactive lymphocytes infiltrate across the blood-brain barrier (BBB) and lead to myelin and axon damage (Compston and Coles, 2008). The aetiology of MS remains unknown, but the disease is thought to develop in genetically susceptible individuals with the influence of environmental risk factors, including infectious agents and smoke constituents (Dendrou et al., 2015). Genome-wide association studies (GWAS) on MS and other immune mediated disease suggest that non-genetic risk factors have a significant contribution, possibly more prominent than genetic risk factors, to immunological heterogeneity in general (Brodin et al., 2015; Dendrou et al., 2015). Exposure to cigarette smoke is a well-established environmental risk factor that has been shown to increase the risk of developing MS and many other chronic inflammatory diseases by affecting the inflammatory responses (Gonçalves et al., 2011; Hagiwara et al., 2001; Wasén et al., 2017). However, the exact mechanism by which cigarette smoke increases the risk of inflammatory diseases is yet to be elucidated.

Biological studies have shown that cigarette smoke impacts both the innate and the adaptive immune responses and has dual effects in the regulation of immunity by either attenuating the defensive immunity or worsening of the pathogenic immune responses. These studies have been performed on different chronic inflammatory diseases; including chronic obstructive pulmonary disease (COPD), asthma, rheumatoid arthritis (RA), psoriasis and, to a lesser extent, multiple sclerosis (MS) (Gonçalves et al., 2011; Perricone et al., 2016; Rennard, 2004; Torii et al., 2011).

Here, we review the immunological effects of cigarette smoking on innate and adaptive immunity that impact different chronic inflammatory diseases; then, we focus on its impact on MS from different aspects, including immunology, epidemiology and epigenetics and propose a model summarizing the potential mechanisms involved in the cigarette smoke associated immunomodulation.

Finally, we review the evidence for the role of smoking in the risk of developing MS, the risk of disability progression in MS and its contribution to early mortality.

2. Cigarette smoke (CS) and inflammation

Cigarette smoke contains over 4000 chemicals, including carbon dioxide, carbon monoxide, nicotine, reactive oxygen species (ROS), reactive nitrogen species (RNS), free radicals, among many others (Rennard, 2004; Sopori, 2002). These chemicals dissolve very quickly

* Corresponding author at: Division of Clinical Neuroscience, Section Clinical Neurology, University of Nottingham, Queen's Medical Centre, South Block C Floor, Nottingham NG7 2UH, UK.
E-mail address: cris.constantinescu@nottingham.ac.uk (C.S. Constantinescu).

https://doi.org/10.1016/j.jneuroim.2018.10.004
Received 18 March 2018; Received in revised form 30 September 2018; Accepted 5 October 2018

in the fluids of oral and airway epithelial linings and are spread into all body tissues through the blood circulation (Lee et al., 2012). Studies have shown that burning of tobacco gives two types or phases of constituents, gaseous and particulate. Reactive oxygen species (ROS) that are not trapped by cigarette filters and do not exist in raw tobacco leaf can be found in the gaseous phase and are short lived, impacting the upper airways; The most toxic CS components are found in the particulate phase, including particulate matter ('tar'), nicotine and others (Huang et al., 2005; Smith and Fischer, 2001; Witschi, 2005). These different constituents of burned tobacco start to react with the immune system in the mucosal surfaces lining the oral cavity, sinuses and airways. Inflammation, lipid peroxidation, oxidative-sensitive cellular pathways and DNA destruction are key pathological processes triggered by smoking (Rom et al., 2013; Yanbaeva et al., 2007).

ROS and many other stimuli can trigger immune cell activation, expansion and secretion of inflammatory mediators which in turn lead to chronic immune cell recruitment and inflammation. Many other adverse consequences of chronic cigarette smoking exposure could also be elucidated by its impact on systemic inflammation.

2.1. CS impact on innate immunity

The innate immunity serves as a primary immune defence that recognises and responds to the environmental pathogens and antigens. Innate immune cells express pattern-recognition receptors (PRRs), including Toll-like receptors (TLRs) and others, which can recognise the pathogen-associated molecular patterns (PAMPs), such as viral nucleic acids and cell wall components of bacteria and fungi, and induce the inflammatory responses (Iwasaki and Medzhitov, 2015). One of the important routes for these pathogens to enter the body are the lungs. Alveolar leukocytes and ciliary epithelial cells lining the alveolar and nasal surfaces are part of the innate immune defence system (Martin and Frevert, 2005). Chemokines and chemokine receptors (CCRs) play an important role in the migration of specific mononuclear cells from the circulation into the areas of inflammation and the regional lymph nodes, leading to the development of an adaptive immune response induction. Chemokines contribute to the pathogenesis of many inflammatory diseases (Charo and Ransohoff, 2006).

2.2. Effects of CS on epithelial cells

Lung epithelial cells play a main role in innate immune responses regulation against a variety of stimuli, such as microbial pathogens and cigarette smoke. They are a target of various respiratory infections as they are the first cells that encounter inhaled pathogens. In smokers, the mucociliary clearance of bacteria and viruses by bronchial epithelium is impaired, allowing the pathogens to reach the lower airways, thus explaining the increased incidence of infections (Leopold et al., 2009; Xavier et al., 2013). Cigarette smoking can impact the lower airway epithelial cells, resulting in an immediate stimulation and inflammatory mediator secretion followed by macrophage and neutrophil recruitment that leads to further damage to the lung tissue. For instance, cigarette smoke condensate has been reported to induce the production of soluble intercellular adhesion molecule 1 (sICAM-1), Granulocyte Monocyte Colony Stimulating factor (GM-CSF), Interleukin-1 β (IL-1β) and neutrophil chemoattractant IL-8 (Duffney et al., 2017; Hellermann et al., 2002). It has been shown that CS exposed mice had a significant reduction in bronchoalveolar lavage fluid (BALF) macrophages, neutrophils, cytokines and chemokines, such as TNF-α, macrophage inflammatory protein (MIP)-2 and matrix metalloproteinase (MMP)-12 after treatment with intranasal anti–GM-CSF mAb (Vlahos et al., 2010).

In addition, danger-associated molecular pattern molecules (DAMPs) or alarmins, endogenous intracellular molecules released by activated or necrotic cells and extracellular matrix molecules, have been recognised to mediate sterile inflammatory responses after cell stress or injury. These DAMPs were found to be recognised by the same host PRRs that are used for PAMPs recognition leading to the same pro-inflammatory cytokines and chemokines upregulation (Rider et al., 2017). Necrotic cells are passively releasing another subset of intracellular proteins that were found to mediate sterile inflammation, including several members of IL-1 family such as IL-33 which is, in contrast with the variety of DAMPs, recognised by the ST2 receptor (IL-1R-Like 1) not PAMP receptors like TLRs (Moussion et al., 2008; Rider et al., 2017). Cigarette smoke was found to increase the expression of IL-33 in bronchial epithelial cells and this increased expression can markedly augment macrophage responses to poly (I:C), a viral PAMP (Kearley et al., 2015; Pace et al., 2014).

2.2.1. Effects of CS on macrophages

Macrophages play an important role in innate host defence against pollutants and elimination of microbial agents, due to their ability to recognise PAMPs antigen presentation, and phagocytosis. The number of alveolar macrophages (AMs) is increased upon cigarette smoke exposure, leading to their activation and production of ROS and inflammatory mediators (Sopori, 2002). Despite the increased activity, the capabilities of macrophages to sense the PAMPs and phagocytose and kill the microbes can be reduced by smoking (Chen et al., 2007; Hodge et al., 2007; Ni et al., 2015; Phipps et al., 2010). Compared to non-smokers, AM of smokers had a decreased surface expression of TLR2, a PRR that recognises (as a heterodimer with TLR1 or TLR6) a range of ligands such as diacyl-lipopeptides, triacyl-lipopeptides and others (Droemann et al., 2005; Zähringer et al., 2008). Neutralization of TLR4, an essential PRR protein that recognises lipopolysaccharide (LPS), a microbial component from gram-negative bacteria, and other endogenous proteins, but not TLR2 led to inhibition of cigarette smoke induced IL-8 secretion by monocytes derived macrophages (Karimi et al., 2006). Doz and colleagues suggested that cigarette smoke induced airway inflammation is mediated by LPS-independent TLR4 activation and myeloid differentiation primary-response gene 88 (MyD88)-dependent pathways, apparently after induction of heat-shock protein 70 (HSP70), which has been suggested as putative TLR4 agonist (Doz et al., 2008). However, although activation of TLR4 by HSP70 remains controversial, its activation by cigarette smoke maybe by LPS in cigarette smoke directly which has been shown to present in a bioactive form in CS (Hasday et al., 1999).

Cord blood mononuclear cells of neonates born of smoker mothers have less TLR-mediated response compared with those of non-smokers mothers (Noakes, 2006). In response to some TLR agonists, cigarette smoking seems to cause a local suppression of AM activity, demonstrated by its ability to affect the gene expression and secretion of some pro-inflammatory cytokines which could contribute to an increased incidence of infection (Chen et al., 2007; Karimi et al., 2006; Metcalfe et al., 2014; Todt et al., 2013). Thus, the effect of smoking on macrophages is complex, with some aspects of inflammation being enhanced, but some defence mechanisms against infection being reduced, overall creating an immune environment that can favour chronic inflammation and autoimmunity.

2.2.2. Effects of CS on dendritic cells

Dendritic cells (DC) are potent antigen-presenting cells (APCs) and vitally important for the initiation of cell-mediated immune responses. (Merad et al., 2013). DC migrate from the circulation towards the lung epithelial surfaces where they can recognise the foreign antigens. After antigen recognition and capture, they migrate back into the regional draining lymph nodes where they present the processed antigens to naïve T lymphocytes via major histocompatibility complex (MHC) class II/T-cell receptor (TCR) ligation, resulting in the initiation, suppression or termination of adaptive immune responses. During migration, DC process the recognised antigens and go through maturation accompanied by upregulation of co-stimulatory molecules expression at the cell surface; such as CD40, CD80 and CD86 (Idoyaga and Steinman, 2011; Liu et al., 2009). The airway epithelial cells surrounded by rich

network of DC, normally control the immunologic homeostasis (Steinman, 2012). Chemokines and their corresponding receptors (CCRs) are key determinants of lymphocytes recruitment into lymphoid follicles. The homing of immature T cells and mature DC to the lymph node is controlled by CCR7, an important receptor that influences the immune responses in the lymph nodes and peripheral tissues via dedicated ligands; including, the lymphoid chemokine ligand (CCL)19 and CCL21 (Förster et al., 2008).

It has been shown that in mice exposed to cigarette smoke and sensitized with ovalbumin (OVA), an inducer of an allergic reaction, the expression of CCR7, MHC class II and CD86 is upregulated and trafficking of DC to the mediastinal lymph node is induced (Robays et al., 2009). Furthermore, the frequency of pulmonary DCs is enhanced by passive smoking, leading to their accumulation, activation and CCL20 expression (Botelho et al., 2012). A significant increase in lung DC in the epithelium of small airways and the expression of CCL20 was reported in patients with chronic obstructive pulmonary disease (COPD) and was associated with disease severity, compared to smokers and non-smokers without COPD (Demedts et al., 2007).

On the other hand, it has been shown that exposure to cigarette smoke or its extract could negatively regulate the frequency and maturation process of DC, and can alter or suppresses the normal DC function and interaction with naïve lymphocytes. In mouse studies, cigarette smoke extract (CSE) was found to reduce the frequency, maturation and stimulation capacity of DC. In addition, this effect was accompanied by diminished surface expression of MHCII, CD80, CD86, CD40 and CD83 in DC. (Givi et al., 2015; Robbins et al., 2008). Similarly, Liao and colleagues found that the frequency of migratory ($CCR7^+$) and mature ($CD83^+$) DC were reduced in the lung tissue of smokers with COPD compared with healthy non-smokers (Liao et al., 2015). In smokers with or without COPD, the expression of $CCR7^+$ and function-associated surface molecules on airway myeloid DC (CD40, CD80 and CD83) were found to be significantly decreased compared to non-smokers but the number of immature DC ($CD1a^+$) was significantly increased in the COPD and healthy smoker groups as compared with healthy non-smokers (Arellano-Orden et al., 2016). In plasmacytoid dendritic cells (pDC) obtained from healthy volunteers, CSE exposure augmented the production of IL-8 and suppressed TLR9 ligand-induced interferon (IFN)-α through attenuation of the PI3K/Akt pathway (Mortaz et al., 2009). These studies indicate that cigarette smoking impacts the maturation process and function of DC, resulting in altered cell-mediated immune responses. Like with macrophages, a dual effect of CSE has been observed, with enhancement of both chronic inflammation and susceptibility to infections. These key components of tissue damage in smokers are relevant to respiratory diseases such as COPD, as well as to MS pathophysiology.

2.3. CS impact on adaptive immunity

As with innate immunity, smoking has been reported to have a direct and indirect effect on both humoral and cell-mediated adaptive immune responses, with the participation of B and T cells, including T-helper (Th)1, Th2, Th17 and regulatory T cells (Treg).

2.3.1. Effects of CS on T cells

Cytokines produced by monocytes, macrophages, neutrophils and DC during innate immune responses, drive differentiation of naïve $CD4^+$ T cells into Th1, Th2, or Th17 (also influencing certain subsets of Treg) reflecting a preferential activation of specific transcription factors and production of cytokines. For example, interleukin (IL)-12, an inflammatory cytokine produced by innate immune cells in response to various stimuli, induces naïve T cells' differentiation into Th1 cells that produce interferon-gamma (IFN-γ) rather than interleukin-4 (IL-4), a Th2 specific cytokine (Kidd, 2003).

Cigarette smoking can suppress certain Th1 and Th17 responses, while promoting Th2 inflammation. For instance, the secretion of IL-12 was reduced by CSE-exposed and LPS-activated DC, resulting in DC function suppression and generation of Th2 inflammatory responses (Vassallo et al., 2005). Recently, CSE was found to have an inhibitory effect on DC capacity to activate antigen specific T-cell response, generating a defective Th1 and Th17 response to bacteria in COPD patients (Le Rouzic et al., 2016). Normally, Th1 cells respond directly to short-chain LPS but this process was shown to be impaired in smokers with or without COPD (Knobloch et al., 2011). Whether Th17 inflammatory responses are stimulated by cigarette smoke is not conclusively proved; however, Shan and colleagues found that Th17 cells were present in the lung parenchyma of patients with emphysema, a disease that affects smokers, and the lung myeloid DC (mDC) were sufficient to direct the generation of adaptive Th1 and Th17 responses to self-antigens in people with emphysema but not normal individuals (Shan et al., 2009). Epidemiologically, the prevalence of Th17-associated inflammatory diseases also suggests that Th17 polarized immune responses might be promoted by cigarette smoke. The cellular mechanisms by which cigarette smoke induces Th2, and potentially Th17 inflammatory responses, are not fully elucidated, although these may include altered activation and antigen presentation by innate immune cells, induction of Th2 polarizing cytokines and inhibition of Th1 polarizing ones, or might be due to a direct effect on T cells (Lee et al., 2012). In animal models, smoking-associated inflammation and autoimmune diseases were shown to be actively associated with Th17 cells. An increase in Th17 cells subset and associated cytokine upregulation (IL-17A, IL-23 and IL-6) were found in the lung tissue and peripheral blood of mice with COPD induced by chronic cigarette smoke exposure (Wang et al., 2012). In an IBD murine model, nicotine, as a major component of cigarette smoke, can worsen the trinitrobenzene sulfonic acid (TNBS/ IL-12 driven)-induced colitis, by skewing Treg/Th17 balance towards pro-inflammatory Th17 cells, or improve the oxazolone colitis by increasing Treg cell number. It has been shown that the dichotomous action of nicotine in both types of IBD, Ulcerative colitis (UC) and Crohn's disease (CD) is a result of downregulation and upregulation of anti-inflammatory Alpha7 nicotinic acetylcholine receptor (a7 nAChR) on colonic CD4 T cells induced by the cytokine environment characteristic of each type of IBD leading to a worsened or improved colitis, respectively (Galitovskiy et al., 2011).

$CD8^+$ T cells are a large subgroup of T cells known as cytotoxic T lymphocytes (CTLs) and play a major role in host immune defence by identifying and killing cells with MHC class I molecules presenting pathogenic antigens. $CD8^+$ T cells have been shown to increase in the lungs of people with COPD (Saetta et al., 1998) and can induce inflammatory cytokines that may contribute to emphysema (Cosio et al., 2002; Majo et al., 2001). Maeno and colleagues reported that CSE could not induce inflammatory response and develop emphysema in $CD8^+$ T cell-deficient ($CD8^{-/-}$) mice (Maeno et al., 2007). In healthy subjects and COPD patients, the exposure of $CD8^+$ T cells to CS condensate was found to increases the protein expression of TLR4 and TLR9 in both lung tissue and peripheral blood mononuclear cells (PBMC), resulting in their activation and production of inflammatory cytokines including IL-1β, IL-6, IL-10, IL-12p70, TNFα and IFN-γ but not chemokine IL-8 (Nadigel et al., 2011).

2.3.2. Effects of CS on B cells

Cigarette smoke may induce abnormal functional changes in B cell responses which can be T cell-independent or T cell-dependent. In healthy current smokers compared to smokers with COPD, Brandsma and colleagues showed that cigarette smoking resulted in higher percentages of total memory B cells as well as class-switched memory B cells in peripheral blood. These class switched cells were mostly IgA expressing B cells which positively correlated with the number of class-switched memory B cells in healthy smokers, while COPD smokers showed more switching to IgG (Brandsma et al., 2009, 2012). In addition, cigarette smoke can induce the expression of Fas receptor (CD95), a transmembrane protein that induces programmed cell death

on peripheral blood cells in general and on B cells in particular (Bijl et al., 2001). This increased sensitivity to apoptotic signals could worsen the clearance mechanisms of apoptotic materials in people who are at risk of autoimmune diseases (Costenbader and Karlson, 2006). Li and colleagues recently found that H. pylori-infected smoking subjects had lower frequency of regulatory B cells ($CD24^+CD38^+$), compared to H. pylori-infected non-smoking subjects. These regulatory B cells (Breg), of H. pylori-infected smoking subjects, showed loss of suppression of pro-inflammatory responses through IL-10 production, when co-cultured with autologous T cells, which was not observed in non-smoking patients (Li et al., 2015). Recent studies on mice have focused on the effect of cigarette smoke on the development and distribution of B cells. Fusby and colleagues found that mice exposed to cigarette smoke had a significant reduction in bone marrow pre-B ($B220^+CD43^-$) cell subsets only, not pro-B cell subsets, with a slight effect on the percentage of splenic transitional T1 B cells (Fusby et al., 2010). In contrast, nicotine has been shown to increase the number of mouse pre-B cells, suggesting that other components of cigarette smoke may counteract the inductive effect of nicotine on B cell lymphopoiesis (Skok et al., 2006).

2.4. Molecular mechanisms underlying the effect of CS

The molecular bases behind the smoking-induced events in both innate and adaptive immune cells are still unclear; however, a variety of mechanisms have been proposed to explain the etiologic link between cigarette smoke and various inflammatory diseases. One of the main pathological mechanisms is the NF-κB signalling pathway activation, that includes inhibitor of NF-IκB kinase (IKK) activation and IκB phosphorylation and degradation, allowing the translocation of NF-κB to the nucleus leading to an induced transcription of different genes involved in inflammatory responses in response to cigarette smoke, such as TNF-α, IL-8 and cyclooxygenase-2 (COX-2), the latter representing an enzyme involved in the inflammatory responses. Histone modifications can impact gene expression by enhancing or halting the accessibility of DNA to transcription factors and co-factors (Anto et al., 2002; Gonçalves et al., 2011). Modulation of NF-κB by cigarette smoke occurs in many ways. First, activation of IKK either by inflammatory mediators (IL-1 and TNF-α) or smoking, results in IκB degradation or stimulation of p65 subunit of NF-κB by acetylation, respectively. Second, Toll-like receptors (TLR) associated activation of NF-κB due to oxidative stress, results in the activation of extracellular signal-regulated kinases ERK1/ERK2 mitogen-activated protein kinase (MAPK) (ERK1/2 MAPK) signalling pathway. Third, there is prolonged NF-κB activation due to smoking-induced reduction of histone deacetylase (HDAC), an enzyme that block the accessibility of DNA to transcription factors (Gonçalves et al., 2011). Histone acetylation which is performed by histone acetylases (HACs), and deacetylation, achieved by histone deacetylases (HDACs) are forms of histone modifications that regulate gene expression by facilitating or blocking DNA accessibility to transcription factors and co-factors, respectively (Yao et al., 2007).

Various studies have linked cigarette smoke with the activation of NF-κB and cytokine expression. The events triggered by cigarette smoke are unlikely to be initiated by short lived ROS alone. Cigarette smoke constituents can contribute to excessive or dysregulated generation of ROS. Among many potential sources of ROS; xanthine oxidase, a final enzyme of purine metabolism, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) have been implicated (Kayyali et al., 2003; Kim et al., 2014; Lee et al., 2012). Ko and colleagues reported that cigarette smoke extract (CSE) induces intracellular ROS, in both human and mouse macrophages due to the activation of NADPH oxidase, which in turn activates AMP-activated protein kinase (AMPK)/MAPK signalling with NF-κB. This effect may be nicotinic acetylcholine receptor (nAChR)-dependent and ROS sensitive (Ko et al., 2015). MAPK signalling activation has three major signalling cassettes; ERK, p38 and c-Jun N-terminal kinase (JNK), which can be activated by a variety of stimuli. For instance, ERK1 and ERK2 are more responsive to growth factors, while stress stimuli can preferentially activate JNK and p38 kinases (Roux and Blenis, 2004). Ex-vivo, Karimi and colleagues found that CSE can activate NF-κB in human monocyte-derived macrophages due to TLR4 ligation and signalling via IRAK-1 phosphorylation, and TRAF6 and IκB-α degradation. Additionally, higher amounts of IL-8 secretion were decreased by blocking p38 MAPK, suggesting the enrolment of p38 as it affects the maximal amounts of IL-8 secretion after CS exposure that can only be produced if the resulting mRNA, after NF-κB translocation, is quickly stabilized by the p38 MAPK pathway (Karimi et al., 2006).

It has been shown that CSE supresses TLR-induced inflammatory cytokines, including TNF-α, IL-6 and IL-10, but not IL-8. This effect was associated with a reduced activation of p38, ERK and p65 upon CSE treatment followed by LPS activation of COPD alveolar macrophages. The lack of IL-8 suppression after LPS treatment was suggested to be due to the initial activation of p38 MAPK pathway by CSE (Metcalfe et al., 2014). Additionally, Castro and colleagues found that CSE was associated with inhibition of viral-induced interferon alpha (IFN-α) secretion, but not IL-8 in human pDCs infected by respiratory syncytial virus (RSV) by downregulating TLR7 expression and decreased activation of interferon regulatory factor(IRF)-7 (Castro et al., 2011). A schematic representation summarizing the pathological effects of cigarette smoke on the inflammatory cytokines gene transcription is shown in Fig. 1.

2.5. CS and autoimmunity

Cigarette smoking is a well-established environmental risk factor that has been shown in many studies to be linked with the development of autoimmune diseases, such as multiple sclerosis (MS), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), psoriatic arthritis, systemic lupus erythematosus (SLE), primary biliary cirrhosis (PBC), Graves' disease and others (Perricone et al., 2016). The microenvironment, such as that present in the lungs, may control the antigen presentation and the destiny of T cells to either effector or regulatory subsets. In the lung, cigarette smoke induces oxidative stress, the imbalance between oxidants and antioxidants in favour of oxidants, and the pro-inflammatory responses causing post-translational protein modifications in the lungs which greatly impact their antigenicity (Cloos and Christgau, 2004).

3. Cigarette smoking and multiple sclerosis

3.1. Epidemiology of smoking in MS

The World Health Organisation (WHO) report estimated that over 1.1 billion people smoked tobacco in 2015. Although the prevalence of smoking is declining worldwide, it appears to be increasing in the Eastern Mediterranean Region and the African Region. In general, significantly more males than females smoke tobacco. Among the WHO regions, Europe has the highest prevalence of tobacco use in adults (28%) and adolescents. In Europe, 19% of wome n over age of 15 used tobacco in 2013. This figure is higher than average tobacco use in females in Africa, South-East Asia, Eastern Mediterranean and Western Pacific Regions (2–3%) (World Health Organisation, 2018) where the prevalence of MS is significantly lower than Europe and North America.

3.1.1. Smoking and risk of developing MS

To date, very few modifiable risk factors have been found to be associated with the risk of MS (Belbasis et al., 2015). Cigarette smoking which is the leading cause of morbidity worldwide, has been shown to play an important role in aetiology of MS. The research has shown that on average first-hand cigarette smoking increases the risk of MS by around 50% (Handel et al., 2011) while exposure to environmental tobacco smoke increases the risk by 30% in adults (Hedström et al.,

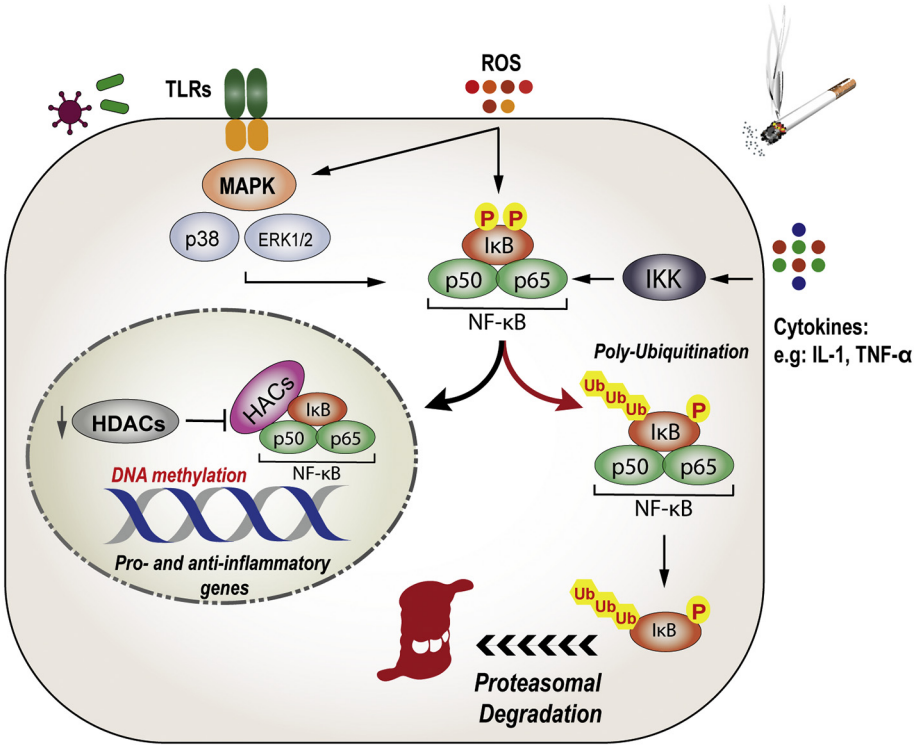

Fig. 1. Molecular mechanisms underlying the effect of cigarette smoke (CS): A schematic model of the impact of cigarette smoke (CS) on immune cells' transcriptional control of inflammatory genes via activation of NF-κB.

2011a) and by more than two times in children who were exposed to parental smoking at home with a clear dose-response association (Mikaeloff et al., 2007).

Despite a marked increase in the number of investigations assessing the link between smoking and MS susceptibility, several aspects of the association including timing of the exposure, its interactions with demographic factors and susceptibility genes as well as the underlying mechanism is not yet fully understood. Several recent multifactorial studies investigated how cigarette smoking interacts with gender and other major environmental and genetic risk factors including tow haplotypes within the human leukocyte antigen (HLA) region (HLA-DRB1*15 and HLA-A*02) and Epstein-Barr virus. Smoking prevalence has markedly increased among women throughout the 20th century to the point that in many high-income countries now women smoke at nearly the same rate as or higher than men (Hitchman and Fong, 2011). Given the significant correlation between the gender ratio of MS with the gender ratio of smoking ($r = 0.16$, $P = 0.002$), it has been suggested that the differential temporal changes in smoking behaviours of men and women, with smoking prevalence in women increasing, may explain in part the recent increase in the female to male ratio of MS (Orton et al., 2006; Palacios et al., 2011; Westerlind et al., 2014). The association between the anti-Epstein-Barr virus nuclear antigens (anti-EBNA) antibody titers and MS risk is also found to be enhanced by two times in smokers (Simon et al., 2010). This may indicate that some component of cigarette smoke possibly modifies either EBV infection or the immune response to the infection. Cigarette smoking has also been shown to significantly interact with the major MS susceptibility genes. In a Swedish case-control study, the interaction between smoking and risk of MS in presence of HLA-DRB1*15 and absence of HLA-A*02 was investigated (Hedström et al., 2011b). While the risk of MS in non-smokers with both genetic risk factors (carriership of HLA-DRB1*15 allele but not HLA-A*02) was 4.9 times higher (95%CI: 3.6 to 6.6), risk was substantially increased to 13.5 times higher (95%CI: 8.1 to 22.6) in ever-smokers with both genetic risk factors compared with never-smokers with neither of the genetic risk factors.

3.1.2. Smoking and worsening of disability in MS

In 1964, Courville first observed the adverse effects of smoking on worsening of symptoms in MS (Courville et al., 1964). Since then, cumulative evidence suggests an influence of smoking on the course of MS and rate of disability accumulation. The research has shown that smokers experience more severe motor symptoms (Emre and de Decker, 1992), have more T2 and gadolinium enhancing lesions on MRI and greater brain atrophy (Healy et al., 2009; Zivadinov et al., 2009), have increased cognitive and psychological impairment (Ozcan et al., 2014; Tanasescu et al., 2017) and lower quality of life (Weiland et al., 2014). Furthermore, smoking has been found to increase the risk of conversion to clinically definite MS in patients with clinically isolated syndrome (CIS) by about 80% (Di Pauli et al., 2008). In a population-based cohort study of patients at Nottingham University Hospital, our group observed that the risk of reaching Expanded Disability Status Scale (EDSS) score milestones of 4.0 (significant disability but able to walk without aid or rest for 500 m) and 6.0 (requires unilateral assistance to walk about 100 m with or without resting) in current smokers was increased by 64% and 49% compared with never smokers, respectively. The risk was not increased in ex-smokers (Manouchehrinia et al., 2013). The risk of converting to secondary progressive MS (SPMS) has also been found to be increased in smokers than in non-smokers (Hernán et al., 2005). Ramanujam et al. showed that for each additional year of smoking after the diagnosis of MS, the risk for transition to SPMS is increased by 4.7% per year (Ramanujam et al., 2015).

3.1.3. Smoking and mortality in MS

Cigarette smoking is the leading cause of preventable death worldwide. WHO has estimated that tobacco use (both smoking and smokeless) is accountable for the death of about six million people worldwide annually with majority dying prematurely. This includes about 600,000 deaths from effects of second-hand smoking (World Health Organisation, 2018). In a prospectively followed cohort of nearly 900 MS patients at Nottingham University Hospital, the risk of all-cause mortality among ever-smokers versus lifetime non-smokers

was more than two times higher (Manouchehrinia et al., 2014), while the standardised mortality ratio was four and two times higher in current and ex-smokers with MS, never smokers with MS did not have an increased mortality rate when compared to the mortality rates in the UK general population. Similarly, in another study from the UK, Lalmohamed et al. found that while the overall risk of death among MS patients was increased by 3.5 times when compared to the non-MS referents in the UK general population, the risk further increased to 6.7 times in current smokers (Lalmohamed et al., 2012).

3.1.4. Effects of smoking cessation

Smoking cessation has been proven to be effective in alleviating some of MS symptoms and slowing down the progression of disabilities (Tanasescu et al., 2017) and risk of SPMS conversion (Ramanujam et al., 2015). We found that in ex-smokers each smoke-free years from MS onset decreases the risk of EDSS score 4.0 and 6.0 by 4% and 3%, respectively (Tanasescu et al., 2017). The clear beneficial effect of smoking cessation on MS clinical course suggests the need for an early intervention in smokers with MS. However, on the other hand, smoking cessation can cause excessive weight gain in some individuals which have been shown to lead to a higher short-term risk of type 2 diabetes mellitus and obesity (Akter et al., 2015; Bush et al., 2016; Yeh et al., 2010).

4. Conclusion

Today, there is ample epidemiological evidence that first and second-hand cigarette smoking and exposure to environmental tobacco, but not other forms of tobacco use (such as chewing tobacco) (Hedström et al., 2009), is a significant risk factor for the development of MS, with substantially larger effects in genetically susceptible individuals. Cumulative epidemiological evidence also suggest that cigarette smoking has pronounce effect on the risk of conversion to clinically definite MS, worsening of physical disability and cognitive impairment and pre-mature death in MS.

4.1. Immunology of smoking in MS

Many mechanisms have been proposed to illustrate the immunopathological role of tobacco in the increased risk of incidence and progression of MS. As the lungs may be a critical site for T cell activation and differentiation, it has been shown in the Lewis rat model of MS, experimental autoimmune encephalomyelitis (EAE), that autoreactive T cells gain the capability to enter the central nervous system (CNS) after residing temporarily within the lung tissues, where they flow within the lymphoid tissues and lung-draining mediastinal lymph nodes and then to the blood stream where they move to the CNS (Odoardi et al., 2012). Therefore, it is more likely that cigarette smoke-induced oxidative stress and TLRs activation by PAMPs in the lung microenvironment may promote the initiation of the pro-inflammatory responses and alter potential autoreactive T cells into pathogenic state. This hypothesis is supported by several recent studies, where active and passive smoking, but not moist snuff (chewing tobacco) are associated with higher MS risk (Arimilli et al., 2017; Hedström et al., 2013; Manouchehrinia et al., 2013; Pasare and Medzhitov, 2004).

In the EAE model, it was shown that CNS professional antigen-presenting $CD11c^+$ DC attract and reactivate infiltrating pathogenic T cells in the CNS, and provoke pro-inflammatory response leading to subsequent monocyte recruitment into the CNS (McMahon et al., 2005; Paterka et al., 2016). Still, different studies have shown that a specific subset of human DC, non-adherent $CD123^+$/CC chemokine receptor 6^+ ($CCR6^+$), are able to induce an immunosuppressive response by expressing indoleamine 2,3-dioxygenase (IDO), resulting in $CD4^+CD25^{high}$ regulatory T cell expansion (Hill et al., 2007; Mellor and Munn, 2004). Among smokers with MS, Correale and colleagues found that cigarette smoking reduces the IDO activity, leading to increased IL-6 and IL-13 production. Furthermore, they found that smoking boosts the activity and the degree of expression of the renin-angiotensin system (RAS), a major endocrine system regulating blood pressure and body fluid homeostasis, leading to increased numbers of IL-17 and IL-22 producing cells as well as chemokines CCL2, CCL3 and CXCL10. These two pathways are involved in the reduction of $CD4^+CD25^+FoxP3^+$ regulatory T cells number among smokers with MS (Correale and Farez, 2015).

The aryl hydrocarbon Receptor (AhR) is a ligand-activated transcription factor that plays a key role in the innate and adaptive immune cells and mediates responses to a multitude of microbial, dietary and environmental toxin stimuli, including cigarette smoke constituents (Quintana and Sherr, 2013). Macrophages, DC, B cells and T cell subsets were found to express AhR, and number of AhR ligands have been reported (Stockinger et al., 2014). It has been shown that the type of AhR ligand can impact the development of either pro-inflammatory Th17 or anti-inflammatory Treg-mediated immune responses, causing different outcomes. For instance, AhR activation with 6-formylindolo[3,2-*b*] carbazole (FICZ) was found to exacerbate EAE by inducing IL-17 producing T cells and interfering with Treg cell development, while activating it with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) led to AhR-dependent induction of $Foxp3^+$ Treg cells, less Th17, IL-17 producing, cells and ultimately suppression of EAE development (Quintana et al., 2008; Veldhoen et al., 2008). Like TCDD, Acrolein, an AhR ligand present in the gaseous phase of the cigarette smoke, was found to exert immunomodulatory effects and led to a relative accumulation of $Foxp3^+$ regulatory T cells in nasal exposed BALB/c mouse allergy model (Roth-Walter et al., 2017). The molecular mechanism by which AhR mediates the immune responsiveness to chemical compounds was shown to be through AhR and its nuclear translocator (AhR-ARNT), p38-MAPK and NF-κB signalling pathways (Nguyen et al., 2013). However, the role of whole cigarette smoke constituents and the molecular mechanisms involved in AhR modulation of T cell differentiation is not completely understood.

Laquinimod is an oral drug and an AhR agonist (not in CS) currently or recently under evaluation for the treatment of relapsing-remitting MS, primary progressive MS and Huntington's disease. It has been shown that laquinimod arrests EAE by AhR-dependent reduction of immune cell migration into the CNS and that was correlated with the clinical symptoms amelioration, which is possibly due to the laquinimod-induced DC and monocytes shift towards an anti- inflammatory phenotype (Berg et al., 2016). The effect of smoking on laquinimod effectiveness is yet to be to be investigated.

4.2. Role of nicotine in MS

It has been proposed that nicotine alone may have a beneficial role in MS pathogenesis. Immune cells that play a crucial role in MS, including T cells, macrophages/microglia and DC express nicotinic acetylcholine receptors (nAChR), suggesting that nicotine may drive immunomodulatory effects in MS incidence and progression (Jin et al., 2012; Razani-Boroujerdi et al., 2007; Wang et al., 2002). This suggestion is supported by the fact that the risk of MS is not increased by tobacco moist snuff but only by smoked tobacco, even when the resulting serum level of nicotine is equal, raising the possibility that other components than nicotine in cigarettes drive the adverse effect of cigarette smoking in MS (Carlens et al., 2010; Hedström et al., 2009). In the EAE model, Gao and colleagues found that nicotine administration after the development of EAE symptoms ameliorates the severity of the disease, while cigarette smoke condensate (CSC) accelerated the severity of the disease in early stages of EAE, suggesting that nicotine and CSC influence the microglial viability, activation and function resulting in different immune responses affecting EAE development (Gao et al., 2014). In addition, it has been shown that α7 nAChRs are expressed by $CD4^+$ T cells and upregulated upon their activation. Treating these $CD4^+$ T cells with nicotine induced a shift to Th2 lineage and reduced

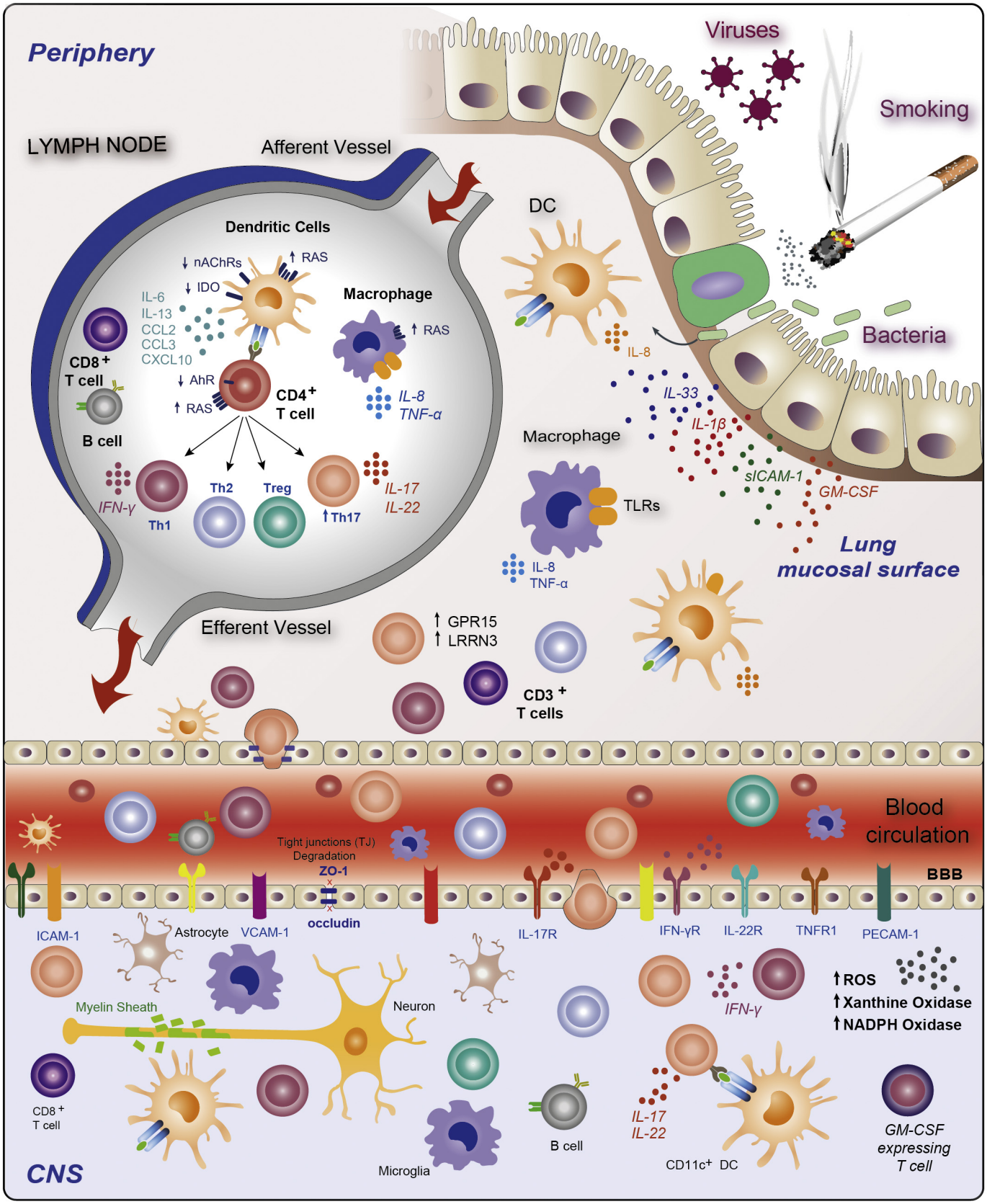

Fig. 2. A schematic model of the immunopathology of cigarette smoking in MS: In the lung microenvironment, cigarette smoke exposure induces oxidative stress, pro-inflammatory responses causing post-translational protein modifications that may control the antigen presentation, the destiny of T and B cells and trigger and alter potential autoreactive T cells into pathogenic state. Cigarette smoking impacts immune responses by enhancing the susceptibility to infections, increasing pro-inflammatory cytokine secretion, shifting T cells to Th17 lineage and altering the BBB integrity.

Th1 and Th17 reactivity, which ultimately reduced T cell infiltration into the CNS (Nizri et al., 2009). However, nicotine has been shown to downregulate the expression of BBB tight junction (TJ) proteins; such as ZO-1, occludin, cadherin and adherens junctional proteins, which may facilitate the immune cell trafficking across the BBB (Abbruscato et al., 2002; Hutamekalin et al., 2008).

4.3. Impact of cigarette smoke on BBB in MS

Cigarette smoke is known for its capability to induce oxidative stress and vascular inflammation that induce pathophysiological changes in the BBB (Naik and Cucullo, 2015). It has been demonstrated that tobacco smoke leads to the degradation of tight junction (TJ) proteins such as ZO-1 and occludin. Furthermore, it induces the production of IL-6 and matrix metalloproteinase-2 (MMP-2) by BBB endothelial cells (ECs), as well as promoting the expression of vascular adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1) and platelet endothelial cell adhesion molecule (PECAM-1), suggesting the ability of cigarette smoking to compromise the function and the integrity of the BBB (Hossain et al., 2011; Larochelle et al., 2011; Naik et al., 2014; Pooja Naik, 2015).

Additionally, the oxidative capacity of cigarette smoke was found to be positively correlated with the extent of BBB damage. It has been demonstrated that high levels of nitric oxide (NO) contributes to the alteration of the BBB integrity, controlling vascular tone and leukocyte-endothelial adhesion (Yamauchi et al., 2007). NO is a component of cigarette smoke. Larochelle and colleagues shown that ROS, in addition to their role in the BBB integrity, modulate BBB function and are involved in the immuno-pathogenesis of MS as they can trigger an inflammatory response by activating a redox signalling pathway such as JAK/STAT pathway leading to TNF-α production in myeloid cells and expression of adhesion molecules (Larochelle et al., 2011). Nuclear factor like 2/antioxidant response element (Nrf2/ARE) pathway is a main player in countering oxidative stress and has been demonstrated to play a cytoprotective role against cigarette smoke exposure at the BBB (Naik et al., 2015).

4.4. Epigenetics of smoking in MS

Epigenetic modifications, such as histone modification and post-translational methylation, depend on the environmental and other influences, including smoking, can result in phenotype plasticity. One mechanism of the epigenetic modification is DNA methylation where methylated cytosines are found mainly at CpG dinucleotides (Huynh and Casaccia, 2013; Sokratous et al., 2016). Recently, tobacco smoking was found to induce CpG methylation changes in peripheral blood mononuclear cells (PBMCs) of healthy cigarette smokers, healthy snuff users and cigarette smokers with or without MS. Aryl-hydrocarbon receptor repressor (AHRR), G Protein-Coupled Receptor 15 (GPR15) and leucine-rich repeat neuronal protein 3 (LRRN3) were found to be hypomethylated leading to their increased expression, which influences the innate and adaptive immune responses (Ammitzboell et al., 2014; Arimilli et al., 2017; Bauer et al., 2016; Zeilinger et al., 2013). Cigarette smoke was reported to facilitate the hypomethylation of GPR15, a chemoattractant receptor involved in effector T cell migration, in $CD3^+$ T cells causing an increased expression of GPR15 by 40% compared to 10% in non-smokers (Bauer et al., 2016). In PBMCs from MS patients, Ammitzboell and colleagues found that GPR15 and LRRN3 are differentially expressed in MS smokers, and by analysing these expressed genes and other 17 genes upregulated upon cigarette smoke exposure, they revealed a network dominated by pro-inflammatory molecules linked to T cell activation and innate immunity (Ammitzboell et al., 2014).

5. Summary and model

Cigarette smoke has severe effects on people's health around the world. CS alters the immune responses either by directly affecting the cells of both the innate and adaptive immune system, or by attenuating the immune recognition and response to pathogenic antigens, increasing the susceptibility to infection that induces the inflammatory changes linked with a wide range of diseases. The mechanism by which CS exposure compromises the immune responses is not completely understood. We have reviewed some of the experimental evidence on CS and its ability to modulate the immune response on key innate and adaptive immune cells that impact different chronic inflammatory diseases; including macrophages, DC, B cells and T cells, and then we focused on its impact on the pathogenesis of multiple sclerosis (MS).

Smoking is one of the best described environmental risk factor for the incidence and disability progression of MS; however, due to the complexity of CS constituents, the mechanism by which it impacts MS is yet to be elucidated. From a clinical point of view, smoking cessation is linked with an evident benefit in people with MS and should be an early intervention.

Recently published studies advanced our understanding about the impact of CS on MS aetiopathogenesis, where its constituents interact with MS risk alleles, host immune system, lung microenvironment, vascular inflammation of BBB, epigenetic modifications as well as the response to pharmaceutical immunomodulatory treatments. The potential effects of CS in MS are summarized in the schematic model shown in Fig. 2. Further investigation of these interactions will grant a better understanding of MS pathogenesis and may unveil novel therapeutic pathways.

Acknowledgment

Work in Prof Constantinescu's laboratory relevant to this paper has been supported by the MS Society of Great Britain and Northern Ireland and the Forman Hardy Charitable Trust via the University of Nottingham.

Declarations of interest

None.

References

Abbruscato, T.J., Lopez, S.P., Mark, K.S., Hawkins, B.T., Davis, T.P., 2002. Nicotine and cotinine modulate cerebral microvascular permeability and protein expression of ZO-1 through nicotinic acetylcholine receptors expressed on brain endothelial cells. J. Pharm. Sci. 2525–2538. https://doi.org/10.1002/jps.10256.

Akter, S., Okazaki, H., Kuwahara, K., Miyamoto, T., Murakami, T., Shimizu, C., Shimizu, M., Tomita, K., Nagahama, S., Eguchi, M., Kochi, T., Imai, T., Nishihara, A., Sasaki, N., Nakagawa, T., Yamamoto, S., Honda, T., Uehara, A., Yamamoto, M., Hori, A., Sakamoto, N., Nishiura, C., Totsuzaki, T., Kato, N., Fukasawa, K., Pham, N.M., Kurotani, K., Nanri, A., Kabe, I., Mizoue, T., Sone, T., Dohi, S., 2015. Smoking, smoking Cessation, and the risk of Type 2 Diabetes among Japanese adults: Japan Epidemiology Collaboration on Occupational Health Study. PLoS One 10, e0132166. https://doi.org/10.1371/journal.pone.0132166.

Ammitzboell, C., Ratzer, R., Börnsen, L., Bekner, F., Sorensen, P.S., Christensen, J.R., Soendergaard, H.B., Sellebjerg, F., 2014. Gene expression in smoking and non-smoking patients with multiple sclerosis. J. Neuroimmunol. 275, 49. https://doi.org/10.1016/j.jneuroim.2014.08.131.

Anto, R.J., Mukhopadhyay, A., Shishodia, S., Gairola, C.G., Aggarwal, B., 2002. Cigarette smoke condensate activates nuclear transcription factor-kappaB through phosphorylation and degradation of IkappaBalpha: correlation with induction of cyclooxygenase-2. Carcinogenesis 23, 1511–1518. https://doi.org/10.1093/carcin/23.9.1511.

Arellano-Orden, E., Calero-Acuña, C., Moreno-Mata, N., Gómez-Izquierdo, L., Sánchez-López, V., López-Ramírez, C., Tobar, D., López-Villalobos, J.L., Gutiérrez, C., Blanco-Orozco, A., López-Campos, J.L., 2016. Cigarette smoke decreases the maturation of lung myeloid dendritic cells. PLoS One 11, e0152737. https://doi.org/10.1371/journal.pone.0152737.

Arimilli, S., Madahian, B., Chen, P., Marano, K., Prasad, G.L., 2017. Gene expression profiles associated with cigarette smoking and moist snuff consumption. BMC Genomics 18, 156. https://doi.org/10.1186/s12864-017-3565-1.

Bauer, M., Fink, B., Thürmann, L., Eszlinger, M., Herberth, G., Lehmann, I., 2016. Tobacco smoking differently influences cell types of the innate and adaptive immune system—indications from CpG site methylation. Clin. Epigenetics 8, 83. https://doi.org/10.1186/s13148-016-0249-7.

Belbasis, L., Bellou, V., Evangelou, E., Ioannidis, J.P.A., Tzoulaki, I., 2015. Environmental risk factors and multiple sclerosis: an umbrella review of systematic reviews and meta-analyses. Lancet Neurol. 14, 263–273. https://doi.org/10.1016/S1474-4422(14)70267-4.

Berg, J., Mahmoudjanlou, Y., Duscha, A., Massa, M.G., Thöne, J., Esser, C., Gold, R., Haghikia, A., 2016. The immunomodulatory effect of laquinimod in CNS autoimmunity is mediated by the aryl hydrocarbon receptor. J. Neuroimmunol. 298, 9–15. https://doi.org/10.1016/j.jneuroim.2016.06.003.

Bijl, M., Horst, G., Limburg, P.C., Kallenberg, C.G.M., 2001. Effects of smoking on activation markers, Fas expression and apoptosis of peripheral blood lymphocytes. Eur. J. Clin. Investig. 31, 550–553. https://doi.org/10.1046/j.1365-2362.2001.00842.x.

Botelho, F.M., Nikota, J.K., Bauer, C.M., Morissette, M.C., Iwakura, Y., Kolbeck, R., Finch, D., Humbles, A.A., Stampfli, M.R., 2012. Cigarette smoke-induced accumulation of lung dendritic cells is interleukin-1alpha-dependent in mice. Respir. Res. 13, 81. https://doi.org/10.1186/1465-9921-13-81.

Brandsma, C.-A., Hylkema, M.N., Geerlings, M., van Geffen, W.H., Postma, D.S., Timens, W., Kerstjens, H.A., 2009. Increased levels of (class switched) memory B cells in peripheral blood of current smokers. Respir. Res. 10, 108. https://doi.org/10.1186/1465-9921-10-108.

Brandsma, C.A., Kerstjens, H.A.M., Van Geffen, W.H., Geerlings, M., Postma, D.S., Hylkema, M.N., Timen, W., 2012. Differential switching to IgG and IgA in active smoking COPD patients and healthy controls. Eur. Respir. J. 40, 313–321. https://doi.org/10.1183/09031936.00011211.

Brodin, P., Jojic, V., Gao, T., Bhattacharya, S., Angel, C.J.L., Furman, D., Shen-Orr, S., Dekker, C.L., Swan, G.E., Butte, A.J., Maecker, H.T., Davis, M.M., 2015. Variation in the human immune system is largely driven by non-heritable influences. Cell 160, 37–47. https://doi.org/10.1016/j.cell.2014.12.020.

Bush, T., Lovejoy, J.C., Deprey, M., Carpenter, K.M., 2016. The effect of tobacco cessation on weight gain, obesity, and diabetes risk. Obesity 24, 1834–1841. https://doi.org/10.1002/oby.21582.

Carlens, C., Hergens, M.-P., Grunewald, J., Ekbom, A., Eklund, A., Höglund, C.O., Askling, J., 2010. Smoking, use of moist snuff, and risk of chronic inflammatory diseases. Am. J. Respir. Crit. Care Med. 181, 1217–1222. https://doi.org/10.1164/rccm.200909-1338OC.

Castro, S.M., Chakraborty, K., Guerrero-Plata, A., 2011. Cigarette smoke suppresses TLR-7 stimulation in response to virus infection in plasmacytoid dendritic cells. Toxicol. Vitr. 25, 1106–1113. https://doi.org/10.1016/j.tiv.2011.03.011.

Charo, I.F., Ransohoff, R.M., 2006. The many Roles of Chemokines and Chemokine Receptors in Inflammation. N. Engl. J. Med. 354, 610–621. https://doi.org/10.1056/NEJMra052723.

Chen, H., Cowan, M.J., Hasday, J.D., Vogel, S.N., Medvedev, A.E., 2007. Tobacco smoking inhibits expression of proinflammatory cytokines and activation of IL-1R-associated kinase, p38, and NF-kB in alveolar macrophages stimulated with TLR2 and TLR4 agonists. J. Immunol. 179, 6097–6106. https://doi.org/10.4049/jimmunol.179.9.6097.

Cloos, P.A.C., Christgau, S., 2004. Post-translational modifications of proteins: implications for aging, antigen recognition, and autoimmunity. Biogerontology 5, 139–158. https://doi.org/10.1023/B:BGEN.0000031152.31352.8b.

Compston, A., Coles, A., 2008. Multiple sclerosis. Lancet 372, 1502–1517. https://doi.org/10.1016/S0140-6736(08)61620-7.

Correale, J., Farez, M.F., 2015. Smoking worsens multiple sclerosis prognosis: two different pathways are involved. J. Neuroimmunol. 281, 23–34. https://doi.org/10.1016/j.jneuroim.2015.03.006.

Cosio, M.G., Majo, J., Cosio, M.G., 2002. Inflammation of the Airways and Lung Parenchyma in COPD. Chest 121, 160S–165S. https://doi.org/10.1378/chest.121.5_suppl.160S.

Costenbader, K.H., Karlson, E.W., 2006. Cigarette smoking and autoimmune disease: what can we learn from epidemiology? Lupus. https://doi.org/10.1177/0961203306069344.

Courville, C.B., Maschmeyer, J.E., Delay, C.P., 1964. Effects of smoking on the acute exacerbations of multiple sclerosis. Bull. Los Angel. Neurol. Soc. 29, 1–6.

Demedts, I.K., Bracke, K.R., Van Pottelberge, G., Testelmans, D., Verleden, G.M., Vermassen, F.E., Joos, G.F., Brusselle, G.G., 2007. Accumulation of dendritic cells and increased CCL20 levels in the airways of patients with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 175, 998–1005. https://doi.org/10.1164/rccm.200608-1113OC.

Dendrou, C.A., Fugger, L., Friese, M.A., 2015. Immunopathology of multiple sclerosis. Nat. Rev. Immunol. 15, 545–558. https://doi.org/10.1038/nri3871.

Di Pauli, F., Reindl, M., Ehling, R., Schautzer, F., Gneiss, C., Lutterotti, A., O'Reilly, E., Munger, K., Deisenhammer, F., Ascherio, A., Berger, T., 2008. Smoking is a risk factor for early conversion to clinically definite multiple sclerosis. Mult. Scler. J. 14, 1026–1030. https://doi.org/10.1177/1352458508093679.

Doz, E., Noulin, N., Boichot, E., Guenon, I., Fick, L., Le Bert, M., Lagente, V., Ryffel, B., Schnyder, B., Quesniaux, V.F.J., Couillin, I., 2008. Cigarette Smoke-Induced Pulmonary Inflammation is TLR4/MyD88 and IL-1R1/MyD88 Signaling Dependent. J. Immunol. 180, 1169–1178. https://doi.org/10.4049/jimmunol.180.2.1169.

Droemann, D., Goldmann, T., Tiedje, T., Zabel, P., Dalhoff, K., Schaaf, B., 2005. Toll-like receptor 2 expression is decreased on alveolar macrophages in cigarette smokers and COPD patients. Respir. Res. 6, 68. https://doi.org/10.1186/1465-9921-6-68.

Duffney, P.F., McCarthy, C.E., Nogales, A., Thatcher, T.H., Martinez-Sobrido, L., Phipps, R.P., Sime, P.J., 2017. Cigarette smoke dampens anti-viral signaling in small airway epithelial cells by disrupting TLR3 cleavage. Am. J. Physiol. Cell. Mol. Physiol. ajplung. 00406, 2017. https://doi.org/10.1152/ajplung.00406.2017.

Emre, M., de Decker, C., 1992. Effects of cigarette smoking on motor functions in patients with multiple sclerosis. Arch. Neurol. 49, 1343–1347.

Förster, R., Davalos-Misslitz, A.C., Rot, A., 2008. CCR7 and its ligands: balancing immunity and tolerance. Nat. Rev. Immunol. 8, 362–371. https://doi.org/10.1038/nri2297.

Fusby, J.S., Kassmeier, M.D., Palmer, V.L., Perry, G.A., Anderson, D.K., Hackfort, B.T., Alvarez, G.K., Cullen, D.M., Akhter, M.P., Swanson, P.C., 2010. Cigarette smoke-induced effects on bone marrow B-cell subsets and CD4 + :CD8 + T-cell ratios are reversed by smoking cessation: Influence of bone mass on immune cell response to and recovery from smoke exposure. Inhal. Toxicol. 22, 785–796. https://doi.org/10.3109/08958378.2010.483258.

Galitovskiy, V., Qian, J., Chernyavsky, A.I., Marchenko, S., Gindi, V., Edwards, R.A., Grando, S.A., 2011. Cytokine-Induced Alterations of 7 Nicotinic Receptor in Colonic CD4 T Cells Mediate Dichotomous Response to Nicotine in Murine Models of Th1/Th17- versus Th2-Mediated Colitis. J. Immunol. 187, 2677–2687. https://doi.org/10.4049/jimmunol.1002711.

Gao, Z., Nissen, J.C., Ji, K., Tsirka, S.E., 2014. The Experimental Autoimmune Encephalomyelitis Disease Course is Modulated by Nicotine and Other Cigarette Smoke Components. PLoS One 9, e107979. https://doi.org/10.1371/journal.pone.0107979.

Givi, M.E., Folkerts, G., Wagenaar, G.T.M., Redegeld, F.A., Mortaz, E., 2015. Cigarette smoke differentially modulates dendritic cell maturation and function in time. Respir. Res. 16, 131. https://doi.org/10.1186/s12931-015-0291-6.

Gonçalves, R.B., Coletta, R.D., Silvério, K.G., Benevides, L., Casati, M.Z., da Silva, J.S., Nociti, F.H., 2011. Impact of smoking on inflammation: overview of molecular mechanisms. Inflamm. Res. 60, 409–424. https://doi.org/10.1007/s00011-011-0308-7.

Hagiwara, E., Takahashi, K.-I., Okubo, T., Ohno, S., Ueda, A., Aoki, A., Odagiri, S., Ishigatsubo, Y., 2001. Cigarette smoking depletes cells spontaneously secreting Th(1) cytokines in the human airway. Cytokine 14, 121–126. https://doi.org/10.1006/cyto.2001.0860.

Handel, A.E., Williamson, A.J., Disanto, G., Dobson, R., Giovannoni, G., Ramagopalan, S.V., 2011. Smoking and multiple sclerosis: an updated meta-analysis. PLoS One 6, e16149. https://doi.org/10.1371/journal.pone.0016149.

Hasday, J.D., Bascom, R., Costa, J.J., Fitzgerald, T., Dubin, W., 1999. Bacterial Endotoxin is an active Component of Cigarette Smoke. Chest 115, 829–835. https://doi.org/10.1378/chest.115.3.829.

Healy, B.C., Ali, E.N., Guttmann, C.R.G., Chitnis, T., Glanz, B.I., Buckle, G., Houtchens, M., Stazzone, L., Moodie, J., Berger, A.M., Duan, Y., Bakshi, R., Khoury, S., Weiner, H., Ascherio, A., 2009. Smoking and disease progression in multiple sclerosis. Arch. Neurol. 66, 858–864. https://doi.org/10.1001/archneurol.2009.122.

Hedström, A.K., Baarnhielm, M., Olsson, T., Alfredsson, L., 2009. Tobacco smoking, but not Swedish snuff use, increases the risk of multiple sclerosis. Neurology 73, 696–701. https://doi.org/10.1212/WNL.0b013e3181b59c40.

Hedström, A.K., Baarnhielm, M., Olsson, T., Alfredsson, L., 2011a. Exposure to environmental tobacco smoke is associated with increased risk for multiple sclerosis. Mult. Scler. J. 17, 788–793. doi:https://doi.org/10.1177/1352458511399610

Hedström, A.K., Sundqvist, E., Baarnhielm, M., Nordin, N., Hillert, J., Kockum, I., Olsson, T., Alfredsson, L., 2011b. Smoking and two human leukocyte antigen genes interact to increase the risk for multiple sclerosis. Brain 134, 653–664. https://doi.org/10.1093/brain/awq371.

Hedström, A., Hillert, J., Olsson, T., Alfredsson, L., 2013. Nicotine might have a protective effect in the etiology of multiple sclerosis. Mult. Scler. J. 19, 1009–1013. https://doi.org/10.1177/1352458512471879.

Hellermann, G.R., Nagy, S.B., Kong, X., Lockey, R.F., Mohapatra, S.S., 2002. Mechanism of cigarette smoke condensate-induced acute inflammatory response in human bronchial epithelial cells. Respir. Res. 3, 22.

Hernán, M.A., Jick, S.S., Logroscino, G., Olek, M.J., Ascherio, A., Jick, H., 2005. Cigarette smoking and the progression of multiple sclerosis. Brain 128, 1461–1465. https://doi.org/10.1093/brain/awh471.

Hill, M., Tanguy-Royer, S., Royer, P., Chauveau, C., Asghar, K., Tesson, L., Lavainne, F., Rémy, S., Brion, R., Hubert, F.-X., Heslan, M., Rimbert, M., Berthelot, L., Moffett, J.R., Josien, R., Grégoire, M., Anegon, I., 2007. IDO expands human CD4+CD25high regulatory T cells by promoting maturation of LPS-treated dendritic cells. Eur. J. Immunol. 37, 3054–3062. https://doi.org/10.1002/eji.200636704.

Hitchman, S.C., Fong, G.T., 2011. Gender empowerment and female-to-male smoking prevalence ratios. Bull. World Health Organ. 89, 195–202. https://doi.org/10.2471/BLT.10.079905.

Hodge, S., Hodge, G., Ahern, J., Jersmann, H., Holmes, M., Reynolds, P.N., 2007. Smoking Alters Alveolar Macrophage Recognition and Phagocytic Ability. Am. J. Respir. Cell Mol. Biol. 37, 748–755. https://doi.org/10.1165/rcmb.2007-0025OC.

Hossain, M., Mazzone, P., Tierney, W., Cucullo, L., 2011. In Vitro Assessment of Tobacco Smoke Toxicity at the BBB: do Antioxidant Supplements have a protective Role? BMC Neurosci. 12, 92. https://doi.org/10.1186/1471-2202-12-92.

Huang, M.-F., Lin, W.-L., Ma, Y.-C., 2005. A study of reactive oxygen species in mainstream of cigarette. Indoor Air 15, 135–140. https://doi.org/10.1111/j.1600-0668.2005.00330.x.

Hutamekalin, P., Farkas, A.E., Orbók, A., Wilhelm, I., Nagyoszi, P., Veszelka, S., Deli, M.A., Buzás, K., Hunyadi-Gulyás, É., Medzihradszky, K.F., Meksuriyen, D., Krizbai, I.A., 2008. Effect of nicotine and polyaromtic hydrocarbons on cerebral endothelial cells. Cell Biol. Int. 32, 198–209. https://doi.org/10.1016/j.cellbi.2007.08.026.

Huynh, J.L., Casaccia, P., 2013. Epigenetic mechanisms in multiple sclerosis: implications for pathogenesis and treatment. Lancet Neurol. 12, 195–206. https://doi.org/10.1016/S1474-4422(12)70309-5.

Idoyaga, J., Steinman, R.M., 2011. SnapShot: Dendritic Cells. Cell 146, 660–660.e2. https://doi.org/10.1016/j.cell.2011.08.010.

Iwasaki, A., Medzhitov, R., 2015. Control of adaptive immunity by the innate immune system. Nat. Immunol. 16, 343–353. https://doi.org/10.1038/ni.3123.
Jin, H.J., Li, H.T., Sui, H.X., Xue, M.Q., Wang, Y.N., Wang, J.X., Gao, F.G., 2012. Nicotine stimulated bone marrow-derived dendritic cells could augment HBV specific CTL priming by activating PI3K-Akt pathway. Immunol. Lett. 146, 40–49. https://doi.org/10.1016/j.imlet.2012.02.015.
Karimi, K., Sarir, H., Mortaz, E., Smit, J.J., Hosseini, H., De Kimpe, S.J., Nijkamp, F.P., Folkerts, G., 2006. Toll-like receptor-4 mediates cigarette smoke-induced cytokine production by human macrophages. Respir. Res. 7, 66. https://doi.org/10.1186/1465-9921-7-66.
Kayyali, U.S., Budhiraja, R., Pennella, C.M., Cooray, S., Lanzillo, J.J., Chalkley, R., Hassoun, P.M., 2003. Upregulation of xanthine oxidase by tobacco smoke condensate in pulmonary endothelial cells. Toxicol. Appl. Pharmacol. 188, 59–68. https://doi.org/10.1016/S0041-008X(02)00076-5.
Kearley, J., Silver, J.S., Sanden, C., Liu, Z., Berlin, A.A., White, N., Mori, M., Pham, T.-H., Ward, C.K., Criner, G.J., Marchetti, N., Mustelin, T., Erjefalt, J.S., Kolbeck, R., Humbles, A.A., 2015. Cigarette Smoke silences Innate Lymphoid Cell Function and Facilitates an Exacerbated Type I Interleukin-33-Dependent Response to Infection. Immunity 42, 566–579. https://doi.org/10.1016/j.immuni.2015.02.011.
Kidd, P., 2003. Th1/Th2 balance: the hypothesis, its limitations, and implications for health and disease. Altern. Med. Rev. 8, 223–246.
Kim, M., Han, C.-H., Lee, M.-Y., 2014. NADPH Oxidase and the Cardiovascular Toxicity Associated with smoking. Toxicol. Res. 30, 149–157. https://doi.org/10.5487/TR.2014.30.3.149.
Knobloch, J., Schild, K., Jungck, D., Urban, K., Müller, K., Schweda, E.K.H., Rupp, J., Koch, A., 2011. The T-Helper Cell Type 1 Immune Response to Gram-negative Bacterial Infections is Impaired in COPD. Am. J. Respir. Crit. Care Med. 183, 204–214. https://doi.org/10.1164/rccm.201002-0199OC.
Ko, H.-K., Lee, H.-F., Lin, A.-H., Liu, M.-H., Liu, C.-I., Lee, T.-S., Kou, Y.R., 2015. Regulation of Cigarette Smoke Induction of IL-8 in Macrophages by AMP-activated Protein Kinase Signaling. J. Cell. Physiol. 230, 1781–1793. https://doi.org/10.1002/jcp.24881.
Lalmohamed, A., Bazelier, M.T., Van Staa, T.P., Uitdehaag, B.M.J., Leufkens, H.G.M., De Boer, A., De Vries, F., 2012. Causes of death in patients with multiple sclerosis and matched referent subjects: a population-based cohort study. Eur. J. Neurol. 19, 1007–1014. https://doi.org/10.1111/j.1468-1331.2012.03668.x.
Larochelle, C., Alvarez, J.I., Prat, A., 2011. How do immune cells overcome the blood-brain barrier in multiple sclerosis? FEBS Lett. https://doi.org/10.1016/j.febslet.2011.04.066.
Le Rouzic, O., Koné, B., Kluza, J., Marchetti, P., Hennegrave, F., Olivier, C., Kervoaze, G., Vilain, E., Mordacq, C., Just, N., Perez, T., Bautin, N., Pichavant, M., Gosset, P., 2016. Cigarette smoke alters the ability of human dendritic cells to promote anti-Streptococcus pneumoniae Th17 response. Respir. Res. 17, 94. https://doi.org/10.1186/s12931-016-0408-6.
Lee, J., Taneja, V., Vassallo, R., 2012. Cigarette smoking and Inflammation: Cellular and Molecular Mechanisms. J. Dent. Res. 91, 142–149. https://doi.org/10.1177/0022034511421200.
Leopold, P.L., O'Mahony, M.J., Lian, X.J., Tilley, A.E., Harvey, B.-G., Crystal, R.G., 2009. Smoking is Associated with Shortened Airway Cilia. PLoS One 4, e8157. https://doi.org/10.1371/journal.pone.0008157.
Li, G., Wulan, H., Song, Z., Paik, P.A., Tsao, M.L., Goodman, G.M., MacEachern, P.T., Downey, R.S., Jankowska, A.J., Rabinowitz, Y.M., Learch, T.B., Song, D.Z., Yuan, J.J., Zheng, S., Zheng, Z., 2015. Regulatory B cell function is suppressed by smoking and obesity in H. pylori-infected subjects and is correlated with elevated risk of gastric cancer. PLoS One 10, e0134591. https://doi.org/10.1371/journal.pone.0134591.
Liao, S.-X., Ding, T., Rao, X.-M., Sun, D.-S., Sun, P.-P., Wang, Y.-J., Fu, D.-D., Liu, X.-L., Ou-Yang, Y., 2015. Cigarette smoke affects dendritic cell maturation in the small airways of patients with chronic obstructive pulmonary disease. Mol. Med. Rep. 11, 219–225. https://doi.org/10.3892/mmr.2014.2759.
Liu, K., Victora, G.D., Schwickert, T.A., Guermonprez, P., Meredith, M.M., Yao, K., Chu, F.-F., Randolph, G.J., Rudensky, A.Y., Nussenzweig, M., 2009. In vivo analysis of dendritic cell development and homeostasis. Science (80-). 324, 392–397. https://doi.org/10.1126/science.1170540.
Maeno, T., Houghton, A.M., Quintero, P.A., Grumelli, S., Owen, C.A., Shapiro, S.D., 2007. CD8+ T Cells are Required for Inflammation and Destruction in Cigarette Smoke-Induced Emphysema in mice. J. Immunol. 178, 8090–8096. https://doi.org/10.4049/jimmunol.178.12.8090.
Majo, J., Ghezzo, H., Cosio, M.G., 2001. Lymphocyte population and apoptosis in the lungs of smokers and their relation to emphysema. Eur. Respir. J. 17, 946–953.
Manouchehrinia, A., Tench, C.R., Maxted, J., Bibani, R.H., Britton, J., Constantinescu, C.S., 2013. Tobacco smoking and disability progression in multiple sclerosis: United Kingdom cohort study. Brain 136, 2298–2304. https://doi.org/10.1093/brain/awt139.
Manouchehrinia, A., Weston, M., Tench, C.R., Britton, J., Constantinescu, C.S., 2014. Tobacco smoking and excess mortality in multiple sclerosis: a cohort study. J. Neurol. Neurosurg. Psychiatry 85, 1091–1095. https://doi.org/10.1136/jnnp-2013-307187.
Martin, T.R., Frevert, C.W., 2005. Innate immunity in the lungs, in: Proceedings of the American Thoracic Society. Am. Thoracic Soc. 403–411. https://doi.org/10.1080/13586840500347277.
McMahon, E.J., Bailey, S.L., Castenada, C.V., Waldner, H., Miller, S.D., 2005. Epitope spreading initiates in the CNS in two mouse models of multiple sclerosis. Nat. Med. 11, 335–339. https://doi.org/10.1038/nm1202.
Mellor, A.L., Munn, D.H., 2004. Ido expression by dendritic cells: tolerance and tryptophan catabolism. Nat. Rev. Immunol. 4, 762–774. https://doi.org/10.1038/nri1457.
Merad, M., Sathe, P., Helft, J., Miller, J., Mortha, A., 2013. The dendritic cell lineage: ontogeny and function of dendritic cells and their subsets in the steady state and the inflamed setting. Annu. Rev. Immunol. 31, 563–604. https://doi.org/10.1146/annurev-immunol-020711-074950.
Metcalfe, H.J., Lea, S., Hughes, D., Khalaf, R., Abbott-Banner, K., Singh, D., 2014. Effects of cigarette smoke on Toll-like receptor (TLR) activation of chronic obstructive pulmonary disease (COPD) macrophages. Clin. Exp. Immunol. 176, 461–472. https://doi.org/10.1111/cei.12289.
Mikaeloff, Y., Caridade, G., Tardieu, M., Suissa, S., 2007. Parental smoking at home and the risk of childhood-onset multiple sclerosis in children. Brain 130, 2589–2595. https://doi.org/10.1093/brain/awm198.
Mortaz, E., Lazar, Z., Koenderman, L., Kraneveld, A.D., Nijkamp, F.P., Folkerts, G., 2009. Cigarette smoke attenuates the production of cytokines by human plasmacytoid dendritic cells and enhances the release of IL-8 in response to TLR-9 stimulation. Respir. Res. 10, 47. https://doi.org/10.1186/1465-9921-10-47.
Moussion, C., Ortega, N., Girard, J.-P., 2008. The IL-1-like Cytokine IL-33 is Constitutively Expressed in the Nucleus of Endothelial Cells and Epithelial Cells in Vivo: a Novel 'Alarmin'? PLoS One 3, e3331. https://doi.org/10.1371/journal.pone.0003331.
Nadigel, J., Préfontaine, D., Baglole, C.J., Maltais, F., Bourbeau, J., Eidelman, D.H., Hamid, Q., 2011. Cigarette smoke increases TLR4 and TLR9 expression and induces cytokine production from CD8+T cells in chronic obstructive pulmonary disease. Respir. Res. 12, 149. https://doi.org/10.1186/1465-9921-12-149.
Naik, P., Cucullo, L., 2015. Pathobiology of tobacco smoking and neurovascular disorders: untied strings and alternative products. Fluids Barriers CNS 12, 25. https://doi.org/10.1186/s12987-015-0022-x.
Naik, P., Fofaria, N., Prasad, S., Sajja, R.K., Weksler, B., Couraud, P.-O., Romero, I.A., Cucullo, L., 2014. Oxidative and pro-inflammatory impact of regular and denicotinized cigarettes on blood brain barrier endothelial cells: is smoking reduced or nicotine-free products really safe? BMC Neurosci. 15, 51. https://doi.org/10.1186/1471-2202-15-51.
Naik, P., Sajja, R.K., Prasad, S., Cucullo, L., 2015. Effect of full flavor and denicotinized cigarettes exposure on the brain microvascular endothelium: a microarray-based gene expression study using a human immortalized BBB endothelial cell line. BMC Neurosci. 16, 38. https://doi.org/10.1186/s12868-015-0173-3.
Nguyen, N.T., Hanieh, H., Nakahama, T., Kishimoto, T., 2013. The roles of aryl hydrocarbon receptor in immune responses. Int. Immunol. 25, 335–343. https://doi.org/10.1093/intimm/dxt011.
Ni, I., Ji, C., Vij, N., 2015. Second-hand cigarette smoke impairs bacterial phagocytosis in macrophages by modulating CFTR dependent lipid-rafts. PLoS One 10, e0121200. https://doi.org/10.1371/journal.pone.0121200.
Nizri, E., Irony-Tur-Sinai, M., Lory, O., Orr-Urtreger, A., Lavi, E., Brenner, T., 2009. Activation of the Cholinergic Anti-Inflammatory System by Nicotine Attenuates Neuroinflammation via suppression of Th1 and Th17 responses. J. Immunol. 183, 6681–6688. https://doi.org/10.4049/jimmunol.0902212.
Noakes, P.S., 2006. Maternal smoking is associated with impaired neonatal toll-like-receptor-mediated immune responses. Eur. Respir. J. 28, 721–729. https://doi.org/10.1183/09031936.06.00050206.
Odoardi, F., Sie, C., Streyl, K., Ulaganathan, V.K., Schläger, C., Lodygin, D., Heckelsmiller, K., Nietfeld, W., Ellwart, J., Klinkert, W.E.F., Lottaz, C., Nosov, M., Brinkmann, V., Spang, R., Lehrach, H., Vingron, M., Wekerle, H., Flügel-Koch, C., Flügel, A., 2012. T cells become licensed in the lung to enter the central nervous system. Nature 488, 675–679. https://doi.org/10.1038/nature11337.
Orton, S.-M., Herrera, B.M., Yee, I.M., Valdar, W., Ramagopalan, S.V., Sadovnick, A.D., Ebers, G.C., 2006. Sex ratio of multiple sclerosis in Canada: a longitudinal study. Lancet Neurol. 5, 932–936. https://doi.org/10.1016/S1474-4422(06)70581-6.
Ozcan, M.E., Asil, T., Ince, B., Bingol, A., Erturk, S., Altinoz, M.A., Karadeli, H.H., Kocer, A., 2014. Association between smoking and cognitive impairment in multiple sclerosis. Neuropsychiatr. Dis. Treat. 10, 1715. https://doi.org/10.2147/NDT.S68389.
Pace, E., Di Sano, C., Sciarrino, S., Scafidi, V., Ferraro, M., Chiappara, G., Siena, L., Gangemi, S., Vitulo, P., Giarratano, A., Gjomarkaj, M., 2014. Cigarette smoke alters IL-33 expression and release in airway epithelial cells. BBA - Mol. Basis Dis. 1842, 1630–1637. https://doi.org/10.1016/j.bbadis.2014.06.009.
Palacios, N., Alonso, A., Brønnum-Hansen, H., Ascherio, A., 2011. Smoking and increased risk of Multiple Sclerosis: parallel Trends in the sex Ratio Reinforce the evidence. Ann. Epidemiol. 21, 536–542. https://doi.org/10.1016/j.annepidem.2011.03.001.
Pasare, C., Medzhitov, R., 2004. Toll-like receptors and acquired immunity. Semin. Immunol. 16, 23–26. https://doi.org/10.1016/j.smim.2003.10.006.
Paterka, M., Siffrin, V., Voss, J.O., Werr, J., Hoppmann, N., Gollan, R., Belikan, P., Bruttger, J., Birkenstock, J., Jung, S., Esplugues, E., Yogev, N., Flavell, R.A., Bopp, T., Zipp, F., 2016. Gatekeeper role of brain antigen-presenting CD11c+ cells in neuroinflammation. EMBO J. 35, 89–101. https://doi.org/10.15252/embj.201591488.
Perricone, C., Versini, M., Ben-Ami, D., Gertel, S., Watad, A., Segel, M.J., Ceccarelli, F., Conti, F., Cantarini, L., Bogdanos, D.P., Antonelli, A., Amital, H., Valesini, G., Shoenfeld, Y., 2016. Smoke and autoimmunity: the fire behind the disease. Autoimmun. Rev. 15, 354–374. https://doi.org/10.1016/j.autrev.2016.01.001.
Phipps, J.C., Aronoff, D.M., Curtis, J.L., Goel, D., O'Brien, E., Mancuso, P., 2010. Cigarette Smoke Exposure Impairs Pulmonary Bacterial Clearance and Alveolar Macrophage Complement-Mediated Phagocytosis of Streptococcus pneumoniae. Infect. Immun. 78, 1214–1220. https://doi.org/10.1128/IAI.00963-09.
Pooja Naik, R.K.S., 2015. Differential Cerebrovascular Toxicity of various Tobacco Products: a Regulatory Perspective. Aust. J. Pharm. 03. https://doi.org/10.4172/2329-6887.1000e130.
Quintana, F.J., Sherr, D.H., 2013. Aryl Hydrocarbon Receptor Control of Adaptive Immunity. Pharmacol. Rev. 65, 1148–1161. https://doi.org/10.1124/pr.113.007823.
Quintana, F.J., Basso, A.S., Iglesias, A.H., Korn, T., Farez, M.F., Bettelli, E., Caccamo, M., Oukka, M., Weiner, H.L., 2008. Control of Treg and TH17 cell differentiation by the

aryl hydrocarbon receptor. Nature 453, 65–71. https://doi.org/10.1038/nature06880.
Ramanujam, R., Hedström, A.-K., Manouchehrinia, A., Alfredsson, L., Olsson, T., Bottai, M., Hillert, J., 2015. Effect of smoking Cessation on Multiple Sclerosis Prognosis. JAMA Neurol. 72, 1117. https://doi.org/10.1001/jamaneurol.2015.1788.
Razani-Boroujerdi, S., Boyd, R.T., Davila-Garcia, M.I., Nandi, J.S., Mishra, N.C., Singh, S.P., Pena-Philippides, J.C., Langley, R., Sopori, M.L., 2007. T Cells Express 7-Nicotinic Acetylcholine Receptor Subunits that require a Functional TCR and Leukocyte-specific Protein Tyrosine Kinase for Nicotine-Induced Ca2+ Response. J. Immunol. 179, 2889–2898. https://doi.org/10.4049/jimmunol.179.5.2889.
Rennard, S.I., 2004. Cigarette Smoke in Research. Am. J. Respir. Cell Mol. Biol. 31, 479–480. https://doi.org/10.1165/rcmb.F284.
Rider, P., Voronov, E., Dinarello, C.A., Apte, R.N., Cohen, I., 2017. Alarmins: Feel the stress. J. Immunol. 198, 1395–1402. https://doi.org/10.4049/jimmunol.1601342.
Robays, L.J., Lanckacker, E.A., Moerloose, K.B., Maes, T., Bracke, K.R., Brusselle, G.G., Joos, G.F., Vermaelen, K.Y., 2009. Concomitant Inhalation of Cigarette Smoke and Aerosolized Protein Activates Airway Dendritic Cells and Induces Allergic Airway Inflammation in a TLR-Independent Way. J. Immunol. 183, 2758–2766. https://doi.org/10.4049/jimmunol.0802204.
Robbins, C.S., Franco, F., Mouded, M., Cernadas, M., Shapiro, S.D., 2008. Cigarette Smoke Exposure Impairs Dendritic Cell Maturation and T Cell Proliferation in Thoracic Lymph Nodes of mice. J. Immunol. 180, 6623–6628. https://doi.org/10.4049/jimmunol.180.10.6623.
Rom, O., Avezov, K., Aizenbud, D., Reznick, A.Z., 2013. Cigarette smoking and inflammation revisited. Respir. Physiol. Neurobiol. 187, 5–10. https://doi.org/10.1016/j.resp.2013.01.013.
Roth-Walter, F., Bergmayr, C., Meitz, S., Buchleitner, S., Stremnitzer, C., Fazekas, J., Moskovskich, A., Müller, M.A., Roth, G.A., Manzano-Szalai, K., Dvorak, Z., Neunkirchner, A., Jensen-Jarolim, E., 2017. Janus-faced Acrolein prevents allergy but accelerates tumor growth by promoting immunoregulatory Foxp3+ cells: Mouse model for passive respiratory exposure. Sci. Rep. 7, 45067. https://doi.org/10.1038/srep45067.
Roux, P.P., Blenis, J., 2004. ERK and p38 MAPK-Activated Protein Kinases: a Family of Protein Kinases with Diverse Biological Functions. Microbiol. Mol. Biol. Rev. 68, 320–344. https://doi.org/10.1128/MMBR.68.2.320-344.2004.
Saetta, M., Di Stefano, A., Turato, G., Facchini, F.M., Corbino, L., Mapp, C.E., Maestrelli, P., Ciaccia, A., Fabbri, L.M., 1998. CD8 + T-Lymphocytes in Peripheral Airways of Smokers with Chronic Obstructive Pulmonary Disease. Am. J. Respir. Crit. Care Med. 157, 822–826. https://doi.org/10.1164/ajrccm.157.3.9709027.
Shan, M., Cheng, H.-F., Song, L.-z., Roberts, L., Green, L., Hacken-Bitar, J., Huh, J., Bakaeen, F., Coxson, H.O., Storness-Bliss, C., Ramchandani, M., Lee, S.-H., Corry, D.B., Kheradmand, F., 2009. Lung Myeloid Dendritic Cells Coordinately Induce TH1 and TH17 responses in Human Emphysema. Sci. Transl. Med. 1, 4ra10-4ra10. https://doi.org/10.1126/scitranlsmed.3000154.
Simon, K.C., van der Mei, I.A.F., Munger, K.L., Ponsonby, A., Dickinson, J., Dwyer, T., Sundstrom, P., Ascherio, A., 2010. Combined effects of smoking, anti-EBNA antibodies, and HLA-DRB1*1501 on multiple sclerosis risk. Neurology 74, 1365–1371. https://doi.org/10.1212/WNL.0b013e3181dad57e.
Skok, M., Grailhe, R., Agenes, F., Changeux, J.-P., 2006. The role of nicotinic acetylcholine receptors in lymphocyte development. J. Neuroimmunol. 171, 86–98. https://doi.org/10.1016/j.jneuroim.2005.09.011.
Smith, C.J., Fischer, T.H., 2001. Particulate and vapor phase constituents of cigarette mainstream smoke and risk of myocardial infarction. Atherosclerosis 158, 257–267. https://doi.org/10.1016/S0021-9150(01)00570-6.
Sokratous, M., Dardiotis, E., Tsouris, Z., Bellou, E., Michalopoulou, A., Siokas, V., Arseniou, S., Stamati, T., Tsivgoulis, G., Bogdanos, D., Hadjigeorgiou, G.M., 2016. Deciphering the role of DNA methylation in multiple sclerosis: emerging issues. Autoimmun. Highlights 7, 12. https://doi.org/10.1007/s13317-016-0084-z.
Sopori, M., 2002. Effects of cigarette smoke on the immune system. Nat. Rev. Immunol. 2, 372–377. https://doi.org/10.1038/nri803.
Steinman, R.M., 2012. Decisions about Dendritic Cells: past, present, and Future. Annu. Rev. Immunol. 30, 1–22. https://doi.org/10.1146/annurev-immunol-100311-102839.
Stockinger, B., Di Meglio, P., Gialitakis, M., Duarte, J.H., 2014. The Aryl Hydrocarbon receptor: multitasking in the immune system. Annu. Rev. Immunol. 32, 403–432. https://doi.org/10.1146/annurev-immunol-032713-120245.
Tanasescu, R., Constantinescu, C.S., Tench, C.R., Manouchehrinia, A., 2017. Smoking Cessation and the Reduction of Disability Progression in Multiple Sclerosis: a Cohort Study. Nicotine Tob. Res. 154, 373–384. https://doi.org/10.1093/ntr/ntx084.
Todt, J.C., Freeman, C.M., Brown, J.P., Sonstein, J., Ames, T.M., McCubbrey, A.L., Martinez, F.J., Chensue, S.W., Beck, J.M., Curtis, J.L., 2013. Smoking decreases the response of human lung macrophages to double-stranded RNA by reducing TLR3 expression. Respir. Res. 14, 33. https://doi.org/10.1186/1465-9921-14-33.
Torii, K., Saito, C., Furuhashi, T., Nishioka, A., Shintani, Y., Kawashima, K., Kato, H., Morita, A., 2011. Tobacco smoke is related to Th17 generation with clinical implications for psoriasis patients. Exp. Dermatol. 20, 371–373. https://doi.org/10.1111/j.1600-0625.2010.01224.x.
Vassallo, R., Tamada, K., Lau, J.S., Kroening, P.R., Chen, L., 2005. Cigarette Smoke Extract Suppresses Human Dendritic Cell Function Leading to Preferential Induction of Th-2 Priming. J. Immunol. 175, 2684–2691. https://doi.org/10.4049/jimmunol.175.4.2684.
Veldhoen, M., Hirota, K., Westendorf, A.M., Buer, J., Dumoutier, L., Renauld, J.-C., Stockinger, B., 2008. The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins. Nature 453, 106–109. https://doi.org/10.1038/nature06881.
Vlahos, R., Bozinovski, S., Chan, S.P.J., Ivanov, S., Lindén, A., Hamilton, J.A., Anderson, G.P., 2010. Neutralizing Granulocyte/Macrophage Colony–Stimulating factor Inhibits Cigarette Smoke–induced Lung Inflammation. Am. J. Respir. Crit. Care Med. 182, 34–40. https://doi.org/10.1164/rccm.200912-1794OC.
Wang, H., Yu, M., Ochani, M., Amella, C.A., Tanovic, M., Susarla, S., Li, J.H., Wang, H., Yang, H., Ulloa, L., Al-Abed, Y., Czura, C.J., Tracey, K.J., 2002. Nicotinic acetylcholine receptor α7 subunit is an essential regulator of inflammation. Nature 421, 384–388. https://doi.org/10.1038/nature01339.
Wang, H., Peng, W., Weng, Y., Ying, H., Li, H., Xia, D., Yu, W., 2012. Imbalance of Th17/Treg cells in mice with chronic cigarette smoke exposure. Int. Immunopharmacol. 14, 504–512. https://doi.org/10.1016/j.intimp.2012.09.011.
Wasén, C., Turkkila, M., Bossios, A., Erlandsson, M., Andersson, K.M., Ekerljung, L., Malmhäll, C., Brisslert, M., Töyrä Silfverswärd, S., Lundbäck, B., Bokarewa, M.I., 2017. Smoking activates cytotoxic CD8+ T cells and causes survivin release in rheumatoid arthritis. J. Autoimmun. 78, 101–110. https://doi.org/10.1016/j.jaut.2016.12.009.
Weiland, T.J., Hadgkiss, E.J., Jelinek, G.A., Pereira, N.G., Marck, C.H., van der Meer, D.M., 2014. The association of alcohol consumption and smoking with quality of life, disability and disease activity in an international sample of people with multiple sclerosis. J. Neurol. Sci. 336, 211–219. https://doi.org/10.1016/j.jns.2013.10.046.
Westerlind, H., Boström, I., Stawiarz, L., Landtblom, A.-M., Almqvist, C., Hillert, J., 2014. New data identify an increasing sex ratio of multiple sclerosis in Sweden. Mult. Scler. 20, 1578–1583. https://doi.org/10.1177/1352458514530021.
Witschi, H., 2005. Carcinogenic activity of Cigarette Smoke Gas phase and its Modulation by Beta-Carotene and N-Acetylcysteine. Toxicol. Sci. 84, 81–87. https://doi.org/10.1093/toxsci/kfi043.
World Health Organisation, 2018. WHO Data and Statistics.
Xavier, R.F., Ramos, D., Ito, J.T., Rodrigues, F.M.M., Bertolini, G.N., Macchione, M., de Toledo, A.C., Ramos, E.M.C., 2013. Effects of Cigarette smoking Intensity on the Mucociliary Clearance of active smokers. Respiration 86, 479–485. https://doi.org/10.1159/000348398.
Yamauchi, A., Dohgu, S., Nishioku, T., Shuto, H., Naito, M., Tsuruo, T., Sawada, Y., Kataoka, Y., 2007. An inhibitory role of nitric oxide in the dynamic regulation of the blood-brain barrier function. Cell. Mol. Neurobiol. 27, 263–270. https://doi.org/10.1007/s10571-007-9139-z.
Yanbaeva, D.G., Dentener, M.A., Creutzberg, E.C., Wesseling, G., Wouters, E.F.M., 2007. Systemic Effects of smoking. Chest 131, 1557–1566. https://doi.org/10.1378/chest.06-2179.
Yao, H., Yang, S.-R., Kode, A., Rajendrasozhan, S., Caito, S., Adenuga, D., Henry, R., Edirisinghe, I., Rahman, I., 2007. Redox regulation of lung inflammation: role of NADPH oxidase and NF-kappaB signalling. Biochem. Soc. Trans. 35, 1151–1155. https://doi.org/10.1042/BST0351151.
Yeh, H.-C., Duncan, B.B., Schmidt, M.I., Wang, N.-Y., Brancati, F.L., 2010. Smoking, smoking Cessation, and risk for Type 2 Diabetes Mellitus: a Cohort Study. Ann. Intern. Med. 152, 10. https://doi.org/10.7326/0003-4819-152-1-201001050-00005.
Zähringer, U., Lindner, B., Inamura, S., Heine, H., Alexander, C., 2008. TLR2 – promiscuous or specific? A critical re-evaluation of a receptor expressing apparent broad specificity. Immunobiology 213, 205–224. https://doi.org/10.1016/j.imbio.2008.02.005.
Zeilinger, S., Kühnel, B., Klopp, N., Baurecht, H., Kleinschmidt, A., Gieger, C., Weidinger, S., Lattka, E., Adamski, J., Peters, A., Strauch, K., Waldenberger, M., Illig, T., 2013. Tobacco smoking leads to Extensive Genome-Wide changes in DNA Methylation. PLoS One 8, e63812. https://doi.org/10.1371/journal.pone.0063812.
Zivadinov, R., Weinstock-Guttman, B., Hashmi, K., Abdelrahman, N., Stosic, M., Dwyer, M., Hussein, S., Durfee, J., Ramanathan, M., 2009. Smoking is associated with increased lesion volumes and brain atrophy in multiple sclerosis. Neurology 73, 504–510. https://doi.org/10.1212/WNL.0b013e3181b2a706.