REVIEW MANUSCRIPT

Smoking and air pollution as pro-inflammatory triggers for the development of rheumatoid arthritis

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Concise title: Smoking and rheumatoid arthritis

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Abstract

Smoking is now well recognised not only as a risk factor for rheumatoid arthritis (RA), but also as a determinant of disease activity, severity, response to therapy, and possibly mortality. Recent studies have provided significant insights into the molecular and cellular mechanisms which underpin the pathogenesis of smoking-related RA. These involve release of the enzymes, peptidylarginine deiminases (PADs) 2 and 4 from smoke-activated, resident and infiltrating pulmonary phagocytes. PADs, in turn, mediate the conversion of various endogenous proteins to putative citrullinated autoantigens. In genetically susceptible individuals, these autoantigens trigger the production of anti-citrullinated peptide/protein pathogenic autoantibodies (ACPA), an event which precedes the development of RA. This review is focused primarily on smoking-mediated harmful chronic inflammatory responses, both local and systemic, which promote the formation of ACPA, as well as the possible involvement of other types of outdoor and indoor pollution in the pathogenesis of RA. This is preceded by a brief overview of the evidence implicating smoking as a risk factor for development of ACPA-positive RA.

Keywords: Anti-citrullinated peptide/protein antibodies; airway microbiota; atmospheric pollution; heavy metals; peptidylarginine deiminases; smoking cessation strategies.

Implications

Chronic inflammatory mechanisms operative in the lungs of smokers lead to the production of anti-citrullinated protein antibodies which, in turn, drive the development of rheumatoid arthritis. These mechanistic insights not only reinforce the association between smoking and risk for rheumatoid arthritis, but also the necessity to increase the level of awareness in those at highest risk.

Introduction

Although identification of the triggering events involved in the immunopathogenesis of rheumatoid arthritis (RA) remain elusive, a considerable and increasing body of evidence supports the contention that these may occur at sites distal to the synovial joints. Prime contenders are the gastrointestinal tract (GIT), and, more recently, the lungs. In the case of the GIT, a number of earlier studies focused on RA and other inflammatory arthropathies proposed a triggering role for Gram-negative intestinal bacterial pathogens. In this setting, immunogenic and pro-inflammatory bacterial products were proposed to access the systemic circulation and joints via translocation across a damaged gut epithelium [1–7]. Potential mechanisms of initiation and/or exacerbation of RA included: i) deposition of bacterial endotoxin in the joints [5, 6]; and ii) production of antibodies and cytotoxic T lymphocytes reactive with cross-reactive epitopes present on both the putative causative bacterial pathogens and host synovial autoantigens [7]. In keeping with these earlier studies, alterations in the GIT microbiome, resulting in replacement of beneficial commensals such as *Bacteroides, Blautia, Lachnospiraceae* and Group XIV Clostridia clades with the pro-inflammatory, Gram-negative, anaerobic rod, *Prevotella copri* have recently been linked to the pathogenesis of RA [8], possibly due to lifestyle factors such as diet and smoking [9].

Recent attention has also focused on the involvement of immunological disturbances in the lungs in the pathogenesis of RA. In this setting, inhalation of cigarette smoke and possibly other indoor and outdoor atmospheric pollutants have been reported to contribute to the development of RA.

Smoking and RA

The association of smoking with development and severity of RA was documented almost 30 years ago [10] and confirmed in many subsequent studies [11–21]. A recent dose-response meta-analysis (encompassing 4,552 RA patients) reported relative risks of 1.26 and 1.96 for the associations of RA with smoking histories of 1–10 and >20 pack years respectively [19]. In addition, others have reported that RA-affected male, current smokers were less likely to experience remission than their

never- or former- smoking counterparts, an association that was not detected in females [22]. These observations are in keeping with several reports on the negative impact of smoking on the response to tumour necrosis factor (TNF) antagonists in particular [23-26], as well as methotrexate [26], in patients with RA [23–26].

It is only more recently, however, that a molecular mechanism underpinning the association between smoking and RA has been unravelled. In this context smoking, and possibly other inhaled pro-inflammatory agents, have been reported to promote protein citrullination in the lungs, a process mediated by peptidylarginine deiminase (PAD) enzymes [27–30]. PADs convert positively charged protein arginine residues to neutral, potentially immunogenic citrulline. In genetically predisposed individuals, protein citrullination poses the potential risk of production of anti-citrullinated peptide/protein antibodies (ACPA), which are strongly associated with development of RA [31,32]. In this context, the combination of current smoking and possession of HLA-DRB1 shared epitope (SE) alleles, both of which are independently associated with RA, is closely associated with the appearance of ACPA, an event which precedes, and is predictive of, the development of RA [33-38]. The specificity of ACPA for their target citrullinated proteins appears to increase closer to disease onset and progression [37]. In the case of patients with early-onset RA, previous smoking is associated with a dose-dependent occurrence of ACPA in both the lungs and circulation [35,39]. Moreover, the combination of a smoking history and double copies of HLA-DRB1 SE genes increases the risk for RA by 21-fold relative to that of non-smokers with no SE genes [35]. The smoking/SE allele interaction is, however, complex [40]. This is clearly illustrated by the findings of a recent study which reported that ever-smoking *per se* is associated with production of ACPA of the IgA isotype, possibly consistent with a pulmonary origin, while SE in the absence of smoking is associated with ACPA of the IgG isotype, and the combination of smoking and SE with seropositivity for both isotypes [41].

Taken together, these findings highlight the putative role of smoking-related inflammatory events in the lungs as potential triggers for development of ACPA and RA [42]. This contention is supported by findings of structural abnormalities of lung parenchyma in patients with untreated, early ACPA-positive RA [41]. These were

associated with high concentrations of ACPA in bronchoalveolar lavage fluid relative to those of blood [35,39].

The oral cavity is also a potential extra-articular site of smoking-associated production of ACPA. In this setting, smoking predisposes for development of chronic periodontitis [43,44]. *Porphyromonas gingivalis*, the major causative pathogen in chronic periodontitis, possesses a bacterial PAD which is capable of citrullinating both host and bacterial proteins, potentially triggering the generation of ACPA in genetically predisposed individuals. Not surprisingly, the prevalence of RA is increased in patients with *P. gingivalis* -associated chronic periodontitis, which correlates with circulating levels of ACPA [45,46]. Citrullination of periodontal proteins such as filaggrin, vimentin and enolase, as well as bacterial antigens, results in a range of different ACPA specificities with antibodies to citrullinated enolase peptides most strongly associated with RA [47].

The remainder of this review is focused on mechanisms which underpin the interaction between smoking, pulmonary inflammation, protein citrullination, ACPA, and RA, as well as the possible involvement of a smokeless tobacco product (snuff) and atmospheric pollution in the pathogenesis of RA.

Potentially harmful constituents of cigarette smoke

The Food and Drug Administration (FDA) of the United States of America has published a list of 96 “harmful and potentially harmful constituents (HPHCs)” present in tobacco products and tobacco smoke [48]. This list of smoking-associated toxicants is, however, likely to be an underestimate given that the gas and tar phases of cigarette smoke collectively contain more than 9600 chemicals [49]. In addition to a range of potentially toxic hydrocarbons such as benzo[a]pyrene, gasses, and heavy metals (Al, As, Cd, Co, Cr, Cu, Fe, Hg, Ni, Pb, V), these include various short-lived and stable toxic free radicals and reactive oxygen species (ROS). Notwithstanding direct damage to airway epithelium and epithelium [50–52], chronic exposure to these smoke-derived toxicants also impacts on cells of the innate and adaptive airway immune systems, as well as on the composition of the airway microbiota, creating a highly pro-inflammatory milieu.

Pro-inflammatory effects of smoking

In the context of a putative role in the immunopathogenesis of RA, it is noteworthy that smoking promotes the recruitment of monocytes and neutrophils to the lungs, with the numbers of alveolar macrophages being about 2 times higher than that of non-smokers [53]. Smoking also causes a chronic, low-grade leukocytosis characterised by increased numbers of immature neutrophils with a pro-inflammatory phenotype which accumulate in the lungs [54]. Migration of circulating neutrophils and monocytes to the lungs is facilitated by smoke-mediated: i) activation of the β2-integrin, CR3, on phagocytes together with upregulated expression of its counter-receptor ,ICAM-1, on vascular endothelium; and ii) increased production of neutrophil/monocyte-attracting chemokines, as well as endothelium-interactive, pro-adhesive cytokines, by smoke-exposed resident airway and infiltrating cells [55,56].

Mechanisms which contribute to the maintenance of a pro-inflammatory environment in the lungs and systemic circulation, of smokers include:

- smoke-mediated, pro-oxidative activation of the transcription factor, nuclear factor kappa B (NFκB), in cells of the airway innate immune system, as well as structural cells, by smoke-derived ROS/radicals and sulphydryl-reactive heavy metals [57-59]. On a cautionary note, however, the extent of the involvement of NFκB in the pro-inflammatory effects of smoking has recently been re-visited and questioned, raising the issue of alternative mechanisms of smoke-activated pulmonary inflammation [60].

- inhibition of release of the anti-inflammatory proteins, suppressors of cytokine signalling (SOCS), SOCS1 and SOCS3, by smoke-exposed alveolar macrophages, consistent with transition of these cells from an anti-inflammatory (M1) to a pro-inflammatory (M2) phenotype. SOCS1 and SOCS3 are released from alveolar macrophages in exosomes and microparticles, respectively. These are then internalised by alveolar epithelial

cells, resulting in attenuation of cytokine signalling, a previously unrecognised mechanism of smoking-mediated inflammatory activity [61].

- smoke-mediated redistribution of the interleukin (IL)-33 receptor, ST2, a member of the IL-1 pro-inflammatory cytokine family, resulting in increased expression on alveolar macrophages and natural killer cells, thereby potentiating the inflammatory potential of these cells [62]

- increased expression of the G-protein-coupled receptor 15 gene (*GPR15*) in the blood of smokers resulting from hypomethylation of DNA [63]. This is an orphan receptor involved in the homing of effector, pro-inflammatory Th1 and Th17 cells to the colon [64]. Although altered expression in the lungs of smokers has not yet been described, it is noteworthy that increased expression of GPR15 has been detected on circulating neutrophils and monocytes fom RA patients, as well as on $CD14^+/CD68^+$ dual-positive synovial macrophages [65]

- chronic inhalation of highly pro-inflammatory bacterial endotoxin, which is present in cured tobacco and remains biologically active, albeit at a lower level, in cigarette smoke [66, 67]. Leakage from the lungs may explain the increased levels of endotoxin present in the blood of “healthy” smokers [68], and possibly the joints of RA patients who smoke [5,6]. Endotoxins have been reported to bind to and to form complexes with procollagen that trigger cartilage inflammation and degradation via inflammatory mechanisms involving activation of NFκB [69].

These pro-inflammatory activities of smoking are summarised in Table 1.

Table 1: Documented and proposed mechanisms of the pro-inflammatory activities of cigarette smoking

Mechanism*	Consequence
Damage to pulmonary epithelium and endothelium resulting in increased lung permeability	Possible leakage of smoke-derived endotoxin and pro-inflammatory cytokines/chemokines, promoting systemic inflammation
Upregulation of expression of adhesion molecules on circulating phagocytes, as well as their counter-receptors on vascular endothelium	Facilitates pulmonary infiltration of neutrophils and monocytes
Activation of NFκB in resident and infiltrating cells of the pulmonary innate immune system, as well as structural cells, by smoke-derived ROS and heavy metals	Increased synthesis of pro-inflammatory cytokines/chemokines
Inhibition of production of SOCS1 and 3 by alveolar macrophages	Increased synthesis of pro-inflammatory cytokines/chemokines
Altered expression of the IL-33 receptor, ST2, on cells of the pulmonary innate immune system	Increased synthesis of pro-inflammatory cytokines/chemokines
Increased expression of the G-protein coupled receptor 15 gene (*GPR15*)	Possible recruitment of pro-inflammatory effector Th1 and Th17 cells and monocytes

*Covered by references 56–59 and 60–67, 80 in the text

Smoking and the microbiota

The chronic inflammatory milieu in the airways of smokers results in chronic, inappropriate activation of innate and adaptive airway host defences, which together with the interactive cytotoxic effects of smoke-derived toxicants, causes immune dysfunction, leading to alterations in the airway microbiota. In this context, alterations in the nasopharyngeal microflora of smokers include reductions in the numbers of competitive aerobic and anaerobic commensals and replacement of these with various pathogens such as *Streptococcus pneumoniae* [70]. Smoking-associated alterations in the airway microbiota are also favoured by the presence of a variety of potential microbial pathogens in cured tobacco the flakes of which translocate to the filter tip [71]. These smoking-related alterations in the airway microbiota are likely to exacerbate airway inflammation and production of ACPA. Given that microorganisms also express citrullinated proteins, it is also possible, albeit speculative, that differential expression of citrullinated proteins on replacement microorganisms may contribute to the pathogenesis of RA [72].

Inflammation and protein citrullination in the lungs of smokers

As mentioned above, PADs, of which there are 5 isoforms (PAD1, 2, 3, 4 and 6), are the key enzymes which mediate the conversion of arginine to citrulline. Two of these enzymes, PAD2 and PAD4, are present at high concentrations in the lungs of smokers, probably originating from infiltrating and resident inflammatory cells, specifically neutrophils, monocytes and macrophages [27-30]. Neutrophils have been reported to contain PADs 2, 3 and 4 [73, 74], monocytes PADs 2 and 4 [75], and macrophages PAD2 only [75]. Neutrophils, not only in the lungs, but also in the synovial fluid, may be the major sources of PAD2 and PAD4, which are released from these short-lived cells during the processes of NETosis and necrosis [73, 74]. Collectively, PAD2 and PAD4 mediate the conversion of a range of host proteins to putative citrullinated autoantigens. These include β- and γ-actins, enolase, fibrinogen, filaggrin and vimentin, all of which are recognised by ACPA [30, 38, 73]. In this context, it is noteworthy that selective knockout of the gene encoding PAD4 in mice has been reported to significantly reduce disease severity in a model of glucose-6-phosphate isomerase-induced arthritis [76].

The weight of evidence clearly supports the link between smoking, pulmonary inflammation, protein citrullination and formation of ACPA in the lungs. However, it should be mentioned that one study to which relatively small numbers of non-smokers and smokers were recruited, failed to confirm this association, with the exception of a sub-group of patients with chronic obstructive pulmonary disease [30].

Although citrullination has received greatest interest with respect to smoking/inflammation-associated, post-translational conversion of host proteins to putative autoantigens, at least two other mechanisms have also been described. These are: i) carbamylation involving the reaction of cyanate present in cigarette smoke with the primary amine group of protein/peptidyl-lysine, resulting in conversion to potentially autoantigenic protein/peptidyl-homocitrulline, which is potentiated by neutrophil/monocyte-derived myeloperoxidase [77]; and ii) ROS-mediated lipid peroxidation, resulting in the formation of malondialdehyde and acetaldehyde which, in turn, form potentially autoantigenic protein adducts via reaction with primary amine groups of amino acids [77, 78].

A proposed mechanism of the inflammatory events involved in the generation of ACPA in the lungs of smokers is shown in Figure 1.

Heavy metals, smoking and RA

Several recent studies have implicated environmental exposure to heavy metals in the pathogenesis of RA. For example, it has been reported that excised nasal polyps from smokers contain significantly higher concentrations of As, Cd and Ni than those measured in polyps of non-smokers [79]. More recently, and of particular relevance to RA, hair and blood samples taken from non-smoking, and smoking RA patients in particular (n=53, 26F:27M, 60% smokers), were found to contain significantly higher concentrations of As, Cd, Hg and Pb than those in the corresponding samples taken from either non-smoking or smoking healthy control subjects [80]. The authors did not, however, address the possible causes of the elevated concentrations of these metals in samples taken from the non-smoking RA patients [80], such as possible exposure to other inhaled atmospheric pollutants [79].

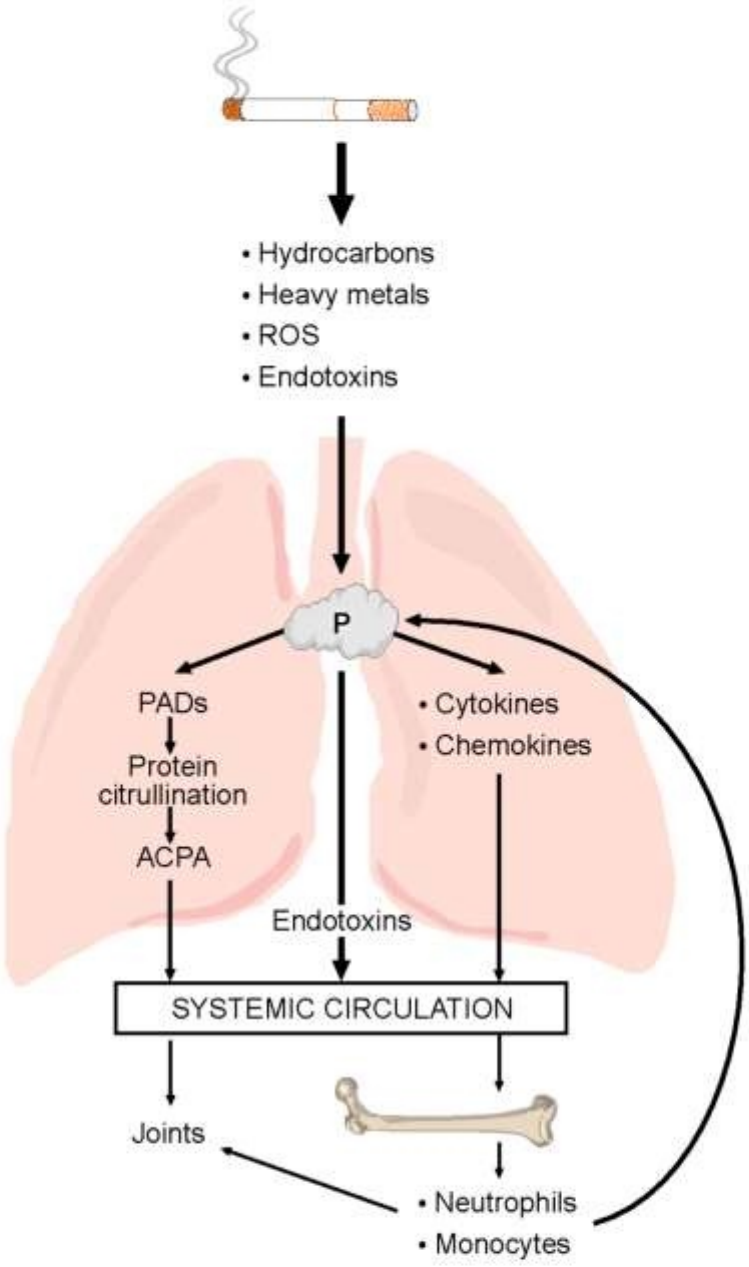

Figure 1: A proposed smoking-activated pulmonary inflammatory cascade leading to the production of anti-citrullinated peptide/protein antibodies (ACPA). Inhalation of cigarette smoke results in exposure of the airways to a range of smoke-derived toxicants, including, but not limited to, hydrocarbons, heavy metals, reactive oxygen species (ROS) and microbial endotoxins. Interactions of these with resident and infiltrating pulmonary phagocytes (P), such as resident alveolar macrophages and infiltrating monocytes and neutrophils, leads to activation of peptidylarginine deiminases (PADs) resulting in citrullination of host proteins, including structural proteins and enzymes. In genetically susceptible individuals, these citrullinated proteins are potential immunogens (autoantigens) which trigger the local production of anti-citrullinated peptide/protein antibodies (ACPA). These, as well as the cells which produce them, migrate to the synovial joints where they promote synovial inflammation and damage to the joints. These events are exacerbated and perpetuated by the sustained production of pro-inflammatory cytokines/chemokines by cells of the pulmonary innate immune system, as well as structural cells. These pro-inflammatory cytokines/ chemokines sustain pulmonary inflammation by promoting the production and trafficking to the lungs of neutrophils and monocytes.

Smokeless tobacco (snuff)

Usage of snuff, which is prepared from dried, pulverised tobacco leaves and is available in the powdered or moistened forms for nasal or oral application respectively, is common in northern European countries, as well as a number of other developed and developing countries including South Africa. Usage of snuff, which may be increasing due to bans on smoking in public places, does not result in exposure to the toxicants that result from the combustion of tobacco. It does, however, carry the risk of exposure to nicotine, heavy metals, and contaminating microorganisms and their products, with the levels of blood and urine nicotine/cotinine being comparable to those of smokers [81–85]. Although studies to date are somewhat limited, those that have been reported did not, however, detect an association between usage of snuff and risk of development of either ACPA-positive or ACPA-negative RA, or for increased disease severity [86–88]. All of these studies were performed in Sweden and involved users of orally-applied moist snuff. Future studies should focus on users of powdered, inhaled snuff products.

Outdoor and indoor atmospheric pollution, pulmonary inflammation and ACPA

Although smoking is a recognised risk factor for development of RA, probably linked to inappropriate immune activation and production of ACPA, in many settings, particularly in some developing world countries such as South Africa, the majority of ACPA-seropositive/SE allele-positive RA patients do not smoke [89, 90]. In this setting, alternative triggering mechanisms of production of ACPA may be implicated. Notwithstanding inhaled snuff products, these include chronic exposure to outdoor, and possibly indoor, atmospheric pollutants as causes of pulmonary inflammation possibly linked to the pathogenesis of RA [91].

Interest in exposure to motor vehicle exhaust fumes, which contain a variety of particulate and non-particulate airway irritants, as a risk factor for RA, was prompted by a study published in 2009 by Hart and colleagues [92]. Based on data derived from the “Nurses’ Health Study,” to which 90,297 U.S. women were enrolled, these authors, using Cox proportional hazard models with “adjustment for a large

number of potential co-founders," including smoking, investigated residing in close proximity to a road as a potential environmental risk factor for RA [92]. They reported that those living within 50 metres of a road, but not further away, had an increased risk of RA, with a hazard ratio (HR) of 1.31 [92]. This association was evident in the following sub-groups: i) non-smokers (HR=1.62); ii) non-smokers with rheumatoid factor (RF)-seropositive RA (HR=1.51); and iii) non-smokers with RF-seronegative RA (HR=1.77) [92]. ACPA were not measured in this study [92]. These findings were confirmed in a more recent study from Canada encompassing 678,361 residents aged 45–48 [93]. The authors reported that residing within ≤50m of motor vehicle traffic was associated with an increased risk for RA [odds ratio (OR) of 1.37], which was not attributable to either traffic-related noise, or, somewhat surprisingly, to specific air pollutants ($PM_{2.5}$, PM_{10}, CO, NO, NO_2, O_3, SO_2) [93]. Other studies have shown a similar lack of association between RA, either seropositive (ACPA/RF) or seronegative disease, and exposure to specific atmospheric pollutants ($PM_{2.5}$, PM_{10}, NO_2 and SO_2) [94, 95].

Although the precise determinants of the link between traffic-related atmospheric pollution and risk for RA remain to be identified, the association is supported, albeit indirectly, by several other lines of evidence. These include:

- a much higher prevalence of RA in urban, as opposed to rural areas of several countries such as China, South Africa and Taiwan. In the case of mainland China, which remains a predominantly rural country, the overall prevalence of RA is considerably lower than that observed in Caucasians (0.28% vs. 1%) [96]. In South Africa, where the epidemiology of RA is changing in relation to ethnicity, the prevalence rates of "definite RA" in rural and urban black South African populations reported in 1975 were reported to be 0.18% and 0.9% respectively [97]; in a later study published in 1988, the prevalence of RA in a defined, remote geographic region of South Africa was estimated to be 0.0026% [98]. The corresponding prevalence rates for Taiwan published in 1994 varied from 0.26 – 0.93%, with the highest rate recorded in an urban region [99, 100]

- As mentioned earlier, even in in non-smoking subjects with RA, the levels of several toxic heavy metals in blood and hair samples were reported to be higher than those of healthy control subjects [60]. In the context of the association of atmospheric pollution and RA risk, two aspects of this study are particularly noteworthy. Firstly, the subjects were resident in a major city (Dublin, Republic of Ireland); secondly, most of the heavy metals tested (As, Cd, Hg) are also present in diesel emissions [60]. In addition, residing in areas with high levels of atmospheric pollution has also been reported to be associated with particularly high concentrations of As in nasal mucosa and nasal polyps [59].

In the context of developing countries, those exposed to high levels of outdoor atmospheric pollution are also likely to have a high probability of exposure to indoor pollution. Sprawling townships and informal settlements with high population densities are often located in close proximity to roads and highways with major traffic flow. Dwellings are often poorly constructed and ventilated, possibly non-electrified, and with lack of access to clean water and sanitation. Notwithstanding active and passive smoking, the major sources of indoor pollution include chronic exposure to house dust contaminated with endotoxin [101], and in some cases, components of smokeless tobacco [102], as well as a variety of particulate, gaseous, heavy metal and other toxicants emanating from woodsmoke and the combustion of paraffin and paraffin wax candles [103, 104]. In addition, those with employment who reside in these environments are likely to be engaged in industries such as construction and mining, involving occupational exposure to inhaled irritants such as silica, which also pose a high risk of development of ACPA-seropositive RA [105,106].

Although current smoking and possibly chronic exposure to outdoor environmental atmospheric pollutants appear to be independent risks for ACPA-seropositive RA, it is likely that interactions between these, as well as with indoor pollution and occupation, pose the greatest risk.

Anti-inflammatory/immunosuppressive therapies

While synthetic and biologic disease-modifying anti-inflammatory drugs remain the cornerstone of the therapy of RA, inhibitors of PADs, which are currently in the developmental pipeline [107], are of potential therapeutic utility in the prevention and/or therapy of RA.

Smoking cessation strategies

Given that smoking is currently recognised as the most significant, avoidable risk for RA, the early identification of RA sufferers who smoke, together with the inclusion of persuasive, anti-smoking counselling as an adjunct to routine care, are clearly priorities. This strategy is underscored by the increased mortality rates in RA, due predominantly to cardiovascular and pulmonary diseases [108, 109]. In this context, it is noteworthy that RA-related increased mortality has been reported to have a strong association with the combination of smoking, SE and ACPA [110]. Overcoming the barriers to successful implementation of anti-smoking strategies in RA does, however, present significant challenges. These include lack of awareness of the risk, as well as dependence on smoking as a distraction from pain, physical inactivity, loneliness and depression [111].

Conclusion

The mechanisms underpinning the pathogenesis of RA are varied, complex and incompletely characterised. Nonetheless, an increasing body of evidence has identified inflammatory mechanisms in the lung, linked to the production of ACPA, as events which precede the development of seropositive RA. Smoking in particular, and possibly exposure to other types of environmental and occupational, atmospheric pollution, trigger these inappropriate inflammatory responses. The implementation of compelling, anti-smoking awareness/education campaigns and cessation strategies is a priority not only to improve the outcome of RA, but also in disease prevention. Future studies should focus on the role of passive smoking, as well as the utility of inclusion of objective, inexpensive measurements of smoke

exposure, in the routine clinical assessment of patients presenting with suspected RA.

Declaration of Interests

None of the authors has a conflict of interest to declare.

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