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Review

# Smoke and autoimmunity: The fire behind the disease

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ABSTRACT

The association between smoke habit and autoimmunity has been hypothesized a long time ago. Smoke has been found to play a pathogenic role in certain autoimmune disease as it may trigger the development of autoantibodies and act on pathogenic mechanism possibly related with an imbalance of the immune system. Indeed, both epidemiological studies and animal models have showed the potential deleterious effect caused by smoke. For instance, smoke, by provoking oxidative stress, may contribute to lupus disease by dysregulating DNA demethylation, upregulating immune genes, thereby leading to autoreactivity. Moreover, it can alter the lung microenvironment, facilitating infections, which, in turn, may trigger the development of an autoimmune condition. This, in turn, may result in a dysregulation of immune system leading to autoimmune phenomena. Not only cigarette smoke but also air pollution has been reported as being responsible for the development of autoimmunity. Large epidemiological studies are needed to further explore the accountability of smoking effect in the pathogenesis of autoimmune diseases.



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## 1. Introduction

The association between smoke habit and autoimmunity has been hypothesized a long time ago [1]. Indeed, within the milestones achieved in the knowledge of the pathogenesis of autoimmune diseases, the discovery of novel autoantibodies possibly triggered by environmental agents has gained the attention of researchers [2]. Moreover, it is now recognized that autoantibodies often precede the development of an overt autoimmune disorder; however, since their presence does not necessarily lead to a full-blown disease, it is still a matter of debate whether they represent epiphenomena, some result of a genetic predisposition, or true risk factors [3]. Nonetheless, in the last years, the concept of "second hit" has been suggested for instance in antiphospholipid syndrome (APS) to explain the occurrence of a full-blown condition in a genetically predisposed individual [4]. Smoke has been found to play a pathogenic role since in certain conditions it may trigger the development of autoantibodies favoring citrullination [5], or acting as the "second hit" responsible for disease manifestation. Indeed, both epidemiological studies and animal models have showed the potential deleterious effect caused by smoke [6,7]. For example, smoke, by provoking oxidative stress, may contribute to lupus disease by dysregulating DNA demethylation, upregulating immune genes thereby leading to autoreactivity [6]. Moreover, it can alter the lung microenvironment, facilitating an exaggerated proinflammatory response to infection [8]. This, in turn, may result in a dysregulation of immune system leading to autoimmune phenomena. Not only cigarette smoke but also air pollution has been reported as being responsible for the development of autoimmunity. Indeed, it has been recently suggested that air pollution may represent a risk factor for rheumatoid arthritis (RA) [9,10]. Nevertheless, the results are still conflicting for some conditions while more clear in other autoimmune diseases such as rheumatoid arthritis. Thus, we aimed to review the role of smoke in the some of the most prominent autoimmune diseases.

## 2. Smoke and rheumatoid arthritis

Rheumatoid arthritis (RA) is a common rheumatologic condition affecting approximately 1% of the adult population [11]. The disease has a complex pathogenesis in which both environmental and genetic factors interplay [12]. The synoviocytes are within the major effectors leading to the formation of pannus and production of proinflammatory cytokines and chemokines [13]. The inflammatory response leads to cartilage degradation and bone damage through the production of proteases and reactive oxygen intermediates, proliferation of synovial fibroblasts, recruitment of inflammatory cells, and neoangiogenesis [14]. The complement system is involved in disease pathogenesis possibly influencing serological phenotype and response to therapy [15–17].

The risk factors suggested so far include diet, coffee intake, alcohol, and body mass index [18]. However, cigarette smoking is the only risk factor clearly associated with disease susceptibility [19]. A number of evidences link cigarette smoking and disease development and outcome in patients with RA [20]. Animal models with collagen-induced arthritis suggest that cigarette smoke can augment the induction and clinical development of arthritis at both young and older mice [21].

In humans, estimations from the Swedish EIRA cohort study indicate that the excess fraction of anti-citrullinated peptide antibody (ACPA) positive RA due to smoking (without considering the HLA-SE status) is 35% (95% CI 25–45). This could indicate that over one-third of RA cases would be prevented if people did not smoke [22].

Back to the late '80s, Vessey et al. [23] found a marked increase in hospital admissions due to RA in smokers. It is not well established whether the association between smoke and RA is more frequent in men or women since there are studies suggesting both scenarios [24,25]. As previously mentioned, there is a correlation between packs smoked in a year and the risk for RA. Indeed, it is more elevated in 10 pack-years or more of smoking and increased linearly with increasing pack-years (HR 1.5e2). Nonetheless, the risk of RA remains substantially elevated even until 10–20 years after smoking ceased [26]. Data from a meta-analysis suggest that the risk for developing RA is about twice for male smokers than non-smokers, while for female smokers, this risk seems to be about 1.3 times higher. This is not valid for heavy smokers (20 pack-years of smoking or more) in which the risk seems equally high for both genders [27].

Smoking seems to influence also the clinical phenotype of patients with RA. Tobacco habit contributes to the occurrence of extra-articular manifestations of RA in European, African-American, and Korean populations. The occurrence of rheumatoid nodules is more frequent in seropositive RA smokers [19]. Even the response to therapy is influenced by smoking status [28]. Those patients who smoke more than 20 pack-years smoke are less likely to improve after treatment; moreover, they seem to need a more aggressive treatment with disease-modifying anti-rheumatic drugs (DMARDs) and have a poor response to anti-TNF treatment. The most important variable is intensity of previous smoking rather than the smoking status at initiation of TNF antagonists [28]. Smokers are more frequently non-responders, as it was recently suggested by data from the Swedish Rheumatology Register cohort [29]. Current smokers were less likely than non-smokers to achieve a good response at 3 months following the start of MTX (27% versus 36%) and at 3 months following the start of TNF inhibitors (29% versus 43%; $P = 0.03$). Such lower likelihood of a good response was still present after at later follow-up visits (6 months, 1 year, and 5 years) with adjusted ORs of 0.65, 0.78, 0.66, and 0.61, respectively.

Hutchinson and colleagues found that [30] heavy smoking was a risk factor for the disease development especially in patients without a family history of RA. When considering the first 7 years of age, maternal smoking during pregnancy can be responsible for infant RA and other inflammatory polyarthritis [31].

Another question is whether RA smokers also do develop a more severe joint damage. If there are studies suggesting they do not [32,33], or even that smoke may ameliorate disease progression [34,35] in others, tobacco exposure has been associated with a more erosive disease [36–38]. In a recent study from patients with early arthritis, the simple erosion narrowing score was found higher in current smokers and former smokers than in never smokers with a statistically significant difference [39].

The exact mechanisms are still unclarified. Lee and colleagues suggested that benzo[a]pyrene may increase the expression of Slug thus upregulating the invasive function of fibroblast-like synoviocytes [40]. This, in turn, may explain the increased radiological progression observed in RA smokers.