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Review

Air pollution as a determinant of rheumatoid arthritis

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ABSTRACT

Pollution has long been incriminated in many cardiovascular and respiratory diseases. More recently, studies evaluated the potential role for particulate pollutants in autoimmune diseases, including rheumatoid arthritis (RA). The incidence of RA was found to be higher in urban areas. Living near air pollution emitters was associated with higher risks of developing RA and of producing RA-specific autoantibodies. Nevertheless, no strong epidemiological evidence exists to link one or more specific air pollution particles to RA. The presence in the bronchi of lymphoid satellite islands (inducible bronchus-associated lymphoid tissue, iBALT) is strongly associated with both inflammatory lung disease and RA-associated lung disease. Diesel exhaust particles can stimulate iBALT formation. The induction by air pollution of an inflammatory environment with high citrullination levels in the lung may induce iBALT formation, thereby causing a transition toward a more specific immune response via the production of anti-citrullinated peptide antibodies. Air pollution not only triggers innate immune responses at the molecular level, increasing the levels of proinflammatory cytokines and reactive oxygen species, but is also involved in adaptive immune responses. Thus, via the aryl hydrocarbon receptor (AHR), diesel exhaust particles can trigger a T-cell switch to the Th17 profile. Finally, in the murine collagen-induced arthritis model, animals whose lymphocytes lack the AHR develop milder arthritis.

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that is mediated by both genetic and environmental factors. Although the joints are the chief targets of RA [1], other tissues – most prominently the lung – can be involved. Lung disease is common in RA, notably during the phase leading up to the disease, when biological markers are found despite the absence of symptoms. Although all the anatomic structures of the lung may be affected, studies suggest predominant involvement of the airways in early asymptomatic RA [2–4]. Vital capacity diminishes, bronchiectasis develops, and an infiltrate of lymphocytes and plasma cells indicates chronic inflammation [2]. These abnormalities are strongly associated with the presence of anti-citrullinated peptide antibodies (ACPAs) in serum, alveolar, and bronchial biopsy specimens. Usual interstitial pneumonitis, (UIP), i.e., diffuse idiopathic interstitial lung disease, is found in nearly 60% of patients with established RA [5].

The posited involvement of the lung in the pathophysiology of RA has received support over the last decade from studies into the effects on the disease of several inhaled environmental factors. The role for smoking is now firmly established [6]: smoking is strongly associated with the development, severity, and treatment response of RA. In HLA-DRB1-positive individuals, cigarette smoke initiates the protein citrullination process that leads to ACPA production. Silica, which is also found in ambient air, has been incriminated in the pathophysiology of RA [7–9].

Air pollution is also a focus of research in the field of autoimmunity. That air pollution is linked to mortality and morbidity from respiratory and cardiovascular diseases was recognized as early as the 1950s [10]. More recently, studies have addressed the potential role for air pollution in the development of autoimmune diseases such as RA. Evidence suggests that, instead of a mere interface between air and the bloodstream, the airway tissues may be capable of transforming air particles and presenting them as antigens. Thus, the particles in ambient air act as precursors and generators of autoimmunity.

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Here, the epidemiological evidence linking air pollution to RA is discussed, as well as the potentially relevant cellular and molecular mechanisms.

2. Effect of air pollution

The pollutants found in air are produced by human activity (e.g., vehicles, manufacturing, smoking, and agriculture) and by natural sources (e.g., forest fires and volcanic eruptions). Both anthropogenic and geogenic pollutants are a mixture of gases (nitrogen dioxide [NO_2], sulfur dioxide [SO_2], ozone [O_3], and carbon monoxide [CO]) and particulate matter (PM). PM can be classified based on the nature of the particles, i.e., chemical (hydrocarbons), metallic (nickel, iron), mineral (silica, quartz), or biological (e.g., pollen and endotoxins). However, particle size is the most relevant classification criterion. Coarse particles (PM_{10}) measure less than 10 μm in diameter, fine particles ($PM_{2.5}$) less than 2.5 μm, very fine particles ($PM_{1.0}$) less than 1 μm, and ultrafine particles ($PM_{0.1}$ or UFPs) less than 100 nm (i.e., are nanoparticles). The World Health Organization has stated that annual mean concentrations per cubic meter of ambient air should not exceed 40 μg for PM_{10} and 25 μg for $PM_{2.5}$ in the European Union [11]. Before the 1980s, the chief sources of PM were wood- and coal-burning heating devices, gasoline, and diesel fuel. These sources produce coarse sulfur-rich particles that are now less abundant proportionally in ambient air, due to advances in industrial emissions control. PUFs have largely taken their place and contribute most of the PM burden. PUFs come chiefly from gas-to-particle conversions but are also produced by internal combustion engines, power plants, incinerators, airplanes, and other sources. PUFs are too small to be cleared effectively by the airway mucociliary apparatus or by alveolar macrophage phagocytosis. They consequently deposit preferentially within the alveoli.

2.1. Epidemiological evidence linking air pollution to rheumatoid arthritis (RA)

RA is a common diseases that occurs throughout the world [12]. Nevertheless, both the incidence and the prevalence of RA vary widely across geographic areas. The estimated incidence is 20–50/100,000 in North America and northern Europe compared to 9–24/100,000 in southern Europe [13]. These differences may be partly ascribable to variations in genetic susceptibility factors and to methodological bias. RA may be less common in developing countries, i.e., in countries with lower levels of industrial activity, suggesting an effect of pollution in the occurrence of RA. Further support for this hypothesis came from evidence that, within a given country, urban areas had a higher incidence of RA compared to rural areas [14,15].

Seven large epidemiological studies have specifically addressed the links between air pollution and the incidence of RA. All of them were conducted in industrialized countries (Canada, Sweden, Taiwan, and US). A study of 90,297 women from the Nurses' Health Study in the US found that traffic exposure assessed as the distance from residence to road was associated with a higher incidence of RA. After adjustment for age, smoking, ethnicity, and body mass index, women living less than 50 m from a road had a 31% higher risk of developing RA compared to women living at more than 200 m from a road [16]. These findings were then partly corroborated by a case-control study from Canada [17]. Living less than 50 m from a road was associated with an odds ratio (OR) of 1.37 (95% confidence interval [95% CI], 1.11–1.68) of developing RA. Distance from industrial emitters of air pollutants was studied in the CARTaGENE cohort from Quebec [18]. For each additional kilometer of distance from emitters of $PM_{2.5}$ and SO_2, the OR for developing RA was 0.81 (95% CI, 0.69–0.96) and the OR for developing ACPAs was 0.92 (95% CI, 0.84–1.00).

These data prompted epidemiological surveys designed to assess direct links between exposures to various pollutants and the incidence of RA [17,19–22]. None of these studies found statistically significant links. Several factors may explain these negative findings. First, cohort studies assessed exposures to pollutants near the place of residence but disregarded potential exposures at the workplace or recreational areas. Second, air pollution is a complex mixture, and focusing on specific components (e.g., gases or PM) may decrease the likelihood of demonstrating significant associations. According to one hypothesis, the higher incidence of RA in people living near roads [16–18] may be ascribable specifically to cadmium exposure and not to other pollutants [23]. Cadmium is a heavy metal that is found in diesel fuels and was used to manufacture tires and brake pads. Cadmium levels are very high within 20 m of asphalt-paved roads and may therefore act as a confounding factor in studies of vehicle-related air pollution. In rats, cadmium exposure was shown to worsen the manifestations of collagen-induced arthritis [24].

2.2. Effect of air pollution on other autoimmune diseases

These conflicting results contrast with the more robust data from studies of lupus and other systemic autoimmune rheumatic diseases (SARDs). The association between $PM_{2.5}$ exposure and the activity of systemic lupus erythematosus (SLE) assessed using the SLE Disease Activity Index version 2000 (SLEDAI-2K) was studied in patients living on the island of Montreal [25]. SLEDAI-2K scores were not associated with $PM_{2.5}$ exposure. However, anti-ds-DNA titers were significantly associated with the $PM_{2.5}$ level measured 24–48 h before blood sampling, suggesting a rapid effect of $PM_{2.5}$ variations on SLE flares.

A genome sequencing study established that living within 300 m of a highway was significantly associated with hypomethylation at three DNA sites in SLE patients but not in controls [26]. These three sites correspond to a single gene, UBE2U, which encodes an enzyme involved in protein ubiquitination and DNA repair.

Another study from Canada assessed associations between air pollution and SARDs, which include SLE, scleroderma, Sjögren's syndrome, dermatopolymyositis, and undifferentiated connective tissue disease [27]. Exposure to $PM_{2.5}$ levels above 5.2 mg/m^3 was associated with a greater risk of developing an SARD (OR, 2.44; 95% CI, 2.32–4.07).

3. The lung is an inducible lymphoid organ

The identification of ACPAs in 1998 was a major stride toward elucidating the pathophysiology of RA. ACPAs are valuable diagnostic aids, given their greater specificity compared to rheumatoid factor. However, their discovery also shed light on the epigenetic modifications that precede the development of RA. ACPAs have strong affinity for citrullinated proteins such as vimentin, fibronectin, histones, α-enolase, fibrinogen, and collagen type II. Citrullination is an epigenetic change produced by enzymes that convert arginine to citrulline. Protein arginine deiminases 2 and 4 are among these enzymes. Bronchoalveolar lavage fluid from smokers without RA contains high levels of PADs [28] and ACPAs [6]. This finding suggests that cigarette smoke or other causes of local inflammation may activate PADs in lung tissue and induce protein citrullination, thereby leading to ACPA production. Furthermore, ACPAs have been proven to exert direct pathogenic effects on joints [29] and have been detected up to 10 years before the onset of RA symptoms [30]. Thus, the lung may be an autoimmunity initiation

Box 1: Inducible bronchus-associated lymphoid tissue (iBALT).

The lymphoid system is composed of primary structures (bone marrow and thymus) and secondary structures (spleen, lymph nodes, and mucosa-associated lymphoid tissue). These structures are constitutively present in humans but can enlarge and acquire greater structural complexity in response to antigenic stimuli. Inducible lymphoid tissues are tertiary structures that can be found in many organs (e.g., pancreas, thyroid, salivary glands, brain, liver, and kidney). They develop only after prolonged exposure to environmental factors (e.g., microorganisms and proinflammatory factors such as cigarette smoke) [31]. Thus, iBALT is a typical tertiary lymphoid structure, as it is absent from the normal lung and develops only in response to antigenic stimuli [32].

The formation of iBALT can be induced by bacterial infections (e.g., due to *Mycoplasma pulmonis*, *Streptococcus*, *Pseudomonas aeruginosa*, or *Mycobacterium tuberculosis*) and viral infections (e.g., by the cytomegalovirus or influenza virus). In this situation, iBALT combats the infection by expediting the clearance or limiting the spread of the pathogens, most notably in tuberculosis. In other conditions, such as inflammatory lung diseases (asthma, pulmonary arterial hypertension, chronic obstructive pulmonary disease, hypersensitivity pneumonitis) and autoimmune diseases (pulmonary manifestations of RA and Sjögren's syndrome), iBALT structures are involved in perpetuating the inflammation and producing autoantibodies [31]. The full spectrum of stimuli responsible for iBALT formation in these diseases has not yet been identified but has been shown to include cigarette smoke [33], inhaled silica [34], and diesel exhaust particles [35]. The iBALT structures are preferentially found near the basal side of the bronchial epithelium and, in some cases, within the perivascular spaces, that is, at sites of contact with antigens that enter the airway lumen then cross through the bronchial wall. As occurs within secondary lymphoid structures, the iBALT leukocytes are organized in B-cell and T-cell zones. The B-cells form follicles, which contain germinal centers in active iBALT areas. Germinal centers also contain activated follicular B-helper T-cells. The T-cell zone comprises CD4+, CD8+, and dendritic cells and surrounds the follicles.

site in RA. Bronchus-associated lymphoid tissue (BALT) may be at the hub of the autoimmunity process.

Inducible BALT (iBALT) (Box 1) develops during infectious, inflammatory, allergic, and tumoral lung diseases. Furthermore, iBALT is more often found, more extensive, and better organized in patients with respiratory disease related to RA or Sjögren's syndrome compared to those with usual interstitial pneumonitis or hypersensitivity pneumonitis [36]. Both the presence and the size of iBALT islands show positive correlations with serum and alveolar ACPA titers. These data argue against the induction of BALT by isolated local inflammation and suggest that an antigenic stimulus is needed. Also, iBALT may be capable of activating and differentiating B-cells into plasma cells with autoantibody-producing potential.

We are aware of a single in vivo study establishing a direct link between diesel emission particles (DEPs) and iBALT formation [35]. Wild-type mice were exposed for 3 months to low or high DEP concentrations (100 $\mu g/m^3$ and 3 mg/m^3, respectively) then killed. The histological examination of the lungs showed iBALT only in the group exposed to high concentrations. ACPAs were not assayed.

This study built on previous experiments demonstrating a role for cigarette smoke and silica in iBALT formation. A study reported as early as 1992 demonstrated iBALT formation in mice exposed to cigarette smoke for 2 months [37]. In human lung, iBALT was identified in 82% of smokers vs. only 14% of non-smokers [38]. Finally, mice exposed to aerosolized silica (70 mg/m^3) for 12 days developed numerous large iBALT structures [34].

Thus, iBALT seems to develop in response to chronic environmental proinflammatory stimuli (silica or PM) and is associated with RA-specific autoantibodies (ACPAs) and RA-related lung disease. The data suggest that iBALT may be a site of antigen presentation and, therefore, of transition from an innate immune response to an antigen-specific adaptive immune response in RA (Fig. 1).

4. Molecular mechanisms

Numerous experimental studies have been conducted in vitro and in animal models to assess the effects of pollution at the cellular and molecular levels. Within iBALT structures, cells involved in both innate and adaptive immune responses coexist and play a role in the formation and function of iBALT upon stimulation by airborne PM.

4.1. Innate immune responses induced by air pollution

PM inhalation leads to a rapid and massive influx of neutrophils and to the release of proinflammatory cytokines (e.g., TNF-α and IL-1 β) [39]. This inflammatory response depends not only on the amount but also on the nature and diameter of the particles. Thus, compared to larger particles, $PM_{0.1}$ induce a stronger inflammatory response [40] and greater IL-6 release, whereas IL-8 release is similar across particle sizes [41].

These data have been corroborated in humans. Changes in proinflammatory cytokine levels induced by various exposures have been evaluated in healthy individuals [42]. A retrospective study showed that O_3 and SO_2 exposure was followed by a significant rise in serum IL-6 levels [43]. The IL-6 elevation was greatest within 4 days after exposure to high O_3 or SO_2 levels and diminished subsequently. Furthermore, TNF-α, prostaglandin, C-reactive protein, and IL-1 β-levels were considerably higher in children living in Mexico city compared to their counterparts in a small town with less air pollution [44].

In addition to local inflammation, air pollution induces oxidative stress. PUFs seem to have the strongest effect in this regard [45,46]. Reactive oxygen species, which are released by neutrophils and macrophages, induce alterations in proteins, particularly those associated with DNA, and cause cell necrosis and apoptosis. Reactive oxygen species are also responsible for the activation and release of neutrophil extracellular traps (NETs), a process known as NETosis. Dying neutrophils release a net of chromatin strands coated with proteins from the granules. NETosis is accompanied with elevation of the levels of IL-23 and IL-17 [47], which are involved in iBALT formation [48]. Interestingly, the molecular structure of NETs can allow exposure of citrullinated peptides [49]. Thus, in RA, NETs may be among the mediators that promote the transition from an innate immune response to an antigen-specific adaptive immune response.

4.2. Adaptive immunity induced by air pollution and role for the aryl hydrocarbon receptor (AHR)

Human T-cells exposed to DEPs in vitro undergo changes in both function and phenotype (Fig. 2). Thus, exposure to nanoparticles from diesel engines led to a significant decline in CD25 expression by CD4+ T-cells, as well as to decreased production of IL-2 and IFN-α suggesting inhibition of regulatory T-cells (Tregs) and Th1 cells [50]. PM exposure also induced changes in lymphocyte phenotype in animal models. In mice, lung CD4+ T-cells chronically exposed to $PM_{2.5}$ switched from the Th1 to the Th17 profile [51].

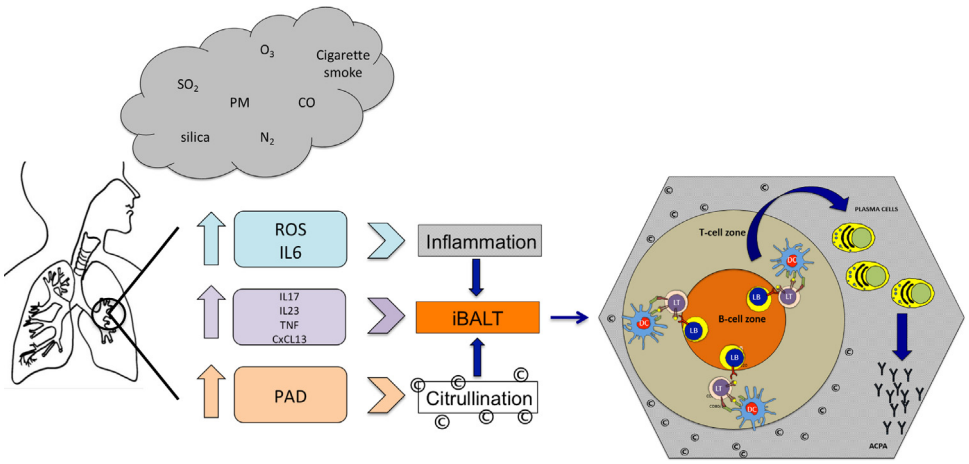

Fig. 1. Potential role for air pollution in the production of anti-citrullinated peptide antibodies (ACPAs) via the formation of inducible bronchus-associated lymphoid tissue (iBALT). ACPA: anti-citrullinated peptide antibody; ©: citrullinated peptide; DC: dendritic cell; FDC: follicular dendritic cell; CO: carbon monoxide; CxCL13: chemokine ligand 13; iBALT: inducible bronchus-associated lymphoid tissue; IL: interleukin; LB: lymphocyte B; LT: lymphocyte T; NO_2: nitrogen dioxide; O_3: ozone; PAD: protein arginine deiminase; PM: particulate matter; ROS: reactive oxygen species; SO_2: sulfur dioxide; TNF: tumor necrosis factor. Air pollutants, most notably fine particles, induce the release of reactive oxygen species (ROS) and IL-6, thereby causing local inflammation. Citrullination of neighboring proteins is promoted not only by the local inflammation, but also by the production of PED induced by fine particles. Exposure to fine particles can also result in the production of other proinflammatory cytokines (IL-17, IL-23, TNF-α) and of several chemokines (including CXCL13) incriminated in the formation of tertiary lymphoid structures known as iBALT. Within the T zone of iBALT structures, citrullinated proteins, acting as antigens, are presented by dendritic cells to naive T-cells. These T-cells then interact with B-cells, which become activated and differentiate into plasma cells. The plasma cells produce anti-citrullinated peptide antibodies, which can be identified in bronchoalveolar lavage fluid.

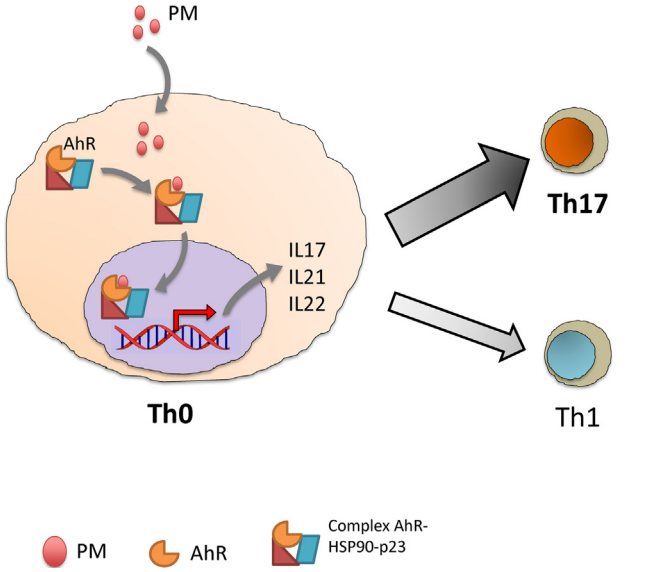

Fig. 2. Effects of the aryl hydrocarbon receptor (AHR) on lymphocyte differentiation. AhR: aryl hydrocarbon receptor; IL: interleukin; PM: particulate matter; Th0: naive helper T-cell; TNF: tumor necrosis factor; HSP: heat shock protein. Fine particles are lipophilic and can therefore cross through the cell membrane. Within the cell, they bind to the aryl hydrocarbon receptor (AHR). Under stable conditions, the AHR is found in the cytosol within complexes with other molecules such as HSP-90 and protein p23. Once the particle is bound to the AHR, the complex translocates to the nucleus, where it binds to xenobiotic response elements (XRE) located within the promoters of target genes such as IL-17, IL-21, and IL-22, which are involved in Th17 differentiation.

After $PM_{2.5}$ exposure, the proportion of Tregs remained very low in the lungs but increased in the bloodstream and spleen. Th17 polarization was investigated in greater detail in a study of cell cultures and in wild-type and $ARH^{-/-}$ mice. $PM_{2.5}$ exposure led to increased IL-17 production and to Th17 expansion both in vitro and in vivo, and these effects were closely related to AHR activation [52].

AHR is a transcription factor belonging to the basic-helix-loop-helix/Per-Arnt-sim (bHLH/PAS) family of proteins. The main function of the AHR is regulation of the expression of xenobiotic-metabolizing enzymes and of their clearance from the body. (Xenobiotics are small molecules not naturally found in the body, such as pesticides and medications.) Under stable conditions, AHR is found in the cytosol, within complexes that also include other molecules such as heat shock protein 90 and protein p23. AHR ligands are lipophilic and therefore readily cross through the cell membrane. AHR bound to a ligand is translocated to the nucleus, where it binds to xenobiotic responsive elements (XREs) located within the promoters of the target genes (such as cytochrome p450). AHR controls the transcriptional activity of the target genes by establishing protein interactions with other transcription factors. Some of these factors exert well-established functions within the immune system. Examples include signal transducers and activators of transcription (STAT), NFκB, and receptors for retinoic acid and estrogens [53]. Many in vivo studies have demonstrated a ubiquitous pattern of AHR expression. Nevertheless, the highest expression levels in adults are found in the placenta, lung, and liver [54].

AHR was first identified as a receptor for dioxins such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, also known as Seveso dioxin), which are released in the environment during natural and industrial combustion processes. Since then, other ligands, both agonistic and antagonistic, have been identified. Many of these ligands are found in food (e.g., fruit, vegetables, and tea). The most abundant are certain flavonoids, i.e., pigments that give their color to flowers and fruit. Other environmental factors, such as ultraviolet radiation, can activate AHR. Thus, AHR is a key mediator of the role for the environment on the metabolism and immune system.

That AHR is involved in inflammatory processes has been established by many studies. Thus, TCDD activates the expression of the genes encoding IL-6 and TNF-α [55]. AHR also plays a role in adaptive immune responses. It is expressed by Langerhans cells and T-cells [56]. AHR controls the expression of IL-21 and IL-22. The binding of AHR to TCDD stimulates the differentiation of Th17 cells [57], which are key actors in autoimmune diseases such as RA, multiple sclerosis, and spondyloarthritis. In keeping with this effect, in vivo activation of AHR by its ligand 6-formylindolo[3,2-b]carbazole

(FICZ) stimulates the Th17 response and worsens the phenotype of experimental autoimmune encephalomyelitis, which is an animal model of multiple sclerosis.

Nevertheless, AHR activation can also induce an antiinflammatory response [58] and expand the Treg cell pool. Thus, binding of TCDD to AHR induces expansion of the CD4+ CD25+ Foxp3+ Treg population, thereby suppressing the development of experimental autoimmune encephalomyelitis [59].

4.3. Role for the aryl hydrocarbon receptor (AHR) and its ligands in rheumatoid arthritis (RA)

In mice with collagen-induced arthritis, intranasal administration of DEPs dose-dependently increased both the incidence and the severity of the joint disease [60]. In the same model, compared to wild-type mice, AHR knockout mice showed lower values for the incidence of arthritis, clinical severity score, IL-6 level, and proportion of Th17 cells [61]. In this Cre-Lox model, the arthritis improved only when the AHR was lacking in the T-cells and not when it was absent from the macrophages [61]. Thus, the development of collagen-induced arthritis is closely dependent on the presence within T-cells of the AHR, whose main ligand is TCDD, a commonly found air pollutant. Finally, AHR expression was higher in synovial tissue from patients with RA than from patients with osteoarthritis [62].

AHR may also be a key player in bone tissue. AHR expression was increased in osteoblasts from mice with collagen-induced arthritis, and TCDD downregulated osteoblast proliferation [63]. This anti-anabolic effect is magnified by a concomitant pro-catabolic effect, as TCDD stimulates bone resorption in vivo by stimulating the proliferation of osteoclasts [64].

Taken together, these experimental data suggest that air pollution may be involved in the initiation of RA and in the structural damage typical of the disease, and that these effects may be mediated by the AHR.

5. Conclusion

Findings from cellular and molecular studies add to epidemiological evidence that PM is involved in the development of iBALT. The role for iBALT in initiating RA highlights the central part played by the lung in the pathophysiology of this disease and the consequences of prolonged inflammation. No evidence is available to date for hierarchizing the effects of intrapulmonary antigen presentations on the initiation or perpetuation of RA.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Ungprasert P, Srivali N, Cheungpasitporn W, et al. Risk of incident chronic obstructive pulmonary disease in patients with rheumatoid arthritis: A systematic review and meta-analysis. Joint Bone Spine 2016;83:290–4.

[2] Fischer A, Solomon JJ, du Bois RM, et al. Lung disease with anti-CCP antibodies but not rheumatoid arthritis or connective tissue disease. Respir Med 2012;106:1040–7.

[3] Metafratzi ZM, Georgiadis AN, Ioannidou CV, et al. Pulmonary involvement in patients with early rheumatoid arthritis. Scand J Rheumatol 2007;36:338–44.

[4] Demoruelle MK, Weisman MH, Simonian PL, et al. Brief report: airways abnormalities and rheumatoid arthritis-related autoantibodies in subjects without arthritis: early injury or initiating site of autoimmunity? Arthritis Rheum 2012;64:1756–61.

[5] Wilsher M, Voight L, Milne D, et al. Prevalence of airway and parenchymal abnormalities in newly diagnosed rheumatoid arthritis. Respir Med 2012;106:1441–6.

[6] Klareskog L, Stolt P, Lundberg K, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum 2006;54:38–46.

[7] Speck-Hernandez CA, Montoya-Ortiz G. Silicon, a possible link between environmental exposure and autoimmune diseases: the case of rheumatoid arthritis. Arthritis 2012;2012:604187.

[8] Caplan A. Certain unusual radiological appearances in the chest of coal-miners suffering from rheumatoid arthritis. Thorax 1953;8:29–37.

[9] Colinet E. [Evolutive chronic polyarthritis and pulmonary silicosis]. Acta Physiother Rheumatol Belg 1953;8:37–41.

[10] Bell ML, Dominici F, Samet JM. A meta-analysis of time-series studies of ozone and mortality with comparison to the national morbidity, mortality, and air pollution study. Epidemiol Camb Mass 2005;16:436–45.

[11] WHO air quality guidelines, global update. Report on a Working Group meeting, Bonn, Germany. Copenhagen, Denmark: WHO Regional Office for Europe; 2005 [http://www.euro.who.int/document/e87950.pdf].

[12] Minichiello E, Semerano L, Boissier M-C. Time trends in the incidence, prevalence, and severity of rheumatoid arthritis: a systematic literature review. Joint Bone Spine 2016;83:625–30.

[13] Tobón GJ, Youinou P, Saraux A. The environment, geo-epidemiology, and autoimmune disease: rheumatoid arthritis. J Autoimmun 2010;35:10–4.

[14] GEO-RA Group. Latitude gradient influences the age of onset of rheumatoid arthritis: a worldwide survey. Clin Rheumatol 2017;36:485–97.

[15] Chiang Y-C, Yen Y-H, Chang W-C, et al. The association between urbanization and rheumatoid arthritis in Taiwan. Int J Clin Pharmacol Ther 2016;54:1–10.

[16] Hart JE, Laden F, Puett RC, et al. Exposure to traffic pollution and increased risk of rheumatoid arthritis. Environ Health Perspect 2009;117:1065–9.

[17] De Roos AJ, Koehoorn M, Tamburic L, et al. Proximity to traffic, ambient air pollution, and community noise in relation to incident rheumatoid arthritis. Environ Health Perspect 2014;122:1075–80.

[18] Bernatsky S, Smargiassi A, Joseph L, et al. Industrial air emissions, and proximity to major industrial emitters, are associated with anti-citrullinated protein antibodies. Environ Res 2017;157:60–3.

[19] Hart JE, Källberg H, Laden F, et al. Ambient air pollution exposures and risk of rheumatoid arthritis. Arthritis Care Res 2013;65:1190–6.

[20] Hart JE, Källberg H, Laden F, et al. Ambient air pollution exposures and risk of rheumatoid arthritis: results from the Swedish EIRA case-control study. Ann Rheum Dis 2013;72:888–94.

[21] Gan RW, Deane KD, Zerbe GO, et al. Relationship between air pollution and positivity of RA-related autoantibodies in individuals without established RA: a report on SERA. Ann Rheum Dis 2013;72:2002–5.

[22] Chang K-H, Hsu C-C, Muo C-H, et al. Air pollution exposure increases the risk of rheumatoid arthritis: a longitudinal and nationwide study. Environ Int 2016;94:495–9.

[23] Hutchinson D. Cadmium, one of the villains behind the curtain: has exposure to cadmium helped to pull the strings of seropositive rheumatoid arthritis pathogenesis all along? Int J Rheum Dis 2015;18:570–3 [quiz 574-6].

[24] Ansari MM, Neha, Khan HA. Effect of cadmium chloride exposure during the induction of collagen induced arthritis. Chem Biol Interact 2015;238:55–65.

[25] Bernatsky S, Fournier M, Pineau CA, et al. Associations between ambient fine particulate levels and disease activity in patients with systemic lupus erythematosus (SLE). Environ Health Perspect 2011;119:45–9.

[26] Lanata C, Nayak R, Nitiham J, et al. Residential proximity to highways, DNA methylation and systemic lupus erythematosus. In: ACR Meeting Abstracts. http://acrabstracts.org/abstract/residential-proximity-to-highways-dna-methylation-and-systemic-lupus-erythematosus/ (accessed 27 Jul 2017).

[27] Bernatsky S, Smargiassi A, Barnabe C, et al. Fine particulate air pollution and systemic autoimmune rheumatic disease in two Canadian provinces. Environ Res 2016;146:85–91.

[28] Makrygiannakis D, Hermansson M, Ulfgren A-K, et al. Smoking increases peptidylarginine deiminase 2 enzyme expression in human lungs and increases citrullination in BAL cells. Ann Rheum Dis 2008;67:1488–92.

[29] Harre U, Georgess D, Bang H, et al. Induction of osteoclastogenesis and bone loss by human autoantibodies against citrullinated vimentin. J Clin Invest 2012;122:1791–802.

[30] Nielen MMJ, van Schaardenburg D, Reesink HW, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis Rheum 2004;50:380–6.

[31] Hwang JY, Randall TD, Silva-Sanchez A. Inducible bronchus-associated lymphoid tissue: taming inflammation in the lung. Front Immunol 2016;7:258.

[32] Tschernig T, Pabst R. Bronchus-associated lymphoid tissue (BALT) is not present in the normal adult lung but in different diseases. Pathobiol J Immunopathol Mol Cell Biol 2000;68:1–8.

[33] Van der Strate BWA, Postma DS, Brandsma C-A, et al. Cigarette smoke-induced emphysema: a role for the B cell? Am J Respir Crit Care Med 2006;173:751–8.

[34] Davis GS, Pfeiffer LM, Hemenway DR. Expansion of interferon-gamma-producing lung lymphocytes in mouse silicosis. Am J Respir Cell Mol Biol 1999;20:813–24.

[35] Hiramatsu K, Azuma A, Kudoh S, et al. Inhalation of diesel exhaust for three months affects major cytokine expression and induces bronchus-associated lymphoid tissue formation in murine lungs. Exp Lung Res 2003;29:607–22.

[36] Rangel-Moreno J, Hartson L, Navarro C, et al. Inducible bronchus-associated lymphoid tissue (iBALT) in patients with pulmonary complications of rheumatoid arthritis. J Clin Invest 2006;116:3183–94.

[37] Escolar Castellón JD, Escolar Castellón A, Roche Roche PA, et al. Bronchial-associated lymphoid tissue (BALT) response to airway challenge with

cigarette smoke, bovine antigen and anti-pulmonary serum. Histol Histopathol 1992;7:321–8.
[38] Richmond I, Pritchard GE, Ashcroft T, et al. Bronchus associated lymphoid tissue (BALT) in human lung: its distribution in smokers and non-smokers. Thorax 1993;48:1130–4.
[39] Aalapati S, Ganapathy S, Manapuram S, et al. Toxicity and bio-accumulation of inhaled cerium oxide nanoparticles in CD1 mice. Nanotoxicology 2014;8:786–98.
[40] Steenhof M, Gosens I, Strak M, et al. In vitro toxicity of particulate matter (PM) collected at different sites in the Netherlands is associated with PM composition, size fraction and oxidative potential – the RAPTES project. Part Fibre Toxicol 2011;8:26.
[41] Hetland RB, Cassee FR, Refsnes M, et al. Release of inflammatory cytokines, cell toxicity and apoptosis in epithelial lung cells after exposure to ambient air particles of different size fractions. Toxicol In Vitro 2004;18:203–12.
[42] Traboulsi H, Guerrina N, Iu M, et al. Inhaled pollutants: the molecular scene behind respiratory and systemic diseases associated with ultrafine particulate matter. Int J Mol Sci 2017:18, http://dx.doi.org/10.3390/ijms18020243.
[43] Thompson AM, Zanobetti A, Silverman F, et al. Baseline repeated measures from controlled human exposure studies: associations between ambient air pollution exposure and the systemic inflammatory biomarkers IL-6 and fibrinogen. Environ Health Perspect 2010;118:120–4.
[44] Calderón-Garcidueñas L, Villarreal-Calderon R, Valencia-Salazar G, et al. Systemic inflammation, endothelial dysfunction, and activation in clinically healthy children exposed to air pollutants. Inhal Toxicol 2008;20:499–506.
[45] Mo Y, Wan R, Feng L, et al. Combination effects of cigarette smoke extract and ambient ultrafine particles on endothelial cells. Toxicol In Vitro 2012;26:295–303.
[46] Li N, Sioutas C, Cho A, et al. Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. Environ Health Perspect 2003;111:455–60.
[47] Stark MA, Huo Y, Burcin TL, et al. Phagocytosis of apoptotic neutrophils regulates granulopoiesis via IL-23 and IL-17. Immunity 2005;22:285–94.
[48] Zhao J, Lin L, Fu L, et al. Neutrophil extracellular Taps play an important role in clearance of Streptococcus suis in vivo. Microbiol Immunol 2016;60:228–33.
[49] Khandpur R, Carmona-Rivera C, Vivekanandan-Giri A, et al. NETs are a source of citrullinated autoantigens and stimulate inflammatory responses in rheumatoid arthritis. Sci Transl Med 2013;5:178ra40.
[50] Pierdominici M, Maselli A, Cecchetti S, et al. Diesel exhaust particle exposure in vitro impacts T lymphocyte phenotype and function. Part Fibre Toxicol 2014;11:74.
[51] Deiuliis JA, Kampfrath T, Zhong J, et al. Pulmonary T cell activation in response to chronic particulate air pollution. Am J Physiol Lung Cell Mol Physiol 2012;302:L399–409.
[52] Van Voorhis M, Knopp S, Julliard W, et al. Exposure to atmospheric particulate matter enhances Th17 polarization through the aryl hydrocarbon receptor. PloS One 2013;8:e82545.
[53] Hankinson O. Role of coactivators in transcriptional activation by the aryl hydrocarbon receptor. Arch Biochem Biophys 2005;433:379–86.
[54] Dolwick KM, Swanson HI, Bradfield CA. In vitro analysis of Ah receptor domains involved in ligand-activated DNA recognition. Proc Natl Acad Sci U S A 1993;90:8566–70.
[55] Kim MJ, Pelloux V, Guyot E, et al. Inflammatory pathway genes belong to major targets of persistent organic pollutants in adipose cells. Environ Health Perspect 2012;120:508–14.
[56] Esser C, Rannug A, Stockinger B. The aryl hydrocarbon receptor in immunity. Trends Immunol 2009;30:447–54.
[57] Veldhoen M, Hirota K, Westendorf AM, et al. The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins. Nature 2008;453:106–9.
[58] Narayanan GA, Murray IA, Krishnegowda G, et al. Selective aryl hydrocarbon receptor modulator-mediated repression of CD55 expression induced by cytokine exposure. J Pharmacol Exp Ther 2012;342:345–55.
[59] Quintana FJ, Basso AS, Iglesias AH, et al. Control of T(reg) and T(H)17 cell differentiation by the aryl hydrocarbon receptor. Nature 2008;453:65–71.
[60] Yoshino S, Sagai M. Enhancement of collagen-induced arthritis in mice by diesel exhaust particles. J Pharmacol Exp Ther 1999;290:524–9.
[61] Nakahama T, Kimura A, Nguyen NT, et al. Aryl hydrocarbon receptor deficiency in T cells suppresses the development of collagen-induced arthritis. Proc Natl Acad Sci U S A 2011;108:14222–7.
[62] Kobayashi S, Okamoto H, Iwamoto T, et al. A role for the aryl hydrocarbon receptor and the dioxin TCDD in rheumatoid arthritis. Rheumatology (Oxford) 2008;47:1317–22.
[63] Yu H, Du Y, Zhang X, et al. The aryl hydrocarbon receptor suppresses osteoblast proliferation and differentiation through the activation of the ERK signaling pathway. Toxicol Appl Pharmacol 2014;280:502–10.
[64] Iqbal J, Sun L, Cao J, et al. Smoke carcinogens cause bone loss through the aryl hydrocarbon receptor and induction of Cyp1 enzymes. Proc Natl Acad Sci U S A 2013;110:11115–20.