Etiological and Biological Aspects of Cigarette Smoking in Rheumatoid Arthritis

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Abstract: Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by the chronic inflammation of the synovium, which develops to joint destruction. Quite interestingly RA has not been present in the world until 17 century. Tobacco has come from today's world, and epidemiological studies revealed cigarette smoking as a major risk factor for the disease. However, the mechanism how cigarette smoking contributes to RA has been unknown. It has been demonstrated that polycyclic aromatic hydrocarbons, constituents of cigarette smoke, and cigarette smoke extracts are able to induce proinflammatory cytokines from RA patient-derived fibroblast-like synoviocytes. Recent studies also suggest an important role of Th17 in RA and contribution of aryl hydrocarbon receptor to the induction and development of Th17 and RA. These new findings lead to uncovering the basis for the etiological role of cigarette smoking in the disease.

Keywords: Cigarette smoking, rheumatoid arthritis, cytokine, inflammation, synovial cell, AhR, Th17.

INTRODUCTION

Rheumatoid arthritis **(**RA) is a systemic inflammatory disease characterized by the chronic inflammation of the synovium, which leads to the destruction of the articular cartilage and ankylosis of the joints. The patients suffer with pain and disability. About 1% of the world's population is affected by the disease, and women are affected three times more than men. Onset of the disease is most frequent in 40 to 50 years, but younger people aged 10-20 years are also affected. Cigarette smoking is a solid risk factor for RA, and recent studies revealed the critical role of proinflammatory cytokines produced by synovial cells in induction and development of RA. However, the mechanisms of cytokine induction relevant to cigarette smoking are largely unknown. In this review I will discuss the etiological and biological aspects of cigarette smoking in RA including historical view of the disease.

WHERE RHEUMATOID ARTHRITIS HAS COME FROM?

Quite interestingly, based on document, excavation, examination of skeletons and paintings RA defined by the current definition has not been found until 17 century in the old world (Europe) [1-3]. This is in quite contrast to the current incidence of RA; many people from young to old are affected by RA. Guillaume Baillou (1558-1616) and Thomas Syndenham (1624-1689) first identified and distinguished RA from the related disease, such as gout and rheumatic fever [4]. However, the reason why RA has suddenly appeared in the ancient times is a big mystery. Therefore, environmental factors are presumed to contribute to the appearance of the disease. In contrast, RA has been observed in habitants who lived 3, 000 to 5, 000 years ago in the new world (America) [2]. Therefore, RA is thought to be introduced from the new world after the discovery at the end of 15 the century.

TOBACCO WAS INTRODUCED TO THE OLD WORLD FROM THE NEW WORLD

Tobacco is a plant native in North and South America. On October 15, 1492, Christopher Columbus was offered dried tobacco leaves as a gift from the American Indians. Soon after, tobacco cultivation was started in Saint-Domingue, Cuba and Brazil by Europeans. From 1556 to 1565, tobacco was introduced into France, Portugal, Spain and England, and then the plant was grown all over Europe, and it became popular mostly as medicine. During the 1600's, tobacco was so popular that it was frequently used as money equivalent to gold. Then some of adverse effects of smoking tobacco were realized, and in 16/17-century there were conflicts against tobacco consumption in different states under threat of punishments [5, 6]. Rothschild, Turner and DeLuca included tobacco among variables that could be responsible for the appearance of RA in Europe [2].

CIGARETTE SMOKING IS A MAJOR RISK FACTOR FOR RA

The etiology of RA is not clear. Infectious agents may act as a trigger for RA, and a number of agents have been suspected of triggering RA, including Epstein-Barr virus [7], parvovirus B19 [8], rubella[9], human T-cell leukemia virus type 1 [10] and some bacteria such as *Erysipelothrix* [11], *Proteus* [12], *Mycobacteria* [13] and *Candida albicans* [14], but these associations have not been supported by epidemiological studies. In addition, infectious agents cannot account for the sudden appearance of RA in Europe at the 17^{th} century, because if so, the strong family, community and area-specific outbreak of the disease should have been observed. In contrast, smoking is a solid environmental risk factor as revealed by many epidemiological studies. Studies indicate an association of cigarette smoking with disease

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outcome in patients with early inflammatory polyarthritis [15] and with increase of rheumatoid factor and nodule formation in patients with RA [16]. A strong association between heavy cigarette smoking and RA, particularly in patients without a family history of RA was also reported [17]. Although male smokers are more associated with the risk for RA, female smokers are also associated with the risk [18]. As expected among North America natives, tobacco smoking was observed to be quite popular, having high prevalence rates. The RA seen in the population is generally severe, seropositive, with an early age of onset, and frequent extraarticular manifestations [19]. Smoking also interacts with genetic factors. Particularly smokers carrying double SE genes in MHC class II related gene (HLA-DRB1allele) have a high risk for RA [20], indicating a strong gene-environment interaction. It is of note that maternal smoking during pregnancy is a determinant of RA and other inflammatory polyarthropathies in an infant during the first 7 years of life [21]. Chemicals in tobacco smoke are adsorbed to tissues, blood, and then transported to fetus [22].

PROINFLAMMATORY CYTOKINES IN SYNOVIAL FLUID ARE CRITICAL FOR THE INDUCTION AND DEVELOPMENT OF RA

In synovial fluids of RA patients many cytokines and chemokines are present, including IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-6, IL-8, IL-15, IL-17, IFN-γ, TNFα, TNFβ, TGFβ, GM-CSF and MIP-3α (CCL20). Macrophage and/or fibroblast derived cytokines like IL-1, IL-6 and TNFα are abundant, whereas T cell products like IL-2, IL-3, IL-4, IFNγ and TNFβ are low. Macrophage-linage cells produce IL-1β and TNFα, and fibroblast-like synovial cells produce IL-6 and IL-1 [22, 23]. Among these cytokines, IL-1, IL-6 and TNFα are important for the induction and development of RA [24, 25]. IL-1 and TNFα increase production of proteases, prostaglandin E2, reactive oxygen intermediates, proliferation of synovial fibroblasts, cartilage degradation, infiltration of inflammatory cells and angiogenesis increase. IL-1 is a major cytokine inducing cartilage degradation, and cartilage degradation caused by TNFα is mediated by IL-1 [26]. IL-6 induces T cell growth and stimulates B cells and also induces acute phase proteins. TNFα, IL-1 and IL-6 are able to induce fever and acute phase proteins. TNFα can induce both IL-1 and IL-6, and IL-1 can induce IL-6. Along with macrophages synovial fibroblast-like cells are the main producers of these cytokines. Primary fibroblast-like synoviocytes or SV40-transformed cell clones are derived from RA patients secrete, constitutively or in response to IL-1or TNFα, proinflammatory cytokines, including IL-1α, IL-1β, IL-6 and IL-8 [27, 28]. There are two types of IL-1, α and β. Although both isoforms appear to play a pivotal role in cartilage destruction, membrane bound IL-1α, but not soluble form, is important for induction of arthritis in IL-1 transgenic mice [29], whereas IL-1β plays a more dominant role in the development of arthritis. The critical role of these proinflammatory cytokines in RA has been verified in animal models and also in RA patients by an improvement of synovial inflammation and demonstrated by the decreased joint destruction following treatment with neutralizing anti-TNFα antibody [30], soluble TNF receptor [31], IL-1 receptor antagonist (IL-1ra) [32] or neutralizing anti-IL-6 antibody [33].

CIGARETTE SMOKE CONDENSATE INDUCES PROINFLAMMATORY CYTOKINES FROM FIBROBLATS-LIKE SYNOVIAL CELLS

In contrast to epidemiological studies, the mechanism how cigarette smoking contributes to RA has been largely unknown. Cigarette smoke condensates (CSC) are able to induce proinflammatory cytokines from lung epithelial cells [34]. Whether CSC or exposure to cigarette smoke is able to induce proinflammatory cytokines from alveolar macrophages is inconsistent [35, 36]. Interestingly, brief exposure (for 1 hr) to second hand smoke increased serum level of proinflammatory cytokines for at least 3 hrs after exposure, particularly in men [37]. Given the fact that synovial cell-derived proinflammatory cytokines are critical for the induction and development of RA, we examined whether CSC or its constituents are able to induce proinflammatory cytokines from fibroblast-like synovial cells. When human fibroblast-like synoviocytes line MH7A was treated with 3-methylcholanthrene (3-MC), Benzo[*a*]pyrene (B[*a*]P) and 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD), these chemicals were able to induce dose- and time-dependently IL-1β mRNA. Most of the effects of these compounds are mediated by the aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor [38]. Upon ligand-induced activation, the AhR releases its chaperoning heat shock protein 90, translocates into the nucleus, and dimerizes with AhR nuclear translocator. The heterodimer complex binds to DNA specific sequences called dioxin responsive elements (DREs), and up- or down-regulates the transcription of genes controlled by DREs [39]. AhR also interacts with a variety of intracellular/nuclear receptors, such as steroid receptors and transcription factor NF-κB and modulates their activities [40]. The augmenting effects of 3-MC, B[*a*]P and TCDD on MH7Acells appeared to be dependent on AhR. CSC, either mainstream or sidestream, also augmented expression levels of IL-1α, IL-1β, IL-6, IL-8 mRNA in both time- and dose–dependent manners. CSC also induced cytokines at protein level and further augmented the effects of TNFα induction of these cytokines at both mRNA and protein levels [41]. As the effect of CSC was partially inhibited by an antagonist for AhR, polycyclic aromatic hydrocarbons (PAHs) as well as other compounds are presumably responsible for the augmenting effect. CSC also exerted similar augmenting effects on primary RA patient-derived fibroblast-like synovial cells (Our unpublished observation). Importantly, the dose of CSC able to induce cytokine mRNA, is reachable if individual with 60 kg body weight takes only 13 (based on mainstream CSC) or 6.7 cigarettes (based on sidestream CSC) and all the smokes were adsorbed. Actually heavy smokers take many more cigarettes in a day and the number reaches up to tremendous for a long time. Significant amount of CSC, especially because PAHs are readily absorbed into adipose tissue, can be accumulated over a long period of time. Side smokers are also affected by the smoke; only brief exposure to side smoke is able to increase serum level of proinflammatory cytokines [37]. In addition, we found that CSC augmented the induction and development of arthritis in the mouse model of collagen type II-induced arthritis (CIA) when CSC was injected with antigen (collagen) into mice [42]. The dose of CSC was also easily reachable in a heavy smoker.

AhR IS INVOLVED IN INDUCTION OF TH17 AND ARTHRITIS

Th17 is a third party of helper T cells which produces IL-17, IL-22, IL-17F, and CCL20. IL-17 stimulates production of proinflammatory cytokines and chemokines such as IL-1, TNFα, IL-6, IL-8, and CCL20 from fibroblasts, endothelial cells, macrophages, and epithelial cells [43, 44]. Th17 cells and these cytokines have been implicated in inflammatory processes and in animal models of autoimmunity or inflammation, such as experimental autoimmune inflammation in animal models of experimental allergic encephalomyelitis (EAE) [45], collagen induced arthritis [46], colitis [47] and steroid resistant airway inflammation and hyper responsiveness [48]. Consistently in human the numbers of Th17 cells or the level of IL-17 are increased in the inflamed tissue sites of patients with multiple sclerosis [49], rheumatoid arthritis [50], inflammatory bowel diseases and psoriatic lesions [51].

There are a number of reports indicating the involvement of Th17 in animal model of arthritis. The incidence of arthritis was partially reduced by the administration of antagonizing IL-17R and Fc fusion protein in adjuvant-induced arthritis [52]. IL-1Ra-deficient mouse developed spontaneous arthritis, which was mediated by the marked production of IL-17 [53]. The incidence of collagen induced arthritis (CIA) was markedly suppressed in IL-17-deficient mice [54]. In humans IL-17 is increased in synovial fluid of RA patients and is produced by T cell clones established from RA patients. RA synovial fluid contained significantly more CCL20 than osteoarthritis (OA). Th17 produces CCL20, and the CCL20 production by fibroblast-like synoviocytes is augmented by IL-1β, IL-17, IL-18 or TNFα [55]. Furthermore, Th17 cells express CC chemokine receptor (CCR) 6, a receptor for CCL20 [56]. Therefore, Th17 is recruited to synovial joint by CCL20 in both human and animal models of arthritis. An accumulation of Th17 relative to Treg was found in synovial fluid of children with arthritis [57], although the increase of Th17 was not confirmed in synovial fluid of adult RA patients [58]. Th17 and Treg cells are differentiated from the same precursor cells by different combinations of cytokines. Treg is generated from naïve T cells by TGF-β, and Th17 is generated by TGF-β and IL-6, IL-21 or IL-1 in the mouse, and IL-1β and IL-6 in the human [59]. Their induction and functions are exclusive of each other.

AhR is linked to Th17-mediated autoimmunity. AhR is exclusively expressed in Th17 cells in the mouse and human. In addition, activation of AhR markedly augmented the development of Th17, and their production of cytokines. AhR activation during induction of EAE caused accelerated onset and increased pathology in wild-type mice, but not AhR-deficient mice [60]. Interestingly, TCDD dependent activation of AhR induced Treg that suppressed EAE, while activation by natural ligand 6-formylindolo[3, 2-b]carbazole interfered with Treg cell development, boosted Th17 cell differentiation and increased the severity of EAE in mice [61]. Therefore, Th17 and Treg are induced by ligand-specific manners *via* AhR. In this regard it is interesting to investigate whether cigarette smoking induces Th17 or Treg. Higher AhR mRNA and protein levels were observed in RA synovial tissue than osteoarthritis (OA) tissue. TCDD up-regulated the expression of IL-1β, IL-6 and IL-8 through binding to AhR in RA patient-derived synovial cells, and AhR expression was up-regulated by TNFα [62]. These findings support that exposure to AhR ligands in cigarette smoke exacerbates RA pathophysiology. Indeed, cigarette smoke exposure appeared to induce AhR activation *in vivo* in AhR/DRE-dependent reporter gene transgenic mice [63].

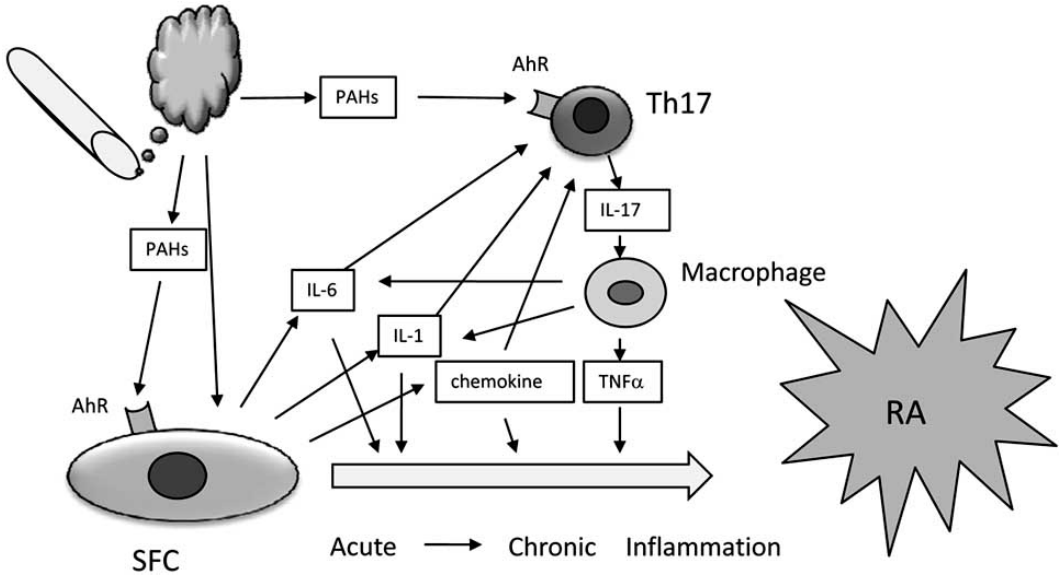

Fig. (1). A possible mechanism of cigarette smoke contribution to the induction and development of RA. Cigarette smoke induces proinflammatory cytokines and chemokines, including IL-1α, IL-1β, IL-6, IL-8 and CCR20 from synovial fibroblast-like cells (SFC), which is partially mediated by aromatic hydrocarbon receptor (AhR) stimulated with polycyclic aromatic hydrocarbons (PAHs) contained in the smoke. IL-1 and IL-6 induce the differentiation and development of Th17. PAHs also accelerate the development of Th17 *via* AhR. CCL20 recruits Th17 into the synovium, and IL-1 activates Th17 for production of IL-17. IL-17 then induces IL-1, IL-6 and TNFα production from macrophages. The acute inflammation leads to chronic inflammation under the influence of sex hormones and genetic factors, which leads to RA.

CONCLUSIONS

Cigarette smoke induces proinflammatory cytokine from synovial cells, and these acute inflammations lead to chronic inflammation by daily cigarette smoking and accumulation of chemicals in the synovium (Fig. **1**). In addition to this direct effect on synovial cells, the compounds in the smoke or synovial cell-derived proinflammatory cytokines, especially IL-1 and IL-6, will accelerate the induction of Th17 or IL-17, which leads to the development of RA. AhR may be involved in this process. This process needs to interact with genetic factors and sex hormones. We found that estrogen favors the induction of IL-1α from synovial cells [64], whereas androgen inhibits the induction of IL-1α [65]. Smoking also affects second hand smokers including their family members, spouse, children and even fetus. We also should be in mind that there are many chemicals in environment, including drugs, pollutants, pesticides, industrial solvents, food additives and fuel exhausts from factories and motorcars. Regarding this aspect the exposure to diesel exhaust particles appeared to enhance collagen-induced arthritis [66], and an elevated risk of RA was found in women living within 50 m of a road, compared with those women living 200 m or farther away [67]. Therefore, it is possible that all these chemicals also contribute to the induction of RA, because hydrophobic chemicals including PAHs are readily absorbed and accumulate in tissues..

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REFERENCES

[1] Short, C.L. The antiquity of rheumatoid arthritis. *Arthritis Rheum.*, **1974**, *17*, 193-205.

[2] Rothschild, B.M.; Turner, K.R.; DeLuca, M.A. Symmetrical erosive peripheral polyarthritis in the Late Archaic Period of Alabama. *Science*, **1988**, *241*, 1498-501.

[3] Altschuler, E.L. Parvovirus B19 and the pathogenesis of rheumatoid arthritis: a case for historical reasoning. *Lancet*, **1999**, *354*, 1026-7.

[4] Abe, T. In *Collagen Disease and Rheumatoid Disease* ; Miyasaka, N. Ed.; Asakura Press: Tokyo, **2001**, pp. 2-5.

[5] History of Tobacco Boston University Medical Center, http://academic.udayton.edu/health/syllabi/tobacco/history.htm#newworld.

[6] History net, http://www.historian.org/bysubject/tobacco1.htm

[7] Balandraud, N.; Roudier, J.; Roudier, C. Epstein-Barr virus and rheumatoid arthritis. *Autoimmun. Rev.*, **2004**, *3*, 362-7.

[8] Cohen, B.J.; Buckley, M.M.; Clewley, J.P.; Jones, V.E.; Puttick, A.H.; Jacoby, R.K. Human parvovirus infection in early rheumatoid and inflammatory arthritis. *Ann. Rheum. Dis.*, **1986**, *45*, 832-8.

[9] Tingle, A.J.; Allen, M.; Petty, R.E.; Kettyls, G.D.; Chantler, J.K. Rubella-associated arthritis. I. Comparative study of joint manifestations associated with natural rubella infection and RA 27/3 rubella immunisation. *Ann. Rheum. Dis*., **1986**, *45*, 110-4.

[10] Nishioka, K.; Maruyama, I.; Sato, K.; Kitaiima, I.; Nakajima, Y.; Osame, M. Chronic inflammatory arthropathy associated with HTLV-I. *Lancet*, **1989**, *1*, 441.

[11] Trautwein, G.; Seidler, D; Schulz, L.C.; Drommer, W.; Weiss, R.; Böhm, K.H. Immunopathology and pathogenesis of chronic erysipelas polyarthritis of swine. *Z. Rheumatol.*, **1976**, *35*, 217-39.

[12] Ebringer, A.; Rashid, T.; Wilson, C. Rheumatoid arthritis: proposal for the use of anti-microbial therapy in early cases. *Scand. J. Rheumatol*., **2003**, *32*, 2-11.

[13] Lydyard, P.; Tsoulfa, G.; Sharif, M.; Broker, B.; Smith, M.; Rook, G.A. Immunity to heat shock proteins in rheumatoid arthritis. *Clin. Exp. Rheumatol.*, **1990**, *Suppl 5*, 69-74.

[14] Hida, S.; Miura, N.N.; Adachi, Y.; Ohno, N. Effect of Candida albicans cell wall glucan as adjuvant for induction of autoimmune arthritis in mice. *J. Autoimmun*., **2005**, *25*, 93-101.

[15] Harrison, B.J.; Silman, A.J.; Wiles, N.J.; Scott, D.J.; Symmons, D.P. The association of cigarette smoking with disease outcome in patients with early inflammatory polyarthritis. *Arthritis Rheum.*, **2001**, *44*, 323-30.

[16] Tuomi, T.; Heliovaara, M.; Palosuo, T.; Aho, K. Smoking, lung function, and rheumatoid factors. *Ann. Rheum. Dis*., **1990**, *49*, 753-6.

[17] Hutchinson, D.; Shepstone, L.; Moots, R.; Lear, J.T.; Lynch, M.P. Heavy cigarette smoking is strongly associated with rheumatoid arthritis (RA), particularly in patients without a family history of RA. *Ann. Rheum. Dis*., **2001**, *60*, 223-7.

[18] Karlson, E.W.; Lee, I.M.; Cook, N.R.; Manson, J.E.; Buring, J.E.; Hennekens, C.H. A retrospective cohort study of cigarette smoking and risk of rheumatoid arthritis in female health professionals. *Arthritis Rheum*., **1999**, *42*, 910-7.

[19] Peschken, C.A.; Esdaile, J.M. Rheumatic diseases in North America's indigenous peoples. *Semin. Arthritis. Rheum*., **1999**, *28*, 368-91.

[20] Padyukov, L.; Silva, C.; Stolt, P.; Alfredsson, L.; Klareskog, L. A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. *Arthritis Rheum.*, **2004**, *50*, 3085-92.

[21] Jaakkola, J.J.; Gissler, M. Maternal smoking in pregnancy as a determinant of rheumatoid arthritis and other inflammatory polyarthropathies during the first 7 years of life. *Int. J. Epidemiol.*, **2005**, *34*, 664-71.

[22] Luck, W; Nau, H; Hansen, R; Steldinger, R. Extent of nicotine and cotinine transfer to the human fetus, placenta and amniotic fluid of smoking mothers. *Dev. Pharmacol. Ther*., **1985**, *8*, 384-95.

[23] Firestein, G.S.; Alvaro-Gracia. J.M.; Maki, R. Quantitative analysis of cytokine gene expression in rheumatoid arthritis. *J. Immunol.*, **1990**, *144*, 3347-53.

[24] Arend, W.P.; Dayer, J.M. Inhibition of the production and effects of interleukin-1 and tumor necrosis factor alpha in rheumatoid arthritis. *Arthritis Rheum.*, **1995**, *38*, 151-60.

[25] Szekanecz, Z.; Koch, A.E.; Kunkel, S.L.; Strieter, R.M. Cytokines in rheumatoid arthritis. Potential targets for pharmacological intervention. *Drugs Aging*, **1998**, *12*, 377-90.

[26] Zwerina, J.; Redlich, K.; Polzer, K.; Joosten, L.; Krönke, G.; Distler, J.; Hess. A.; Pundt, N.; Pap, T.; Hoffmann, O.; Gasser, J.; Scheinecker, C.; Smolen, J.S.; van den Berg, W.; Schett, G. *Proc. Natl. Acad. Sci. U. S. A.*, **2007**, *104*, 11742-7.

[27] Buchan, G.; Barrett, K.; Turner, M.; Chantry, D.; Maini, R.N.; Feldmann, M. Interleukin-1 and tumour necrosis factor mRNA expression in rheumatoid arthritis: prolonged production of IL-1 alpha. *Clin. Exp. Immunol.*, **1988**, *73*, 449-55.

[28] Shimozato, O; Watanabe, N.; Goto, M.; Kobayashi, Y. Cytokine production by SV40-transformed adherent synovial cells from rheumatoid arthritis patients. *Cytokine*, **1996**, *8*, 99-105.

[29] Niki, Y.; Yamada, H.; Kikuchi, T.; Toyama, Y.; Matsumoto, H.; Fujikawa, K.; Tada, N. Membrane-associated IL-1 contributes to chronic synovitis and cartilage destruction in human IL-1 alpha transgenic mice. *J. Immunol.*, **2004**, *172*, 577-84.

[30] Lipsky, P.E.; van der Heijde, D.M.; St Clair, E.W.; Furst, D.E.; Breedveld, F.C.; Kalden, J.R.; Smolen, J.S.; Weisman, M.; Emery, P.; Feldmann, M.; Harriman, G.R.; Maini, R.N. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N. Engl. J. Med*., **2000**, *343*, 1594-62.

[31] Moreland, L.W.; Margolies, G.; Heck, L.W. Jr.; Saway, A.; Blosch, C.; Hanna, R.; Koopman, W.J. Recombinant soluble tumor necrosis factor receptor (p80) fusion protein: toxicity and dose finding trial in refractory rheumatoid arthritis. *J. Rheumatol*., **1996**, 23, 1849-55.

[32] Furst, D.E. Anakinra: Review of recombinant human interleukin-I receptor antagonist in the treatment of rheumatoid arthritis. *Clin. Therap.*, **2004**, *26*, 1960-75.

[33] Choy, E.H.; Isenberg, D.A.; Garrood, T.; Farrow, S.; Ioannou, Y.; Bird, H.; Cheung, N.; Williams, B.; Hazleman, B.; Price, R.; Yoshizaki, K.; Nishimoto, N.; Kishimoto, T.; Panayi, G.S. Therapeutic benefit of blocking interleukin-6 activity with an anti-interleukin-6 receptor monoclonal antibody in rheumatoid arthritis: a randomized, double-blind, placebo-controlled, dose-escalation trial. *Arthritis Rheum*., **2002**, *46*, 3143-50.

[34] Rusznak, C.; Mills, P.R.; Devalia, J.L.; Sapsford, R.J.; Davies, R.J.; Lozewicz, S. Effect of cigarette smoke on the permeability and IL-1beta and sICAM-1 release from cultured human bronchial epithelial cells of never-smokers, smokers, and patients with chronic obstructive pulmonary disease. *Am. J. Respir. Cell Mol. Biol*., **2000**, *23*, 530-6.

[35] Ito, K.; Lim, S.; Caramori, G.; Chung, K.F.; Barnes, P.J.; Adcock, I.M. Cigarette smoking reduces histone deacetylase 2 expression, enhances cytokine expression, and inhibits glucocorticoid actions in alveolar macrophages. *FASEB J*., **2001**, *15*, 1110-2.

[36] Gaschler, G.J.; Zavitz, C.C.; Bauer, C.M.; Skrtic, M.; Lindahl, M.; Robbins, C.S.; Chen, B.; Stämpfli, M, R. Cigarette smoke exposure attenuates cytokine production by mouse alveolar macrophages. *Am. J. Respir. Cell Mol. Biol.*, **2008**, *38*, 218-26.

[37] Flouris, A.D.; Metsios G.S.; Carrillo A.E.; Jamurtas A.Z.; Gourgoulianis K.; Kiropoulos T.; Tzatzarakis M.N.; Tsatsakis A.M.; Koutedakis Y. Acute and short-term effects of secondhand smoke on lung function and cytokine production. *Am. J. Respir. Crit. Care Med*., **2009**, *79*, 1029-33.

[38] Tamaki, A.; Hayashi, H.; Nakajima, H.; Takii, T.; Katagiri, D.; Miyazawa, K.; Hirose, K.; Onozaki, K. Cigarette smoke condensate upregulates the gene and protein expression of proinflammatory cytokines in human fibroblast-like synoviocyte line. *Interferon Cytokine Res.*, **2008**, *28*, 509-21.

[42] Chujo, S.; Okamoto, S.; Sunahara, R.; Itoh, Y.; Hayashi, H.; Takii, T.; Hayakawa, K.; Onozaki, K. Study on cigarette smoking and rheumatoid arthritis. *Proceeding of the 129th Annual Meeting of Pharmaceutical Society of Japan*, **2009**, *27*, p. 168.

[43] Steinman, L. A brief history of T_H17, the first major revision in the T_H1/T_H2 hypothesis of T cell–mediated tissue damage. *Nat. Med*., **2007**, *13*, 139-145.

[44] Fouse, L.A.; Wright, J.F.; Dunussi-Joannopoulos, K.; Collins, M. Th17 cytokines and their emerging roles in inflammation and autoimmunity. *Immunol. Rev*., **2008**, *226*, 87-103.

[45] Park, H.; Li, Z.; Yang, X.O.; Chang, S.H.; Nurieva, R.; Wang, Y.H.; Wang, Y.; Hood, L, ; Zhu, Z.; Tian, Q.; Dong, C. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. *Nat. Immunol.*, 2005, *6*, 1133-41.

[46] Lubberts, E.; Joosten, L.A.; Oppers, B.; van den Bersselaar, L.; Coenen-de Roo, C.J.; Kolls, J.K.; Schwarzenberger, P.; van de Loo, F.A.; van den Berg, W.B. IL-1-independent role of IL-17 in synovial inflammation and joint destruction during collagen-induced arthritis. *J. Immunol.*, **2001**, *167*, 1004-13.

[47] Zhang, Z.; Zheng, M.; Bindas, J.; Schwarzenberger, P.; Kolls, J.K. Critical role of IL-17 receptor signaling in acute TNBS-induced colitis. *Inflamm. Bowel Dis.*, **2006**, *12*, 382-8.

[48] McKinley L.; Alcorn, J.F.; Peterson, A.; Dupont, R.B.; Kapadia, S.; Logar, A.; Henry, A.; Irvin, C.G.; Piganelli, J.D.; Ray, A.; Kolls, J.K. TH17 cells mediate steroid-resistant airway inflammation and airway hyperresponsiveness in mice. *J. Immunol.*, **2008**, *181*, 4089-97.

[49] Matusevicius, D.; Kivisäkk, P.; He, B.; Kostulas, N.; Ozenci, V.; Fredrikson, S.; Link, H. Interleukin-17 mRNA expression in blood and CSF mononuclear cells is augmented in multiple sclerosis. *Mult. Scler*., **1999**, *5*, 101-4.

[50] Kotake, S.; Udagawa, N.; Takahashi, N.; Matsuzaki, K.; Itoh, K.; Ishiyama, S.; Saito, S.; Inoue, K.; Kamatani, N.; Gillespie, M.T.; Martin, T.J.; Suda, T. IL-17 in synovial fluids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis. *J. Clin. Invest.*, **1999**, *103*, 1345-52.

[51] Pène, J.; Chevalier, S.; Preisser, L.; Vénéreau, E.; Guilleux, M.H.; Ghannam, S.; Molès, J.P.; Danger, Y.; Ravon, E.; Lesaux, S.; Yssel, H, ; Gascan, H. Chronically inflamed human tissues are infiltrated by highly differentiated Th17 lymphocytes. *J. Immunol*., **2008**, *180*, 7423-30.

[52] Bush, K.A.; Farmer, K.M.; Walker, J.S.; Kirkham, B.W. Reduction of joint inflammation and bone erosion in rat adjuvant arthritis by treatment with interleukin-17 receptor IgG1 Fc fusion protein. *Arthritis Rheum.*, **2002**, *46*, 802-5.

[53] Nakae, S.; Saijo, S.; Horai, R.; Sudo, K.; Mori, S.; Iwakura, Y. IL-17 production from activated T cells is required for the spontaneous development of destructive arthritis in mice deficient in IL-1 receptor antagonist. *Proc. Natl. Acad. Sci. U. S. A.*, **2003**, *100*, 5986-90.

[54] Nakae, S.; Nambu, A.; Sudo, K.; Iwakura, Y. Suppression of immune induction of collagen-induced arthritis in IL-17-deficient mice. *J. Immunol*., **2003**, *171*, 6173-7.

[55] Ruth, J.H.; Shahrara, S.; Park, C.C.; Morel, J.C.; Kumar, P.; Qin, S.; Koch, A.E. Role of macrophage inflammatory protein-3alpha and its ligand CCR6 in rheumatoid arthritis. *Lab. Invest.*, **2003**, *83*, 579-88.

[56] Hirota, K.: Yoshitomi, H.; Hashimoto, M.; Maeda, S.; Teradaira, S.; Sugimoto, N.; Yamaguchi, T.; Nomura, T.; Ito, H.; Nakamura, T.; Sakaguchi, N.; Sakaguchi, S. Preferential recruitment of CCR6-expressing Th17 cells to inflamed joints via CCL20 in rheumatoid arthritis and its animal model. *J. Exp. Med*., **2007**, *204*, 2803-12.

[57] Nistala, K.; Moncrieffe, H.; Newton, K.R.; Varsani, H.; Hunter, P.; Wedderburn, L.R. Interleukin-17-producing T cells are enriched in the joints of children with arthritis, but have a reciprocal relationship to regulatory T cell numbers. *Arthritis Rheum*., **2008**, *58*, 875-87.

[58] Yamada, H.; Nakashima, Y.; Okazaki, K.; Mawatari, T.; Fukushi, J.I.; Kaibara, N.; Hori, A.; Iwamoto, Y.; Yoshikai, Y. Th1 but not Th17 cells predominate in the joints of patients with rheumatoid arthritis. *Ann. Rheum. Dis*., **2008**, *67*, 1299-304.

[59] Acosta-Rodriguez, E. V.; Napolitani G.; Lanzavecchia, A.; Sallusto, F. Interleukins 1beta and 6 but not transforming growth factor-beta are essential for the differentiation of interleukin 17-producing human T helper cells. *Nat. Immunol.*, **2007**, *8*, 942-9.

[60] Veldhoen, M.; Hirota, K.; Westendorf, A.M.; Buer, J.; Dumoutier, L.; Renauld, J.C.; Stockinger, B. The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins. *Nature*, **2008**, *453*, 106-9.

[61] Quintana, F.J.; Basso, A.S.; Iglesias, A.H.; Korn, T.; Farez, M.F.; Bettelli, E.; Caccamo, M.; Oukka, M.; Weiner, H.L. Control of T(reg) and T(H)17 cell differentiation by the aryl hydrocarbon receptor. *Nature*, **2008**, *453*, 65-71.

[62] Kobayashi, S.; Okamoto, H.; Iwamoto, T.; Toyama, Y.; Tomatsu, T.; Yamanaka, H.; Momohara, S. A role for the aryl hydrocarbon receptor and the dioxin TCDD in rheumatoid arthritis. *Rheumatology*, **2008**, *47*, 1317-22.

[63] Kasai, A.; Hiramatsu, N.; Hayakawa, K.; Yao, J.; Maeda, S.; Kitamura, M. High levels of dioxin-like potential in cigarette smoke evidenced by in vitro and in vivo biosensing. *Cancer Res*., **2006**, *66*, 7143-50.

[64] Itoh, Y.; Hayashi, H.; Miyazawa, K.; Kojima, S.; Akahoshi, T.; Onozaki K. 17beta-estradiol induces IL-1alpha gene expression in rheumatoid fibroblast-like synovial cells through estrogen receptor alpha (ERalpha) and augmentation of transcriptional activity of Sp1 by dissociating histone deacetylase 2 from ERalpha. *J. Immunol.*, **2007**, *178*, 3059-66.

[65] Itoh, Y.; Hayashi, H.; Xu, J.; Takii, T.; Miyazawa, K.; Ariga, H.; Akahoshi, T.; Waguri-Nagaya, Y.; Otsuka, T.; Okamoto, T.; Onozaki, K. Dihydrotestosterone inhibits tumor necrosis factor alpha induced interleukin-1alpha mRNA expression in rheumatoid fibroblast-like synovial cells. *Biol. Pharm. Bull*., **2007**, *30*, 1140-3.

[66] Yoshino, S.; Sagai, M. Enhancement of collagen-induced arthritis in mice by diesel exhaust particles. *J. Pharmacol. Exp. Ther*., **1999**, *29*, 524-9.

[67] Hart, J.E.; Laden, F.; Puett, R.C.; Costenbader, K.H.; Karlson, E.W. Exposure to traffic pollution and increased risk of rheumatoid arthritis. *Environ. Health Perspect.*, **2009**, *117*, 1065-9.

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