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Smoking and the Microbiome in the Pathogenesis of Rheumatoid Arthritis

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Commentary

Rheumatoid arthritis (RA) is a chronic, destructive, inflammatory, polyarticular joint disease, characterized by infiltration of inflammatory cells, followed by the destruction of cartilage and bone [1]. Inflammatory cytokines such as tumor necrosis factor-α (TNF- α), interleukin-6 (IL-6) and interleukin-1 (IL-1) as well as chemokines such as pulmonary and activation-regulated chemokine /CCL18 and monocyte chemoattractant protein-4 /CCL13 play important roles in the pathogenesis of RA. These cytokines have emerged as important pro-inflammatory mediators and dominant molecular targets for the therapeutic strategies [2]. The nuclear factor κB (NF-κB) family of transcriptional activators regulates the expression of a variety of cytokines involved in the pathology of RA, including TNF- α, IL-6 and IL-1 [3]. Thus, NF-κB is also an important target of RA treatment [4].

Although the etiology of RA has not been fully understood yet, both genetic and environmental factors have been identified and the interplay between predisposing genetic factors and environmental conditions have been suggested to trigger disease manifestation. One of the key findings to elucidate the pathogenesis of RA is the discovery of autoimmunity to citrullinated protein/peptide antigens (ACPA). This discovery has led to the concept that ACPA might be the essential link between disease genetic factors and the production of cytokines/chemokines.

To date, numerous genetic risk factors leading to RA have been identified including a group of MHC class II alleles, such as HLA-DR4, -DR1 and -DR10 [5]. Shared epitopes (SEs) which share variants of the Q/R-K/R-R-A-A amino acid motif present in the third hypervariable region of the DRβ1 chain. This component constitutes of the peptide binding groove [6]. Although the pathological role of SE has not be elucidated yet, SE is suggested to have roles in enhanced affinity and presentation of autoantigens, resulting in the activation of self-reactive T cells [7-10]. Another genetic risk factor for RA patients with ACPA positive is the susceptibility allele 620W of *PTPN22*, a gene encodes a tyrosine phosphatase and a gene in the TNF receptor-associated factor 1-C5 (TRAF1-C5) region. Polymorphisms in the human *PADI4* gene were associated with RA in Asian cohorts [11].

On the other hand, a number of environmental factors have reported to be linked to RA, such as smoking and infections. Smoking is extensively studied and Sugiyama et al. used meta-analysis to conclude that smoking is a risk factor for RA, especially rheumatoid factor-positive RA men [12]. Klareskog et al. reported that both the SE positivity and smoking habits were risk factors for anti-CCP antibody positive RA but not anti-CCP negative. The presence of both factors were closely associated with the development of RA. They proposed that smoking activates an antigen specific autoimmune response to citrullinated proteins in the presence of the HLA-DR SE alleles, resulting in the development of RA [13]. Mahdi et al. has discovered that a SE, PTPN22 and smoking showed the strongest association with the anti-citrullinated α-enolase-positive subset and concluded that citrullinated alpha-enolase links smoking to genetic risk factors in the development of RA [14]. It seems that smoking and a SE interaction enhances immunity to various different citrullinated epitopes resulting in the autoimmune response associated with RA [15]. While the molecular mechanisms responsible for the influence of smoking in RA are not fully elucidated yet, some studies have shown an association between RA and toxic compounds found in cigarette smoke, such as 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), nicotine and reactive oxygen species. We found that aryl hydrocarbone receptor (AhR) mRNA and protein levels were higher in RA synovial tissue than in OA tissue, and that TCDD enhanced the expression of IL-1β, IL-6, and IL-8 through binding to AhR, with this effect transmitted through the NF-κB and ERK signaling pathways. In addition, AhR expression in synovial cells was up-regulated by TNF- α. These data suggest that TNF- α activates AhR expression in RA synovial tissue, and thus cigarette smoking and exposure to TCDD enhances the RA inflammatory processes. Thus, TCDD exposure, such as during smoking, appears to exacerbate RA pathogenesis [16]. As tobacco smoke is a rich source of planar polycyclic aromatic hydrocarbons, many of which are AhR agonists (e.g. benzo[a]pyrene) it is possible that the activation of the AhR may play a significant role in disease progression [17]. Furthermore, smoking has been shown to modulate the immune system by altering Th-17 cell-mediated responses in a manner consistent with the ability of AHR activation to influence Th-17 cell differentiation [18,19].

DNA sequence-based analyses of gut microbial and a development of the studies in mucosal immunology suggest that the microbiome represents an important environmental factor that can influence the development of autoimmune diseases [20]. The term microbiome defines the ecological communities of commensal, symbiotic, and pathogenic micro-organisms that share human body space. Intestinal epithelial cells expressing Toll-like receptors (TLRs) in their cellular membrane recognized of pathogen-associated molecular patterns.This interaction activates the signaling adaptor molecule myeloid differentiation primary-response protein 88, and ultimately resulting in the induction of downstream inflammatory responses. In addition, alteration of the microbiome may contribute to the disturbance of the delicate balance between type 1 T helper cells, type 2 T helper cells, type 17 T helper cells and regulatory T cells, thereby resulting in systemic auto-immune responses. Recently, Scher JU et al. have reported that the presence of *Prevotella copri* is strongly correlated with new-onset untreated rheumatoid arthritis subjects [21]. They also found that the increases in *Prevotella* abundance correlated with a reduction in *Bacteroides* and a loss of reportedly beneficial microbes, such as Group XIV Clostridia, Blautia, and *Lachnospiraceae clades*. These findings may understand how the alteration of the microbiome contributes redox and reactive oxygen species in the pathogenesis of RA. Therefore, we can speculate that cross-talk between the microbiome and the human body in terms of genetic predisposing

factors might contribute to the development of auto-immune diseases, such as RA. Further studies are required to elucidate the role of the interaction between genetic and environmental factors in the development of RA.

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