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Invited Perspective: Air Pollutants, Genetics, and the Mucosal Paradigm for Rheumatoid Arthritis Risk

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Rheumatoid arthritis (RA) is a chronic, debilitating inflammatory condition that is triggered by a combination of environmental and genetic factors.[1–3] Several decades of RA research have contributed to the development of the "mucosal paradigm" of RA disease pathogenesis, which posits that local inflammation of the mucosa in airways and other mucosal sites leads to the loss of immune tolerance and the production of autoantibodies.[4,5] This process often occurs years before patients develop the joint-related symptoms that are the clinical hallmarks of RA.

Support for the mucosal origins hypothesis derives from several sources. Respiratory exposures, such as cigarette smoking and silica dust, have been associated with RA risk, demonstrating that airway damage and inflammation likely serve as key drivers of RA autoantibody formation and disease pathogenesis.[6–8] Cigarette smoking in particular has been shown to strongly interact with known genetic risk factors for RA, including the major histocompatibility complex, class II, DR beta 1 (*HLA-DRB1*) "shared epitope," suggesting that people with specific genetic variants may be more likely to generate autoantibodies that place them on the path toward RA development.[9–11] Recent evidence showing an association between childhood passive smoking and future development of adult-onset seropositive RA further emphasizes the potential for a long latency period for environmental exposures and the development of clinical RA symptoms.[12] However, because many people who develop RA do not smoke cigarettes or have significant exposure to secondhand smoke, there has been intense interest in identifying other inhalants that may also affect RA risk.

In this issue of *Environmental Health Perspectives*, Zhang et al. report on their comprehensive study investigating ambient air pollution, genetic factors, and RA risk.[13] They found that higher levels of specific pollutants and a higher overall air pollution score were each associated with increased RA risk. They noted a strong dose effect for the air pollution score on RA risk among subjects with low and intermediate RA genetic risk.

These findings contribute to the growing literature investigating the impact of inhalants other than cigarette smoke on RA risk. An investigation in the Nurses' Health Study of 90,297 women found that living within 50 m of a road conferred increased risk of RA compared with living 200 m or farther away.[14] A study of 640,041 people in the British Columbia Border Air Quality Study found a similar association between traffic proximity and RA risk.[15] However, the data linking specific pollutants to RA risk have been conflicting. In both the Nurses' Health Study and the British Columbia study, specific pollutants, including particulate matter with aerodynamic diameters of $\leq$2.5 μm or $\geq$10 μm, nitrogen dioxide, and sulfur dioxide, were not associated with RA risk.[15,16] Similarly, there was no significant association between pollutants and RA risk after adjustment for smoking and education in a large case–control study of 1,497 incident RA cases and 2,536 age- and sex-matched controls in the Swedish Epidemiological Investigations of Rheumatoid Arthritis study.[17] In contrast, large population-based studies of 322,301 people in Taiwan[18] and 230,034 people in South Korea[19] did find associations between specific pollutants and RA. However, none of these previous studies incorporated genetic factors to investigate possible gene–pollutant interactions as in the study by Zhang et al.[13]

Although Zhang et al. included several single-nucleotide polymorphisms of the human *HLA* genes in the RA genetic risk score,[13] they did not specifically determine shared epitope status or other classical HLA alleles. Because these HLA proteins play a central role in the presentation of neoantigens to T cells,[20] it is possible that the lack of strong gene–pollutant interaction could be due to omission of this important RA genetic risk factor. Important future directions include the incorporation of *HLA* into RA genetic risk scores, as well as investigating occupational inhalants and seropositive RA, while integrating RA genetic risk.

In conclusion, it is increasingly clear that air pollutants and genetic factors each likely contribute to RA risk. The important findings reported by Zhang et al.[13] offer more rationale to encourage policies to improve air quality to lower risk of RA and other autoimmune conditions that have been associated with respiratory exposures. These findings also provide additional evidence of the mucosal paradigm of RA risk related to pulmonary mucosal injury from air pollutants, which will continue to be a key area of mechanistic RA research.

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