



# Environmental exposures and biomarkers predictive of rheumatoid arthritis and the pathway to precision medicine

Sasha M. Bernatsky<sup>1</sup>, Jean C. Pfau<sup>2</sup>, Marvin J. Fritzler<sup>3</sup>

<sup>1</sup>Research Institute of the McGill University Health Centre, McGill University, Montreal, Quebec, Canada; <sup>2</sup>Department of Microbiology and Immunology, Montana State University, Bozeman, MT, USA; <sup>3</sup>Cumming School of Medicine, University of Calgary, Calgary, Canada

*Correspondence to:* Marvin J. Fritzler, PhD, MD. Cumming School of Medicine, University of Calgary, 3330 Hospital Dr. NW, Calgary, AB, T2N 4N1, Canada. Email: fritzler@ucalgary.ca.

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Rheumatoid arthritis (RA) is regarded as a systemic autoimmune rheumatic disease (SARD) where the major clinical manifestations involve symmetrical arthrodial joints and are associated with increased direct and indirect health care costs (1). Few of the other SARD (i.e., systemic lupus erythematosus (SLE), systemic sclerosis, autoimmune inflammatory myopathies) have been the benefactors of the tremendous progress in understanding RA disease onset, pathogenesis, diagnostic approaches, and therapeutic options (1,2). Indeed, related to this progress, there are emerging efforts to identify at risk individuals (3-6), arrive at an early and accurate diagnosis of “pre-RA” and then initiate evidence-based disease interventions (7,8). Implicit in the approach to disease prevention is the need for precision medical approaches such as the ‘systems biology based P4 model’ (Predictive, Preventive, Personalized, Participatory) espoused by Flores *et al.* (9) and others.

A key to the P4 approach is an understanding of elements that predate the development of clinically obvious RA. Certainly, dating to the 1970s, there is a fulsome literature on the biomarkers that attend the diagnosis of RA. These include genomic markers such as HLA-DRB1 and the so-called shared epitope (10), epigenetic markers such as modifications of chromatin (i.e., methylation and acetylation) (10-12), autoantibodies that historically include rheumatoid factor, but more recently focused on autoantibodies directed to citrullinated peptides (ACPA), as well as cytokines and interleukins such as IL-1, IL-15 and IL-17 (13).

If they are to be used to ‘predict’ RA and enter a

medical management pathway of precision medicine, it is imperative that there is a thorough understanding of how these biomarkers are represented in unselected populations. In this light, a recent study by van Zanten *et al.* from the Netherlands provides important insight into the clinical utility of ACPA through a population-based study of >40,000 individuals that are part of a larger prospective “Lifelines” study in their country ([www.Lifelines.net](http://www.Lifelines.net)) (14).

In RA, environmental factors appear to play a more significant role than genetic factors and may be the ‘second hit’ that is needed to convert an individual into the RA disease trajectory. The rather small influence of genetic factors in RA is exemplified by the concordance rate of RA in monozygotic twins of approximately 14% and only 4% in dizygotic twins [reviewed in (15)]. Of the environmental factors implicated in RA, periodontitis and cigarette smoking are best established as risk factors for the disease [reviewed in (14)] and emerging evidence has implicated air pollution and other routes of exposure (16,17) in the form of silica (16,18), traffic emissions (19,20) and particulates (21) as significant co-factors. Other risk factors implicated in RA include occupation (17,22,23), obesity (24), socioeconomic (22), dietary carbohydrates (25), seasonal effects (26), pesticides (17), and alcohol may actually be protective (27). Other factors (physical and psychological trauma, surgery, infections) have also been reported but are poorly substantiated [reviewed in (26,28)].

In the benchmark study of van Zanten *et al.* (14), the link of ACPA to self-reported disease that could be taken as either established or pre-RA was the focus, and many

of the factors referred to above were addressed. It is important to appreciate that this study utilized an adjusted cut-off for ACPA because, as the authors explain, the ACPA cut-offs appropriate for a healthy population are not clearly established. Since they desired “to use the test to detect ACPA and not as a diagnostic test for RA”, a 99-centile cut-off value of  $\geq 6.2$  U/mL was chosen, whereas the manufacturer’s cut-off value for RA diagnostics was recommended to be  $\geq 10$  U/mL. Using this cut-off for the non-RA group, older age, smoking and joint complaints remained significantly more frequently present in ACPA-positive compared with ACPA-negative participants. For example, in this unselected population study 1.0% had ACPA levels that were higher than an adjusted cutoff. Notably, a positive ACPA was significantly associated with older age, female sex, smoking, joint complaints, RA and first degree relatives (FDR) with rheumatism. Further, in the Lifelines study, of the ACPA-positive participants, 22.4% had RA (15.2% with defined RA and 7.2% self-reported RA only). However, in participants without RA, 0.8% were ACPA-positive. When the manufacturer’s recommended cutoff of  $\geq 10$  U/mL was used, ACPA-positive participants reported significantly less use of sugar-sweetened soft drinks, and women were less often nulliparous. Other previously-reported risk factors for RA and ACPA were not significantly associated with ACPA positivity. For example, body mass index (BMI) and being overweight were previously associated with RA (24) but in this study BMI was not associated with ACPA positivity. In addition, an association with alcohol non-use and ACPA positivity and/or higher ACPA titers, self-reported periodontitis, dietary fish intake as a protective factor or sugar-sweetened soft drinks as an aggravating factor for RA was not detected.

Despite the valuable insight that this remarkable study provides, the possible geographic clustering of disease and potential or observed exposure to pollution were not reported. This is of importance because if RA is to be prevented or mitigated, remediation of environmental factors should be one of the major considerations.

While ACPA-positivity is clearly an important marker for early detection of RA, the Lifelines study confirms other studies demonstrating that a significant subset of RA patients is ACPA-negative. One potentially helpful model of RA etiology proposes that environmental triggers of RA should be defined in categories. Within this model emerges the possibility that different sets of triggers drive ACPA-positive *vs.* ACPA-negative RA. In this case, the Lifelines database and cohort may provide an invaluable tool for

testing this hypothesis. For example, there is evidence that cigarette smoking is associated with an increased risk of ACPA-positive RA, but not ACPA-negative RA, and cigarette smoking in the context of the *HLA-DRB1* genetic background is associated with a high-risk for ACPA-positive RA [reviewed (29)]. The discovery that smoking increases expression of enzymes associated with protein citrullination, which could trigger development of ACPA, led to further studies to identify environmental RA triggers that were (or were not) associated with ACPA. Although not apparent in the Lifelines study (14), in other recent studies periodontitis linked to *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* has been associated with ACPA-positive RA, and significant protein citrullination (30,31). However, RA associated with inhalation exposures to silica or asbestos tend to be ACPA-negative in the absence of smoking, despite the ability of silica nanoparticles to increase citrullination in lung cells [reviewed (32)]. An association between RA and exposure to crystalline silica (quartz) has become well established, and more recently asbestos has also been reported as a trigger for RA (33). The mechanism whereby these silicate mineral dust exposures drive RA may be different than environmental triggers that lead to ACPA-positive RA (32), and likely a SARD-permissive genetic environment will be necessary for full disease development.

Ambient air pollution and other occupational exposures, as possible triggers for the development of SARD, has been the focus of other studies. Notable industrial emissions include fine particulate matter ( $PM_{2.5}$ ) and sulfur dioxide ( $SO_2$ ). Most particulate matter is formed from gases emitted from power plants, industries and automobiles motor vehicles, although some particulate matter is directly emitted from smokestacks and other sources. Industrial activities are the largest sources of  $SO_2$  emissions followed by combustion of fossil fuels at power plants and other emissions from motor vehicles and industrial facilities. Since particulate matter may trigger a host of non-rheumatologic health problems (34) it would be intriguing to confirm whether some components of air pollution trigger rheumatic disease encompassing RA as well. Links between  $PM_{2.5}$  levels and SLE activity have been reported (35), as well as evidence supporting an increased risk of certain SARD with  $PM_{2.5}$  (36). Analysis of death certificates in 26 USA states concluded that death from SARD were associated with occupational exposures encountered in farming and industry (23) and analysis of data extracted from the Nurses’ Health Study found an association

between exposure to traffic pollution and RA suggesting that pollution from traffic in adulthood may be a newly identified environmental risk factor for RA (19). Studies of a Swedish cohort reported that exposure to NO<sub>2</sub>, but not particulate matter, was associated with RA risk (22). One study reported that measures of air pollution levels were associated with a 60% increased risk of juvenile idiopathic arthritis in young children (21). However, other studies did not find any clear links between RA onset and traffic-related NO<sub>2</sub> levels or regional PM<sub>2.5</sub> levels (20). As mentioned earlier, there is convincing evidence that tobacco smoking may induce ACPA but to date no publications have clearly linked air pollution and ACPA.

In conclusion, the application of precision medicine to the prediction and effective intervention leading to prevention of RA is still in its early stages. The factors described above implicated as triggers for onset and perpetuation of RA provide an approach that may help to detect environmental triggers for RA and to better understand gene/environment interactions in RA. Many other environmental triggers may still be identified. In some instances, variability in research approaches and discordant results strongly suggest that additional, thorough, coordinated research efforts are required in the future. Variability in measurement of air pollution, both in terms of types and timing, may in part explain the inconsistencies in these reports. In addition, it is well known that no one environmental or xenobiotic factor alone induces SARD; multiple genes appear to be susceptible to xenobiotic-induced epigenetic modifications leading to a SARD-permissive state where multiple exposures (i.e., second and third “hits”) are likely required to trigger RA. Therefore, the development and progression of RA may depend on synergistic effects of environmental factors such as air pollution, cigarette smoking, and infections on a susceptible genetic background. A fulsome understanding of these factors is important on a clinical care pathway for RA that embraces precision medicine.

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