

VIEWPOINT

Mining the pathogenesis of rheumatoid arthritis, the leading role of the environment

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ABSTRACT

The environment plays a crucial role in the pathogenesis of various diseases, including rheumatic musculoskeletal diseases (RMDs). Chronic exposure to air pollution has been associated with a number of detrimental effects on the immune system, including direct activation of autoimmunity and autoantibodies production. Rheumatoid arthritis (RA) is a paradigmatic example of the link between environmental stimuli and development of autoimmunity. Recent evidence has confirmed such association and provided further indication of the strict relationship between the lungs and the synovial tissue. Hard rock mining and chronic exposure to airborne fine particulate matter have been associated with higher risk of developing RA. In addition, new evidence showed a peculiar association between acute exposure to toxic inhalants and risk of RA flare. In conclusion, the environment is the straw that breaks the camel's back, unfortunately the "straws" are rapidly accumulating, and their burden is projected to increase accordingly.

In 1952, Dr Anthony Caplan first described 51 cases of coal miners affected by a bizarre pneumoconiosis and simultaneously by rheumatoid arthritis (RA). In the original paper, Dr Caplan reported a striking association between chronic exposure to coal-mining dust and multiple, well-defined, round opacities in lungs of patients with RA, this involvement was not seen in non-RA workers.¹ 70 years later we have learnt much more. Many studies have examined the relationship between exposure to toxic inhalants and pulmonary diseases² and many others have linked the respirable silica to RA, with or without interstitial lung disease (ILD).³ Indeed, the scientific community has made many steps forward in the understanding of the pathogenesis of ILD in inflammatory musculoskeletal diseases. Lungs and joints are intimately connected, and this connection seems to work in both ways.⁴ RA-ILD is clearly triggered by systemic/joint inflammation, but it

is also true that synovitis might be triggered by inflammatory phenomena starting in the lungs. Post-translational modification of lung proteins (i.e., citrullination) leads to the formation of self-antigens and eventually of autoantibodies (i.e., anti-citrullinated protein antibodies [ACPA]), which are pathogenetic of RA in many ways.⁵ Notably, Lugli and colleagues in 2015 demonstrated that the citrullination process is secondary to lung inflammation itself and there are only minimal differences between smokers and non-smokers.⁶ The latter finding is of the utmost importance and might explain why and how numerous environmental triggers, other than cigarette smoking, have been associated to RA risk.

Last of this long list is the exposure to hard rocks (ie, minerals containing heavy metals like uranium, zircon, gold). Blanc *et al* had recently published, in *JAMA Network Open*, a cross-sectional study aimed to test the hypothesis that hard rock mining is associated with greater risk of RA.⁷ The authors surveyed, telephonically, nearly 2000 men from the southwest of the USA, a region characterised by elevated incidence of pneumoconiosis. The questionnaire covered countless aspects of the lifestyle and working habits as well as medical history and medications. Among the overall sample 790 (39.7%) had some exposure to silica or mining activities and 118 (5.9%) were hard rock miners. In aggregate, exposure to mining activity of any kind was associated with greater risk of RA (either using more stringent or non-stringent definition of RA diagnosis). Remarkably, hard rock mining was associated with a threefold higher risk of developing RA and interestingly, the point estimate for soft rock mining (ie, coal mining) was even greater (ninefold higher risk). The latter finding might suggest that the nature of the inhaled small particles



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might not be as relevant as previously assumed. In line with such hypothesis, chronic exposure to fine particulate matter (PM), which is a mixture of dust and other carbon-derived compounds, has been associated to higher risk of RA.⁸ Moreover, militaries with RA exposed to burn pits and waste disposal had nearly twice the risk of having ACPA-positive arthritis.⁹ Interestingly, such association stand true even for systemic sclerosis, vasculitis and myositis.¹⁰ At the end of the day, it is not all due to respirable silica!

What is even more interesting and thought-provoking in the study by Blanc *et al* is the association between mining activities and the risk of non-RA arthritis. The latter result, which was not entirely discussed in the article, might deserve some special considerations. We are somehow inclined to assume that cigarette smoking and/or environmental pollution are associated to RA alone. Nothing could be further from the truth. Although RA is a paradigmatic example of the environment affecting the immune system, there have been many studies linking toxic environmental exposure and immune-mediated diseases.⁸ As an example silica exposure has been consistently associated with systemic lupus erythematosus (SLE) risk's.¹¹ Again, PM exposure has been linked to higher risk of connective tissue diseases and multiple sclerosis.⁸ In this scenario, the study by Blanc *et al* adds to the body of literature pointing towards a more holistic effect of air pollution on the immune system.

Blanc *et al*, alongside many other authors, focused on chronic exposure to environmental factors (or at least proxies of chronic exposure) and the risk of developing arthritis. However, recent evidence has shown that transient and acute exposure to toxics might trigger flares of autoimmune diseases such as RA, psoriasis or SLE.^{12–15} In other words, hazardous components of air pollution (both gaseous and particulate) can exert negative effects on the immune system that seem to be both permanent and transitory. Moreover, air pollution is also harmful on a wide variety of body systems and tissues. As an example, heavy metals contained in PM can transfer from alveoli to the blood stream and bind to hydroxyapatite crystals in the skeleton with direct toxic consequences on bone cells.¹⁶ Air pollution exposure has been indeed linked to higher risk of osteoporosis and fractures.^{17 18} Cardiovascular risk as well is dramatically increased by exposure to environmental pollutants,¹⁹ a finding that is of particular concern for patients with RA, who face a more than doubled cardiovascular risk compared with healthy individuals even under normal conditions.²⁰ Moreover, pain (independently from inflammation) might be correlated with the fluctuation of pollutants.²¹

According to the WHO, air pollution is a major cause of morbidity and mortality, which is, at least in part, preventable.²² Compliance with air pollution exposure guidance would ensure a dramatic reduction of mortality across Europe; more than 50 000

deaths can be prevented, especially in highly polluted regions (northern Italy or central Europe).²³ Regrettably, air pollution seems to disproportionately impact low-income populations and patients with chronic diseases.²⁴ Pollution takes its toll on health every day, especially in patients with rheumatic musculoskeletal diseases but, even if the paint is as dark, we should act immediately to counteract what seems to be inevitable. Short-term coping strategies are at our fingertips. We can minimise the exposure in various ways, from indoor air filters to personal protective equipment for high-risk workers. Still, we are waiting for a more profound change to come.

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