Pulmonary infection in Wegener’s granulomatosis and idiopathic pulmonary fibrosis

Nicholas Kim Harrison

Friederich Wegener’s original paper “On generalised septic vessel disease” suggests he thought likely there was an infectious cause for the condition which now bears his eponym. The characteristic pathological features of Wegener granulomatosis (WG) are: a necrotising granulomatous inflammation of the respiratory tract with vasculitis affecting both arteries and veins; focal necrotising glomerulonephritis; and a varying degree of systemic vasculitis—the so-called “Wegener’s triad”. The granulomatous inflammation is conspicuous for the absence of any obvious microorganism, although granulomatous infections can sometimes be misdiagnosed as WG. During the 70 years since Wegener’s description there have been some remarkable advances in both the diagnosis and treatment of this condition and in our understanding of its pathogenesis. However, the precise nature of the initiating factor(s) remains elusive.

What we do know is that there is a strong association between WG and the human leukocyte antigen (HLA)-DPB1*0401 allele, suggesting that there is an inherited predisposition for the condition. Interestingly, there is also an association with α-1 antitrypsin deficiency. We also know that virtually all patients who subsequently develop the systemic disease have circulating antineutrophil cytoplasmic antibodies (ANCAs) and these are mainly directed against proteinase-3 (PR3), the so-called “Wegener’s autoantigen”—a serine protease which regulates cell proliferation, differentiation and death. This antibody has proved to be a useful biomarker for the diagnosis of WG, although less so for the likelihood of relapse. Furthermore, our increasing knowledge of its biological properties has provided new insights into the pathogenesis of WG. Specifically, whilst PR3 is the target antigen for ANCA’s, the observation that elevated levels of PR3 at sites of granulomatous inflammation correlate with increased tumour necrosis factor α (TNFα) has led to the hypothesis that PR3 is directly involved in the modulation of cytokines associated with an aberrant immune response (see Csernok et al. for a review).

Following tissue injury, increased levels of PR3, released from activated or dying neutrophils, might act as a danger/alarm
signal interacting with proteinase-activated receptor-2 (PAR-2), the so-called “gateway receptors” on dendritic cells. This would result in their maturation and instruction to initiate an innate T helper 1 (Th1) immune response. However, PR3 also has further effects on inflammation mediated by two distinct actions on interleukin 32 (IL32), a recently identified cytokine which induces production of TNFα, IL1β, IL6 and 2CXC chemokines by immune cells. It is known that PR3 activates IL32 by enzymatic cleavage, thereby enhancing its proinflammatory effects. However, PR3 is also known to be a specific binding protein for IL32α, independently of its enzymatic activity. It has been speculated whether this may be one, neglected factor, responsible for the alveolar epithelial injury observed in IPF. Certainly, recurrent “microinfections” would be consistent with the observed temporal and spatial heterogeneity of lung fibrosis seen in usual interstitial pneumonia. The observation that a patient with IPF given empirical treatment with co-trimoxazole (for presumed Pneumocystis jiroveci) showed considerable clinical improvement led to a recent, small, pilot study of this antibiotic in patients with pulmonary fibrosis. The results are encouraging and a bigger trial is currently underway in the UK to examine this observation further.

It is tempting to speculate that in both WG and IPF, co-trimoxazole treatment may exert a beneficial effect by reducing bacterial colonisation and, thereby, halting the, downstream cellular and molecular interactions which ensue. Whatever agent(s) initiate and/or perpetuate these conditions remains elusive. The study by Richter et al is a timely reminder that the complex relationship between microorganisms and the respiratory tract has yet to yield all its secrets.

**Competing interests:** None.


**REFERENCES**

Where there’s smoke... there’s tuberculosis

Stephen Gordon, Jamie Rylance

Recent observations have demonstrated precisely the increased life expectancy associated with clean environmental air in the USA. This dramatic health benefit has been achieved at levels of pollution very much lower than those found indoors in underdeveloped countries. Traditional cooking fires using biomass (organic material) fuel are inefficient and the smoke levels measured in poorly ventilated homes are often 100 times that regarded as dangerous in the affluent industrial world. High levels of indoor air pollution have been associated in epidemiological studies with upper and lower respiratory tract acute infections (ALRIs), chronic obstructive pulmonary disease (COPD) and lung cancer. There has been less evidence to support an association of indoor air pollution with biomass fuel use and tuberculosis, and so the report by Kolappan and Subramani (see page 705) in this issue is most welcome. Three billion people use biomass fuel globally, almost entirely in areas with high rates of tuberculosis. The confounding effects of poverty, crowding, malnutrition and increased exposure make an association between biomass fuel use and tuberculosis very hard to disintegrate. In a well-conducted study in Chennai, India, the authors report that 56% of proven tuberculosis cases can be associated with biomass fuel usage. Confounding factors including cigarette smoking, alcohol use, socioeconomic status and case-contact are also examined. This study is likely to underestimate the true burden of tuberculosis transmission as young children are intensely exposed to biomass smoke in the home and are a very difficult group in which to diagnose tuberculosis.

Given the association of ALRIs with biomass smoke exposure, and the association of cigarette smoking with tuberculosis, the finding of this study is not surprising. Two major unanswered questions are immediately provoked. First: what is the mechanism behind this association? Secondly: what can be done to protect biomass smoke-exposed adults and children in areas with high tuberculosis transmission?

The mechanism by which biomass smoke exposure results in increased tuberculosis disease is likely to relate to the established effects on alveolar macrophages and pulmonary epithelium. Smoke particle size, form and surface chemistry initially promote a proinflammatory state and oxidative damage to the lung. Laboratory models have demonstrated upregulation of tumour necrosis factor α (TNFα), interleukin 6 (IL6) and IL8; nuclear factor-kΒ (NF-kΒ) activation and cellular lipid peroxidation. Apoptosis of alveolar macrophages is also increased, and, although this is usually considered a positive host defence response, cytotoxic effects may predominate. Phagocytosis is reduced in some non-tuberculosis bacterial studies, and pulmonary mycobacterial load is increased by diesel exhaust particulates. Peak respiratory burst activity may be decreased, but inducible nitric oxide synthase (iNOS) expression is upregulated. There is no clear narrative to this disruption, and many are yet uninvestigated possibilities. As the epidemiological evidence becomes stronger, there is a need to strengthen mechanistic explanations using relevant in vitro models of biomass particulates.

More importantly to the 7 million people per year who are diagnosed as having tuberculosis in underdeveloped countries, what can be done to prevent this burden of disease? The answer here can be stated with more certainty. Multiple new technologies exist to improve fuel efficiency and domestic ventilation, even in the most resource-deprived situations (www.hedon.info). At the Partnership for Clean Indoor Air Forum in Kampala in March 2009 (www.pciaonline.org), 265 non-governmental organisations (NGOs) re-asserted their intention to improve indoor air quality not only because of the environmental imperative to do so, but also because of the probable health benefits of improved stove technology.

As chest physicians, we look forward to the results of the RESPIRE trial from Guatemala, due to be published this year, which is expected to show for the first time a direct health benefit from an indoor air intervention. A stove intervention alone, however, will not reduce the global burden of tuberculosis.

Reducing biomass smoke-related disease will require multifaceted action to improve fuel security, health education (particularly for women), diet and environmental conservation coupled with excellent tuberculosis case management. These are exciting and challenging times.

Competing interests: None.


REFERENCES

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