Effect of air pollution on the human immune system

Inhaled particulates from environmental pollutants accumulate in macrophages in lung-associated lymph nodes over years, compromising immune surveillance via direct effects on immune cell function and lymphoid architecture. These findings reveal the importance of improved air quality to preserve immune health against current and emerging pathogens.

This is a summary of:
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The question

The world population is aging, and the majority of healthcare costs, morbidity and mortality that are associated with diseases concern individuals in the sixth decade of life and older[1]. Thus, we need to improve our understanding of the underlying mechanisms that exacerbate disease susceptibility in elderly individuals. As starkly observed in the SARS-COV-2 pandemic, elderly individuals have increased susceptibility to respiratory infections as well as other lung diseases, such as chronic obstructive pulmonary disease and cancer[2]. This susceptibility is attributed to senescent changes in immune cells, which result in systemic inflammation and functional impairments in adaptive immunity[3]. However, the immune system is localized in mucosal and lymphoid tissues throughout the body, and the effect of aging on local immune responses has not been well-studied. The lung has continuous exposure to the environment, and the effect of this exposure on the immune system over age is not known. In this study, we investigated the role of atmospheric particulate matter in lung-associated immunity over the human lifespan.

The discovery

In our studies of human tissue immunity that used samples that were obtained from deceased human organ donors[4], we consistently observed that lymph nodes (LNs) associated with the lungs were black in color, owing to the presence of black particulate matter, whereas gut-associated LNs were the expected beige color, with no particulates. Thus, we began to investigate the effect of particulates on immune cells and LN architecture in these different LN sites using quantitative imaging and cellular and functional assays. We found that atmospheric particulate matter accumulated with age specifically in lung-associated LNs but not in gut-associated LNs, and this accumulation increased remarkably after age 40 (Fig. 1). Because lymphatic vessels connect LNs and tissues, one might expect that black particulates would disperse across other types of tissue-draining LNs; however, the fact that particulates became entrapped in lung-associated LNs suggested local effects of particulate matter on lung immunity. We found that particulates were contained within a specific subset of macrophages that was located in the T cell zone of the LN and not within follicles. Importantly, particulate-containing macrophages exhibited reduced activation, impaired production of pro-inflammatory cytokines and significantly reduced phagocytic capacity, whereas macrophages in the same LN that did not contain particulates did not exhibit these functional alterations. Particulate accumulation in lung-associated LNs further led to age-associated alterations in LN structural integrity, owing to the disruption of B cell follicles and lymphatic drainage. These results show that inhaled particulates have direct and cumulative effects on innate and adaptive immune processes that take place in the lymphoid organs that carry out immune surveillance of the lungs and respiratory tract.

The interpretation

Our study shows that pollutants in our environment have a direct and detrimental effect on the human immune system, and specifically the immune organs that are associated with the respiratory tract. LNs filter impurities and coordinate the clearance of harmful antigens and pathogens, but over decades the LNs connected to the lungs become clogged with particulates, and as a result they are not able to carry out essential functions of host defense and immune surveillance. In addition, the effects of pollutants are cumulative and can in part account for the worse outcome of respiratory infections in elderly individuals compared with younger populations.

Our study raises important questions concerning the mechanisms by which particulates are contained by specific macrophage subsets in the LNs. It is unknown whether these macrophages are resident in the LN or whether they are derived from lung macrophages that migrate to the associated LN. It will be interesting to assess whether targeting certain macrophage populations may facilitate the clearance of particulate matter. Moreover, we showed that particulates impair the phagocytic capacity that is mediated by scavenger receptors that are expressed by macrophages. However, the effects of particulates on other pathways for phagocytosis of pathogens and cellular debris remain to be established.

In addition, it will be important to understand the full effect of inhaled particulates in the resident immune cell populations in the lung itself, which is an area of ongoing investigation.

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EXPERT OPINION

"While the approach undertaken here is classical in its methodology, having access to human material from large numbers of donors can be very challenging and has to be commended. The manuscript is very well-written, and the data are very interesting, robust and well-presented."
Thomas Marichal, Liège University, Liège, Belgium

FIGURE

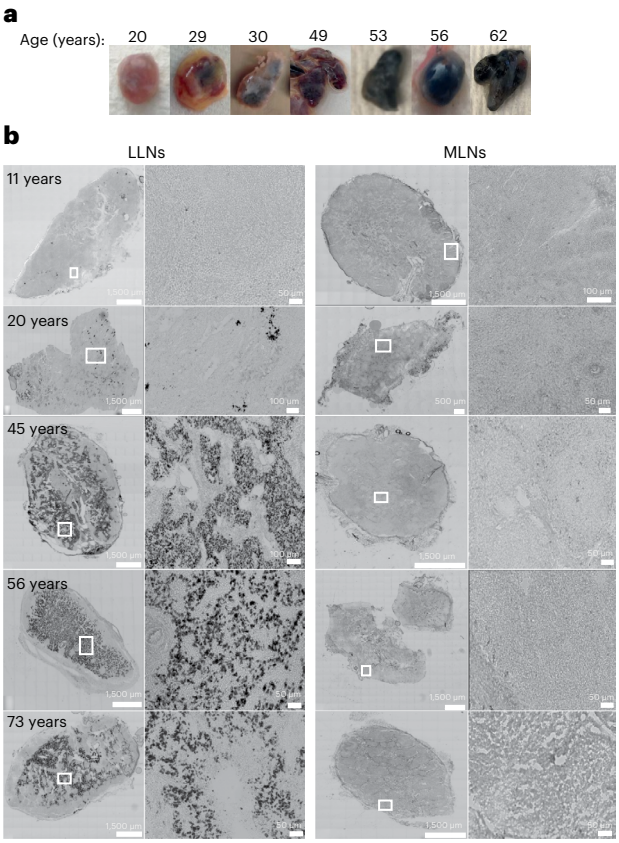

Fig. 1 | Lung-associated lymph nodes accumulate carbon particulates with age. a, Gross appearance of lung-associated LNs (LLNs) over age. **b**, Brightfield confocal images of human LLNs and mesenteric LNs (MLNs) obtained from organ donors of various ages. Images of whole LN sections were reconstructed from 70–400 individual 20X images; magnified images show areas in white boxes. Black regions show particulate contents.

BEHIND THE PAPER

In 2011, we set up a tissue resource from human organ donors, with the goal of investigating tissue-resident immune cells in mucosal sites and lymphoid organs[5]. During the course of these studies, we observed that lung-associated LNs were black in donors with no history of smoking, whereas LNs in other sites, such as those associated with the gut, exhibited a beige color that is typical of leukocytes. We investigated this phenomenon further and found that the black color was due to carbon particulates, which showed increased accumulation with age. Our ability to control for particulates, age and location through the sampling of LNs from different sites in donors of all ages enabled us to uncover a mechanism for how environmental pollutants interact with the immune system. **D.L.F.**

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FROM THE EDITOR

"This work by Ural and colleagues stood out because it examined the effects of age on human immune system function using LN samples, rather than blood samples as is common, and because it offered new insight into how environmental pollutants may alter immune activity. The results will hopefully motivate further research into how carbon emissions and other forms of pollution affect immune responses." **Editorial Team, *Nature Medicine***