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EDITORIAL

Studying smoking benefit in farmer's lung to understand Covid-19

It was observed, first in China, and then in France, that the proportion of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) patients was significantly lower in active smokers compared to the proportion of active smokers in the general population. The protection conferred by smoking for a respiratory disease has so far only been described for hypersensitivity pneumonitis (HP), especially for farmer's lung, and to a lesser degree, for bird fancier's lung. We compared the similarities and differences between farmer's lung and SARS-CoV-2 and the relationship between smoking and SARS-CoV-2 and farmer's lung.

Farmer's lung is the most common form of HP [1]. HP is characterized by a Th1 immune response, the production of immune complexes and the 'hyper production' of precipitating antibodies. Magnus was the first to suggest that smoking may confer protection against farmer's lung in the 16th century. Since then, several epidemiological studies reported that active smokers were under-represented among HP patients, from 2.2 to 12% [1–4]. The prevalence of active smokers is estimated at 28.2% in the general population and at 20.6% in farmers. There is currently a relatively high prevalence of smoking in the farmers compared to the general population. A significantly reduced antibody response was observed in active smokers with HP [2,4]. Amongst all the studies on the beneficial effect of smoking against HP, Cormier *et al.* has the largest cohort, with a 888 cases in dairy farmers [4]. They found a strong negative relationship between smoking and positive precipitins [4].

The findings strongly support the hypothesis that smoking may have a protective effect against HP. However, no likely putative immunological mechanism has been postulated for this. This may be due to a reluctance to fund studies investigating a possible protective role of smoking. Currently only epidemiological studies are available on the lower precipitin prevalence in active smokers [1–4].

Smoking has adverse effects on cardiovascular mortality and morbidity and is a category 1 IARC carcinogen [5]. Suggesting that smoking may have positive health effects is a provocative concept. However, tobacco would not be the only controversial substance studied. We sought to understand better the relationship between smoking and HP or SARS-CoV-2.

A lower prevalence of active smokers in SARS-CoV-2 patients compared to non-smokers has been reported worldwide [6,7]. First in China, then in Korea, in the USA and in France. French data from Salpétrière University Hospital of Paris reported that out of 480 SARS-CoV-2 patients, only 5% were current smokers. There were ~80% fewer active smokers in SARS-CoV-2 patients than in the general population after adjusting for age and sex (unpublished data by Pr. Zahir Amoura on Cnews). At Besançon University Hospital (Eastern France), since mid-March 2020, out of 130 ICU patients with SARS-CoV-2 only 4% were active smokers (unpublished personal data). The under-representation of active smokers in SARS-CoV-2 patients suggests a protective effect of smoking, similar to that in the farmer's lung. That this finding is consistent suggests that it is not a coincidence but a specific association, whose mechanism is still unknown. One hypothesis is that smoking may reduce susceptibility to SARS-CoV-2 infection, for example by modifying the expression of receptors, such as ACE2, as proposed by Propper [6].

The Covid-19 pandemic has also highlighted other similarities between HP and SARS-CoV-2. Chen *et al.* showed that Covid-19 was characterized by a Th1-driven immune response and especially by the production of interleukin (IL)-6 [8], which is similar to the immunological mechanism of HP [1].

Other researchers found that the SARS-CoV-2 immune response could lead to the development of immune complexes [8]. As immune complexes and precipitating antibodies may be preferably produced in response to Covid-19, this may explain why the development of serological tests was difficult and why the reliability of serological tests was uncertain [9]. Several treatments commonly used to treat HP, such as rituximab and steroids (e.g. dexamethasone), were used in SARS-CoV-2 patients with encouraging results [1,10,11]. Low doses of dexamethasone had a real benefit in the management of SARS-CoV-2 patients by the Recovery study. The Recovery study included 11 500 SARS-CoV-2 patients in the UK and as early as 8 June 2020, the study investigating the effect of low doses of dexamethasone

was discontinued because evidence of efficacy was clear: one death avoided for eight patients with mechanical ventilation or for 25 patients on oxygen. These impressive results could be due to the anti-inflammatory effect of steroids limiting the 'cytokine storm' described during SARS-CoV-2 [8]. Steroids are recognized as effective for the treatment of HP, especially during the acute phase [1,10,11].

However, important differences remain: HP is a semi-delayed allergic disease without IgE, whereas SARS-CoV-2 is an infection of the pulmonary cells by a virus accompanied by an overproduction of pro-inflammatory cytokines.

As being an active smoker may protect against SARS-CoV-2, it would be useful to better understand the relationship between smoking and SARS-CoV-2. However, it is difficult to carry out *in vitro* or *in vivo* experiments for non-specialized teams (Directive 2000/54/EC-biological agents at work). In contrast, *in vitro* and *in vivo* experiments with fungi or bacteria involved in farmer's lung are accessible to all research teams.

Two experimental designs may be helpful. *In vivo* assays on mice, which would allow investigation of the modulation of the immune response due to tobacco smoke after chronic exposure; or *in vitro* assays on cells from healthy donors, which would allow investigation of the early impact of tobacco smoke.

Working on cellular models (epithelial cells, dendritic cells) exposed to mould, actinomyces and mycobacteria involved in HP was previously performed successfully. Similar assays could be developed to investigate if smoking decreases the early inflammatory response.

We chose to highlight the most obvious similarities between SARS-CoV-2 and farmer's lung but there are probably others, especially concerning the hyperactive immune response described as 'cytokine storm'. The lack of knowledge about the mode of action of smoking in farmer's lung disease limits comparisons with SARS-CoV-2 and more research is required.

Once the mechanisms are understood, this could increase the therapeutic options for HP and prevent job loss which often remains the only way to alleviate symptoms and prevent worsening of the disease. Future research should include funding for studies on smoking and the development of HP and SARS-CoV-2.

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References

1. Soumagne T, Chardon ML, Dournes G *et al*. Emphysema in active farmer's lung disease. *PLoS One* 2017;**12**:e0178263.
2. Morgan DC, Smyth JT, Lister RW, Pethybridge RJ. Chest symptoms and farmer's lung: a community survey. *Br J Ind Med* 1973;**30**:259–265.
3. Cormier Y, Bélanger J, Durand P. Factors influencing the development of serum precipitins to farmer's lung antigen in Quebec dairy farmers. *Thorax* 1985;**40**:138–142.
4. Baldwin CI, Todd A, Bourke S, Allen A, Calvert JE. Pigeon fanciers' lung: effects of smoking on serum and salivary antibody responses to pigeon antigens. *Clin Exp Immunol* 1998;**113**:166–172.
5. Corona G, Sansone A, Pallotti F, *et al*. People smoke for nicotine, but lose sexual and reproductive health for tar: a narrative review on the effect of cigarette smoking on male sexuality and reproduction. *J Endocrinol Invest* 2020. doi:10.1007/s40618-020-01257-x.
6. Propper RE. Does cigarette smoking protect against SARS-CoV-2 infection? *Nicotine Tob Res* 2020. doi:10.1093/ntr/ntaa073.
7. Farsalinos K, Barbouni A, Niaura R. Systematic review of the prevalence of current smoking among hospitalized COVID-19 patients in China: could nicotine be a therapeutic option? *Intern Emerg Med* 2020. doi:10.1007/s11739-020-02355-7.
8. Chen G, Wu D, Guo W *et al*. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020;**130**:2620–2629.
9. Theel ES, Slev P, Wheeler S, Couturier MR, Wong SJ, Kadkhoda K. The role of antibody testing for SARS-CoV-2: is there one? *J Clin Microbiol* 2020. doi:10.1128/JCM.00797-20.
10. Tamm AM, Kremens K. Rituximab for salvage therapy of refractory hypersensitivity pneumonitis. *WMJ* 2019;**118**:95–97.
11. Guilpain P, Le Bihan C, Foulongne V *et al*. Rituximab for granulomatosis with polyangiitis in the pandemic of Covid-19: lessons from a case with severe pneumonia. *Ann Rheum Dis* 2020. doi:10.1136/annrheumdis-2020-217549.