Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the current COVID-19 disease pandemic. In some patients, the symptoms are mild, and a fraction of SARS-CoV-2-infected individuals develop severe illness with a high fatality rate due to lung damage and acute respiratory distress syndrome.\(^1\)

Innate lymphoid cells (ILCs) are a recently identified type of effector immune cells that rapidly sense environmental stimuli and participate in early immune responses by promptly secreting large amounts of cytokines.\(^2\) The ILC2 subpopulation was shown to mediate Type 2 responses and to recruit eosinophils upon the release of alarmins (e.g., IL-33) by damaged epithelial cells\(^3\,\,^4\). ILC2s were also shown to participate in the termination of inflammatory responses and tissue repair by amphiregulin secretion. In addition, ILC2s are critical in the early phases of allergic lung inflammation, including that induced by the protease allergen papain.\(^5\) Based on the essential function of the papain-like protease PLpro in regulating SARS-CoV-2\(^7\) (Fig. 1a), we hypothesized a similar mechanism for PLpro and papain is known to act by stimulating epithelial cells to secrete IL-5 and IL-13.\(^6\) The ILC2 subpopulation was shown to drive alarmin secretion (Fig. 1b). Next, by performing multi-parametric flow cytometry-based immune monitoring of circulating ILCs, defined as Lin\(^-\)CD127\(^+\) cells, we detected a reduction in ILCs in severely ill patients, with a significant relative increase in the ILC2 subpopulation but no significant changes in other subpopulations (Fig. 1b). The proportions of cKit\(^{\text{high}}\) and cKit\(^{\text{dim}}\) ILC2s were comparable between HDs and mild COVID-19 patients. However, the cKit\(^{\text{dim}}\) subset was expanded in severe patients, which was compatible with an increase in fully mature ILC2s. Furthermore, we observed overall low but elevated levels of the Type 2 cytokines IL-5 and IL-13 in patients compared to those in HDs (Fig. 1b), while Type 1 and Type 17 cytokine levels were comparable across cohorts (data not shown). In line with the current literature, IL-6 levels were also increased in severe COVID-19 patients.

Upon activation, ILC2s modulate their phenotype by up/downregulating cell surface proteins. Therefore, we screened the expression of activating and inhibitory receptors on ILC2s in mild and severe patients. The ILC2s in severe patients showed an increase in the NKG2D\(^+\) population compared to those in mild patients and controls and a significant decrease in CD25 and KLRG1 (Fig. 1c). No differences in NKG2D, KLRG1, or CD25 expression were observed in ILC1s or ILCPs in patients (data not shown). The levels of other markers, such as PD-1, NKG2A, and Nkp46, were similar on ILC2s from HDs and patients.

Of note, NKG2D, which is the activating C-type lectin-like molecule abundantly expressed by cytotoxic NK cells, has not been previously reported on ILC2s. However, its expression is known to be induced in NK cells by IL-33 and other members of the IL-1 family of cytokines, such as IL-18. Notably, serum IL-18 levels were significantly higher in severe COVID-19 patients than in patients with mild illness and HDs (Fig. 1d). Furthermore, ILC2s were previously reported to express IL-18R in the skin, lung and bone marrow\(^10\) and to react to IL-18 produced by Type 2 cytokine secretion. To verify whether NKG2D expression in ILC2s can be induced by elevations of the IL-33 or IL-18 concentrations in COVID-19 patients (Fig. 1b, d), we stimulated HD peripheral blood mononuclear cells (PBMCs) in vitro with recombinant human (rh) IL-33 or rhIL-18 alone or in combination for 48 h and monitored the ILC2 phenotype. We observed an increase in NKG2D expression in ILC2s exposed to IL-18 (Fig. 1d) but not in ILC2s exposed to IL-33, suggesting a direct link between IL-18 and NKG2D\(^+\) ILC2s in severe COVID-19 patients. To explore the potential clinical relevance of NKG2D\(^+\) ILC2s in anti-COVID-19 immune responses, we stratified patients based on the median expression of NKG2D on ILC2s (Fig. 1e). We observed a significantly reduced effect in patients with high NKG2D expression compared to those with low expression. This suggests that NKG2D may have a role in the evasion of the adaptive immune response by SARS-CoV-2.

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Received: 2 November 2020 Accepted: 12 November 2020
Published online: 14 December 2020
proportion of patients requiring mechanical ventilation in the severe group with high numbers of NKG2D$^+$ ILC2s, indicating the protective role of this cell subset in the response against the virus. In line with this finding, the hospitalization length was drastically reduced in these patients (Fig. 1e).

Overall, our study shows an increase in ILC2s in COVID-19 patients in parallel with elevated serum Type 2 cytokine levels. These anti-inflammatory mediators might be produced particularly by NKG2D$^+$ ILC2s upon engagement of the NKG2D receptor with its ligands, which are known to be upregulated on infected cells in the context of viral diseases.

**ACKNOWLEDGEMENTS**

We are grateful to the patients for their dedicated collaboration and to the healthy donors for their blood donation. The Jandus laboratory at the University of Geneva is supported by the Swiss National Science Foundation (PRIMA PR00P3_179727), the Swiss Cancer League (KFS-4402-02-2018), the Fondazione San Salvatore and the Helmut Horten Foundation. The UMR1098 RIGHT Laboratory is supported by the Etablissement Français du Sang Bourgogne Franche-Comté, University of Bourgogne Franche-Comté, INSERM and the University Hospital of Besançon.

**AUTHOR CONTRIBUTIONS**

A.G.-C. and L.S. conducted experiments and carried out data analysis; R.L. and C.J. initiated and designed the research; R.L., C.J., A.G.-C., L.S., M.K., M.B.K., K.B., G.V., S.T., and C.B. discussed the results and wrote and/or reviewed the manuscript.

**FUNDING**

Open Access funding provided by University of Geneva.

**ADDITIONAL INFORMATION**

The online version of this article (https://doi.org/10.1038/s41423-020-00596-2) contains supplementary material.

**Competing interests:** The authors declare no competing interests.

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