

Correspondence

Polyfunctionality of *bona fide* resident lung CD69⁺ natural killer cells

To the Editor:

We read with great interest the recent article from Marquardt et al.¹ dedicated to the detailed characterization of human lung natural killer (NK) cells. On the basis of the expression of CD69, they nicely distinguished *bona fide* resident CD69⁺ from circulating CD69[−] CD56^{dim} NK cells in a large cohort of patients undergoing pulmonary lobectomy. They have shown that NK cells in the lung are highly differentiated and predominantly circulating ones, which contrasts with lung CD3⁺ T cells.

Although we do appreciate their comprehensive work, we would like to express 2 comments and queries.

In accordance with some of our previous works, the authors reported that NK cells were hypofunctional:

- In patients with lung carcinoma, we analyzed the phenotype and functions of lung NK cells and observed that the intratumoral NK cells were significantly hypofunctional and more commonly CD69 positive as compared with other NK cell populations.² In light with Marquardt et al.,¹ we could then suggest that most of these intratumoral NK cells are resident.
- In patients with antisynthetase syndrome (aSS)—a rare autoimmune connective tissue disease characterized with interstitial lung disease (ILD) in the foreground³—peripheral blood NK cells are highly differentiated and hypofunctional as well, irrespective of the IL-15 serum titers.^{4,5} Immunohistological studies in the lungs showed a massive infiltration of NK cells.⁴ In addition, we recently observed in a 39-year-old woman with active aSS that the proportion of CD69⁺ CD3[−] CD56⁺ NK cells was higher in bronchoalveolar lavage as compared with blood (37% vs 16%, respectively). In respect with Marquardt et al.,¹ this would suggest that NK cell infiltration in aSS-related-ILD mainly consists of resident NK cells.

We thus regret that the authors studied lung NK cell functions as a whole, regardless of their status of circulating or resident lung NK cells. We would be very interesting in knowing whether the authors showed any differences in polyfunction assays, according to the CD69 expression of the lung NK cells. Furthermore, hypofunctionality of lung NK cells was determined after *in vitro*

stimulation with nonspecific stimuli, including K562 target cells and phorbol 12-myristate 13-acetate and ionomycin or IFN- α . We think it would be of interest to evaluate the proliferation and polyfunctional capacities of both CD69[−] and CD69⁺ lung NK cells, following IL-15 stimulation. Indeed, IL-15 is locally produced within the lung^{1,6} and involved in NK cell regulation (differentiation and functionality).⁷

We think that such complementary results might expand our knowledge about the distinct role of circulating and resident lung NK cells. Furthermore, these comprehensive data might help in understanding the involvement of NK cells in different diseases commonly affecting the lung, including cancer and ILD, and thus could lead to the development of new lung-targeted therapeutic strategies.⁷

Baptiste Hervier, MD, PhD^{a,b}

Isabelle Cremer, PhD^c

Vincent Vieillard, PhD^a

From ^aSorbonne Universités, Centre d'Immunologie et des Maladies Infectieuses (CIMI-Paris), Paris, France; ^bAP-HP, Hôpital Pitié-Salpêtrière, Département de Médecine Interne et Immunologie Clinique, Centre National de Référence des Maladies Musculaires, Paris, France; and ^cUniversité Paris Descartes-Paris 5, Centre de Recherche des Cordeliers, Paris, France. E-mail: baptiste.hervier@psl.aphp.fr.

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REFERENCES

1. Marquardt N, Kekäläinen E, Chen P, Kvedaraitė E, Wilson JN, Ivarsson MA, et al. Human lung natural killer cells are predominantly comprised of highly differentiated hypofunctional CD69[−]CD56^{dim} cells. *J Allergy Clin Immunol* 2017;139:1321-30.e4.
2. Platonova S, Cherfils-Vicini J, Damotte D, Crozet L, Vieillard V, Validire P, et al. Profound coordinated alterations of intratumoral NK cell phenotype and function in lung carcinoma. *Cancer Res* 2011;71:5412-22.
3. Hervier B, Benveniste O. Clinical heterogeneity and outcomes of antisynthetase syndrome. *Curr Rheumatol Rep* 2013;15:349.
4. Hervier B, Perez M, Allenbach Y, Devilliers H, Cohen F, Uzunhan Y, et al. Involvement of NK cells and Nkp30 pathway in antisynthetase syndrome. *J Immunol* 2016;197:1621-30.
5. Collison J. Inflammatory myopathies: NK cell function linked to antisynthetase syndrome. *Nat Rev Rheumatol* 2016;12:562.
6. Muros S, Taha R, Tscopoulos A, Olivenstein R, Tonnel AB, Christodoulou P, et al. Expression of IL-15 in inflammatory pulmonary diseases. *J Allergy Clin Immunol* 2001;108:970-5.
7. Patidar M, Yadav N, Dalai SK. Interleukin 15: a key cytokine for immunotherapy. *Cytokine Growth Factor Rev* 2016;31:49-59.

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