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Spotlight

CD8$^+$ T cells: An ineffective armor against prolonged COVID-19 in cancer patients

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In a diverse cohort of cancer patients, Lyudovyk et al.[1] show that persistent COVID-19 infection is associated with weaker humoral responses and increased CD8$^+$ T cell responses that are ineffective in clearing virus, particularly in patients receiving B cell-depleting therapies.

Patients with cancer, especially those with hematologic malignancies, are at a higher risk of severe infection and death associated with COVID-19.[2–4] Prior reports suggest that adverse outcomes are not limited only to the acute phase of the infection: in some cases, they can be attributed to prolonged SARS-CoV-2 infection and compromised viral clearance, resulting in additional episodes of symptomatic decompensation or interruption of cancer treatment. This has been reported to be particularly common in cancer patients receiving B cell-depleting therapy, a mainstay of treatment in lymphoid malignancies.[5,6]

In a cohort of hospitalized patients with COVID-19 infection, Bange et al. previously reported that cytotoxic CD8$^+$ T cell responses play a critical role to control the acute-phase disease, particularly in patients with impaired B cell function.[7] Patients with depleted T cell responses had the highest mortality. However, how the immune dysfunction in cancer patients (intrinsic to the disease itself as well as due to immunosuppressive treatments) impacts viral clearance and long-term immune responses to SARS-CoV-2 in this vulnerable population is not fully understood.

To characterize the factors impacting immune recovery from COVID-19, Lyudovyk et al. performed a multimodal analysis on blood samples collected longitudinally in a mixed cohort of more than 100 solid-tumor and heme-malignancy patients who developed COVID-19 and recovered clinically.[1] Prolonged SARS-CoV-2 positivity (i.e., a positive SARS-CoV-2 PCR test $\geq$30 days after the initial positive test) was observed in 22% of patients overall but was significantly more common in the patients with hematologic malignancies. The clinical relevance of persistent PCR positivity is highlighted by the fact that 18% of patients who initially were considered convalescent subsequently required re-hospitalization, and that 8% of patients ultimately died of COVID-19.

Serologic analyses of antibody levels against the SARS-CoV-2 nucleocapsid and spike proteins demonstrated that patients with hematologic malignancies have lower peak antibody levels and a more transient serological response, consistent with prior reports. B cell-depleting therapy and a low (nucleocapsid) antibody level were significantly associated with prolonged viremia. Interestingly, viral persistence was not associated with a specific B cell phenotype or total B cell count determined through flow cytometry. Furthermore, solid-tumor patients with low circulating B cell counts were generally able to mount a robust IgG response. Together, these findings support the notion that an intact humoral immune response, i.e., the production of sufficient levels of high-quality antibodies, is critical for efficient and expedient viral clearance.

How, then, do patients with an impaired humoral response clear the virus (or why do some fail to do so)? The authors performed an unsupervised, high-dimensional analysis of blood lymphocytes to characterize the cellular immune response and identify four major subgroups based on immune cell phenotype. They complement this with functional studies and T cell receptor (TCR) sequencing to better understand the quality of the cellular immune response in these groups.

Remarkably, persistent SARS-CoV-2 positivity was observed most frequently in the group of patients with B cell depletion and a CD8-dominant T cell response (Figure 1). These CD8$^+$ cytotoxic T cells were associated with an increased effector differentiation phenotype, with a persistent cytokine response to SARS-CoV-2 peptide stimulation but with limited memory characteristics. TCR sequencing in these patients showed a broad SARS-CoV-2-specific CD8$^+$ T cell repertoire with minimal convergence over time. Interestingly, patients who maintained functional CD4$^+$ T cell responses (as shown by cytokine analysis and TCR sequencing), even in the presence of B cell depletion, retained the ability to clear the virus and avoid persistent PCR positivity. Together, these data support the conclusion that, in absence of humoral control, a vigorous and long-lasting antigen-specific CD8$^+$ T cell response alone is insufficient for viral clearance.

The work by Lyudovyk et al. has several strong points that help us understand the mechanisms driving persistent COVID-19 infection in cancer patients, including longitudinal sampling and analysis of the immune response comprehensively, i.e., taking both humoral and T cell response into consideration. This valuable effort is

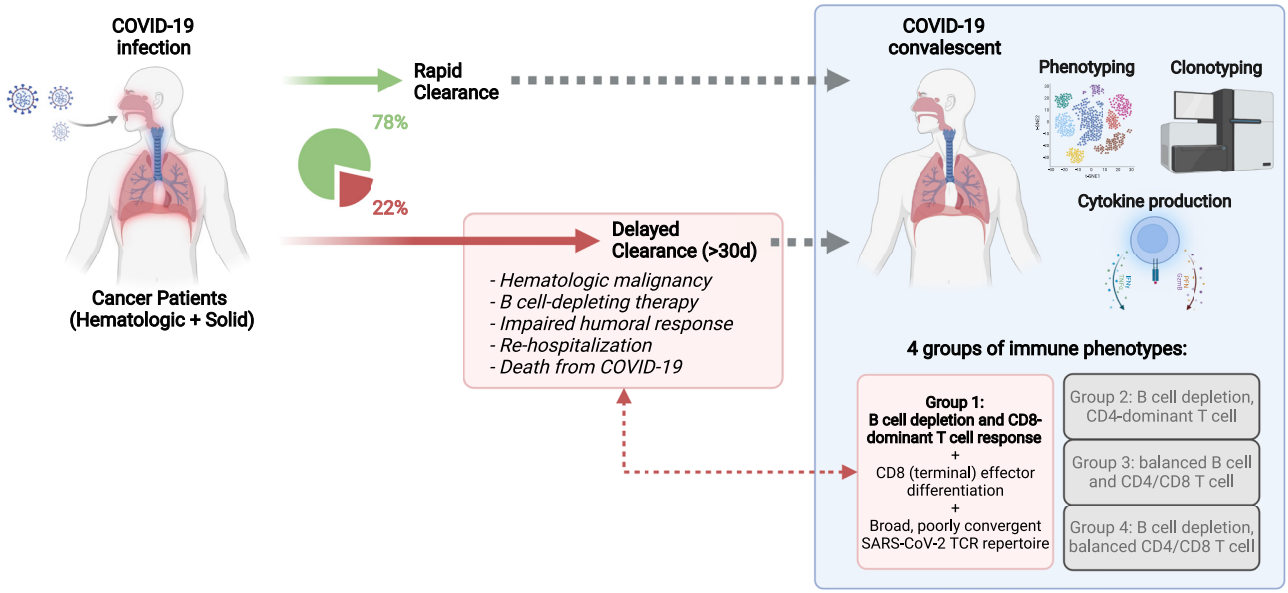

Figure 1. B cell depletion with a CD8-dominant T cell response is associated with delayed clearance of SARS-CoV-2 in cancer patients

complemented with unbiased phenotypic analysis, functional data, and T cell clonality, which enrichen our understanding of the quality of the observed immune phenotypes.

Some important questions and areas of further research remain outstanding. The study does not address why and how the $CD8^+$ T cells become dysfunctional (i.e., unable to achieve clearance) and why a $CD4^+$ T cell response is absent in these patients. Furthermore, prior results have suggested a critical role for $CD8^+$ T cell responses during the acute phase of COVID-19, with patients' lack of $CD8^+$ T cell response as an indicator of poor prognosis.[7] It now appears that different arms of an adaptive immune response might be responsible for acute control versus long-term clearance.

These findings highlight the coordinated role of various immune cell populations in the response to COVID-19. The findings are timely, especially in the context of novel viral variants that have shown an increased tendency to escape antibody-mediated neutralization.[8] It will be important to understand how these findings translate to vaccine-induced immune responses. The lack of antigen persistence in this context might explain different effects observed between natural SARS-CoV-2 infection and vaccination. SARS-CoV-2 vaccines appear to elicit durable B and $CD4^+$ T cell responses, with $CD8^+$ T cell responses being more transient and variable.[9,10] Studies in that context, particularly with boosters and new variants, would be useful to follow up these results.

Understanding the role of a coordinated immune response to a respiratory pathogen in cancer patients with varying degrees of immune dysregulation has important implications beyond the ongoing COVID-19 pandemic. In this context, it would be interesting to confirm the findings in other (respiratory) viral infections that can cause severe illness in cancer patients. Similar mechanistic studies would be valuable in specific immunocompromised cancer populations (e.g., multiple myeloma) and non-cancer patients (e.g., organ transplant and multiple sclerosis) that face similar challenges with prolonged COVID-19 infection.

DECLARATION OF INTERESTS

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REFERENCES

1. Lyudovyk, O., Kim, J.Y., Qualls, D., Hwee, M.A., Lin, Y.-H., Boutemine, S.R., Elhanati, Y., Solovyov, A., Douglas, M., Chen, E., et al. Impaired humoral immunity is associated with prolonged COVID-19 despite robust CD8 T-cell responses. Cancer Cell 10.1016/j.ccell.2022.05.013.
2. Dai, M., Liu, D., Liu, M., Zhou, F., Li, G., Chen, Z., Zhang, Z., You, H., Wu, M., Zheng, Q., et al. (2020). Patients with cancer appear more vulnerable to SARS-COV-2: a Multicenter study during the COVID-19 Outbreak. Cancer Discov. https://doi.org/10.1158/2159–8290CD-20-0422
3. Wang, B., Van Oekelen, O., Mouhieddine, T.H., Del Valle, D.M., Richter, J., Cho, H.J., Richard, S., Chari, A., Gnjatic, S., Merad, M., et al. (2020). A tertiary center experience of multiple myeloma patients with COVID-19: lessons learned and the path forward. J. Hematol. Oncol. *13*, 94. https://doi.org/10.1186/s13045-020-00934-x.
4. Robilotti, E.V., Babady, N.E., Mead, P.A., Rolling, T., Perez-Johnston, R., Bernardes, M., Bogler, Y., Caldararo, M., Figueroa, C.J., Glickman, M.S., et al. (2020). Determinants of COVID-19 disease severity in patients with cancer. Nature Medicine. https://doi.org/10.1038/s41591-020-0979-0.
5. Arcani, R., Colle, J., Cauchois, R., Koubi, M., Jarrot, P.-A., Jean, R., Boyer, A., Lachamp, J., Tichadou, A., Couderc, A.-L., et al. (2021). Clinical characteristics and outcomes of patients with haematologic malignancies and COVID-19 suggest that prolonged SARS-CoV-2 carriage is an important issue. Ann. Hematol. *100*, 2799–2803. https://doi.org/10.1007/s00277-021-04656-z.
6. Lee, C.Y., Shah, M.K., Hoyos, D., Solovyov, A., Douglas, M., Taur, Y., Maslak, P., Babady, N.E., Greenbaum, B., Kamboj, M., and Vardhana, S.A. (2022). Prolonged SARS-CoV-2

infection in patients with lymphoid malignancies. Cancer Discov. *12*, 62–73. https://doi.org/10.1158/2159-8290.cd-21-1033.

7. Bange, E.M., Han, N.A., Wileyto, P., Kim, J.Y., Gouma, S., Robinson, J., Greenplate, A.R., Hwee, M.A., Porterfield, F., Owoyemi, O., et al. (2021). CD8+ T cells contribute to survival in patients with COVID-19 and hematologic cancer. Nature Medicine. https://doi.org/10.1038/s41591-021-01386-7.
8. Aleman, A., Van Oekelen, O., Upadhyaya, B., Beach, K., Kogan Zajdman, A., Alshammary, H., Serebryakova, K., Agte, S., Kappes, K., Gleason, C.R., Srivastava, K., PVI/MM/Seronet Study Group, Almo, S., Cordon-Cardo, C., Krammer, F., Merad, M., Jagannath, S., Wajnberg, A., Simon, V., and Parekh, S. (2022). Augmentation of humoral and cellular immune responses after third-dose SARS-CoV-2 vaccination and viral neutralization in myeloma patients. Cancer Cell *40*, 441–443. https://doi.org/10.1016/j.ccell.2022.03.013.
9. Goel, R.R., Painter, M.M., Apostolidis, S.A., Mathew, D., Meng, W., Rosenfeld, A.M., Lundgreen, K.A., Reynaldi, A., Khoury, D.S., Pattekar, A., et al. (2021). mRNA vaccines induce durable immune memory to SARS-CoV-2 and variants of concern. Science *374*, abm0829. https://doi.org/10.1126/science.abm0829.
10. Painter, M.M., Mathew, D., Goel, R.R., Apostolidis, S.A., Pattekar, A., Kuthuru, O., Baxter, A.E., Herati, R.S., Oldridge, D.A., Gouma, S., et al. (2021). Rapid induction of antigen-specific $CD4^+$ T cells is associated with coordinated humoral and cellular immunity to SARS-CoV-2 mRNA vaccination. Immunity *54*, 2133–2142.e3. https://doi.org/10.1016/j.immuni.2021.08.001.