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Unexpected tumor reduction in metastatic colorectal cancer patients during SARS-Cov-2 infection: effect of ACE-2 expression on tumor cells or molecular mimicry phenomena? Two not mutually exclusive hypotheses

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Dear Editor,

We read with great interest the recent paper by Ottaiano *et al.*[1] about unexpected tumor reduction in metastatic colorectal cancer patients following SARS-CoV-2 infection published in this journal. The authors describe three patients that underwent a significant reduction of the disease after mild to severely symptomatic COVID-19.

The authors hypothesize that this reduction might be due to the direct viral infection of tumor cells *via* the ACE-2 receptor (the cell's gateway for the virus) because this receptor is expressed by a variety of human cytotypes, including colorectal ones. In turn, the entrance of the virus into the tumor cells would trigger an immune response against them.

This is a fascinating hypothesis that prompted us to propose another, different but not exclusive, which we recently published in another journal.[2] We propose to consider a role for molecular mimicry, namely viral proteins mimic human molecules (e.g., molecular chaperones/heat shock proteins or Hsps) and, thus, elicit immunity not only against themselves but also against the human proteins expressed on the tumor cells. This would be a case of autoimmunity caused by foreign antigens against crossreactive epitopes on host's cells.

SARS-CoV-2 may elicit autoimmunity in the host because of molecular mimicry of human proteins that share immunogenic epitopes with viral proteins. Among the human molecules that share epitopes with viral molecules are the chaperones Hsp60, Hsp70, and Hsp90.[3] These chaperones are typically increased in colorectal cancer tissue, in which they are distributed with a pattern different from that characterizing normal cell counterparts, being also on the plasma-cell membrane and accessible to the immune system and, thus, can be targets for immunotherapy.[4–6]

We would like to prompt clinical studies to test the hypothesis that the disease reduction in patients affected by colorectal cancer is caused by an immune reaction against chaperones/Hsps initiated by SARS-CoV-2 infection through molecular mimicry. For example, serum from cancer patients ought to be examined to determine whether the levels of antibodies against chaperones/Hsps are different from those of proper controls and if they are cytotoxic/cytolytic for cancer cells. Other assays are possible, involving cells of the immune system and appropriate targets. Confirmation of this hypothesis would probably

boost efforts to develop efficacious immunotherapy of cancer,[2] in Coley's[7] footsteps of many years ago.[8]

Conflict of interest statement

The authors declare that there is no conflict of interest.

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References

1. Ottaiano A, Scala S, D'Alterio C, *et al.* Unexpected tumor reduction in metastatic colorectal cancer patients during SARS-Cov-2 infection. *Ther J Med Oncol* 2021; 13: 17588359211011455.

2. Burgio S, De Macario EC, Macario AJ, *et al*. SARS-CoV-2 in patients with cancer: possible role of mimicry of human molecules by viral proteins and the resulting anti-cancer immunity. *Cell Stress Chaperones*. Epub ahead of print 11 May 2021. DOI: 10.1007/s12192-021-01211-7.

3. Gammazza AM, Légaré S, Bosco GL, *et al.* Human molecular chaperones share with SARS-CoV-2 antigenic epitopes potentially capable of eliciting autoimmunity against endothelial cells: possible role of molecular mimicry in COVID-19. *Cell Stress Chaperones* 2020; 25: 737–741.

4. Campanella C, Rappa F, Sciumè C, *et al*. Heat shock protein 60 levels in tissue and circulating exosomes in human large bowel cancer before and after ablative surgery. *Cancer* 2015; 121: 3230–3239.

5. Gastpar R, Gehrmann M, Bausero MA, *et al*. Heat shock protein 70 surface-positive tumor exosomes stimulate migratory and cytolytic activity of natural killer cells. *Cancer Res* 2005; 65: 5238–5247.

6. Milicevic Z, Bogojevic D, Mihailovic M, *et al*. Molecular characterization of hsp90 isoforms in colorectal cancer cells and its association with tumour progression. *Int J Oncol* 2008; 32: 1169–1178.

7. Coley WB. The treatment of malignant tumors by repeated inoculations of erysipelas. With a report of ten original cases. 1893. *Clin Orthop Relat Res* 1991; 262: 3–11.s

8. McCarthy EF. The toxins of William B. Coley and the treatment of bone and soft-tissue sarcomas. *Iowa Orthop J* 2006; 26: 154–158.