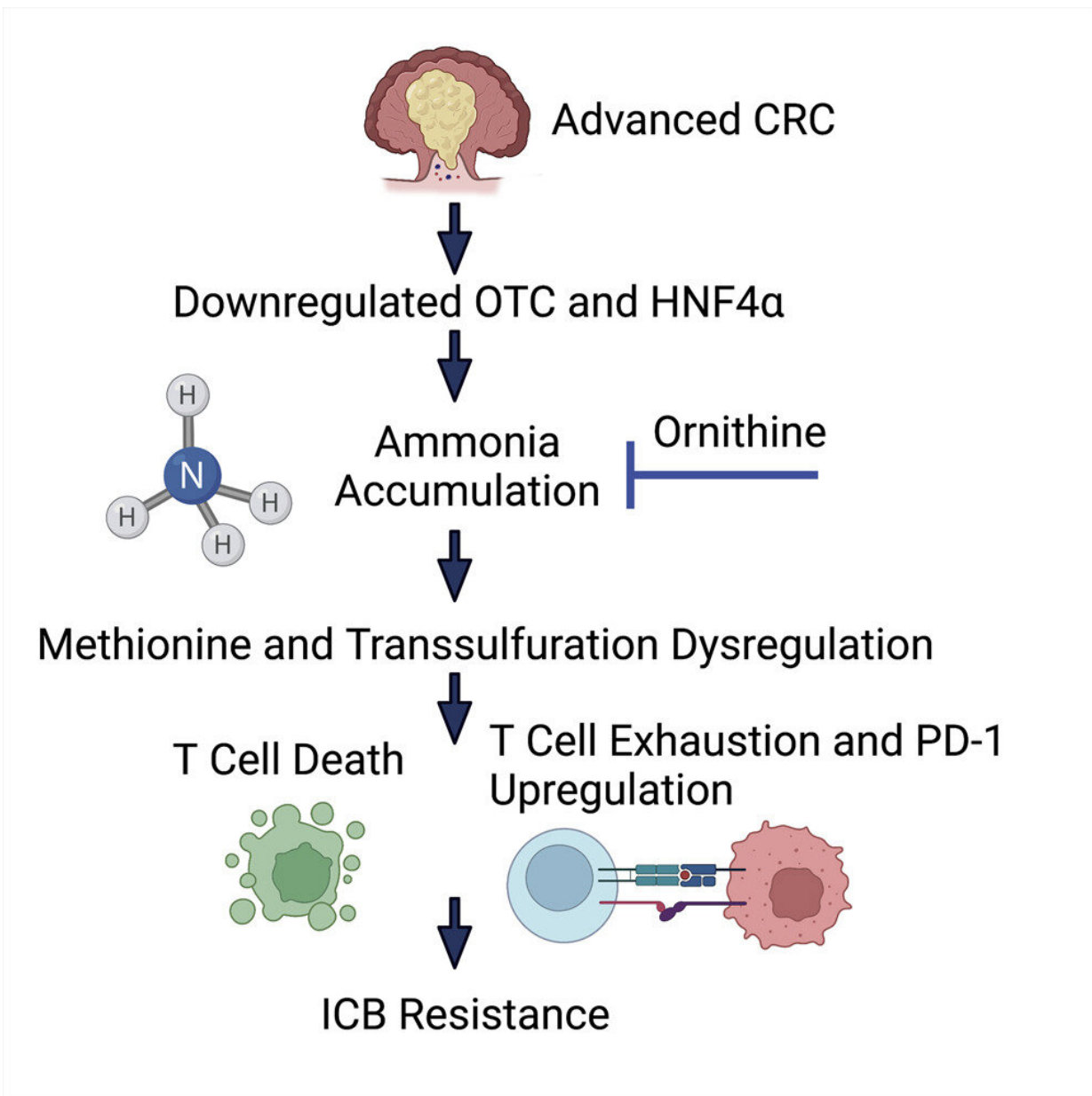


Tumor ammonia levels inhibit T cell growth, impact immunotherapy: Study

December 23 2022, by Anna Megdell



Graphical abstract. Credit: *Journal of Clinical Investigation* (2021). DOI: 10.1172/JCI143691

High levels of ammonia in tumors leads to fewer T cells and immunotherapy resistance in mouse models of colorectal cancer, new findings from the University of Michigan Rogel Cancer Center revealed. Researchers found that ammonia inhibits the growth and function of T cells, which are vital for anti-tumor immunity. The findings appear in *Cell Metabolism*.

"We identified the mechanism of how ammonia dysregulates T cell function and showed that reducing ammonia levels using FDA-approved drugs for hyperammonemia can reduce [tumor size](#) in several different models including [metastatic colorectal cancer](#)," says Hannah Bell, Ph.D., a postdoctoral fellow in [cancer biology](#) and author on this paper. "Use of this drug also synergizes with immunotherapy. If you treat the mice with immunotherapy when you also treat them with this ammonia reducing agent, you're able to sensitize the tumors to treatment."

"Most [colorectal cancers](#) are insensitive to immune therapies," adds Yatrik Shah, Ph.D., Horace W. Davenport Collegiate Professor of Physiology and first author of the study. "We've found that one of the mechanisms that leads to this resistance is likely the high level of ammonia that accumulates in the microenvironment."

Bell explains that while there are many factors that contribute to immunotherapy resistance, there are few therapeutic interventions that can reactivate therapy sensitivity. "Our study shows that this is a relatively safe and FDA-approved method that could work alongside immunotherapy to make treatment more effective for patients. This new method provides a potentially direct avenue to treat tumors and

reactivate the immune system."

How does ammonia accumulate in colorectal tumors in the first place? Ammonia levels are regulated by a balance of production and cellular detoxification. Most ammonia is generated by the microbiota, but Bell and Shah's work suggests that increased production of ammonia is not what results in accumulation. "Our work demonstrates that tumors have lost the ability to detoxify ammonia leading to build up," said Shah.

Further, the accumulation of [ammonia](#) is likely not isolated to just colorectal tumors. Shah says this discovery may open doors in explaining resistance to other cancer types as well. "Only about 20-30% of all [cancer patients](#) are sensitive to immunotherapy. 70% of patients don't derive any benefit from it," Shah said. "Now, we have a mechanism that could explain this resistance in tumors beyond colon cancer."

More work needs to be done before researchers can bring these findings into the clinic.

More information: Hannah N. Bell et al, Microenvironmental ammonia enhances T cell exhaustion in colorectal cancer, *Cell Metabolism* (2022). [DOI: 10.1016/j.cmet.2022.11.013](https://doi.org/10.1016/j.cmet.2022.11.013)

Provided by University of Michigan

Citation: Tumor ammonia levels inhibit T cell growth, impact immunotherapy: Study (2022, December 23) retrieved 6 May 2023 from <https://medicalxpress.com/news/2022-12-tumor-ammonia-inhibit-cell-growth.html>

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