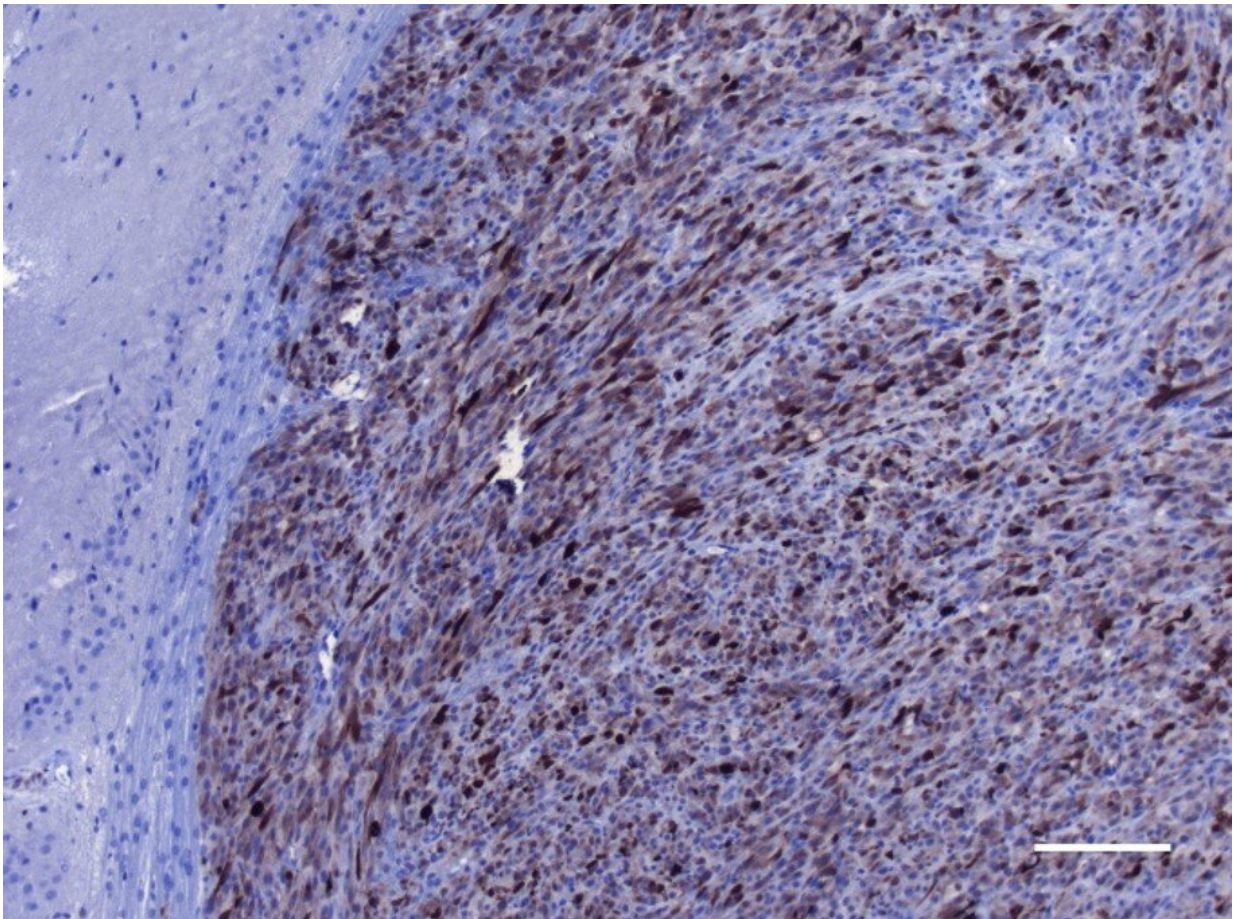


# Revising theory of cancer-induced immune suppression

September 30 2021, by Will Doss

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Glioblastoma. Brown staining indicates IDO expression. Credit: Northwestern University

Many cancers produce an enzyme called IDO that suppresses immune

system activity, but the long-held hypothesis of how this mechanism operates requires revision, according to a study published in *Clinical Cancer Research*.

In addition to engaging tryptophan metabolism, IDO enhances immunosuppressive factors of the complement [immune system](#). This finding likely explains in part why immunotherapy efforts in incurable cancers such as glioblastoma have fallen flat, according to Derek Wainwright, Ph.D., assistant professor of Neurological Surgery and senior author of the study.

"We have opened up new possibilities into understanding how IDO suppresses the anti-[cancer immune response](#) that is independent of its historical and predominant association with tryptophan metabolism," said Wainwright, who is also a professor of Medicine in the Division of Hematology and Oncology and of Microbiology-Immunology.

Many difficult-to-treat cancers, including glioblastoma, prostate cancer and pancreatic cancer, show high levels of IDO expression. The enzyme converts tryptophan, an [essential amino acid](#) that can only be absorbed through diet, into a metabolite called kynurenine. The depletion of tryptophan and the accumulation of kynurenine is the historical mechanism for how IDO suppresses the anti-tumor immune response—primarily based on studies conducted in petri dishes.

"For greater than 20 years, we have assumed this is how IDO affects the immune response," Wainwright said.

Many clinical trials using pharmacologic IDO enzyme inhibitors in combination with immunotherapy have failed to show an improvement in patient survival as compared with immunotherapy alone. This led Wainwright and his collaborators to go back to the drawing board with IDO. In the current study, investigators deleted IDO entirely in mice

with cancers similar to glioblastoma, then re-activated IDO, either with a normal form or a form where enzyme activity was nullified.

They found that IDO, regardless of its ability to metabolize tryptophan, was associated with decreased survival of experimental animals with [brain tumors](#) and enhanced immunosuppressive cell accumulation.

During their investigation of IDO in tumor cells, one particular pathway caught their attention: the complement cascade. The complement cascade is part of the basic innate immune system where hepatocytes in the liver create a complement factor that binds to invaders or inflamed tissue to help neutralize a pathogen or damaged tissue. Complement factor H (CFH), which normally acts as an inhibitor of the complement cascade to prevent over-activation of complement-mediated protection against foreign invaders, is also regulated by IDO.

CFH is a ripe target for creating new inhibitors that could be deployed alongside immunotherapy, according to Wainwright. Large chemical-genetic screens are now being deployed to identify ligands that can bind to and inhibit CFH with an effort to create a new class of drugs.

"This system is poorly studied and the association between IDO and CFH has never been discovered for any cancer prior to our study," Wainwright said.

Wainwright added that this mechanism may be present in other IDO-enriched cancers besides glioblastoma, including pancreatic and prostate cancer.

**More information:** Lijie Zhai et al, Tumor cell IDO enhances immune suppression and decreases survival independent of tryptophan metabolism in glioblastoma, *Clinical Cancer Research* (2021). [DOI: 10.1158/1078-0432.CCR-21-1392](https://doi.org/10.1158/1078-0432.CCR-21-1392)

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