# COX-2 inhibitors may reverse IDO1-mediated immunosuppression in some cancers

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In preclinical studies, tumors that consitutively expressed the protein indoleamine 2,3-dioxygenase (IDO1) responded to the cyclooxygenase-2 (COX-2) inhibitor celecoxib (Celebrex) and had improved infiltration of certain subsets of T cells, making them more likely to respond to anti-PD1 therapies.

The study is published in *Cancer Immunology Research*, a journal of the American Association for Cancer Research, by Benoit J. Van den Eynde, MD, PhD, professor at Ludwig Institute for Cancer Research at de Duve Institute and Université catholique de Louvain in Brussels, Belgium.

"A key challenge in cancer immunotherapy is to understand why some patients respond to immunotherapy but many others do not," said Van den Eynde. "If we understand why, we can then select and treat only those patients who will benefit from the treatment, but most importantly, we can devise strategies to make immunotherapy work in those who are not currently responding."

Many tumors use IDO1 as a shield to protect themselves from immune attack, explained Van den Eynde. Some of them start building and raising their shields when they are being attacked by T cells, which is called adaptive resistance. In such tumors, IDO1 expression is associated with inflammation and T-cell infiltration.

However, some tumors produce IDO1 constitutively (continuously) and have their shields ready and raised before any immune attack. Such tumors are fully protected and can prevent T-cell attack by disabling the T cells right away. "This is what we call intrinsic resistance and may explain why some tumors are 'cold,' meaning, not infiltrated by T cells," Van den Eynde said.

"We wanted to understand the molecular mechanisms that make some tumors express IDO1 constitutively," he added.

Using two human melanoma cell lines, Van den Eynde and colleagues first demonstrated that COX-2 and its product, prostaglandin E2 (PGE2), caused the constitutive expression of IDO1 by utilizing the MAPK, PKC, and PI3K cell-signaling pathways. These results held true in other human tumor cell lines as well, including lung, ovarian, and head and neck cancer cell lines. "These data provide evidence that COX-2 drives tumor-induced immunosuppression through constitutive expression of IDO1," Van den Eynde noted.

Next, they showed that immunodeficient mice reconstituted with human lymphocytes and bearing human ovarian tumor xenografts with constitutive IDO1 expression responded to celecoxib as well as the IDO1 inhibitor, epacadostat. "The outcomes we observed with COX-2 inhibitors and IDO1 inhibitors were identical, which came as a surprise," Van den Eynde said. "It is always very useful to have two compounds acting on the same pathway with two different modes of action: In case tumors start resisting one compound, they may still be sensitive to the other."

By mining the transcriptomics data of 1,041 different human tumor cell lines from the Broad Institute, the researchers found a correlation between IDO1 expression and activation of the COX-2/PGE2 axis in several cancer types, including stomach, pancreatic, liver, and lung

cancers, and sarcoma.

"Our studies provide a clear rationale to test, in the clinics, combinations of anti-PD1 immunotherapy and COX-2 inhibitors," Van den Eynde said. "This should be straightforward given the fact that both anti-PD1 and COX-2 inhibitors are already approved for clinical use in different contexts." Initial analysis by the team indicated that about 10 to 50 percent of human tumors express IDO1 constitutively, depending on tumor type.

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