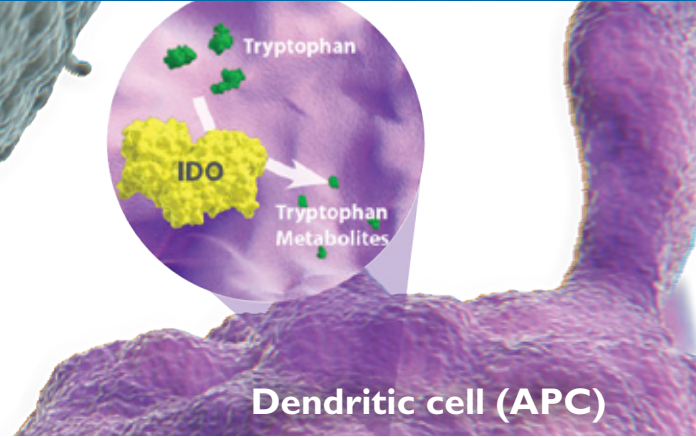


Indoleamine 2,3-dioxygenase (IDO) Immune Pathway

Inactive T cell



Dendritic cell (APC)

About IDO

Indoleamine 2,3-dioxygenase (IDO) is an intracellular enzyme that initiates the breakdown of tryptophan in the tumor microenvironment.^{1,2} Tryptophan is an essential amino acid obtained from the diet that is a fuel required by the body to build proteins needed for cellular growth as well as immune function.³



IDO and Immune Function

- IDO regulates immune function through control of tryptophan levels.
- In a healthy person, IDO ensures the immune system does not over-respond to threats.
- By reducing the level of tryptophan, IDO removes the fuel needed for immune activity and acts to suppress the immune system through two mechanisms:⁴
 - Suppression of effector T cell activity which signals to stop the immune response
 - Promotion of T regulatory cell (Treg) activity which acts to actively suppress the immune response



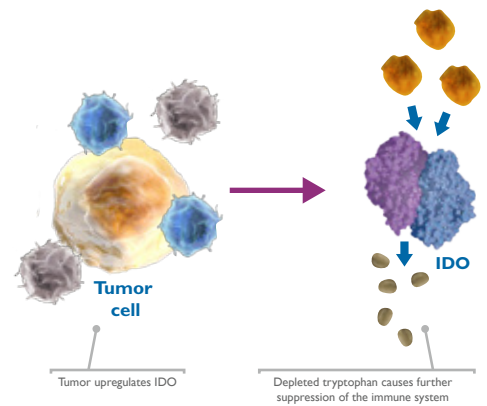
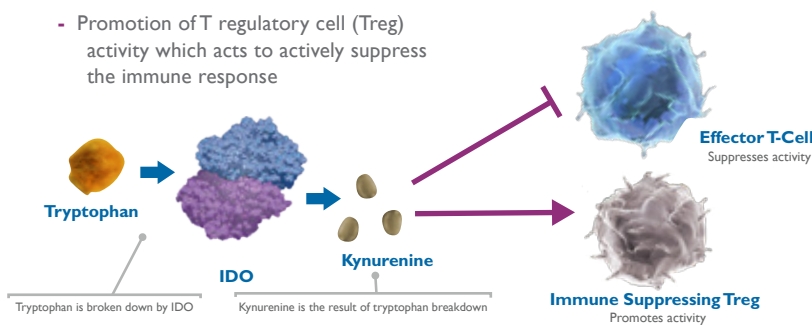
IDO and Cancer

- Tumor cells hijack this immunosuppressive process by upregulating IDO activity and depleting tryptophan in the tumor microenvironment.
- Without tryptophan to fuel the immune cells, cytotoxic T cells starve and immunosuppressive Tregs are upregulated^{5,6,7,8} leading to a failure of the immune system to respond appropriately to the cancer.⁶
- IDO expression is upregulated in several types of cancer.⁹



Clinical Implications and Interactions

- Preclinical studies suggest that targeting the IDO pathway in combination with other potentially complementary immune pathways may be a key strategy to more effectively activate the antitumor immune response.



The IDO pathway is just one of many immune pathways under investigation at Bristol-Myers Squibb. Learn more about our work in Immuno-Oncology by visiting:

<https://iopathway.web.bms.com>

¹ Mellor AL, Munn DH. Tryptophan catabolism and T-cell tolerance: immunosuppression by starvation? *Immunol Today*. 1999;20(10):469-473. ² Munn DH, Sharma MD, Lee JR, et al. Potential regulatory function of human dendritic cells expressing indoleamine 2,3-dioxygenase. *Science*. 2002;297(5588):1867-1870. ³ Richard DM, Dawes MA, Mathias CV, et al. L-Tryptophan: Basic Metabolic Functions, Behavioral Research and Therapeutic Indications. *Int J Tryptophan Res*. 2009; 2:45-60. ⁴ Johnson TS, Munn DH. Host indoleamine 2,3-dioxygenase: contribution to systemic acquired tumor tolerance. *Immunol Invest*. 2012;41(6-7):765-97. doi:10.3109/08820139.2012.689405. ⁵ Löb S, Königsrainer A, Zieker D, et al. IDO1 and IDO2 are expressed in human tumors: levo- but not dextro-1-methyl tryptophan inhibits tryptophan catabolism. *Cancer Immunol Immunother*. 2009;58(1):153-157. ⁶ Liu P, Xie BL, Cai SH, et al. Expression of indoleamine 2,3-dioxygenase in nasopharyngeal carcinoma impairs the cytolytic function of peripheral blood lymphocytes. *BMC Cancer*. 2009;9:416. doi: 10.1186/1471-2407-9-416. ⁷ Wainwright DA, Balyasnikova IV, Chang AL, et al. IDO expression in brain tumors increases the recruitment of regulatory T cells and negatively impacts survival. *Clin Cancer Res*. 2012;18(22):6110-6121. ⁸ Fallarino F, Grohmann U, You S, et al. The combined effects of tryptophan starvation and tryptophan catabolites down-regulate T cell receptor C-chain and induce a regulatory phenotype in naive T cells. *J Immunol*. 2006;176(11):6752-6761. ⁹ Uytendhoeve C, Pilotte L, Théate I, et al. Evidence for a tumoral immune resistance mechanism based on tryptophan degradation by indoleamine 2,3-dioxygenase. *Nat Med*. 2003 Oct; 9(10):1269-74.



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