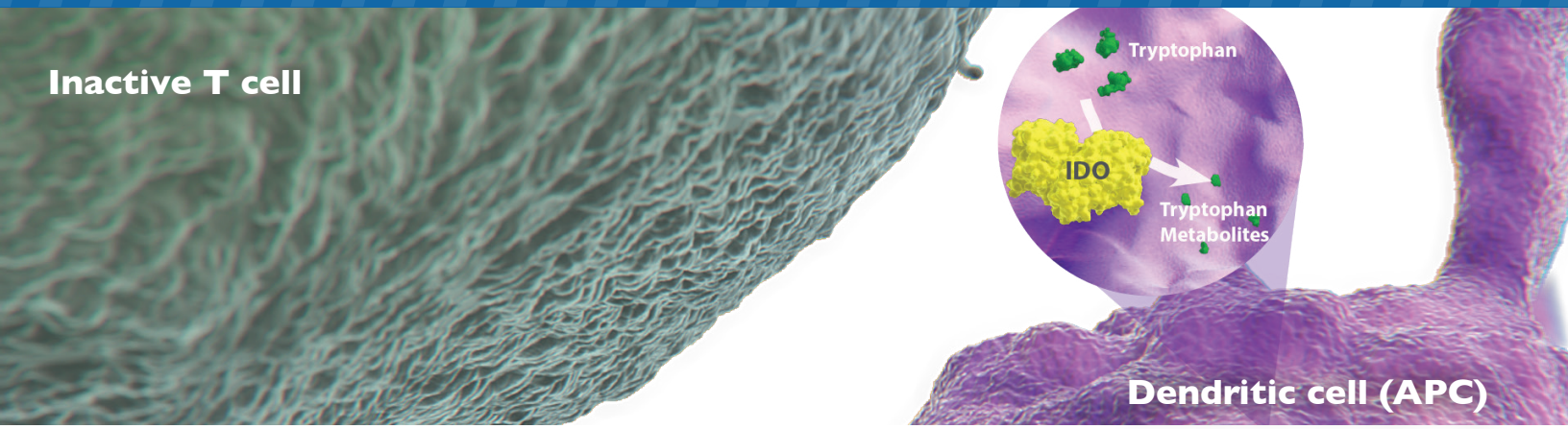
Indoleamine 2,3-dioxygenase (IDO) Immune Pathway



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

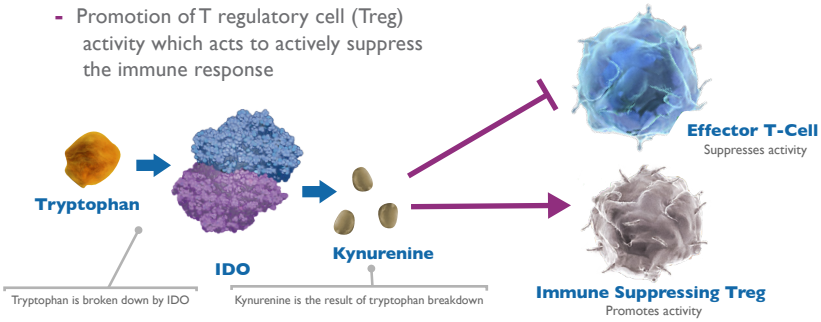
- IDO regulates immune function through control of tryptophan levels.
- In a healthy person, IDO ensures the immune system does not over-respond to threats.
- By reducing the level of tryptophan, IDO removes the fuel needed for immune activity and acts to suppress the immune system through two mechanisms:[4]
  - 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

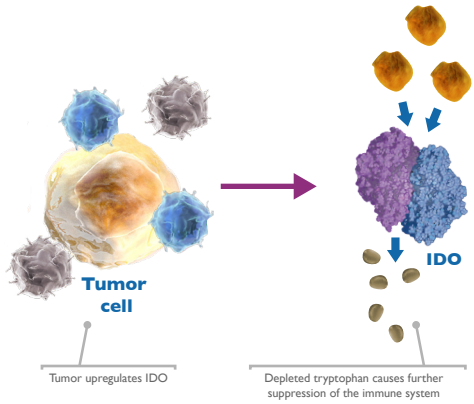
IDO and Cancer

- 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://www.bms.com/life-and-science/science/immuno-oncology-pathway.html

[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 CW, 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 ζ-chain and induce a regulatory phenotype in naive T cells. J Immunol. 2006;176(11):6752-6761. [9] Uyttenhove 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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