



# **Cancer Immunotherapy: Chapter 32. IDO in Immune Escape: Regulation and Therapeutic Inhibition**

*Alexander J. Muller, Courtney Smith, Richard Metz, George C. Prendergast*

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Indoleamine 2,3-dioxygenase (IDO) is an enzyme that degrades the essential amino acid tryptophan independent of the process that maintains normal tryptophan homeostasis. In recent years, interest in IDO and the tryptophan catabolic pathway it feeds into has grown rapidly with the discovery that IDO activity is critical for generating tolerance to foreign antigens in a variety of tissue microenvironments. In cancer, IDO is overexpressed in both tumor cells and stromal cells where it promotes the establishment of peripheral tolerance to tumor antigens. By helping tumor cells escape T-cell-dependent immune attack, IDO contributes to pathogenic inflammatory states which permit tumor survival and outgrowth. In preclinical studies, small molecule inhibitors of IDO can reverse this mechanism of immune escape. Notably, in combinatorial treatment regimens, IDO inhibition strongly leverages the efficacy of classical cancer chemotherapeutic agents, causing the regression of tumors that are otherwise largely resistant to treatment. Based on these findings, clinical evaluation of IDO inhibitors for cancer treatment is currently ongoing. After presenting a historical background on the discovery and early studies of this enzyme, this chapter focuses on work that defines IDO as an important mediator of pathogenic inflammation and cancer, and summarizes the development of IDO inhibitors as potential anticancer modalities.

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