

## **A Novel Dendritic Cell Subset that Regulates T cell Responses by Catabolizing Tryptophan**

Andrew L. Mellor, Babak Baban, Phillip R. Chandler, David J. Kahler, Anna K. Manlapat,  
Juan-Juan-Wu, Madhav D. Sharma and David H. Munn  
Immunotherapy Center, Medical College of Georgia, Augusta, Georgia, 30912, USA

The conserved intracellular heme-containing enzyme indoleamine 2,3 dioxygenase (IDO) catabolizes the first, rate-limiting step of oxidative tryptophan catabolism. Minor populations of human and murine dendritic cells (DCs) can be induced to express IDO (IDO-competent DCs), which acquire potent and dominant T cell suppressive functions as a consequence. In mouse spleen, B7 (CTLA4-Ig) and TLR9 (CpG-ODNs) ligands induce IDO expression in a novel DC subset co-expressing the B cell marker CD19 (CD11c<sup>HIGH</sup>B220<sup>+</sup>CD19<sup>+</sup>120G8<sup>NEG</sup>). A closely related IDO<sup>+</sup> DC population also accumulates in tissues associated with tumor growth. CD19<sup>+</sup> DCs comprise <10% of splenic DCs, display plasmacytoid morphology and produce interferon type 1 (IFN $\alpha$ ), which is essential to signal IDO up-regulation. However, CD19<sup>+</sup> DCs are phenotypically and functionally distinct from plasmacytoid DCs (pDCs, CD11c<sup>LOW</sup>B220<sup>+</sup>CD19<sup>NEG</sup>120G8<sup>+</sup>), which they resemble. CTLA4-Ig treatment stimulates rapid (<5 hrs) IDO transcription in DCs, and IDO enzyme activity is essential for subsequent IFN $\alpha$  production by DCs, which amplifies IDO expression at later times (>18 hrs). In contrast, TLR9 ligands (CpG-ODNs) stimulate IDO-independent IFN $\alpha$  production by CD19<sup>+</sup> DCs. Spontaneous and induced IDO activity in CD19<sup>+</sup> DCs overrides innate T cell stimulatory functions of CD19<sup>+</sup> DCs, as well as other T cell stimulatory DCs in the same cultures. In the presence of IDO<sup>+</sup> CD19<sup>+</sup> DCs, activated T cells undergo cell cycle arrest, exhibit increased apoptosis rates, and become functionally anergic in vivo. IDO activity in DCs from tumor-bearing mice activates the GCN2-kinase dependent integrated stress response (ISR) to amino acid (tryptophan) withdrawal in T cells. Increased concentrations of uncharged tRNA trigger GCN2-kinase activation that modifies ribosomal complexes containing the translation initiation factor eIF2. These signaling mechanisms in IDO-competent DCs and effector T cells constitute a versatile and potent immunoregulatory mechanism that can be manipulated to improve outcomes in a range of T cell-mediated inflammatory diseases and syndromes, including chronic infectious and autoimmune diseases, cancer and tissue transplant survival. These studies were supported by NIH grants awarded to ALM (HD41187, AI63402) and to DHM (CA103320 and CA096651).

### **Citations:**

1. Mellor, A.L., and Munn, D.H. (2004). Indoleamine 2,3 dioxygenase expression in dendritic cells: Tolerance and tryptophan catabolism. *Nature Rev. Immunology*. 4, 762-774.
2. Munn, D.H., Sharma, M.D., Baban, B., Harding, H.P., Zhang, Y., Ron, D. and Mellor, A.L. (2005). GCN2 Kinase in T Cells Mediates Proliferative Arrest and Anergy Induction in Response to Indoleamine 2,3-Dioxygenase. *Immunity*, 22: 1-10.
3. Baban, B., Hansen, A.M., Chandler, P.R., Manlapat, A., Bingaman, A, Kahler, D.J., Munn, D.H. and Mellor, A.L. (2005). A minor population of splenic dendritic cells expressing CD19 mediates IDO-dependent T cell suppression via type I IFN signaling following B7 ligation. *International Immunology*. 17: 909-19.
4. Mellor, A.L., Baban, B., Chandler, P.R., Manlapat, A., Kahler, D.J. and Munn, D.H. (2005) CpG oligonucleotides induce splenic CD19<sup>+</sup> dendritic cells to acquire potent indoleamine 2,3 dioxygenase-dependent T cell regulatory functions via interferon type 1 signaling. *J. Immunol. (Cutting Edge)*, 175: 5601-5605.