Langerhans cells (LC) are a special subset of dendritic cells integrating cutaneous immunity. The study of LC function is of major interest not only for efforts of vaccine design and immunotherapy but also for gaining an insight into the pathogenesis of immune-mediated cutaneous diseases and neoplasias. Recently, defined antigen-presenting cells were described that express indoleamine 2,3-dioxygenase (IDO) and inhibit T cell proliferation in vitro and in vivo. Here, we show that stimulation with interferon-gamma (IFN-gamma) induces the expression of functionally active IDO in highly purified human epidermal LC. The induction of IDO after stimulation of LC with IFN-gamma seems to follow a defined kinetic with rapid upregulation followed by a downregulation after about 24 h of culture. Accordingly, proliferation of T cells induced by anti-CD3 antibodies was modulated by supernatants of IFN-gamma-activated human epidermal LC. Importantly, downregulation of T cell proliferation by supernatants of 24 h IFN-gamma-activated LC was prevented by inhibition of IDO. These results indicate that LC not only have the capacity to stimulate but also to inhibit T cells, and suggest that LC possess an immunoregulatory function in promoting T cell tolerance by production of IDO.