IDO inhibits T-cell function through suppressing Vav1 expression and activation

Xiubao Ren

Department of Immunology, Tianjin Medical University Cancer Institute and Hospital, China

Introduction:
The tumor microenvironment plays a key role in regulating malignant development. Immune cells serve as important regulators in the microenvironment, which lead to both preventing and enhancing tumor growth. Recent studies have revealed that immune escape serves as a fundamental trait of cancer. Immune escape which represents the defeat of immune surveillance is a critical pathway to malignance. Therefore, studies focusing on mechanisms and regulation of immune escape may provide insights into potential cancer therapy.

Purpose:
Indoleamine 2,3-dioxygenase (IDO), a tryptophan catabolic enzyme, plays an important role in immune escape through suppressing T-cell function. Since Vav1 signaling pathway regulates T cell homeostasis, this study was designed to test the hypothesis that IDO induces T-cell immunosuppression through inhibiting Vav1 signaling.

Results:
We found that IDO produced by IDO stably expressing CHO cells significantly inhibited interleukin (IL)-2 expression and proliferative response in T cells and increased apoptosis of T cells. IDO suppressed Vav1 mRNA and protein production in T cells. Furthermore, IDO inhibited TCR activation-induced Vav1 phosphorylation, which represents Vav1’s activation state in T cells. These effects on T-cells induced by co-culture of CHO/IDO with T cells were attenuated by 1-MT.

Materials and methods:
Chinese hamster ovary (CHO) cells were stably transfected with human IDO (CHO/IDO). CD3+T cells were isolated from human peripheral blood mononuclear cells. After co-culture of CHO/IDO cells with T cells in the presence or absence of an anti-CD3 antibody to activate T cell receptor (TCR) and/or 1-methyl-L-tryptophan (1-MT) to inhibit IDO activity, T cell proliferation and apoptosis were determined. T cell total RNA and cellular protein samples were isolated for etecting Vav1 gene and protein expression and activation state.

Conclusions:
The inhibitory effects of IDO on T cell immune responses may be through downregulation of Vav1 protein expression and activation. These studies provide insight into understanding the mechanisms of immune escape induced by IDO and therapeutic application of IDO inhibitors for cancer treatment.