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Editorial OMICS International

Concise Remarks on Tolerogenic Dendritic Cells

Haiyan Xu*

Department of Urinary Surgery, Third Affiliated Hospital of Soochow University, Changzhou 213003, China

***Corresponding author:** Xu H, Department of Urinary Surgery, Third Affiliated Hospital of Soochow University, Changzhou 213003, China, Tel: (86)51968870351; E-mail: xuhaiyan09@163.com

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Editorial

In 1996, Steptoe and Thomson described dendritic cells (DCs) in detail with focus on the induction of tolerance, and they proposed the concept of tolerogenic DCs (tDCs) [1]. Since then, tDCs have drawn more and more attention due to their suppressive effect on the field of allograft rejection and autoimmune disorders.

tDCs are a type of dendritic cells with special functions, because they can render other cells immunologically tolerant depending on their status. Biomarkers may indicate their capacity for tolerogenic induction. The low expression of co-stimulators, such as CD80, CD86, MHC II, and CD40, and the expression of suppressive molecules, such as programmed cell death ligand-1 (PD-L1) and immunoglobulin-like transcript (ILT)-3 and -4, are common characteristics of tDCs. tDCs include immature DCs, activated DCs, and DCs that have lost the ability to undergo normal differentiation [2]. *In vitro*, tDCs strongly inhibit the activation and proliferation of T cells, and they show strong capacity for the uptake, processing, and presenting of antigen [3]. Transplantation animal models have produced some successful reports of prolonging the survival time of allografts using tDC; the models have included heart, pancreatic gland, hind limb, islet, skin flap, and kidney grafts. tDCs have also shown good results in autoimmune disease models, such as the collagen-induced arthritis (CIA) mouse, the experimental autoimmune encephalomyelitis (EAE) mouse, the non-obese diabetic (NOD) mouse, and the type I diabetic mouse.

There are several potential main mechanisms underlying the action of tDC [4,5]:

1. The production, secretion, or amplification of natural or adaptable regulatory T cells (Treg).
2. The expression of interleukin-10, indoleamine 2,3-dioxygenase (IDO), or tumor growth factor (TGF)-β1, and establishment of the suppression feedback loop with Treg.

tDCs are widely distributed in vivo, but their overall numbers are very small. It is very difficult to directly isolate tDCs from organisms. tDCs used in research are always induced from autogenic or xenogenic bone marrow or peripheral blood mononuclear cells through genetic engineering technology, cytokines, or chemical reagents. Rapamycin, dexameth, vitamin A, and vitamin D can successfully induce tDC production. These cytokines, TGF-β, granulocyte colony-stimulating factor, vascular epithelial growth factor, and vasoactive intestinal polypeptide have been found to be able to induce precursors to transform into tDCs. Auto antigen loading can induce the production of tDCs in precursors that do not respond to antigen stimulation. The first-in-human phase I trial of tDCs was performed using this method to enrich and infuse the disease-specific citrullinated peptide-loaded tDCs, designated "Rheumavax".

Some studies have provided new and promising treatments for rheumatoid arthritis, but they also raised a number of questions [6,7]. The One Study, a multicenter clinical trial that is designed to evaluate the effect of tDCs on the establishment of immune tolerance in kidney transplantation recipients, is currently under way [4]. In this trial, tDCs are induced from autogenic peripheral blood mononuclear cells, stimulated by low quantities of GM-CSF or immunosuppressive agents, and administered in a large quantity (1×10^6/Kg). We here analyzed the results of the current research. One key point affecting the clinical use of tDCs is their stability and ability to migrate. The tDCs must migrate to the site of the inflammation and remain non-responsive after they engulf necrotic or stressed cells. One goal of this work is to find an ideal approach to maintain their inactive status and sustain their migratory ability.

Studies have suggested that tDCs produced through different induction methods have different characteristics, sharing only their tolerogenic function. The rapid development of gene editing techniques and the identification of suitable checkpoints within the metabolic pathway may help identify ideal tDCs. Considerable progress has been made in the study of chimeric antigen receptor-modified T cells and associated therapies. This has brought not only good news for some cancer patients but also new hope for the further development of cell therapies. Someday tDCs transfer may be used to treat organ transplantation and autoimmune patients.

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