IMMUNE TOLERANCE AND HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Immune Tolerance after Transplantation

The success of transplantation, specifically hematopoietic stem cell transplantation (HSCT), is directly correlated with the level of immune tolerance. The failure of reaching new immunological homeostasis leads to host versus graft reaction and then graft rejection as well as graft versus host reaction that leads to graft versus host disease (GVHD) after HSCT. Understanding the post-transplant immune tolerance mechanisms might help to generate new therapeutic strategies that might overcome these post-transplant problems and improve the outcome of transplant.

T lymphocytes play a critical role in the immune response including graft rejection and GVHD. Other lymphocytes and immune regulatory cells including B cells, NK –T cells, dendritic cells (DC), myeloid cells, mesenchymal cells are also involved in the development of transplant tolerance (reviewed in [1]).

T cells and Immune Tolerance

Immune tolerance is defined as a condition that the immune system is not able to mount an immune response to certain antigens [2], which is directly linked to T cell tolerance. T cells become unresponsive to immune stimulation with two different mechanisms: i) central and ii) peripheral tolerance. Central tolerance may occur by elimination of self-reactive clones during the thymic maturation [3]. Clonal T cells with T cell receptors (TCRs) recognizing self-antigens are deleted by positive and negative selection before releasing of T cells from the thymus. Peripheral tolerance, the deletion/elimination of activated T cell clones in the periphery includes suppression of T cells by regulatory cells or inhibitory molecules [4].

1. Central Tolerance

Lymphoid precursors from the BM migrate to the thymus and then will undergo subsequent differentiation under the control of factors including Interleukin-7 (IL-7) and Notch-1 [5]. During thymic maturation, T cells progress through different developmental stages from T cell precursor to mature T cells while they are gaining normal T cell receptor formation on their surface. Thymocytes are divided 4 major subgroups according to CD4 and CD8 expression on their surface; double negative (DN), double positive (DP), CD4-single positive (CD4-SP) and CD8- single positive (CD8-SP). DN populations arise from early thymic precursors includes different developmental stages. TCR development starts in the DN stage and completes normal structure in DP stage. Thymocytes with T cell receptors (TCRs) recognizing self-antigens and nonfunctional TCRs are deleted by negative and positive selection respectively before releasing from the thymus (reviewed in [2, 3]). Only 1-2 % of thymocytes are able to reach a mature T cell status before they are released from the thymus.

2. Peripheral Tolerance

In normal host small amount of self-reactive T lymphocytes escape from the selection in the thymus and that can be eliminated in the periphery by deletion and suppression. After transplantation, transplanted organ/tissue is easily recognized as a non-self, which stimulates the generation of a large amount of alloreactive T cell clones in the periphery. Alloreactive T cell clones cannot be controlled by central tolerance in the early period of HSCT because there is no presentation of the donor-associated MHC's in the thymus. Therefore, alloreactive T cells should be eliminated and/or suppressed in the periphery.

Clonal deletion of alloreactive T cells, development of T cell anergy and suppression of alloreactive T cells by regulatory cells and inhibitory cytokines are the mechanisms of the peripheral tolerance. The presence of a large amount of alloreactive T cells after allogeneic HSCT requires clonal deletion by T cell apoptosis, which can be induced via two pathways;

(i) Activation of death receptors, such as the Fas (CD95)/Fas ligand (CD95L) pathway, essential for the regulation of activation induced cell death (AICD), which occurs after antigenic stimulation of mature T cells [6] and

(ii) The loss of growth factors or nutrient deprivation [7], which is called passive cell death, leading to a shift in balance toward the pro-apoptotic Bcl-2 family members such as Bax and Bad [8]

T cell anergy and inhibitory costimulatory molecules

T cell activation requires two signals: i) TCR signal ii) costimulatory signal. T cells are not able to mount an immune response without a second costimulatory signal. CD28 is the main co-stimulatory receptor and has two ligands; B7.1 (CD80) and B7.2 (CD86) that are expressed on APCs. Activation of T cells in the absence of CD28 results in an anergic state with defective T cell signaling.

CTLA-4, a member of the immunoglobulin superfamily, was the first discovered inhibitory molecule and has a similar structure to CD28. Both molecules bind to CD80 and CD86 on antigen-presenting cells. CTLA-4 inhibits CD28 dependent T cell activation, cell cycle progression and IL-2 production of T cells. CTLA-4 is a critical molecule for regulatory T cell function. PD-1 is another inhibitory molecule with two ligands (PD-L1 and PD-L2) that are expressed on T cells, B cells, antigen-presenting cells, endothelial cells, and tumor tissues. PD-1/PD-L1 interactions lead to inhibitory signals and results in the inhibition of T cell activation and function.

Regulatory cells

A number of immunologically active cells with suppressive functions on the immune system have been reported since 1970s including suppressor T cells, myeloid cells, veto cells, B cells, dendritic cells and mesenchymal cells. Regulatory T cells has been clearly defined in mid 90s that play a significant role in the development of tolerance (reviewed in [9]). Approximately 5-10 % of peripheral CD4+ cells express IL-2 receptors on their surface. The depletion of CD4+CD25+ cells results in development of autoimmune disease. Naturally occurring T_{reg} specifically express a transcription factor (Foxp3), which is the major inducer, regulator, and survival factor in T_{reg} development and function [10, 11].

Regulatory T cells can suppress the immune response with different mechanisms;

1. Activation of inhibitory costimulatory molecules; CTLA-4
2. Activation of indoleamine 2,3-dioxygenase (IDO), which results in both a local deprivation of tryptophan and the production of inhibitory molecules.
3. Increased secretion of inhibitory hormones and cytokines; TGF-beta and IL-10.
4. Increased cytotoxic molecules (granzyme A), stimulates cytotoxicity against to activated T cells by perforin dependent mechanism.

Inducing tolerance after HSCT

Induction of transplant tolerance improves the outcome of the transplant**.** Some of the therapeutic strategies have been used in the clinic as written below.

1. T cell depletion; The removal of the T cells from the graft is the one of the well-known methods, which decreases the incidence of graft versus host disease, but may result in increased frequency of life threatening viral and fungal infections after HSCT.
2. Selective depletion of alloreactive T cells
3. Immunotherapy with regulatory T cells or other suppressor cells; mesenchymal cells, facilitating cells, dendritic cells, etc.
4. Using mega dose of CD34+ cells with veto activity
5. Pre or post transplant chemotherapy (Cyclophosphamide, Campath)
6. Costimulatory molecule blockade; CTLA-Ig

Clinically applicable transplant tolerance induction methods will broaden options to treat GVHD, facilitate anti-tumor effects, and shorten the period of post-transplant immune deficiency.

References

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