Monitoring for tolerance in kidney transplant patients before and after conversion from CNI to Rapamycin based therapy

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Abstract

Costimulation is a key determinant of the outcome of T-cell activation on exposure to foreign antigen. The best characterized T-cell costimulatory pathway involves the CD28 receptor on the T cells, which binds to two costimulatory molecules, B7-1 (CD80) and B7-2 (CD86) on the antigen presenting cell (APCs). The interaction of B7-l and B7-2 with CD28, in concert with T cell receptor signaling, promotes the expansion of antigen stimulated T-cells and their differentiation into effector and memory cells. CD28 is the Major costimulatory receptor for T cells ***(Greenwald et al., 2005)***

Key Words :

antigen – Azathioprine - hepatitis C virus .

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List of abbreviations

Ag: antigen

APC: antigen presenting cell

ATG: Anti thymocyte globulin

AZA: Azathioprine

Cad: Cadaveric kidney transplantation

CADI: chronic allograft damage index

CAN: chronic allograft nephropathy

CD: cluster of differentiation

CRF: chronic renal failure

CTLA-4: cytotoxic T lymphocyte antigen-4

DBMI: donor bone marrow infusion

DC: dendritic cell

FasL: Fas ligand

GVHD: graft versus host disease

HCV: hepatitis C virus

ICAM: intercellular adhesion molecule

ICOS: Inducible co-stimulator

IFN: interferon

Ig: immunoglobulin

IL: interleukin

IL-2R: interleukin-2 receptor

LFA: Leukocyte function associated antigen

LRD: Live related donor

MAP: Mitogen activated protein

MHC: major histocompatability complex

MMF: mycophenolate mofetil

NK: natural killer

PCR: Polymerase chain reaction

PD-1: programmed death-1

PD-L: programmed death ligand

PMNs: polymorphonuclear cells

T reg: regulatory T lymphocyte.

TCR: T-cell receptor

TGF: transforming growth factor

TH: T helper

TLRs: toll like receptors

TNF: Tumor necrosis factor

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Introduction

The immune system has the remarkable ability to defend against diverse microbial pathogens and yet not to respond to self. T cells are key mediators of the immune response, and their activation is tightly regulated to prevent autoreactivity. T-cell activation requires two signals that are delivered by antigen-presenting cells (APCs). The first signal is antigen displayed by APCs in the form of peptides bound to histocompatability molecules; the recognition of antigen by T-cell receptors provides specificity to the response. The second signal, called the "costimulatory signal" because it stimulates T cells in conjunction with antigen, is provided by molecules on APCs that engage particular costimulatory receptors on T-cells ***(Arlene and Abbas, 2006)***.

In the absence of costimulation, T cells that recognize antigen either fail to respond and die or enter in a state of unresponsiveness known as anergy. Thus, costimulation is a key determinant of the outcome of a T cell's encounter with antigen. The best characterized T-cell costimulatory pathway involves the CD28 receptor, which binds to two costimulatory molecules, B7-1 (CD80) and B7-2 (CD86) ***(Greenwald et al., 2005).***

The interaction of B7-1 and B7-2 with CD28, in concert with t- cell receptor signaling, promotes the expansion of antigen stimulated T cells and their differentiation into effector and

memory cells. CD28 is the major costimulatory receptor for naïve T cells and is therefore important for initiating T cell responses. Cytotoxic T lymphocyte associated antigen-4 (CTLA-4) is a CD28 homologue that also binds to B7-1 and B7-2 but is expressed in an inducible fashion after T- cell activation. Unlike CD28, CTLA-4 shuts off T- cell responses by inhibiting interleukin-2 production and blocking cell cycle progression. Thus, CTLA-4 is involved in the induction and maintenance of T- cell tolerance ***(Bluestone et al, 2006).***

Aim of the work

This study aimed at evaluating the Cytotoxic T lymphocyte associated antigen-4 (CTLA-4) level of expression in stable transplant patients and consider its value as a marker of immune tolerance regarding their immunosuppressive medications.

Chapter 1

Innate versus Adaptive immunity

The innate and adaptive immune responses both function to protect against invading organisms, but they differ in a number of ways. (1)The innate immune system is constitutively present and reacts immediately to infection. The adaptive immune response to an invading organism takes some time to develop.(2)The innate immune system is not specific in its response and reacts equally well to a variety of organisms, whereas the adaptive immune system is antigen specific and reacts only with the organism that induced the response.(3)The adaptive immune system exhibits immunological memory. It "remembers" that it has encountered an invading organism (antigen) and reacts more rapidly on subsequent exposure to the same organism. The innate immune system does not possess a memory. ***(Vilches and Parhan, 2002)***

➢**Functions of the innate immune system:**

(1)Recruiting immune cells to sites of infection and inflammation, through the production of chemical factors, including specialized chemical mediators, called cytokines.(2)Activation of the complement cascade to identify bacteria, activate cells and to promote clearance of dead cells or antibody complexes.(3)The identification and removal of foreign substances present in organs, tissues, the blood and lymph, by

specialized white blood cells.(4)Activation of the adaptive immune system through a process known as antigen presentation. ***(Mayer Gene, 2006)***

➢**Functions of the adaptive immune system:**

(1) The recognition of specific (non self) antigens in the presence of (self) during the process of antigen presentation. (2) The generation of responses that are tailored to maximally eliminate specific pathogens or pathogen infected cells (3) The development of immunological memory, in which each pathogen is "remembered" by a signature antigen. These memory cells can be called upon to quickly eliminate a pathogen should subsequent infections occur. ***(Pancer and Cooper, 2006)***

➢**Cells of the immune system:**

B-cells: The major function of B lymphocytes is to develop into antibody-secreting plasma cells following stimulation by foreign antigens of bacteria, viruses and tumor cells. Antibodies are specialized proteins that specifically recognize and bind to specific antigens that caused their stimulation. Antibody production and binding to foreign antigens is often critical as a means of signaling other cells to engulf, kill or remove that substance from the body. ***(Bowers and William, 2006)***

T-cells: T lymphocytes are usually divided into two major subsets that are functionally and phenotypically different. T helper (TH) cells, also called CD4+ T cells, are involved in coordination and regulation of immunological responses. They

function to mediate responses by the secretion of lymphokines that stimulate or otherwise affect other cells involved in the immune responses. The second subset types of T lymphocytes are cytotoxic T lymphocytes (Tc cells or CTLs) or CD8+ T cells. These cells are involved in directly killing certain tumor cells, virus-infected cells, transplant cells, and sometimes eucaryotic parasites. CD8+ T cells are also important in down-regulation of immune responses. ***(Marrack and Kappler, 2004)***

Natural Killer cells: (NK) cells are similar to cytotoxic T lymphocytes CTLs (CD8+ T cells). They function as Effector cells that directly kill certain tumors such as melanomas, lymphomas and Virus infected cells, most notably herpes and cytomegalovirus infected cells. However, NK cells, unlike the CD8+ (Tc) cells, kill their target cells without need for recognition of antigen in association with MHC molecules. NK cells that have been activated by secretions from CD4+ T cells will kill their tumor or viral infected targets more effectively. ***(Natarajan et al., 2002)***

Macrophages: Macrophages are important in the regulation of immune responses. Besides their role in phagocytosis, they may function as antigen presenting cells (APCs) because they ingest foreign materials and present these antigens to other cells of the immune system such as T cells and B cells. This is one of the important first steps in the initiation of an immunological response.