The characterization of T cells that reside in kidney transplants

Published: 18-03-2013
Last updated: 26-04-2024

The characterization of T cells that reside in kidney transplants.The characterization of the T cell-mediated antiviral responses in kidneysThe role of kidney-resident T cells in acute and chronic allograft rejection

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Nephropathies
Study type	Observational invasive

Summary

ID

NL-OMON39128

Source
ToetsingOnline

Brief title
Kidney transplant-residing T cells

Condition

- Nephropathies

Synonym
n.a.

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Nierstichting

Intervention

Keyword: Kidney, T cell, transplantation

Outcome measures

Primary outcome

T cell phenotypes

Specificity of circulating and renal-residing T cells

Function of kidney-resident T cells

Cross-reactivity of kidney-resident T cells

Secondary outcome

Renal biopsies contain renal tubular epithelial cells, which seem to play a role in shaping the immuneresponse against viruses. We will isolate renal tubular epithelial cells, after T cell isolation and use these cells to elucidate the role of renal epithelial cells in immunresponses against virusses and in allograft rejection.

Study description

Background summary

It is becoming increasingly apparent that memory T cells of the peripheral circulation are phenotypically and functionally distinct from memory T cells that reside in specific organ systems such as the central nervous system, the skin, the gut and the lungs. Upon priming of naïve T cells with their cognate antigens, as presented by specialized dendritic cells (DCs), T-cells undergo tissue-specific programming that allows them to home to, and reside in the organ system where they are most needed. There, these cells provide a first line of defence against microorganisms that have a propensity for invading that specific organ system.
For example, T cells that have been instructed by specialized DCs present in the Peyer*s patches and the mesenteric lymph nodes in the intestine, start expressing several localizing molecules such as CCR9 and α4β7 integrin by which

they home and bind to their ligands, CCL25 and MadCAM-1 that are exclusively expressed by endothelial cells and epithelial cells also located in the intestine, thereby transforming them into *gut-homing T cells*. Recently, our group showed that there are specialized CD8+ T cells that reside in the lung. These cells expressed the αE inetgrin CD103 which mediates binding to lung epithelium. Interestingly, this subset of T cells is not present in the peripheral circulation and is specific only for the respiratory influenza virus,but not for the systemic viruses Epstein-Barr virus (EBV) and Cytomegalovirus. As such, these cells seem to provide a localized first line of response to respiratory viruses.
Taken together, we now hypothesize that there are also T cells with a unique phenotype that confer a localized protection against renotrope viruses in the kidney. For example, polyomavirus BK (BKV) is strongly renotrope and latently infects 70 to 90 percent of the population. Normally it does not cause any known disease in immunocompetent individuals. However, in immunocompromised patients, such as renal transplant recipients, BKV frequently (re)activates and may cause BKV-associated nephropathy (BKVN). Currently, with no other therapeutic strategy available other than tapering the immunosuppressive regimen, BKVN is a major cause of graft loss in renal transplantation. Moreover, tapering of the immunosuppressive regimen, in order for the patient*s immune system to mount an antiviral response, is a double-edged sword since it will also lead to more rejection of the allograft. Therefore, more specific treatments targeting BKV are direly needed to improve the outcome of kidney transplantation. Given the strong association between BKV-associated disease and immunodeficiency, and conversely, the lack of BKV-associated disease in immunocompetent individuals, the normal, mostly T cell-mediated immune response, seems to be of particular value in keeping BKV at bay. As such, knowledge about the T cell response may lead to new therapeutic insights where BKV is specifically targeted rather than also compromising the allograft by the tapering of immunosuppressive medication. Examples of highly specific therapeutic strategies that have used such knowledge and that are currently already applied in transplantation medicine, are vaccination and the adoptive transfer of EBV- and CMV-specific T cells.
In kidney transplant recipients, kidney-resident T cells could also be of importance in allograft rejection due to so called heterologous immunity. It is known that virus-specific T cells can cross-react with human leukocyte antigen (HLA)-antigenic peptide complexes. Such cross-reactive T cells would be harmless in a healthy individual where they confer protection against their cognate antigen, but might respond to a *foreign* allograft in the context of transplantation, as such mediating allograft rejection. Viral (re)activation is not uncommon in renal transplant patients due to the immunosuppressive medication, pre-existing antiviral and cross-reactive T cells will expand owing to the antigenic pressure. Indeed, both acute and chronic allograft rejection has been associated with several viral infections, amongst which importantly CMV. The significance of cross-reactive T cells as a negative influence on graft survival was further established in several mouse models. In pathogen-free mice, tolerance to the allograft was readily induced by treatment

with monoclonal antibodies that block T cell co-stimulation, such as anti-CD154. However, this effect was abrogated by inducing viral infections. Also, mice that were previously infected with multiple viruses proved to be refractory to tolerance, whilst uninfected mice or mice infected with only a single virus, were still susceptible to tolerance induction.
Given the above, it is important to gain knowledge about T cells present the kidney. The technology to extract these T cells from small tissue samples is available in our research group and we have extentive experience with the analyses of the phenotype and function of virus and allo-specific T cells. Therefore, we ask permission to obtain additional tissue samples during renal allograft biopsies in kindey transplant recipients that occur on standard clinical indications or for research purposes.

Study objective

The characterization of T cells that reside in kidney transplants.
The characterization of the T cell-mediated antiviral responses in kidneys
The role of kidney-resident T cells in acute and chronic allograft rejection

Study design

If transplant recipients undergo a kidney biopsy after transplantation because of standard clinical evaluation, they will be asked to donate one extra tissue sample. In addition, transplant recipients will be asked to donate 57 ml of peripheral venous blood and an urine sample on the same day. In this way, T cells residing in the kidney can be compared to peripherally circulating T cells from the same individual. If biopsy moments coincide with a blood-withdrawal in context of the Allegro study (CCMO registration number NL32205.042.10) or BK virus study (CCMO registration number NL39356.018.12), no extra blood sample will be obtained. Peripheral blood mononuclear cells (PBMCs) will be isolated and stored in liquid nitrogen until further use. Function , phenotype and specificity of peripheral and renal T cells will be analyzed by flow cytometry as described in the research protocol.

Study burden and risks

A kidney biopsy bears the risk of the formation of a hematoma in the biopted kidney. We regard this additional risk on the formation of hematoma due to the extra biopsy to be small.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

A patient must be over 18 years of age.
A patient must have undergone a kidney transplantation and must be treated by nephrologists from the Renal Transplant Unit in the Academic Medical Centre.
A patient must be eligible for a kidney biopsy in the context of standard clinical indications.

Exclusion criteria

All patients who do not meet any of the inclusion criteria
All patients who experience any serious adverse events will be excluded from further participation in this study
All patients for whom it is regarded unsafe for any reason, by the treating transplant nephrologist, to undergo the interventions described in detail in the study protocol.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-08-2013
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	18-03-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL41165.018.12