In Vitro Characterization and Enhancement of HIV-Specific CD8+ T Cells

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1. To examine whether epigenetic inhibitors can reverse exhaustion of HIV-specific CD8+ T cells.2. To determine whether HIV-specific CD8+ T cells have altered expression of post-transcriptional regulators.

Ethical review	Not approved
Status	Will not start
Health condition type	Viral infectious disorders
Study type	Observational invasive

Summary

ID

NL-OMON42584

Source
ToetsingOnline

Brief title
CD8+ T cells in HIV

Condition

- Viral infectious disorders

Synonym
AIDS, HIV infection

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: CD8+ T cells, HIV, Post-transcriptional control, T cell exhaustion

Outcome measures

Primary outcome

This is a discovery study aiming to study exhaustion in HIV-specific CD8+ T cells and how these functional defects can be modified by epigenetic inhibitors. The main study parameters are a) phenotypic and functional characterization of HIV- and CMV-specific CD8+ T cells from HIV-infected individuals; b) Increase of function and reverse of exhaustion phenotype by epigenetic inhibitors; c) Expression pattern of select post-transcriptional modifiers in HIV- and CMV-specific CD8+ T cells from HIV-infected individuals.

Secondary outcome

Non applicable

Study description

Background summary

Antigen-specific cytotoxic CD8+ T cell responses are considered to be major players in the protective immune response against acute and chronic viral infections. In infections with the human immunodeficiency virus (HIV) the key role of CD8+ T cells was indicated by several studies. Although the immune response in HIV infected individuals can control HIV replication for several years, ultimately, HIV-specific CD8+ T cells fail to clear or control HIV infection and AIDS develops. This failure of HIV-specific CD8+ T cells to eradicate or control long-term HIV raises the question whether HIV-specific CD8+ T cells become exhausted, leading to the functional loss of virus-specific CD8+ T cells in chronic viral infections. Mechanisms regulating gene activity include epigenetic modification and post-transcriptional regulations. Epigenetic modification leads to chances in chromatin structure through methylation of DNA and modification of histones. Epigenetic-mediated gene silencing was recently also linked to CD8+ T cell exhaustion. Since epigenetic

modulations are reversible, inhibiting enzymes involved in epigenetic modifications may represent a new approach to modulate the function of T cells in viral infections. Post-transcriptional regulation is another mechanism controlling the activity of genes. So far, microRNA, long noncoding RNA and RNA-binding proteins have been indicated as altering gene expression in a network by mechanism like silencing translation, destabilizing mRNA, preventing degradation and modulating localization. Very little is known about the role these post-transcriptional regulators play in immune responses and specifically cytotoxic CD8+ T cells although dysregulated post-transcriptional regulators may contribute to the exhausted phenotype of HIV-specific CD8+ T cells.
In this study, we will analyze the effect epigenetic inhibitor have on the function of HIV- and CMV-specific CD8+ T cells. We will also characterize the expression profile of several posttranscriptional regulators in HIV- and CMV-specific CD8+ T cells from HIV-infected controls. We will take advantage of having the ability to analyze two different virus-specific CD8+ T cells in the same HIV-infected individual: HIV-specific CD8+ T cells are exhausted virus-specific CD8+ T cells which fail to control chronic viral infection whereas CMV-specific CD8+ T cells successfully control chronic CMV infection. This will allow us to directly compare the effect of epigenetic inhibitors and the expression of post-transcriptional regulators in these two CD8+ T cell population and determine which will restore the function and behavior of the failed HIV-specific CD8+ T cells to the level of the successful CMV-specific CD8+ T cells.

Study objective

1. To examine whether epigenetic inhibitors can reverse exhaustion of HIV-specific CD8+ T cells.
2. To determine whether HIV-specific CD8+ T cells have altered expression of post-transcriptional regulators.

Study design

This is a research study that uses peripheral blood received through venipuncture from HIV-infected individuals. In vitro experiments are performed on isolated lymphocytes. Chronically HIV-infected volunteers will be asked to donate blood (maximum 50 ml, 5 tubes) either during their scheduled physician visit or during a scheduled visit for the blood donation. PBMC will be isolated from peripheral blood and either analyzed or cultured in vitro. For the epigenetic inhibitor studies we will treat PBMC in culture with different epigenetic inhibitors and then the phenotype and function of HIV-specific and CMV-specific CD8+ T cells will be analyzed. The phenotype of HIV-specific CD8+ T cells will be determined by flow cytometry (memory differentiation, cytokine production and inhibitory receptor expression) immediately after isolation or after peptide stimulation. In some instances HIV-specific CD8+ T cells will be peptide-stimulated and proliferation will be measured. In some experiments we

will examine the rate of cell death of HIV-specific CD8+ T cells. For the post-transcriptional regulator analysis, we will sort HIV- and CMV-specific CD8+ T cells from PBMC and analyze the expression of select post-transcriptional regulators (miRNA, lncRNA and RBP) by RT-PCR and RNAseq. For some of these post-transcriptional regulators, we will measure their intracellular expression by flow cytometry when the assay is available.

Study burden and risks

There are no benefits for participants in this in vitro research study. The only potential risk of participation in this study is the minor risk connected to blood donation through venipuncture.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Age >18 years
Confirmed HIV-1 infection
Treatment or viral loads that fit into one of the study groups

Exclusion criteria

Inability to donate 50 ml of blood
Pregnancy or breastfeeding
Major comorbidities

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	396
Type:	Anticipated

Ethics review

Not approved

Date:	08-09-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL53938.078.15