Identifying the underlying mechanisms and consequences of the loss of nasal T cells in vital and frail older individuals

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Primary Objective: To compare nasal CD8+ T cell frequency between young adults and frail older adults.Secondary Objective(s): 1. In depth profiling of T cells in nose and blood of young adults and older adults with and without frailty.2. Assess the...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Infections - pathogen unspecified
Study type	Observational invasive

Summary

ID

NL-OMON54081

Source
ToetsingOnline

Brief title
T cells in Nose of Older adults (TINO)

Condition

- Infections - pathogen unspecified

Synonym
respiratory infections in elderly

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: NWO

Intervention

Keyword: Aging, Immunesystem, recurrent respiratory infections, Tissue-resident T cells

Outcome measures

Primary outcome

Frequency of nasal CD8+ T cells in young adults and frail older adults.

Secondary outcome

• Phenotype (subsets, activation status), functionality, transcriptomic state, clonality and frequency of nasal and blood T cell populations in young adults, healthy older adults and frail older adults that suffer from recurrent respiratory tract infections or not.

• Stability of T cells and other immune parameters, as described for main study parameter, during a second sample after 3 months.

• Analysis of other immune populations as for main study parameter

• Concentration of nasal and systemic factors (e.g. cytokines and metabolites) and their association with T cells and other immune populations

• Respiratory tract microbiota profiles and presence of asymptomatic viral infections and their association with T cells and other immune parameters

• Chronological and biological age, sex, and other immunologically relevant parameters with T cell populations and other immune parameters

• Alteration of T cell phenotype, during and following respiratory tract infections. Levels of antigen-specific T cells and other immune parameters in nose and blood post infection. Aetiological agent will be characterized using standard diagnostics tests.

Study description

Background summary

Individuals with advanced age are at a progressively increasing risk of acquiring lower respiratory tract infections. Over the coming decades, as the population ages, the incidence of respiratory infections and community-acquired pneumonia is expected to substantially increase. The current outbreak of SARS-CoV-2 demonstrates the global urgency of understanding the effect of age on local mucosal immunity given the increased susceptibility of the elderly. With advanced age, increased inflammation (*inflammaging*), immunosenescence and reduced naïve and expanded memory lymphocyte pools have been described in peripheral blood. In addition to calendar age, the degree of frailty also is important for susceptibility to severe infections as this associates with increased risk of hospital admission in elderly with community-acquired pneumonia. Frailty has been shown to also be associated with alterations in the immune system in peripheral blood, although this association and its role in the susceptibility to infections remains poorly characterized. While many studies have investigated how the immune system changes with age, most of these have been conducted in peripheral blood, which poorly reflects the immune system at mucosal surfaces. Indeed, whether and how alterations in the mucosal immune system with age predispose to infections in the very old remains unclear as access to relevant tissue samples is limited. Increased understanding of local immunity could thus be critical in the development of new vaccines against respiratory pathogens. Recent developments in minimally-invasive nasal sampling techniques now allow us to address this knowledge gap. Recently, we already observed that in healthy older adults, both CD4+ T cells and CD8+ T cells are selectively lost from the nasal mucosa.

However, the exact phenotype, underlying mechanisms, key molecules and consequences of this have not yet been investigated. We also do not currently know whether specific mucosal T cell populations are associated with the increased susceptibility to infection seen in advanced age. Nor do we know whether these reduced T cells indicate a limited ability of older adults to mount robust mucosal T cell responses. Addressing these knowledge gaps could be beneficial to develop vaccines or interventions that increase mucosal resident-memory T cells, which are crucial for protection against respiratory viral infections. For example, if reduced migration to the nose underlies this paucity, it is conceivable to add chemo-attractants to nasal vaccines that lead to an increased efflux of T cells at time of vaccination. Alternatively, if increased apoptosis is present in the nasal mucosa of older adults, because of limited availability of specific metabolites or tissue factors, prophylactic local administration could sustain good mucosal immunity.

Study objective

Primary Objective:
To compare nasal CD8+ T cell frequency between young adults and frail older adults.

Secondary Objective(s):
1. In depth profiling of T cells in nose and blood of young adults and older adults with and without frailty.
2. Assess the stability of T cell populations and other immune populations over time.
3. Compare blood and nasal T cells between older adults with and without recurrent respiratory tract infections.
4. Compare other nasal and systemic immune populations and parameters between young adults, vital older adults and frail older adults (with or without recurrent infections).
5. Associate nasal and systemic factors (e.g. cytokines and metabolites) and with T cells.
6. Associate respiratory tract microbiota with T cells and other immune parameters.
7. Associate covariates, such as biological age, HLA type and sex with T cells and other immune parameters.
8. Assess the impact of acute respiratory tract infection on (antigen-specific) T cell populations and other immune parameters in nose and blood.
eters in nose and blood.

Study design

This is a prospective follow-up study.

Four patient groups (healthy young adults, vital older adults, older adults with frailty without recurring respiratory tract infections and older adults with frailty with recurring respiratory tract infections) will be included and provide samples of nose and blood immunology (see figure 1). This will allow for immunological cross-sectional comparisons. Up to 30 participants per group will be asked to return after 2-4 months to provide the same set of samples to be able to analyze stability of T cells.

Participants will be asked to contact the study team if they experience symptoms of respiratory tract infection, such as a sore throat or runny nose, OR fever, OR test positive for SARS-CoV-2, within the 3 months from start of study. For these participants we will collect additional samples to identify aetiological agents and perform immunological analysis at that time (within 7 days of onset). If a causative agent (Viral: RSV / influenza A or B, Human Rhinovirus, Metapneumovirus, Parainfluenza virus 1-4, SARS-CoV-2, Human Coronavirus 229E, NL63, HKU1, OC43, Bocavirus, Adenovirus and/or bacterial, e.g. Staphylococcus aureus / Streptococcus pneumoniae, H. influenzae) is identified they will be asked to return 3 more times to provide samples to longitudinally monitor immunity.

Healthy young adults and older adults will be recruited from LUMC*s vaccination clinic. (Frail) elderly will be recruited from the geriatric outpatient clinic, emergency department and acute admittance ward in the LUMC. Participants who provide informed consent to participate in the study and meet all of the inclusion criteria and none of the exclusion criteria are included in the study.

Participants will be asked to provide samples as indicated in figure 1. If they are unable to come to LUMC for the visit, a member of the study team will perform a home visit.

For participants who develop symptoms the maximum study duration is 8 months (symptom at any point in first 3 months and then 5 months follow-up), for other participants, the study duration is either single timepoint or 2-4 months.

Study burden and risks

The following samples will be collected: 80mL of peripheral blood, nasal curettage, nasosorption, nasopharyngeal and oropharyngeal swab. Also a questionnaire will be taken to collect relevant information. A subset of people (up to 30/group) that do not develop symptoms during the study will be asked to come back after 2-4 months to compare the stability of T cells over time.. If people develop symptoms congruent with respiratory infection they will be asked to contact the study team and give samples to identify the causative agent and study nasal and systemic responses. If a common respiratory tract viral or bacterial pathogen is identified as causative, blood and nasal samples will be collected 3 more times at 1, 3 and 5 months. There are no direct benefits to taking part, but this study can provide information that ultimately could lead to improved vaccination or prophylaxis in the elderly against respiratory tract infections. Risks associated with the study are minimal.

Contacts

Public
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333 ZA
NL
Scientific
Leids Universitair Medisch Centrum

Albinusdreef 2

Leiden 2333 ZA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Age, frailty score and self-reported respiratory tract infections in previous year, ability to provide informed consent

Exclusion criteria

• Incompetence to provide informed consent
• Current smoker or >40 pack year history
• History of severe nose bleedings
• Diagnosed with asthma, COPD or chronic rhinosinusitis
• Use of inhalation corticosteroids or antibiotics in the past 6 weeks
• Current use of anti-coagulants (to prevent nosebleeds). Platelet inhibitors like acetylsalicylzuur (Ascal) are allowed
• Respiratory tract infection or common cold in the past 2 weeks
• Immunocompromised individuals (with primary immune deficiency or secondary immune deficiency)
• Life expectancy <28 days in the opinion of study physician
• Vaccination in the 2 months prior to study start

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-01-2022
Enrollment:	170
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	10-09-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	21-12-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	06-05-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	16-03-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL77841.058.21