Immune ageing in health and disease

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Primary Objective: To study changes of T cell subsets (Th1/Tc1, Th2/Tc2, Th17/Tc17, regulatory T cells and senescent T cells) in healthy ageing and unhealthy ageing. Secondary Objective(s): - To study the immune risk phenotype in healthy persons...

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

Summary

ID

NL-OMON39532

Source
ToetsingOnline

Brief title
Immune ageing in health and disease

Condition

- Other condition

Synonym
ageing and frailty

Health condition

gezonde veroudering en ongezonde veroudering/frailty

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Ageing, Frailty, Immunology, T cell

Outcome measures

Primary outcome

Main study parameter/endpoint

Which changes of T cell subsets (Th1/Tc1, Th2/Tc2, Th17/Tc17, regulatory T cells and senescent T cells) can be observed during healthy ageing versus unhealthy ageing.

Secondary outcome

Secondary study parameters/endpoints (if applicable)

Does the immune risk phenotype apply to unhealthy, frail elderly individuals rather than healthy, non-frail elderly individuals?

Is healthy ageing characterized by better maintenance of T cell function compared to unhealthy ageing?

Construct validity of GFI compared to TFI and Fried.

Other study parameters (if applicable)

We will also determine the presence of HLA-DR4 and CMV/EBV status since these factors may influence ageing of the immune system. Biomarkers of inflamm-ageing

will be assessed (such as crp and ESR and cytokine levels).

Study description

Background summary

Immune-ageing
Aging of the immune system has been associated with failing immune responses directed to new pathogens or tumour antigens [1]. Conversely, an overactive immune system is thought responsible for the development of cardiovascular disease and auto-immunity (e.g. rheumatoid arthritis, giant cell arteritis and polymyalgia rheumatica) [2].
Of the leukocyte subsets, T lymphocytes seem to be most influenced by aging due to the gradual loss of their specific maturation organ, the thymus [3]. Besides thymic involution, immune senescence may result from: 1) shrinkage of the T cell repertoire through continuous antigen stimulation favouring the development of functionally altered, oligoclonal, senescent T cells (identified by CD28/CD27 loss and telomeric erosion) and 2) a chronic low degree of inflammation (termed inflamm-ageing) evidenced by increased serum levels of inflammatory cytokines and acute phase proteins [2,4,5]. Longitudinal studies (that included healthy octo-, nono- and centenarians) have identified a so called immune risk phenotype (IRP) that is associated with poor immune function and increased mortality risk: a CD4+/CD8+ T cell ratio < 1, low CD19+ B cell counts and a poor lymphocyte proliferative response [6,7].
Besides senescent T cells, other subsets of CD4+ and CD8+ T cells have been described (table 1). Historically, CD4+ T cells were divided into T helper 1 cells and T helper 2 cells. More recently Th17 and regulatory T cells were identified. Similar to CD4+ T cells, CD8+ T cells can be divided into three subsets (T cytotoxic 1, 2 and 3) based on IFN-gamma, IL-4 and IL-17 production. However, little is known about whether these cell subsets alter during healthy versus unhealthy ageing.

Health status: SENIEUR protocol
To study age-related changes of the immune system, it is important to recruit elderly donors who are truly healthy. Many elderly people have diseases or drugs that influence the immune system. In order to study the effect of ageing (instead of disease) on the immune system, the SENIEUR protocol has been developed [8]. This protocol encompasses careful history taking, physical examination and a series of mandatory blood and urine tests. Using this method for recruitment of healthy elderly individuals in immunological studies is important, as it allows differentiation of healthy ageing (SENIEURs) from less-/non-healthy ageing (non-SENIEURs) [8]. The SENIEUR protocol has been further validated in other studies, and is currently regarded as the best protocol to assess health status of elderly individuals in a standardized way

[9,10].

Frailty
As stated, elderly people are more susceptible to infections, autoimmunity and cancer. This general age-associated susceptibility to diseases in elderly people is currently known as *frailty*. The concept of frailty is important, as it recognizes that in elderly populations a wide individual disparity is present regarding morbidity and mortality risks. Notably, these risks cannot be entirely explained by chronological age, as some 60 year old persons are more frail when compared to some 90 year old persons [11].
Various instruments have been devised to identify frail elderly people.
Early instruments to measure frailty were the protocol of Fried et al. and the Groningen Frailty Indicator (GFI) [11,12]. The Fried protocol mainly focuses on physical components of functioning in the elderly, such as grip strength and gait speed. In contrast, the GFI relies more heavily on psychosocial components of functioning. To date, the Fried protocol is the most widely used instrument internationnaly to assess frailty, and has been shown to predict mortality in cohorts of elderly people [13]. In addition to the GFI (mainly used in the UMCG), the Tilburg Frailty Indicator (TFI) has been developed. The TFI is a modification of the GFI, and has been more extensively validated compared to the GFI [14,15]. The Fried protocol and the TFI represent two different models of frailty and they measure different modalities. The Fried protocol measures fysical strength whereas the TFI, which is a questionnaire, measures psychological and social functioning.
So far, it remains unclear whether the adaptive immune system of frail elderly people differs from that in non-frail elderly people.

Study objective

Primary Objective: To study changes of T cell subsets (Th1/Tc1, Th2/Tc2, Th17/Tc17, regulatory T cells and senescent T cells) in healthy ageing and unhealthy ageing.

Secondary Objective(s):
- To study the immune risk phenotype in healthy persons versus frail and diseased persons.
- To study T cell function in healthy persons versus frail and diseased persons.
- To assess the construct validity of the Groningen Frailty Indicator to more extensively validated measures of frailty (Fried and TFI)

Study design

Observational study with determination of health status, frailty status and T cell subsets and cytokines in peripheral blood.

Study burden and risks

Donors from the different age groups/elderly groups will gain no direct benefit from the study. In times of rising age expectancies and demographic shifts towards older populations, we believe that more insights in the role of the immune system in the ageing process, will be useful to develop healthy ageing strategies in the future.
In addition, we hope to better understand which changes occur in the (adaptive) immune system with ageing, and which of these changes are associated with poor health (SENIEUR status) or frailty (Fried, TFI, GFI) later in life.
We do not expect that questionnaires and venapuncture will put study participants at risk.

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

Group 1: Healthy young donors
1. Having no chronic diseases
2. Healthy according to SENIEUR protocol
3. Not-frail according to frailty instruments (Fried)
4. Age 19-39 years
5. Being able to give informed consent;Group 2: Healthy intermediate-age donors
1. Having no chronic diseases
2. Healthy according to SENIEUR protocol
3. Not-frail according to frailty instruments (Fried)
4. Age 40-60 years
5. Being able to give informed consent;Group 3: Non-frail, SENIEUR elderly donors
1. Healthy according to SENIEUR protocol
2. Not-frail according to frailty instruments (Fried, TFI, GFI)
3. Age >= 60 years
4. Being able to give informed consent;Group 4: Non-frail, non-SENIEUR elderly donors
1. Not fully healthy according to SENIEUR protocol
2. Not-frail according to frailty instruments (Fried, TFI, GFI)
3. Age >= 60 years
4. Being able to give informed consent;Group 5: Low-Frail, non-SENIEUR elderly donors
1. Not fully healthy according to SENIEUR protocol
2. Low/intermediate frail according to frailty instruments (Fried, TFI, GFI)
3. Age >= 60 years
4. Being able to give informed consent;Group 6: High-Frail, non-SENIEUR elderly donors
1. Not healthy according to SENIEUR protocol
2. High or fully frail according to frailty instruments (Fried, TFI, GFI)
3. Age >= 60 years
4. Being able to give informed consent

Exclusion criteria

In general:
1. No informed consent
2. Clinical signs of severe anaemia, or persons known to have anaemia defined as a hemoglobulin level of less than 6,0 g/dL
3. Pregnancy;Non-SENIEUR elderly donors
1. Disease that has been reported to influence the immune system (active infection, inflammatory disease, malignancy, dementia, alcohol or drug abuse)
2. Drugs that have been reported to influence the immune system (corticosteroids, other immuno suppressive therapy, vaccination in prior 4 weeks)

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-11-2012
Enrollment:	300
Type:	Actual

Ethics review

Approved WMO

Date:	17-07-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL42467.042.12