Immune regulation by microRNA implications for diagnosis and treatment of chronic disease development in aging people with rheumatoid arthritis (RA) and osteoarthritis (OA) as disease models.

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

Summary

ID

NL-OMON33895

Source
ToetsingOnline

Brief title
Immune regulation by microRNA in HC, RA and OA.

Condition

- Autoimmune disorders

Synonym
immune mediated chronic diseases

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: co-multimorbidity, immune regulation, microRNA, RA/OA

Outcome measures

Primary outcome

First, is there a relation between multi-morbidity and a certain IRP/ microRNA

profile and the GFI.

Secondary outcome

What changes in miRNA/ IRP are instrumental for the development of

multi-morbidity? Such mechanistic insight could be useful to help or better

define the IRP and could be a potential lead for therapeutic intervention.

Study description

Background summary

Many chronic diseases with an increased prevalence in elderly are known to cluster and have a strong relation with characteristic, complex, changes in the immune response which may occur as a result of aging. Specifically, immunological aging is presumed to be causally related to autoimmunity, cancer, cardio vascular disease (including atherosclerosis), sarcopenia, Alzheimer*s disease, diabetes, a generally increased vulnerability to infection and a decreased responsiveness to vaccination. The age dependent deterioration of the immune function (immunosenescence) is characterized by a reduced CD4/CD8 T-cell ratio, loss of costimularory and proliferative capacity and increased production of pro- and anti-inflammatory cytokines. Collectively, these phenotypic age related changes are denoted by the term *immune risk profile* (IRP).
A better understanding into the nature of risk factors as well as the

association of risk factors, such as IRP, with multi-morbidity is central for improvement of treatment, early diagnosis and prevention of chronic diseases. In this respect, two important issues need to be addressed: First, how can patients at risk be recognized, e.g. what are the indicators that relate to the development of IRP and multi-morbidity. Second, what are the mechanistic fundaments of the age related aggregation of risk factors, e.g. what age related molecular mechanisms are instrumental for the development of an IRP and co-morbidity.
In respect to the first issue, indicators aimed at the identification of patients at risk for multi-morbidity or complex care, such as provided by the Groningen Frailty Indicator (GFI), provide an easy and inexpensive basis for the standardized screening of patients at risk for the development of multi- and co-morbidity such as possibly associated with immunosenescence. As such, it would be most relevant to investigate immunological characteristics of elder individuals that present with a high GFI. In respect to the second issue, one class of molecules, so-called microRNAs (miRNAs), are of specific interest. MiRNAs are endogenous small RNAs (approximately 22 nucleotides) that have recently emerged as key factors in regulating and fine-tuning homeostatic cellular processes such as fundamental to a proper functioning immune response. Specifically, recent studies have shown the profound impact of miRNAs on immune receptor responsiveness, cytokine production and germinal centre formation, underlining the importance of miRNAs in immunocompetence. In general, miRNAs are important epigenetic regulator molecules involved in normal tissue development and cell biological processes. miRNAs act by controlling protein expression at the level of mRNA protein translation. By complementary pairing with specific target mRNAs in their 3* untranslated region (3*UTR), miRNAs allow translational repression and/or degradation of the target mRNA and, as such, protein expression. The differential expression of miRNAs in, sometimes, closely related subsets of cells and their differential expression through developmental stages of cells and tissues is now recognized as an important epigenetic factor in normal and patho-physiological aspects of aging, including immunological aging. E.g. disregulation of miRNA expression results in lymphomagenesis and immunosenescence. Thus, miRNAs may be regarded both as phenotypically relevant biomarkers, specifically for complex, chronic, age related morbidities, and leads for therapeutic intervention.

Study objective

In this project we will set out to investigate characteristics of the aged immune response, with a particular focus on the role of microRNAs (miRNAs) herein. Specifically we will address two aims:
1) We aim to characterize the differences in the miRNA profile of immune cells associated with an IRP in relation to multi-morbidity (part 1 of the study).
2) We aim to delineate how miRNAs associated with patho-immunological aspects of aging relate to the devlopment of multimorbidity. (part 2 of the study).

Study design

Observational study with assessment of microRNA in blood.

Study burden and risks

The burden for patients lies in the fact that during regular visits at the outpatient clinic they have to fill in questionnaires and extra blood will be drawn during regular vena puncture. For healthy controls the burden lies within the fact that they have to visit the outpatient clinic, fill in questionnaires and have a vena puncture. To decrease their burden we will recruit as much as possible HC by asking partners of patients if they are willing to participate in the present study.

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

RA patients with comorbidity
1.Fulfilling the ACR classification criteria for RA
2.Age > 65 years
3.No treatment with DMARD (Disease Modifying Antirheumatic Drugs)
4.Presence of co-morbidity;Healthy Controls
1.Have no chronic disease
2.Age > 65 years;RA patients without comorbidity
1.Fulfilling the ACR classification criteria for RA
2.Age > 65 years
3.No treatment with DMARD (Disease Modifying Antirheumatic Drugs)
4.No co-morbidity at start of the study;For OA patients
1.Fulfilling the ACR classification criteria for OA
2.Age >65 years
3.No co-morbidity at start of the study

Exclusion criteria

For all groups (RA, OA and HC)
1.No informed consent
2.Severe anaemia defined as a Hb of less than 6.0 gr/l

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):	30-11-2009

Enrollment:	80
Type:	Actual

Ethics review

Approved WMO 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	NL25505.042.09