Focus of research group (I)

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Department, UMC: Medical Biochemistry, AMC
Size of research group: 1 Technician, 5 OIO

Current mission, vision and aims

Basic scientific research is the one and only foundation for novel therapeutic interventions in cardiovascular disease

We aim to understand the underlying mechanism of vascular disease and diet-induced diabetes with the ultimate goal to apply our novel insight in clinical practice

Focus on nuclear receptor Nur77 and its co-regulator FHL2
Focus on Nur77

- Inhibits the growth of smooth muscle cells
- Promotes angiogenesis
- Is anti-inflammatory in macrophages

Perfect target in in-stent restenosis
-> find small-molecule drugs
Inflammatory response: different phases

- Acute phase:
  - NFkB↑
  - Succinate↑
  - ROS↑
  - Cytokines↑

- Resolution phase:

Resolution
Inflammatory response: different phases

- NFκB ↑
- Succinate ↑
- ROS ↑
- Cytokines ↑

Resolution phase

Chronic inflammation
Inflammatory response: different phases

- **Acute phase**
  - NFκB ↑
  - Succinate ↑
  - ROS ↑
  - Cytokines ↑

- **Resolution phase**

- **Chronic inflammation**

- **Resolution?**

Graph showing inflammation levels over time with peaks for Sepsis and Chronic inflammation.
Nur77 crucial in resolution of inflammation
Leaving acute phase intact!
Nur77 remodels mito metabolism in macrophages

Wild-type macrophage

LPS

Cytokines

Glucose

IDH

TCA

ETC

HIF-1α

Nur77

Idh

Lactate

NO

Glutamine

Succinate

Duco Koenis
Nur77 remodels mito metabolism in macrophages
FHL2 modulates signal transduction
LIM-domain only protein

Role of FHL2 in T2D:
- FHL2-KO mice in diet-induced obesity/diabetes

Maria Clemente - Rembrandt
Jayron Habibe - ACS

Ed Eringa, Daniel van Raalte, Max Nieuwdorp, Carlie de Vries
Hilde Herrema, Torsten Scheithauer, Mariska Vos
FHL2−/− mice gain less weight after high fat diet
FHL2\(^{-/-}\) HFD:
Clear glucose faster, release more insulin

![Graph showing area under curve (AUC) for ipGTT](image)

**Insulin quantification**

![Image of insulin quantification](image)
FHL2\(^{-/-}\) mice after high fat diet

FHL2\(^{-/-}\) mice
- Gain less weight
- Move less
- Produce more heat
- Clear glucose faster
- Produce more insulin

What is the underlying mechanism??
Focus of research group (II)

Current expertise

Nuclear Receptor Nur77 and its cofactor FHL2
Primary smooth muscle cell (SMC) culture human / mouse
Primary macrophages mouse bone marrow / metabolism
Molecular biology / protein expression bacteria / lentivirus
Mouse models on SMC pathology / obesity / atherosclerosis

Collaboration in ACS

De Waard: smooth muscle cells in Marfan / Nur77 in heart
Van Raalte/Nieuwdorp: FHL2 in type 2 diabetes
Eringa: perivascular fat function / diabetes - clamping
Huveneers: FHL2 cellular localization and role in endothelial cells
Zelcer: cholesterol metabolism and Nur77

Current funding
Rembrandt, ACS, NWO, AMC
Future plans

Short term (1-2 year) plan

• Unravel the mechanism of the anti-inflammatory role in macrophages of Nuclear Receptor Nur77: does its effect on metabolism require DNA-binding/dimerisation.

• Understand the role of FHL2 in diet-induced obesity and diabetes

Necessary infrastructure:

  Up to date molecular biology infrastructure
  Animal facility with ‘easy’ forms/rules and CRISPR/Cas facility

Long term (>2 year) plan

Identify small-molecules to modulate Nur77 and FHL2 activity

Necessary infrastructure:

  Protein purification and modelling
Upregulation of lipid metabolism-related genes in Brown Adipose Tissue (BAT)

**Thermogenic genes**

**Lipid metabolism-related genes**

[Diagram showing mRNA relative expression levels for different groups: Chow – WT, Chow – FHL2−/−, HFD – WT, HFD – FHL2−/−]