



Heart Failure & Arrhythmias



Pulmonary Hypertension
& Thrombosis



Atherosclerosis
& Ischemic Syndromes



Diabetes & Metabolism



Microcirculation

Focus of research group (I)

Name PI: Carlie de Vries

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**



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Microcirculation

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



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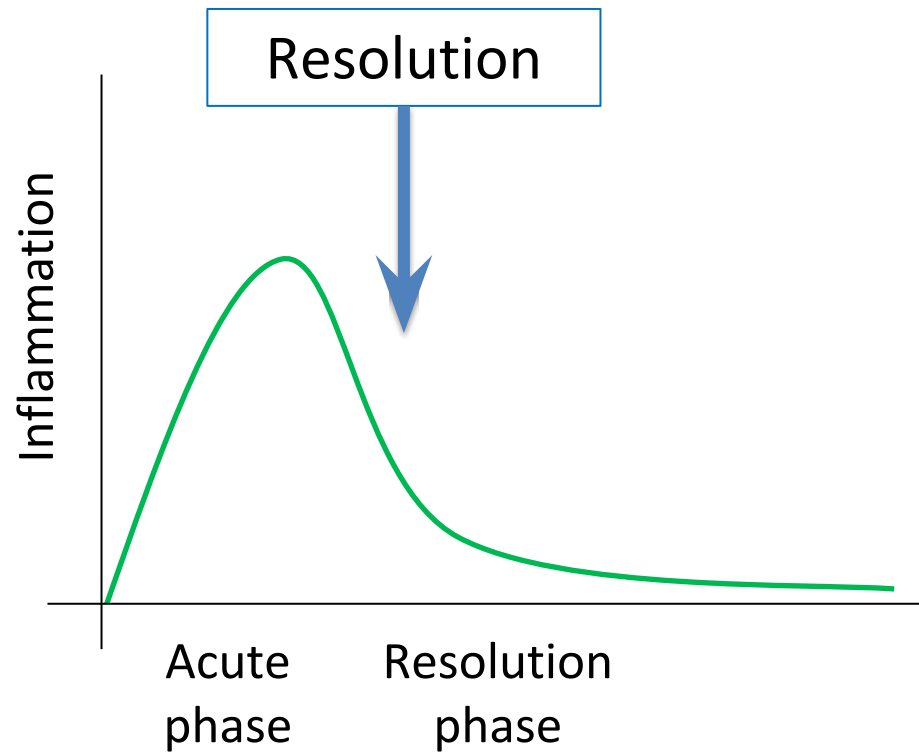


Diabetes & Metabolism



Microcirculation

NFKB ↑
Succinate ↑
ROS ↑
Cytokines ↑



Inflammatory response: different phases



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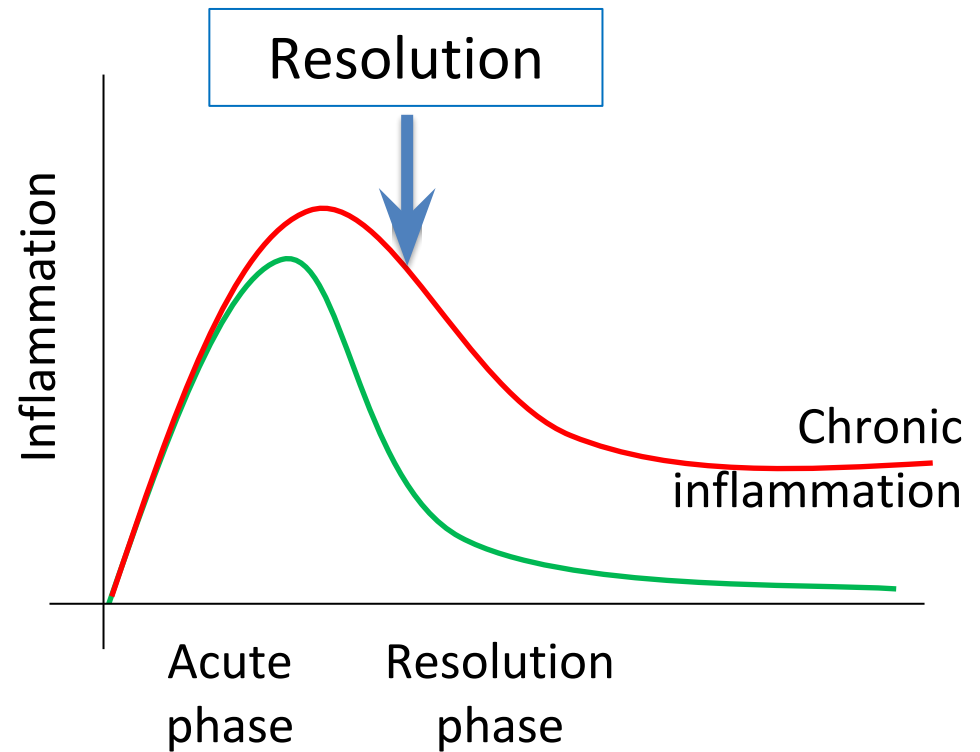


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Inflammatory response: different phases



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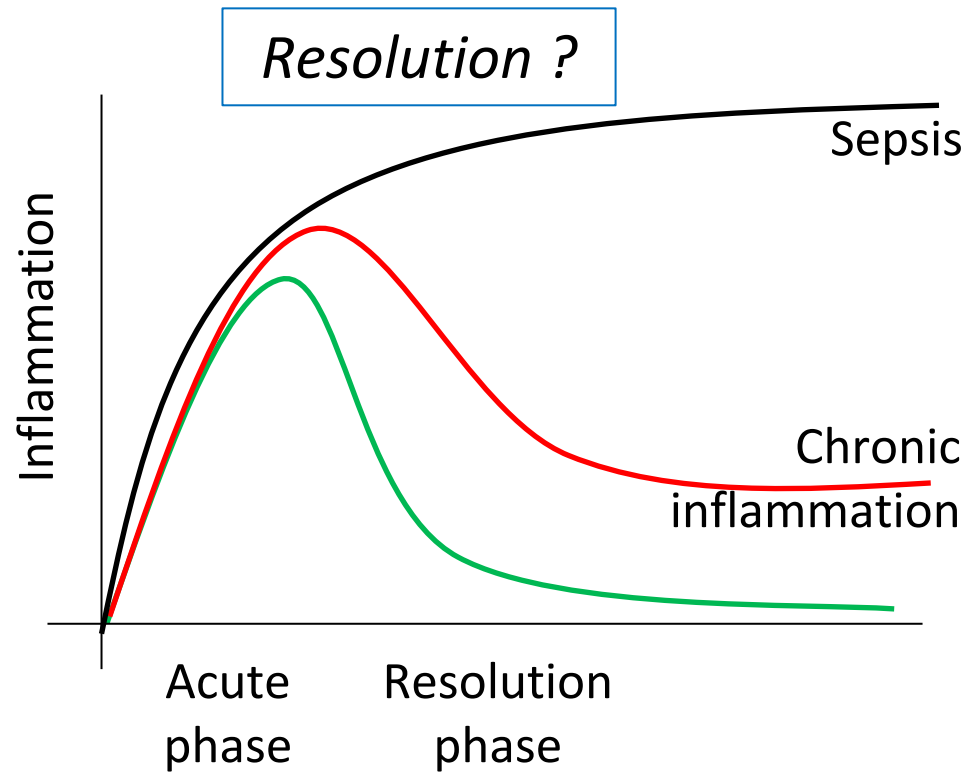


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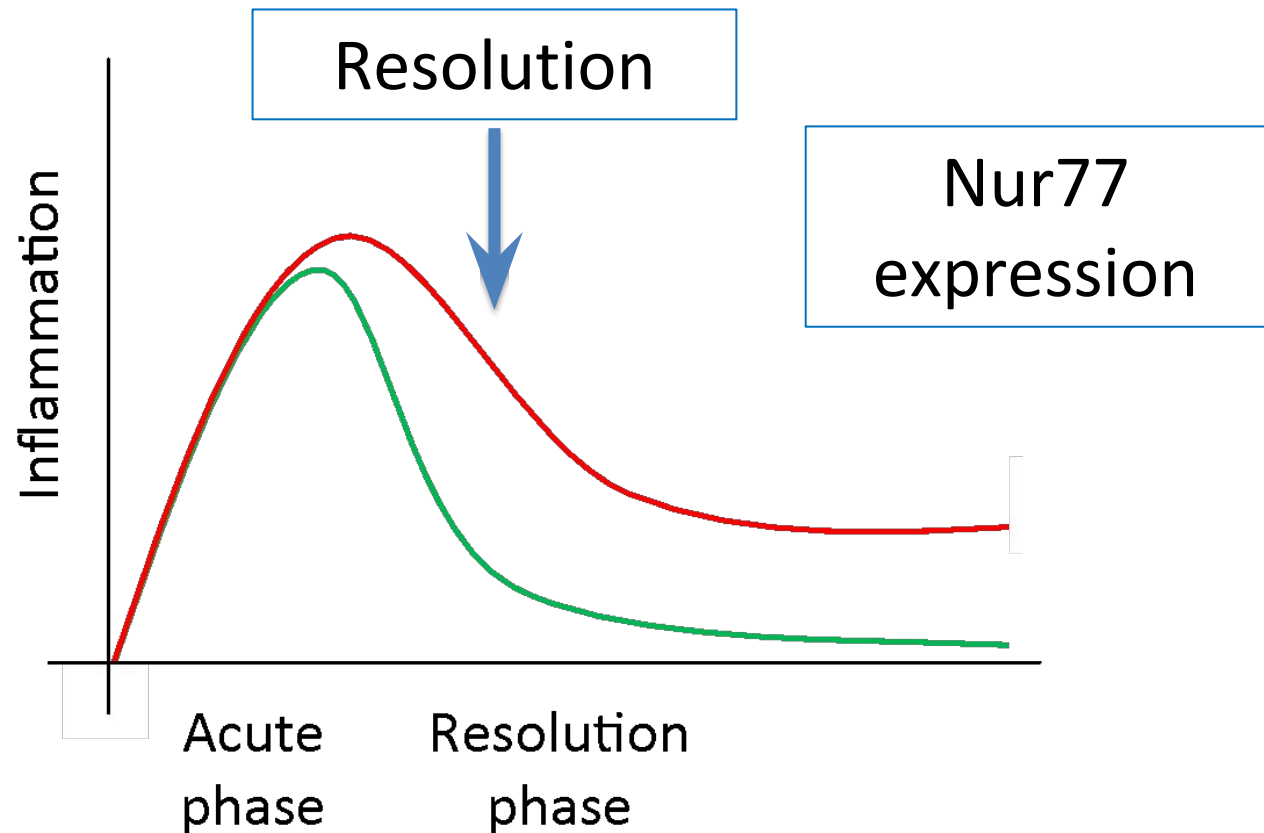
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Microcirculation

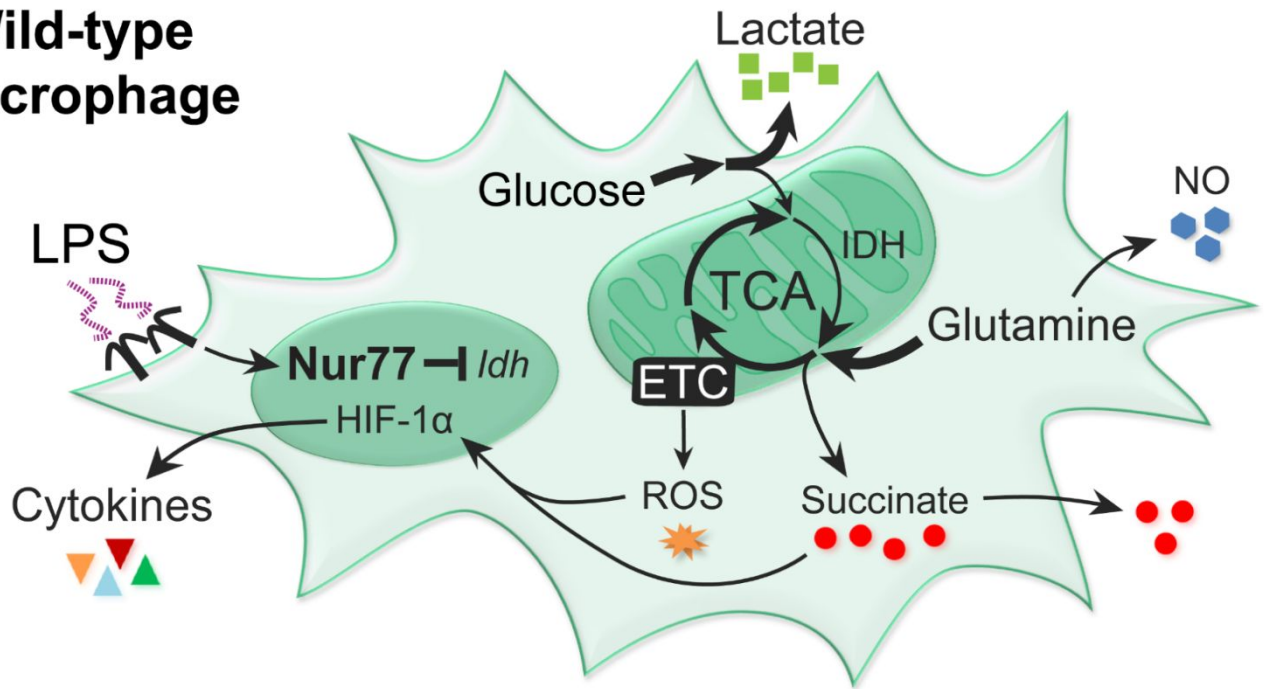
Nur77 crucial in resolution of inflammation

Leaving acute phase intact!



Nur77 remodels mito metabolism in macrophages

Wild-type macrophage



Duco Koenis



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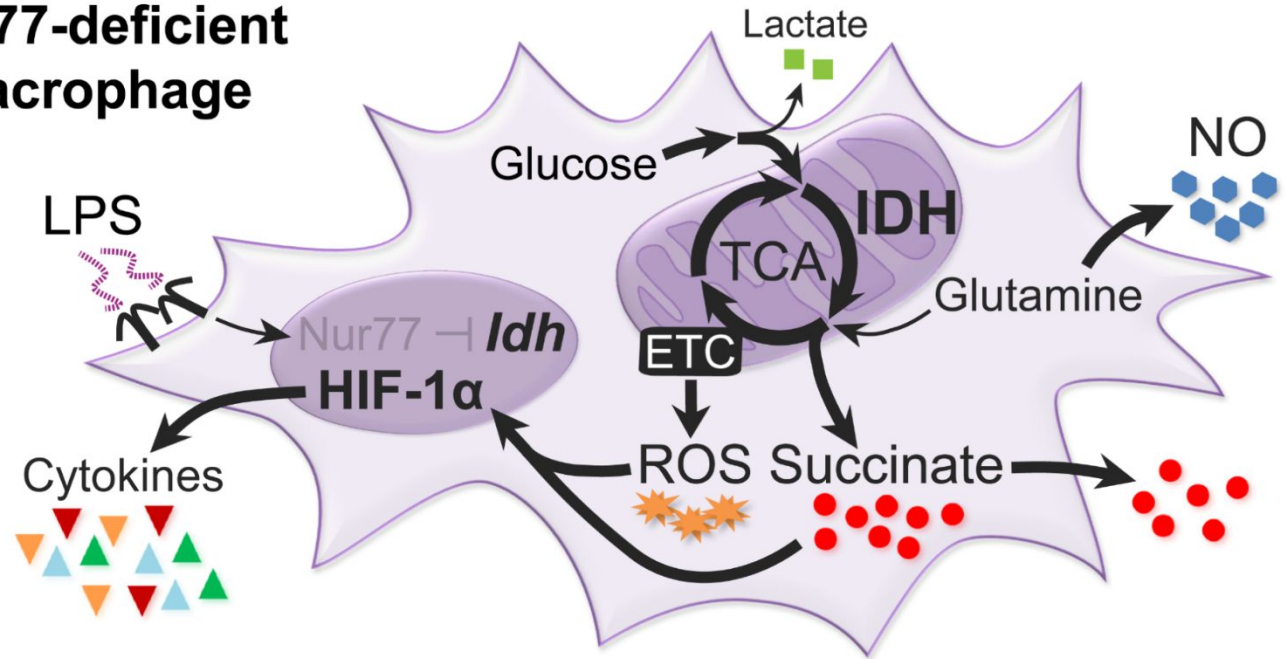


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Microcirculation

Nur77-deficient macrophage



Duco Koenis



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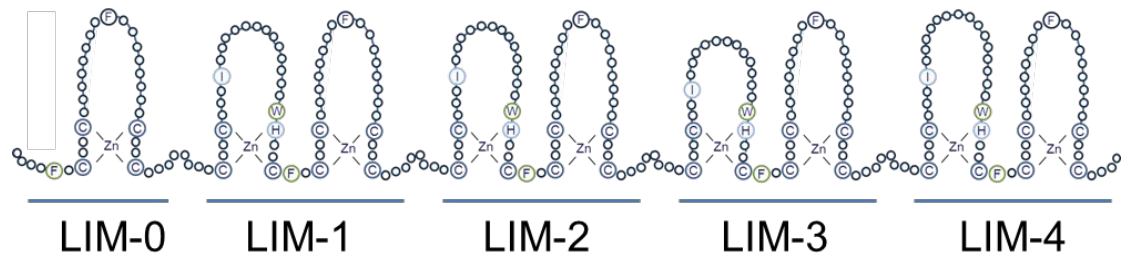
Diabetes & Metabolism



Microcirculation

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



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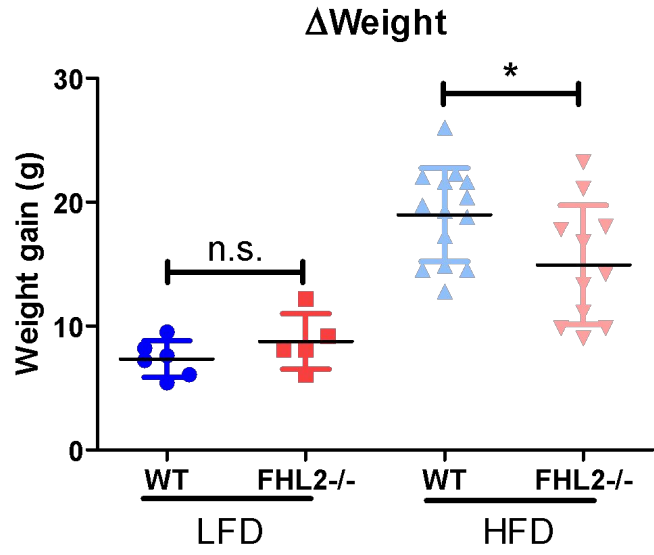
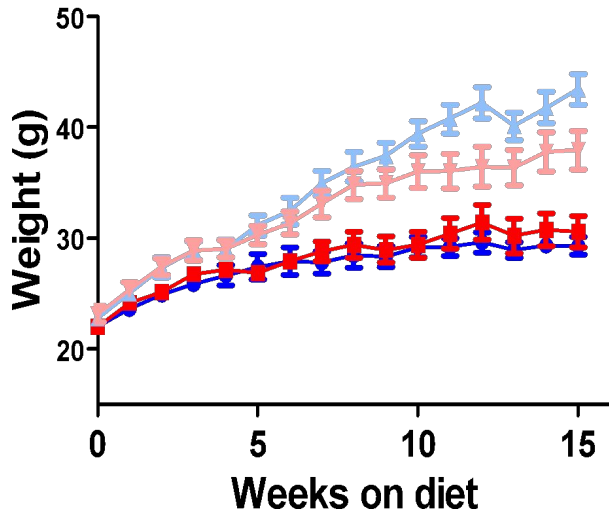
Atherosclerosis & Ischemic Syndromes



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Microcirculation



- Chow - WT
- Chow - FHL2^{-/-}
- HFD - WT
- HFD - FHL2^{-/-}



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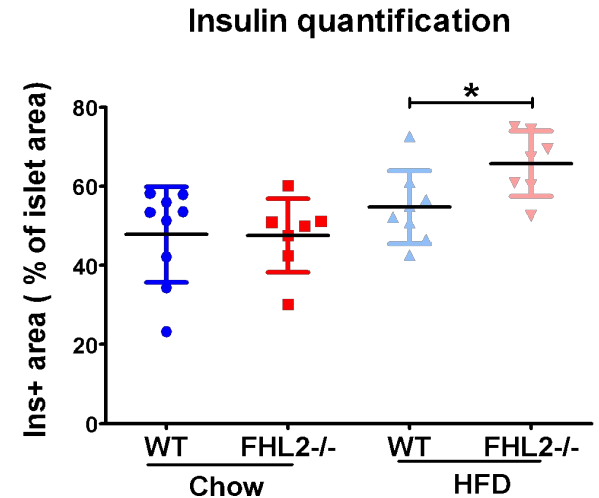
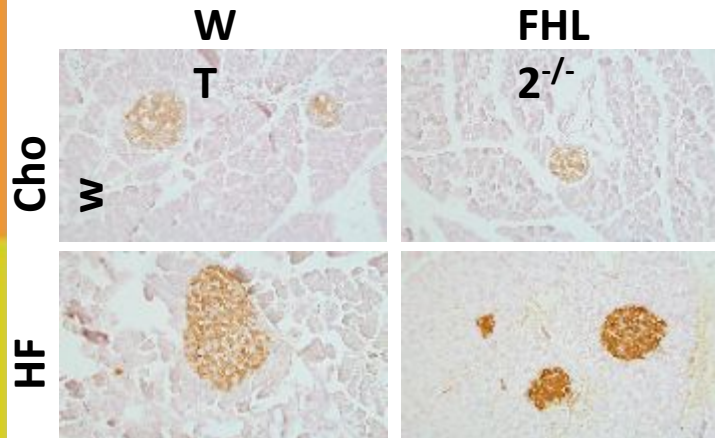
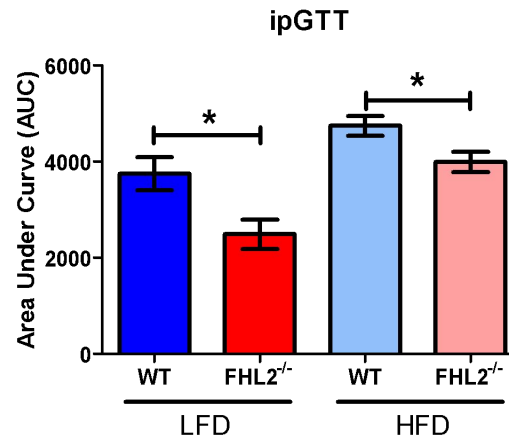
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Microcirculation

FHL2^{-/-} HFD:

Clear glucose faster, release more insulin





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Microcirculation

FHL2^{-/-} mice after high fat diet

FHL2^{-/-} mice

- Gain less weight
- Move less
- Produce more heat
- Clear glucose faster
- Produce more insulin

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What is the underlying mechanism??



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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



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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

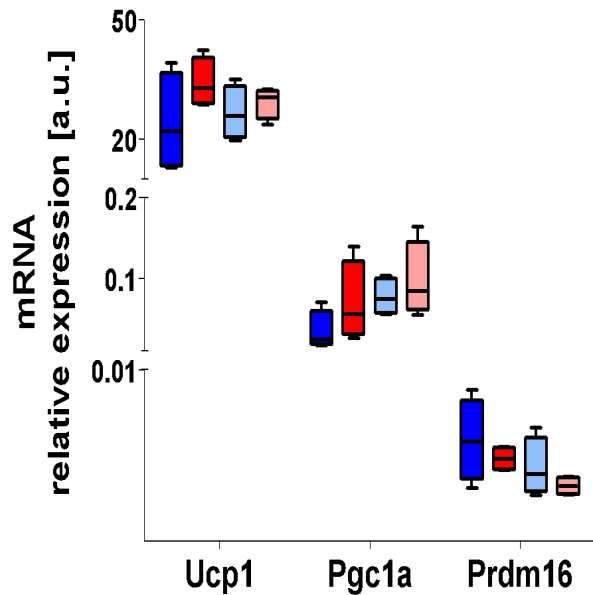
Identify small-molecules to modulate Nur77 and FHL2 activity

Necessary infrastructure:

Protein purification and modelling

Upregulation of lipid metabolism-related genes in Brown Adipose Tissue (BAT)

Thermogenic genes



Lipid metabolism-related genes

