AARHUS UNIVERSITY

Press release

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Basic information

Name: Stine Gunnersen Email: stine.gunnersen@clin.au.dk Phone: 20845570

Department of: Clinical Medicine

Main supervisor: Jacob Fog Bentzon

Title of dissertation: Functional Roles of Smooth Muscle Cells in Neointima and Atherosclerosis Formation

Date for defence: 13-12-2019 at (time of day): 14.30 Place: Auditorium B, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Aarhus University Hospital, Skejby, Denmark.

Press release (Danish)

Glatte muskelcellers rolle i udviklingen af åreforkalkning og andre sygdomme i karvæggen.

I et nyt PhD projekt fra Aarhus Universitet, Health, undersøges glatte muskelcellers rolle for inflammation i udviklingen af åreforkalkning og den sygdom, der opstår efter skade på karvæggen. Projektet undersøger dette ved hjælp af genetisk modificerede mus, der mangler vigtige inflammatoriske gener i glatte muskelceller og der undersøges hvorvidt det påvirker udviklingen af åreforkalkning og sygdom i karvæggen efter karskade. Projektet er gennemført af læge Stine Gunnersen, der forsvarer sit PhD projekt d. 13. december 2019.

Åreforkalkning er den underliggende årsag til langt de fleste tilfælde af blodprop i hjertet og i hjernen. Det er en kronisk, inflammatorisk sygdom, der er karakteriseret ved aflejring af cholesterol i karvæggen. Behandlingen består primært af cholesterol-sænkende medicin og livsstilsændringer, men trods denne behandling, udvikler mange mennesker sygdommen. Forskning i åreforkalkning er vigtig for at forstå de underliggende mekanismer, der driver udviklingen, og for at finde nye behandlingsmuligheder, der kan bremse åreforkalkningen i at udvikle sig til blodpropper i hjertet og i hjernen.

En vigtig celletype i udviklingen af åreforkalkning er den glatte muskel celle. Den glatte muskelcelle er i celleforsøg vist at bidrage til den inflammatoriske proces og formålet med denne afhandling er, at undersøge den glatte muskelcelles rolle for inflammation i udviklingen af åreforkalkning ved at fjerne vigtige inflammatoriske gener specifikt i de glatte muskelceller i en musemodel, der udvikler åreforkalkning.

Afhandlingen er delt i tre projekter. Det første projekt omhandler MyD88, et adaptor-molekyle, som formidler signalering i den inflammatoriske proces. Vi fandt, at mangel på MyD88 i glatte muskelceller i en mus ikke påvirker udviklingen af åreforkalkning, men reducerede antallet af glatte muskelceller i avancerede åreforkalkningslæsioner. Det andet projekt handler om CCL2, som er et vigtigt signalerings molekyle i den inflammatoriske signalering. I dette projekt fandt vi overraskende, at mus, der mangler CCL2 i de glatte muskelceller har højere cholesteroltal end mus, der fortsat udtrykker CCL2 i de glatte muskelceller. Sidste projekt handler om VCAM1, der også er et vigtigt signalerings molekyle i inflammationsprocessen. Vi fandt, at mangel på VCAM1 i glatte muskelceller ikke påvirkede væksten af glatte muskelceller i mus udsat for karskade, men derimod reducerede udviklingen af brusk-lignende celler i den skadede karvæg. Til sidst fandt vi, at at mangel på VCAM1 i glatte muskelceller reducerede dannelsen af åreforkalkning i mus.

Forsvaret af ph.d.-projektet er offentligt og finder sted den 13. december 2019 kl. 14.30 i Auditorium B, Aarhus Universitetshospital, Skejby, Palle Juul-Jensens Boulevard 99, Aarhus. Titlen på projektet er "Functional roles of Smooth Muscle Cells in Neointima and Atherosclerosis Formation". Yderligere oplysninger: Ph.d.-studerende Stine Gunnersen, e-mail: stine.gunnersen@clin.au.dk, tlf. 20845570.

Bedømmelsesudvalg:
Associate professor, Simon Glerup, Department of Biomedicine, Aarhus University.

Senior Lecturer, Helle Jørgensen, Division of Cardiovascular Medicine, University of Cambridge, Cambridge Biomedical Campus.

Associate professor, Daniel Ketelhuth, Kardiovaskulær og Renal Forskning, SDU, Odense.

Press release (English)

Functional roles of Smooth Muscle Cells in Neointima and Atherosclerosis Formation.

In a new PhD project from Aarhus University, Health, the role of smooth muscle cells in inflammation during atherosclerosis development and upon arterial injury are investigated. By using genetic modificed mouse models lacking important genes in the pro-inflammatory pathway specifically in smooth muscle cells, the influence of these genes on the development of atherosclerosis and arterial injury induced neointima was investigated. The project was carried out by Stine Gunnersen, MD, who is defending her PhD dissertation on the 13th of December 2019.

Atherosclerosis is the underlying cause of heart attatch and stroke. It is a chronich inflammatory disease driven by retention of cholesterol particles in the arterial wall. The treatment options for atherosclerosis primary consist of cholesterol-lowering drugs and life-style interventions, but still, many people develop the disease. Research of the underlying mechanisms and the importance of inflammation for atherosclerosis development is important to find new drug targets with the potential to inhibit the disease progression.

In the initiation and progression of atherosclerosis and other arterial diseases, smooth muscle cells play an important role. Smooth muscle cells have also in cell studies been shown to contribute to the inflammatory process. The purpose of the current PhD project was to investigate the influence of smooth muscle cells on inflammation during atherosclerosis development by deleting important genes in the proinflammatory pathway specifically in smooth muscle cells in mice that develops atherosclerosis.

The PhD dissertation consists of three projects. In the first project, we investigate atherosclerosis development in a mouse with smooth muscle cell specific deletion of MyD88, an adaptor molecyle that facilitates signaling in the proinflammatory pathway. We found, that lack of MyD88 in smooth muscle cells does not influence the development of atherosclerosis, but reduces the number of smooth muscle cells in advanced atherosclerotic lesions. In the second project, we investigate atherosclerosis development in a mouse model with smooth muscle cells specific deletion of CCL2, a cytokine in the proinflammatory pathway. Suprisingly, we found lack of CCL2 in smooth muscle cells, to increase plasma cholesterol levels and thereby increase atherosclerosis development. In the last project, we investigated the importance of VCAM1 expression in smooth muscle cells for development of neointima in response to arterial injury and for atherosclerosis development in mice. VCAM1 is an adhesion molecyle important for monocyte recruitment and for the infmammatory process. We found that lack of VCAM1 did not influence proliferation of smooth muscle cells in response to arterial injury, but reduced development of chondrocyte-like cells in the injured arterial wall. Last, we found lack of VCAM1 in smooth muscle cells to reduce atherosclerosis development in hypercholesterolemic mice.

The defence is public and takes place on the 13th of December 2019 at 14.30 in Auditorium B, Aarhus University Hospital, Skejby, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N. The title of the project is "Functional roles of Smooth Muscle Cells in Neointima and Atherosclerosis Formation". For more information, please contact PhD student Stine Gunnersen, email: stine.gunnersen@clin.au.dk, Phone +45 20845570.

Assessment committee:
Associate professor, Simon Glerup, Department of Biomedicine, Aarhus University.

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