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Title of project: Unraveling the role of apoM in diabetic nephropathy – implication of glycocalyx formation and S1P signaling on kidney fibrosis

ABSTRACT

Diabetic nephropathy is one of the most common complication within diabetes. It is a disease characterised by a progressive formation of kidney fibrosis and decreased kidney function, both common features for chronic kidney disease (CKD). Besides dialysis, treatment options are poor and there are no good biomarkers for disease progression. My vision is to investigate the role of apolipoprotein M (apoM) on kidney fibrosis via effects on glycocalyx formation and sphingosine-1-phosphate (S1P) signaling.

ApoM is a ~25 kDa apolipoprotein bound to high density lipoproteins that carries the bioactive lipid S1P in plasma. The apoM/S1P complex preserves endothelial barrier function, but the mechanism is not known. Glycocalyx is a network of proteins and advanced sucker molecules on the surface of endothelial cells. This network is central for maintaining the barrier function, and is interestingly, reduced in patients with diabetes. We have preliminary data indicating that lack of apoM reduces glycocalyx components in mice. Thus, in the present project I will address whether plasma apoM/S1P affects the glycocalyx barrier and thereby the formation of fibrosis in the kidney - and whether this is augmented in a diabetic setting. These studies will be performed by using unique apoM mouse models. Also, I will unravel whether possible effects on kidney fibrosis are due to plasma derived or kidney specific apoM.

In patients, the degree of kidney fibrosis is today determined by taking a kidney biopsy. This introduces a risk for the patient and reduces the number of times the degree of fibrosis can be determined, which highlights the need for new biomarkers. S1P is part of a bigger sphingolipid family that is derived from ceramide. An imbalance in the levels of sphingolipid intermediates has, among others, been associated with fibrosis. Such imbalances have been found in patients with type-2-diabetes. Thus, to address whether imbalances in the sphingolipid composition could serve as biomarkers, I will measure the sphingolipid profile in patients with CKD and associate these patterns with the degree of kidney disease. This will be done in collaboration with experts within the field (the SLING group, Singapore University) and the department of Nephrology, Rigshospitalet.

Overall, the proposed project will uncover new aspects of apoM/S1P in kidney fibrosis in a diabetic setting and will potentially add valuable knowledge on new, much needed, new target and diagnostic tools in the treatment of kidney fibrosis.

ABSTRAKT

Diabetisk nefropati er en af de komplikationer, der oftest ses hos patienter med diabetes. Sygdommen er karakteriseret af en progressiv fibrosedannelse i nyrerne og nedsat nyrefunktion, hvilket er to centrale kendetegn ved kronisk nyresydom (chronic kidney disease, CKD). Udover dialyse er behandlings-mulighederne dårlige, og der er ingen gode biomarkører for sygdomsprogression. Min vision er at undersøge hvorvidt apolipoprotein M (apoM) spiller en rolle i udviklingen af nyrefibrose via effekter på glycocalyx-dannelse og sphingosine-1-phosphate (S1P) signallering.

ApoM er et ~25 kDa apolipoprotein bundet til HDL, der fungerer som transportør af det bioaktive lipid S1P i plasma. ApoM/S1- komplekset opretholder en normal endothelcelle-barriere, men mekanismen bag dette er ukendt. Glycocalyx er et netværk af proteiner og avancerede sukkermolekyler på endothelcellens overflade. Dette netværk er centralt for opretholdelsen af barrierefunktionen og er højst interessant reduceret i patienter med diabetes. Vi har præliminære data, der indikerer at mangel på apoM reducerer niveauet af visse glycocalyx-komponenter i mus. I projektet ønsker jeg derfor at undersøge, om plasma apoM/S1P påvirker glycocalyx-barrieren og dermed fibrosedannelse i nyren - og hvorvidt dette er øget i sammenhæng med diabetes. Disse studier vil blive foretaget i unikke apoM musemodeller. Samtidig vil jeg undersøge om mulige effekter på fibrose skyldes apoM i plasma eller nyrespecifikt apoM.

Graden af nyrefibrose i patienter bestemmes i dag ved hjælp af en nyrebiopsi. Det introducerer en risiko for patienten og begrænser antallet af gange fibrosegraden kan bestemmes, hvilket understreger behovet for nye biomarkører. S1P er en del af en større sphingolipid-familie der dannes ud fra ceramid. En ubalance i niveauerne af de enkelte sphingolipid-intermediater er blandt andet blevet associeret med fibrose. Sådanne ubalancer er blevet fundet i patienter med type-2-diabetes. For at adressere om ubalancer i spingolipidprofilen kan fungere som biomarkører, vil jeg måle sphingolipidprofilen i patienter med CKD og associere disse mønstre med graden af nyresygdom. Det vil blive gjort i samarbejde med eksperter indenfor feltet (SLING gruppen, Singapore Universitet) og Nefrologisk Klinik, Rigshospitalet.

Samlet vil det foreslåede projekt afdække helt nye aspekter af apoM/S1P's rolle i nyrefibrose i sammenhæng med diabetes og vil potentielt kunne give os værdifuld viden om nye targets og diagnostiske værktøjer i behandlingen af nyrefibrose.