**Press release**

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**Basic information**

Name: Stine Aarhus Mikkelsen Email: smik@biomed.au.dk Phone: 29260840

Department of:

Main supervisor: Jens Peter Andersen

Title of dissertation: Mutational studies of structure-function relationship in the mammalian flippase ATP8A2 and SERCA - “The giant substrate problem” of flippases and the mechanism underlying Darier Disease mutation E917K”

Date for defence: 28-11-2017 at (time of day): 13 Place: in auditorium 6, building 1170, Aarhus University, 8000 Aarhus C.

Press release (Danish)

Mutationsstudier af struktur-funktions forhold i den mammale flippase ATP8A2 og SERCA- "The giant substrate problem" i flippaser og mekanismen bag Darier sygdommen.

Et nyt ph.d.-projekt fra Aarhus Universitet, Health, bidrager til forståelse af den molekylære mekanisme, hvormed flippaseenzymet flytter fosfolipider over cellemembranen og den tilgrundliggende mekanisme for en mutation i SERCA enzymet, som fører til Darier hudsygdommen. Projektet er gennemført af cand. scient. Stine Aarhus Mikkelsen, der forsvarer afhandlingen d. 28/11 2017

Flippaser og SERCA er begge medlemmer af P-type ATPase enzym familien. Flippaser opretholder den vigtige asymmetriske lipid fordeling i cellemembranen ved at flytte bestemte fosfolipider fra den ene side af membranen til den anden, men mekanismen bag dette er endnu ukendt. Fosfolipider er ca. 10 gange større end ioner, og derved er det et mysterium, hvordan flippaseenzymet bliver i stand til at flytte dem. SERCA flytter Ca-ioner over endoplasmisk retikulum membranen inde i cellen og sørger for at opretholde den korrekte hvile Ca-koncentration i cellen, som ellers flukturerer ved forskellige cellulære processer.

I dette projekt er flipasens mekanisme blevet belyst ved mutagenese studier, hvormed vigtige aminosyrer er identificeret i flippasens membrandomæne. Dette danner grundlag for at foreslå en mekanisme, som kan forklare flippasens flytning af fosfolipider ved hjælp af en transportvej centralt placeret i membrandomænet, meget analogt til de iontransporterende P-type ATPaser som f.eks. SERCA, til trods for lipidernes størrelse. Den sygdomsfremkaldende mutation i SERCA enzymet har afsløret et vigtigt hydrogen-bindings-netværk, som bidrager til at kontrollere enzymets hastighed, desuden har det ført til belysning af isoformspecifikke ligheder og forskelle i SERCA.

Forsvaret af ph.d.-projektet er offentligt og finder sted den 28/11 kl. 13 i auditorium 6, bygning 1170, Aarhus Universitet, Ole Worms Allé 3 , 8000 Aarhus C. Titlen på projektet er ”Mutational studies of structure-function relationship in the mammalian flippase ATP8A2 and SERCA - “The giant substrate problem” of flippases and the mechanism underlying Darier Disease mutation E917K””. Yderligere oplysninger: Ph.d.-studerende Stine Aarhus Mikkelsen, e-mail: smik@biomed.au.dk, tlf. 29260840.

Bedømmelsesudvalg:

Natalya Fedosova (formand for bedømmelsesudvalget)

Department of Biomedicine, Aarhus University, Denmark

Thomas Günther-Pomorski

University of Bochum / Department of Biochemistry II, Germany

Howard S. Young

Department of Biochemistry, University of Alberta, Canada

Press release (English)

Mutational studies of structure-function relationship in the mammalian flippase ATP8A2 and SERCA - “The giant substrate problem” of flippases and the mechanism underlying Darier Disease mutation E917K”

A new PhD-project from Aarhus University, Health, contributes to understanding how the flippases move phospholipids across the cell membrane and the underlying mechanism of a Darier disease-causing mutation in SERCA.

The project has been carried out by MSc Stine Aarhus Mikkelsen, who is defending her thesis on November 28th, 2017.

Flippases and SERCA both belong to the P-type ATPase enzyme family. Flippases maintain the essential asymmetric lipid distribution in the cell membrane by moving specific phospholipids from one side to the other side of the membrane, however the underlying mechanism is still unknown. Phospholipids are about 10 times the size of ions and this makes a mystery of how the flippase manages this process. SERCA moves Ca-ions across the ER-membrane inside the cell and maintains the resting Ca concentration in the cell, which fluctates during different cellular processes.

Mutational analysis was used to elucidate the flippase mechanism in this project, and critical amino acid residues have been identified in the flippase membrane domain. On this basis a mechanism has been suggested by which the flippase moves phospholipids through the most central part of the membrane domain analogously to ion transporting P-type ATPases such as SERCA, despite the giant nature of the lipid substrate.

The disease-causing mutation in the SERCA enzyme has revealed a important hydrogen bonding network contributing to control the velocity of the enzyme, as well as isoform specific similarities and differences in SERCA.

The defence is public and takes place on November 28th at 1 pm in auditorium 6, building 1170, Aarhus University, Ole Worms Allé 3, Aarhus C. The title of the project is "Mutational studies of structure-function relationship in the mammalian flippase ATP8A2 and SERCA - “The giant substrate problem” of flippases and the mechanism underlying Darier Disease mutation E917K”. For more information, please contact PhD student Stine Aarhus Mikkelsen, email: smik@biomed.au.dk, Phone +45 29260840.

Assessment committee:

Natalya Fedosova (chairman and moderator of the defence)

Department of Biomedicine, Aarhus University, Denmark

Thomas Günther-Pomorski

University of Bochum / Department of Biochemistry II, Germany

Howard S. Young

Department of Biochemistry, University of Alberta, Canada

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