Press release

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Basic information

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Department of: Biomedicine

Main supervisor: Anders Børglum

Title of dissertation: Molecular characterization of the schizophrenia associated ZEB1 and ZEB2 genes

Date for defence: 03/10/2017 at (time of day): 13:00 Place: Edward Biermann,Søauditorium (Building 1252-204).

Press release (Danish)
ZEB1 og ZEB2 iddragelse i skizofreni.

Skizofreni er en invaliderende og kompleks psykiatrisk lidelse med meget begrænset kendskab til de bagvedliggende årsagsfaktorer. Det vides dog, at arvelige faktorer er den væsentligste årsagskomponent og de senere års forskning har resulteret i identifikation af en række risikogener for skizofreni. Blandt de identificerede kandidater er Zink finger E-box bindende homeobox 2(ZEB2) og Zink finger E-box bindende homeobox 1 (ZEB1) generne. Der er begrænset viden om disse gener og deres rolle i patogenesen af skizofreni. Formålet med denne afhandling var at identificere molekylære interaktioner for ZEB1 og ZEB2 i humane celler, hvilket kan øge forståelsen af deres rolle i udviklingen af skizofreni. I de to første studier blev nye protein-protein interaktioner af henholdsvis ZEB1 of ZEB2 identificeret ved brug af co-immunopræcipitation og massespektrometri (LC-MS/MS). I det første studie fandt vi, at sphingomyelin syntase 2 (SGMS2) og Eh domain containing 4 (EHD4) binder til ZEB2. Da sphingomyelin er beriget i myelinskederne dannet af oligodendrocytter og Schwannske celler, var fundet med til at danne en hypotese om, at denne interaktion er vigtig i disse celletyper. I det andet studie identificerede vi 46 nye proteininteraktioner med ZEB1. Den stærkeste interaktion var med basic helix-loop-helix transkriptionfaktor, HES6, som er vigtig for dannelse og differentiering af nerveceller. Disse resutater giver ny information om de underliggende sygdomsmekanismer og anledning til at danne nye hypoteser om ZEB1's molekylære funktion.
Det tredje og sidste studie var et hypotese-baseret studie. Et tidligere studie har indikeret, at ekspressionen af ZEB1 kan påvirkes af hypoxia induced factor, HIF1A. Derudover har en mindsket mængde af juntion zonula occludens 1, ZO1, vist sig at føre til forstyrrelser i endotelbarrieren i hjernen. Disse informationer var med til at forme hypotesen, at hypoxi opregulerer ekspressionen af ZEB1, som så vil påvirke ZO1 udtrykket. Studiet havde derfor til formål at udersøge sammenhængen mellem hypoxi, Zeb1 og Zo1 ekspression i endotelceller fra musehjerner. Vi fandt en positiv korrelation mellem Zeb1 og Zo1, som imidlertid var uafhængig af oxygenniveauet.
Disse studier har dannet ny biologisk indsigt i ZEB1 og ZEB2-funktionerne og bidraget til forståelsen af deres rolle i udviklingen af skizofreni.

Resultaterne er sammenfattet i et nyt ph.d.-projekt fra Aarhus Universitet, Health. Projektet er gennemført af Desirée Leduc, der forsvarer d. 03/10-2017.

Forsvaret af ph.d.-projektet er offentligt og finder sted den 03/10 kl. 13:00 i Edward Biermann,Søauditurim, Aarhus Universitet, Bartholins Allé 3, Aarhus C. Titlen på projektet er "Molekylær karakterisering af skizofreni-associerede ZEB1 og ZEB2 gener". Yderligere oplysninger: Ph.d.-studerende Desirée Leduc, e-mail: leduc@biomed.au.dk, tlf. 22309625.

Bedømmelsesudvalg:
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Press release (English)

ZEB1 and ZEB2 involvement in schizophrenia

Schizophrenia , is a disabling psychiatric disorder with a complex and not well understood etiology. It is belived that the etiology is an elaborate interplay between genetic, epigenetic and envrionmental factors. Major efforts over the years especially in the genetic field have resulted in the identification of many risk genes, among others the Zinc finger E-box binding homeobox 2(ZEB2) and Zinc finger E-box binding homeobox 1 (ZEB1) gene. The role of these two genes in the pathogenesis of schizophrenia is limited. The general aim of this thesis was to unravel the molecular role of ZEB2 and ZEB1 in human cells. In the first two studies, the protein-protein interactions of ZEB1 and ZEB2 in were explored using co-immunoprecipitaion and nano liquid chromatography and mass spectromety (LC-MS/MS). In the first study,we identified sphyngomyelin synthatase 2(SGMS2) and Eh domain containing 4 (EHD4) to be inetarcting with ZEB2. Sphyngomyelin is particularly abundandt in the myelin sheaths of oligodendrocytes and Shwan cells, by which we hypothesised that this interaction may play a role in this cell type. In the second study, we identidied 46 new protein interactions for ZEB1. The strongest interaction detected was the basic helix -loop-helix transcription factor, HES6, which is important for the formation and differentiation of nerve cells. These results provide new information on the underlying disease mechanisms and the opportunity to form new hypothesis about the molecular function of ZEB1. The third and last study, was a hypothesis based study. An earlier study had identified that ZEB1 expression is affected by the hypoxia induced factor , HIF1A. Addtitionally, a decreased amount of junction zonula occludens 1, ZO1, has been shown to cause diruption in the endothelial barrier in the brain. This information helped in shaping the hypothesis that hypoxia upregulates the expression of ZEB1 , which will affect the ZO1 expression. The study aimed at exploring the relationship between hipoxia, Zeb1 and Zo1 expression in endothelial cells of mouse brain. We found a positive correlation between Zeb1 and Zo1, although independet of the oxygen levels. These studies have provided new biological insights into the ZEB1 and ZEB2 function, and contributed to the understanding of their role in the development of schizophrenia.

The project was carried out by Desiree Leduc , who is defending her/his dissertation on the 03 /10.

The defence is public and takes place on Edward Bierman/Søauditorium at 13:00, Aarhus University, Whilhem Myeres Alle, Aarhus. The title of the project is "Molecular characterization of schizophrenia associated ZEB1 and ZEB2 genes". For more information, please contact PhD student Desiree Leduc , email: leduc@biomed.au.dk, Phone +45 22309625.

Assessment committee:
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