Press release

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Basic information

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Department of: Biomedicine

Main supervisor: Associate Professor Mette Madsen

Title of dissertation: Large endocytic receptors in development and disease –
Investigations of LRP1 and LRP2 in placental maturation and metastatic competence of malignant melanoma.

Date for defence: 23 at (time of day): 11 AM Place: 1115-151B Meeting room 22, Skou building, Aarhus University.

Press release (Danish)

Ph.d. forsvar med titlen: Store endocytiske receptorer i udvikling og sygdom - Undersøgelser af LRP1 og LRP2 i placental modning og metastatisk kompetence i malignt melanom

Forsvaret omhandler et nyt ph.d.-projekt fra Aarhus Universitet, Health. Projektet er gennemført af Julie Nelly Christensen der forsvarer det d. 23 September

Ph.d. projektet havde til formål at undersøge ekspressionen og rollen af de to store endocytiske receptorer LRP1 og LRP2 under henholdsvis placentaudvikling og progression af modermærkekræft. Unormal placentaudvikling og funktion er forbundet med ændringer i moderens fysiologiske tilstand, som det f.eks. ses i tilfælde af fedme, hvilket øger risikoen for patologiske placentatilstande. Ud over sundhedsrisikoen forbundet med placentapatologi direkte under graviditeten, har studier også vist øget tilbøjelighed til udvikling af sygdom senere i livet for både mor og foster. I øjeblikket findes der ingen pålidelige screenings-, forebyggelses- eller behandlingsmuligheder for patologiske placentatilstande. Øget forståelse af de molekylære ændringer, der er involveret i udviklingen af placentasygdom, kan være med til at drive fremskridt inden for forebyggelses og behandlingsfeltet. Den endocytiske receptor LRP1 er højt udtrykt i placenta og vist at være vigtig for fosterudvikling. Vi undersøgte ekspressionen af LRP1 i placentaprøver fra 1. trimester fra normalvægtige og overvægtige kvinder på gen- og proteinniveau. Vi observerede ændret ekspression af LRP1 hvilket indikerer at receptoren muligvis spiller en rolle i den tidlige udvikling af placentaen i tilfælde af abnorm maternel fysiologi. Analyse af offentlige genekpressions data fra normale og intra uterin vækstbegrænsede placentaer viste ændret ekspression af LRP1. Yderligere fandt vi ved in vitro-undersøgelser en sammenhæng mellem LRP1-ekspression og placentamodning.
Malignt melanom er en meget aggressiv kræftform på grund af tidlig spredning af sygdommen. Spredning er relateret til fænotype ændringer i melanomcellerne til mindre differentierede celletyper. LRP2 ekspression er tidligere beskrevet som et karakteristika af en proliferativ fænotype og samtidig er proliferation blevet associeret til differentiering gennem ekspressionsmønstre som samlet beskriver mindre aggressive melanomceller. Vi undersøgte ekspressionen af LRP2 i to kohorter af primære melanomtumorer og korrelerede ekspressionen med kliniske data. For yderligere at undersøge LRP2's rolle i melanom udførte vi in vitro fjernelse af receptoren ved hjælp af CRISPR/Cas9-teknologi. LRP2-KO-modellen blev evalueret ved anvendelse af teknikker, som tester metastatisk potentiale, herunder Boyden-kammer, sfæredannelses-assay og co-kulturer med immunceller. Samlet viste vores analyser, at LRP2 spiller en vigtig rolle i de indviklede netværk, der styrer melanomprogression.
Forsvaret af ph.d.-projektet er offentligt og finder sted den 23 September kl. 11 i 1115-151B, Møderum 22, Skou bygningen, Aarhus Universitet, Høegh Guldbergsgade 10, 8000 Aarhus C. Titlen på projektet er ”Store endocytiske receptorer i udvikling og sygdom - Undersøgelser af LRP1 og LRP2 i placental

modning og metastatisk kompetence i malignt melanom". Yderligere oplysninger: Ph.d.-studerende Julie Nelly Christensen, e-mail: jnc@biomed.au.dk.

Bedømmelsesudvalg: Henrik Hager, konsulterende patolog og klinisk lektor ved Vejle Hospital, Afdeling for klinisk patologi og Lukas Sommer, Professor ved Zurich Universitet, Anatomisk Institut Institute of Anatomy. Udvalgets formand: Hanne B. Møller, MD Ph.d., Lektor, Aarhus Universitet, Biomedicinsk Institut.
Hovedvejleder: Mette Madsen, Ph.d., Lektor, Aarhus Universitet, Biomedicinsk Institut.

Press release (English)

PhD defence entitled: Large endocytic receptors in development and disease – Investigations of LRP1 and LRP2 in placental maturation and metastatic competence of malignant melanoma.

The project was carried out by Julie Nelly Christensen, who is defending her dissertation on the 23nd of September.

The PhD project aimed to investigate the expression and role of the two large endocytic receptors LRP1 and LRP2 during placental development and melanoma skin cancer progression, respectively. Abnormal placental development and function is associated with altered maternal physiological conditions, like seen in obesity, increasing the risk of placental pathology. In addition to the immediate health risk associated with placental pathologies, studies have also shown predisposition of both mother and fetus to disease later in life. Currently no reliable screening, prevention or management options exist for placental pathologies thus, understanding the molecular changes involved in the development of placental disease might enable advancement within the field of prevention and treatment. The endocytic receptor LRP1 is highly expressed in the placenta and shown to be important for fetal development. We investigated the expression of LRP1 in 1st trimester placental samples from normal weight and obese women at gene and protein level. Altered expression of LRP1 was identified indicating a possible role for receptor in early placental events linked to abnormal maternal physiology. Altered expression of placental LRP1 was identified by analysis of public data of gene expression in normal and intra uterine growth restricted placentaes. In vitro investigations of LRP1 expression during placental maturation events indicated an association between the two.
Malignant melanoma is a very aggressive cancer due to early dissemination. Dissemination is related to phenotypic changes in the melanoma cells to less differentiated cell types. LRP2 have previously been described as a trait of a proliferative phenotype and the proliferation of melanoma cells has been linked to differentiation through expressional patterns, which describe less aggressive melanoma cells. We investigated the expression of LRP2 in two cohorts of primary melanoma tumors and correlated the expression to clinical data. To further investigate the role of LRP2 in melanoma, we performed in vitro ablation of the receptor using CRISPR/Cas9 technology. The LRP2-KO model was evaluated using techniques testing metastatic potential including Boyden chamber analysis, spheroid assays and immune cell co-cultures. Collected the analyses showed LRP2 to play an important role in the intricate networks controlling melanoma progression.
The defence is public and takes place on the 23nd of September at 11 AM in 1115-151B Meeting room 22, Skou building, Aarhus University, Hoegh Guldbergsgade 10, 8000 Aarhus C. The title of the project is 'Large endocytic receptors in development and disease –
Investigations of LRP1 and LRP2 in placental maturation and
metastatic competence of malignant melanoma'. For more information, please contact PhD student Julie Nelly Christensen, email: jnc@biomed.au.dk.

Assessment committee:
Henrik Hager, Consultant Pathologist and associate clinical professor at Vejle Hospital, Dept. of Clinical Pathology and Lukas Sommer, Professor at the University of Zurich, Institute of Anatomy.
Chair of the committee: Hanne B. Møller, MD PhD, Associate Professor Aarhus University, Department for Biomedicine.
Main supervisor and non-voting member of committee: Mette Madsen, PhD, Associate Professor Aarhus University, Department for Biomedicine.

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