AARHUS UNIVERSITY

Press release

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Basic information

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Department of: Forensic Medicine

Main supervisor: Professor MSO Mogens Johannsen

Title of dissertation: Elucidation of the Hotspots for Advanced Glycation - The Missing Links between AGE and Aging-related Diseases

Date for defence: March 6th 2019 at (time of day): 3:15 PM Place: Aud-I (1514-213), Department of Chemistry, Aarhus University

Press release (Danish)

Kortlægning af hotspots for glykering - De manglende forbindelser mellem slutprodukter for glykering og aldersbetingede sygdomme

Methylglyoxal er et biprodukt fra glykolysen – en metabolit som er kendt for sin høje reaktiveret og for at reagere med endogene makromolekyler så som proteiner, DNA og lipider. Denne reaktion skaber strukturelle ændringer i de ramte molekyler, hvilket potentielt kan lede til dysfunktion. Afgiftningsmekanismer eksisterer for at minimere niveauet af methylglyoxal, men i tilfælde af ubalanceret dannelse og afgiftning, kan methylglyoxal have en skadelig effekt på det biologiske system. Evidens peger på, at modifikationer afledt af methylglyoxal er forbundet med molekylære ændringer ved aldring og i udviklingen af flere aldersbetingede sygdomme. Dog mangler en bredere viden omkring hvilke biomolekyler, der bliver modificeret af methylglyoxal, for at opnå en mere omfattende forståelse af dets skadelige virkninger i biologien. Dette er nærmere studeret i et nyt ph.d.-projekt fra Aarhus Universitet, Health. Projektet er gennemført af Anne-Mette Schou Oxvig, der forsvarer det d. 6/3-2019

I dette Ph.d.-projekt har vi profileret proteiner, der modificeres af methylglyoxal. Disse undersøgelser er blevet udført ved hjælp af en kemisk probe, som i sin struktur ligner den naturlige metabolit, men som er designet som et værktøj til at studere følgerne af methylglyoxal. Vi har demonstreret, at proben er egnet til at studere methylglyoxal i generelle biologiske sammenhænge. Proben er blevet anvendt til at undersøge methylglyoxalmetabolisme og proteinmodifikationer i blod. Vi har udviklet en metode til sideløbende at følge fluxen til de to processer; afgiftning og proteinmodifikation, i den samme biologiske prøve. I prøver af fuldblod og plasma viste vi, at graden af proteinmodifikation er afhængig af den enzymatiske afgiftning fra glyoxalasesystemet i blodceller. Herudover har vi kortlagt proteiner, der modificeres af methylglyoxal, for nu at præsentere den første generelle opgørelse af hvordan blodproteomet rammes. Derudover anvendte vi proben til at profilere modificerede proteiner i cellelysat. Dette studie blev udført som en reaktivitetsbaseret profilering for at kortlægge potentielle "hotspots" for methylglyoxal. Disse hotspots – proteiner der udviser hyperreaktivitet for modifikation – var af særlig interesse, da vores hypotese går på, at deres modifikation spiller en vigtig rolle i de biologiske konsekvenser af methylglyoxal. Med dette studie, kan vi derfor, foruden at præsentere den første globale kortlægning af proteiner modificeret af methylglyoxal i cellelysat, også præsentere en profil af potentielle hotspots for methylglyoxal-modifikationer. Vi evaluerede de identificerede modificerede proteiner og fandt modifikation af flere funktionelt vigtige aminosyrer. Desuden observerede vi, at modifikationen afhænger af specifikke aminosyresekvenser rundt om den modificerede aminosyre. Dette kunne tyde på at sekvensmotivet kan spille en rolle for både produktet af modifikationen og reaktiviteten af aminosyren. .

Forsvaret af ph.d.-projektet er offentligt og finder sted den 6/3 kl. 15:15 i Aud-I (1514-213), Aarhus Universitet, Langelandsgade 140, Aarhus C. Titlen på projektet er "Elucidation of the Hotspots for

Advanced Glycation - The Missing Links between AGE and Aging-related Diseases". Yderligere oplysninger: Ph.d.-studerende Anne-Mette Schou Oxvig, e-mail: annemette.oxvig@forens.au.dk, tlf. 28303447.

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Press release (English)

Elucidation of the hotspots for advanced glycation - The missing links between advanced glycation end-products (AGE) and aging-related diseases

Methylglyoxal, a metabolic byproduct from the glycolytic pathway, is known to be highly reactive and to react with endogenous macromolecules such as proteins, DNA, and lipids. This reaction causes structural modifications in the target molecules, which may lead to dysfunction. Detoxification mechanisms exist to minimize the level of methylglyoxal; however, in cases of unbalanced formation and detoxification, methylglyoxal may have deleterious effects on the biological system. A growing body of evidence suggests that methylglyoxal-derived modifications are linked to molecular changes during aging and in the development of several aging-related diseases. However, a deeper knowledge into the targets of methylglyoxal is needed for a more comprehensive understanding of its deleterious impact in biology. This is further investigated in a new project conductet at Aarhus University, Health. The project was carried out by Anne-Mette Schou Oxvig, who is defending her dissertation on March 6th 2019.

In this PhD study, we have profiled protein targets for methylglyoxal-modifications. Investigations have been performed using a chemical probe, which structurally resembles the native metabolite but is designed as a tool to study the actions of methylglyoxal. We have demonstrated that the probe is a suitable proxy for methylglyoxal in biological studies. The probe has further been used to investigate methylglyoxal metabolism and protein modification in blood. We developed a method to simultaneously monitor the flux to the two processes; detoxification and protein modification, in the same biological sample. Using whole blood and plasma, we demonstrated that the degree of protein modification is dependent on the enzymatic detoxification by the glyoxalase system in blood cells. Furthermore, proteins modified by methylglyoxal were elucidated, to reveal the first general inventory of blood proteome targets. The probe was additionally used to profile protein targets in cell lysates. This experiment was performed as reactivity-based profiling to elucidate potential "hotspots" for methylglyoxal. These hotspots – targets which show hyperreactivity toward modification – were of special interest as we hypothesize their modification to be important for the biological consequences of methylglyoxal. Hence, with this study, we may not only present the first global elucidation of methylglyoxal targets in cell lysates, but also a profile of potential hotspots for methylglyoxal-derived modifications. We evaluated the identified target sites of our probe and detected several functionally important residues to be modified. Furthermore, we observed the modification to be dependent on specific patterns in the amino acid sequence surrounding the target residue. This suggests that the sequence motif may play a role, both for the modification product and the reactivity of the amino acid residue.

The defence is public and takes place on March 6th 2019 at 3:15 PM in Aud-I (1514-213), Aarhus University, Langelandsgade 140, Aarhus C. The title of the project is "Elucidation of the Hotspots for Advanced Glycation - The Missing Links between AGE and Aging-related Diseases". For more

information, please contact PhD student Anne-Mette Schou Oxvig, email: annemette.oxvig@forens.au.dk, Phone +45 2830 3447.

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