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Title of project: Discovery and study of hot-spots for proteome advanced glycation

ABSTRACT

During glycolysis a ubiquitous toxic byproduct methylglyoxal (MG) is formed. MG is a reactive α-oxoaldehyde that reacts non-enzymatically with arginine and lysine residues in proteins to form advanced glycation end-products (AGEs). AGE causes structural and functional changes to proteins, and it is becoming increasingly clear that MG and the generated AGEs are both common factors in the development and progression of diabetes and age-related diseases. This is supported by human association studies between MG or AGE and diabetic complications such as kidney and cardiovascular disease for both *diabetes mellitus* type 1 and type 2. Additionally, the correlation has been shown in animal studies, where elevated levels of MG are associated with different late diabetic complications. Despite the connections between MG or AGE and disease, are well established, the molecular details usually remain elusive and only in a limited number of cases a direct link between a specific AGE modified protein and diabetic complications have been elucidated. The reason is that AGE formation is a non-enzymatic process, where MG reacts with thousands of proteins. Without knowing which proteins that are particular susceptible for AGE formation and accordingly gets modified to a level where its function is impaired, it is inherently difficult to elucidate the detailed pathological mechanisms and move the field forward. We have recently developed a unique tool that allows us to map proteins particularly susceptible to AGE formation *in vivo.* Our objective is now to identify these hyper-reactive proteins to generate a map of those proteins most likely to be involved in AGE-related cellular dysfunction. Furthermore, we aim to perform functional studies of a selected number of these hyper-reactive proteins in order to increase our understanding of non-enzymatic glycation in diabetes. We hope that the results of our studies will become a unique tool for researchers working with diabetes and AGE that will help to understand the molecular details of these diseases, and help the field to move forward.

ABSTRAKT

Med forskningsprojektet ønskes afdækning og undersøgelse af de spontane ændringer, der sker på humane proteiner som følge af forhøjet blodsukker. Ændringer som over tid kan lede til aldersrelaterede sygdomme såsom diabetes og hjerte-kar-sygdomme. På molekylært plan opstår de ved, at et biprodukt fra sukkerstofskiftet kaldet methylglyoxal reagerer med proteinerne under dannelse af såkaldte avancerede glykeringsslutprodukter (AGEs). Methylglyoxal forandrer således tusindvis af proteiner i den humane organisme. Hvilke af disse forandringer der påvirker udviklingen af diabetes og sendiabetiske komplikationer, er dog stadig uklart. Denne uvished hæmmer forskning og udvikling på området væsentligt, da man ganske enkelt ikke ved, hvor fokus skal rettes hen, dvs. hvilke proteiner der er værd at undersøge for at bremse sygdomsudviklingen. For at afklare dette har vi udviklet en kemisk methylglyoxal-probe, et molekyle der med høj præcision kan kortlægge de forskellige typer af AGEs, såvel som, ved stigende koncentration, også

identificere de mest reaktive proteiner, såkaldte hotspots. Disse hotspot-proteiner vil med stor sandsynlighed være centrale i udviklingen af diabetes- og aldringsrelaterede sygdomme. Ved at afdække denne gruppe af proteiner, håber vi således at kunne fokusere forskningen, og dermed bidrage til at området flytter sig væsentligt i fremtiden. I samarbejde med udenlandske specialister vil vi selv undersøge, hvorledes modifikation af centrale hotspot-proteiner leder til dysfunktionelle celler og metabolisme i diabetes. Hvis vi kan afdække mekanismer centrale for udvikling af diabetes og sendiabetiske komplikationer, vil det i fremtiden være lettere at dirigere en indsats for tidlig behandling og evt. forebyggelse til gavn for den enkelte patient.