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Title of project: Resolving the contribution of subcellular ROS sources to muscle insulin resistance

ABSTRACT

Background: Reactive oxygen species (ROS) from mitochondria may contribute to muscle insulin resistance but are likely modulators rather than initiators of this pathology. NADPH oxidase (NOX)2 is another myocellular ROS source activated by exercise and perhaps insulin, which also responds to a range of insulin-resistance-inducers. NOX2 has been suggested to signal upstream of mitochondria in other cell-types, including heart muscle. My work until now suggests that NOX2 is a major ROS source during in vivo exercise in mice and humans and required for exercise-training stimulated changes in mitochondrial network morphology. However, NOX2 in skeletal muscle remains poorly studied due to a lack of suitable models and methodological shortcomings. This is even more true in humans.
Hypothesis: I hypothesize that NOX2 is hyper-activated in insulin-resistance and required for insulin resistance in skeletal muscle, in part via extensive cross talk between NOX2 and mitochondrial ROS production. In addition, we predict NOX2 to be required some of the health-beneficial effects of exercise in both mice and humans.
Methodology: An international collaborative effort with basic and clinical scientists, combining novel NOX2 mouse models and muscle biopsy material from NOX2-deficient or insulin-resistant human subjects, with innovative subcellular ROS and protein imaging tools and muscle redox proteomics.
Impact: This project will provide the first subcellular insight into the mechanistic role of NOX2 in insulin-resistance and exercise-metabolism in mice and humans, and identify novel redox-signaling targets downstream of NOX2 and mitochondria. This is expected to significantly advance our current understanding of how muscle insulin-resistance develops.

ABSTRACT

En nedsat evne for insulin til at øge sukkeroptagelsen i muskel, kaldet insulinresistens, er en tidlig og væsentlig defekt i udviklingen af type 2 sukkersyge. Overproduktion af frie iltradikaler fra muskelcellernes kraftværk, mitokondrier, er blevet foreslået at spille en rolle i udviklingen af insulinresistens i mange celletyper, herunder muskel, men mitokondriers bidrag er fortsat omstridt. Dette kan skyldes at iltradikaler også kan produceres andre steder i cellerne end mitokondrier, at de forskellige kilder kan kommunikere indbydes, og at de eksisterende metoder og modeller oftest måler på hele muskler og ikke kan skelne mellem forskellige kilders bidrag.

I dette internationale samarbejde med grundvidenskabelige og kliniske forskere vil vi anvende nye redskaber og modeller der muliggør en systematisk visualisering og måling af frie iltradikalproduktionen fra forskellige kilder i muskler fra mus og mennesker med forstyrret iltradikal-signalering. Specifikt vil vi undersøge en stærk formodning om det iltradikal-

producerende enzym NADPH oxidase 2 er et tveægget sværd der både er nødvendigt for musklens udvikling af insulinresistens og for visse gavnlige tilpasninger til motion, bl.a. ved at styre sukkerstofskifte og mitokondrie-tilpasninger. Derudover vil vi ved hjælp af massespektrometri på forskellige dele af muskelcellerne kortlægge hvilke ændringer der sker under påvirkning af fri iltradikaler fra forskellige kilder i dette væv.

Den nye viden og de nye metoder udviklet i dette projekt forventes at kunne bidrage til at afklare frie iltradikalers bidrag til muskelfunktion og insulinresistens og dermed bidrage til mere præcise medicinske forebyggelses og behandlingsstrategier.