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Abstract

Every year, millions of people are diagnosed with cancer, and cancer is one of the leading causes of premature death. Cancer is described as a group of diseases defined by uncontrolled cellular growth. Here, many patients diagnosed with cancer will develop complications in addition to the cancer disease itself. One of these complications is the development of metabolic dysfunction, including insulin resistance. As the development of metabolic dysfunction in patients increases the risk of cancer reoccurrence and death, there is a necessity for treating such conditions. There is currently limited molecular knowledge regarding the pathology of cancer-induced metabolic dysfunction. Thus, the primary aim of the current PhD project was to investigate the mechanisms underlying metabolic dysfunction in cancer.

Using a pre-clinical model of cancer, the Lewis lung carcinoma model, it was showed that especially muscle with an oxidative phenotype developed insulin resistance compared to muscle with a glycolytic phenotype, that did not develop insulin resistance. This was associated with the development of "selective insulin resistance". More specifically, parts of the insulin signaling cascade were abrogated in the oxidative muscle, where several phosphorylation-sites on the protein TBC1D4 were reduced. Additionally, it was showed that subunits of the metabolic stress-sensor, AMP-activated protein kinase (AMPK), were upregulated in skeletal muscle of patients with cancer-induced muscle loss, known as cachexia (non-small cell lung carcinoma). Lacking functional AMPK in muscle during tumor-development in mice aggravated cancer-induced metabolic dysfunction, where treatment with an AMPK activator alleviated insulin intolerance in tumor-bearing mice. In skeletal muscle, cancer led to changes in proteins involved in glucose metabolism in an AMPK-dependent manner. This included the phosphorylation of TBC1D4 and the increase in the protein expression of pyruvate dehydrogenase. Thus, these data suggest that muscle AMPK has a protective role in cancer-induced metabolic dysfunction.

Collectively, the current project provides a greater molecular understanding of the alterations of skeletal muscle seen in the context of cancer in the lung. Furthermore, data of the current PhD project suggest that AMPK may be a possible pharmacological target in treatment of cancer-associated metabolic dysfunction.

Resumé (Dansk)

Millioner af mennesker bliver hvert år diagnosticeret med cancer i verden, hvor cancer er en af de ledende årsager til tidlig død. Sygdommen cancer er en gruppe af sygdomme, som er karakteriseret ved ukontrolleret cellevækst. Cancer kan lede til flere forskellige komplikationer, hvor metabolisk dysfunktion, herunder insulinresistens, er en af disse komplikationer. Udviklingen af metabolisk dysfunktion hos patienter med en cancerdiagnose kan have fatale konsekvenser, hvor der ses en øget dødelighed og en større chance for at canceren vender tilbage. Vi ved meget lidt omkring, hvorfor metabolisk dysfunktion udvikler sig hos patienter med cancer. Formålet ved dette PhD projekt var at undersøge de molekylære mekanismer der leder til metabolisk dysfunktion ved cancer.

Ved brug af en cancer-musemodel, Lewis lung carcinoma, viste indeværende projekt, at det især er muskler med en oxidativ fænotype, som udvikler insulinresistens ved cancer. Dette var modsat muskler med en glykolytisk fænotype, som ikke blev insulinresistente. Molekylært observerede vi, at denne insulinresistens var associeret med "selektiv insulinresistens", hvor det var specifikke dele af insulinsignaleringskaskaden, som var negativt påvirket. Herunder var fosforyleringen af proteinet TBC1D4 nedsat flere steder på. Ydermere viste PhD projektet også, at den metaboliske stress-sensor, proteinet AMP-aktiveret protein kinase (AMPK), var opreguleret i muskler fra patienter med cancer-induceret muskeltab. Dernæst viste vi, at cancer i mus, der mangler funktionel AMPK i musklerne, leder til en forværring af de metaboliske dysfunktioner, som ses ved cancer. Modsat førte farmakologisk aktivering af AMPK til en forbedring af den nedsatte insulin tolerance set i mus med cancer. Molekylært viste data også, at cancer ændrede ekspressionen af flere proteiner, hvilket var afhængigt af AMPK. Dette gjaldt blandt andet fosforyleringen af TBC1D4 og opreguleringen af proteinet, pyrovat dehydrogenase. Det blev konkluderet, at AMPK i musklerne har en beskyttende effekt med den metaboliske dysfunktion, som ses ved cancer.

Dette PhD projekt har øget vores forståelse for de molekylære mekanismer, som ændrer sig ved udviklingen af metabolisk dysfunktion i cancer. Ydermere viste data fra projektet, at AMPK potentielt kan bruges farmakologisk til at behandle metabolisk dysfunktion i cancer.

Publication list during the PhD

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