

PostDoc Linn Gillberg, MSc, PhD

Place of enrolment: University of Copenhagen, Xlab, Department of biomedical Sciences

Principal supervisor: Professor, DMSc Flemming Dela, University of Copenhagen, Xlab, Department of Biomedical Sciences

Title of project: Metabolic and epigenetic changes after adjuvant chemotherapy in patients with early breast cancer

ABSTRACT

Breast cancer is the most common cancer in Danish women and has an average of around 5,000 new cases a year. Patients treated for early (non-metastatic) breast cancer (EBC) comprise, due to earlier diagnosis and improved treatment, a large and growing group of cancer survivors. However, many patients experience treatment-related endocrine side-effects such as dyslipidemia, insulin resistance and hypertension increasing the risk of metabolic diseases including Type 2 diabetes (T2D). Moreover, chemotherapy increases the risk of mutations in hematopoietic stem cell and thereby risk of age-related clonal hematopoiesis and blood cancer. The most common age-related mutations affect epigenetic regulators and may, besides increasing the risk of blood cancer, cause increased inflammation of peripheral tissues and thereby cardiometabolic diseases. The overall *purpose* of this postdoc project is to understand the underlying molecular (epigenetic, transcriptional, mutational and mitochondrial) mechanisms responsible for chemotherapy-induced metabolic derangements in EBC patients. As the responsible investigator on this project, I aim to investigate epigenetic and mutational effects in whole blood from 80 postmenopausal EBC patients before and after chemotherapy and relate these to their clinical metabolic characteristics. Moreover, I aim to study genome-wide epigenetic and transcriptional (focus on metabolism and inflammation gene sets) alterations as well as macrophage infiltration and mitochondrial respiratory capacity in subcutaneous adipose tissue from 16 EBC patients after chemotherapy and 10 healthy age-matched controls. All together this project will bridge basic biomedical research with clinical research by associating clinical and physiological characteristics with molecular markers in blood and adipose tissue from EBC patients after adjuvant chemotherapy. This project will increase our understanding of chemotherapy-related metabolic side-effects and thereby allow clinicians to follow up, initiate interventions and possibly prevent that these otherwise healthy women develop T2D and other metabolic diseases secondary to cancer treatment. 3

ABSTRACT

Brystkræft er den mest almindelige form for kræft hos danske kvinder med ca. 5000 nye tilfælde om året. Grundet tidligere diagnose og forbedret behandling tilhører brystkræftpatienter en voksende gruppe af kræftoverlevende. Imidlertid oplever mange patienter bivirkninger ved behandlingen såsom øget vægt, en stigning i blodsukker og kolesterol samt forhøjet blodtryk, hvilket medfører en øget risiko for bl.a. type 2-diabetes. Endvidere øger kemoterapien risiko for aldersrelaterede mutationer i blodcellerne. Disse genetiske forandringer påvirker DNA'ets struktur og cellernes evne til at specialisere sig. Ud over at øge risikoen for blodkræft kan disse mutationer

også forårsage inflammation i fedtvæv og blodkar, og dermed bidrage til udviklingen af hjertekarsygdomme og type 2-diabetes.

Det overordnede formål med mit postdoc-projekt er at forstå de underliggende molekulære mekanismer, der er ansvarlige for kemoterapi-inducerede metaboliske forstyrrelser hos brystkræftpatienter. Jeg vil undersøge genetiske ændringer i blodprøver fra 80 kvinder med brystkræft før og efter kemoterapi-behandling, og relatere disse fund til patienternes metaboliske sundhed. Desuden vil jeg undersøge fedtvævet for molekulære ændringer med fokus på metabolisme, energidannelse og inflammation. Dette vil undersøges i 16 brystkræftpatienter efter kemoterapibehandling samt 10 raske aldersmatchede kvinder. Alt i alt vil dette projekt bygge bro mellem klinisk og basal biomedicinsk forskning ved at forbinde kliniske markører og biologiske egenskaber i blod- og fedtvævsprøver. Dette projekt vil øge vores viden om bivirkningerne ved kemoterapi og derved give mulighed for at iværksætte interventioner der forhindrer at kvinder udvikler type 2-diabetes og andre metaboliske sygdomme i forlængelse af deres brystkræft.