Liquid Biopsies for Type 2 Diabetes Mellitus: Biomarkers for Disease Risk and Diagnosis

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Place: Remote

Abstract

Background: Type 2 diabetes mellitus (T2DM) has reached epidemic proportions in the United States. There is a critical need for earlier and more effective screening and diagnostic tools. Innovative liquid biopsy technologies may play a key role in meeting this need. Liquid biopsies are a non-invasive, adjunctive tool for determining diagnosis, prognosis, and therapeutic response. This dissertation focuses on two potential applications of liquid biopsy technologies to T2DM: (1) epigenome-wide association studies to identify epigenetic markers of risk for T2DM, and (2) extracellular vesicle (EV)-based biomarker studies to identify and detect markers associated with T2DM development and progression. Dissertation studies: The body of research reported in this dissertation establishes important groundwork for the development of liquid biopsy assays for T2DM. The first manuscript is a scoping review focusing on the biology of EVs in the etiology of pancreatic β-cell dysfunction and failure in diabetes. This review maps evidence that enhances understanding of disease mechanisms and collates EV-derived biomarker candidates from the studies reviewed. The second manuscript investigates the utility of liquid biopsies for detection of epigenetic markers of T2DM risk. This secondary analysis of data from the Upstate KIDS study examines associations between in vitro exposure to gestational diabetes mellitus (GDM) and DNA methylation changes in newborn blood samples. Offspring exposed to GDM in utero are at high risk for developing T2DM, and epigenetic modifications during fetal development may contribute to elevated risk. Significant associations between DNA methylation and GDM exposure were not detected among study participants after correction for multiple testing. However, the study was underpowered to detect small differences in methylation; oversampling of GDM exposure cases is needed. Further study is required to validate epigenetic marker candidates for T2DM risk identified in prior studies. The third manuscript investigates methods for detection of low-abundance EV RNA biomarkers, preliminary to optimizing workflows for EV-based liquid biopsies. Two single-cell, ultra-low input RNA-sequencing methods were tested, using intact EVs as library inputs. Findings of this study were that random-priming, pico-scale SMART-Seq methods are effective for generating robust RNA-seq data, using input of 10⁶ EVs.