Diabetic Complications Consortium

Application Title: Epigenetic Harbingers of Vascular Endothelial Dysfunction in Type 2 Diabetes

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1. Project Accomplishments:

Given the strong association between T cell inflammation and T2D vascular endothelial dysfunction, we proposed a series of studies to test the hypothesis that epigenetic mechanisms regulate the cytokine-mediated T cell inflammation that drives T2D-associated loss of endothelial function. We planned to team up with an established clinical investigator and expert in endothelial cell dysfunction to analyze blood samples from patients with known endothelial function, measured as part of his ongoing NIH-funded studies. However, due to issues with his previously approved IRB protocol, we were unable to secure the samples required for this project. We instead moved forward with our initial plan to use bioinformatics to understand inflammation in type 2 diabetes, taking advantage of my existing approved IRB protocols. Using a combination of stimulated blood cells (PBMCs) and bioinformatics analyses, we have identified three different inflammatory signatures from T cells in obese patients that uniquely identify non-diabetes, pre-diabetes, or type 2 diabetes subjects. These T cell signatures predict clinical group of individuals based on inflammation alone, in the absence of additional information on metabolic health. The signature highlighted Th17 cells as important sources of T2D-associated inflammation. We followed up with mechanistic analyses by using IL-17A and IL-17F blocking antibodies to link these Th17 cytokines to a more classical diabetogenic cytokine, TNFa, for the first time. These results are detailed in Ip et al, Obesity (2016); see full reference below.

2. Specific Aims:

Original Aim 1: To identify associations between DNA methylation and vascular endothelial dysfunction, we will identify methylated DNA domains from T cells of subjects that have been characterized for endothelial phenotype, inflammation and metabolic health.
Original Aim 2: We will determine relationships among T cell DNA methylation, endothelial function, inflammation and metabolic health.

Revised Aim 1: To identify T cell inflammatory signatures that associate with development of inflammatory complications in type 2 diabetes, we will stimulate T cells in the context of peripheral blood mononuclear cells and measure cytokine production. Multivariate bioinformatics approaches will identify signature cytokines and cytokine networks that uniquely identify non-diabetes, pre-diabetes, and type 2 diabetes subjects. **Results**-Ip et al., 2016
Revised Aim 2: We will perform partial least squares analyses to use data from Aim 1 to built a model for cytokine networks that underlie inflammatory-mediated complications of type 2

diabetes. We will independently query the model with existing data sets from type 2 diabetes and obese/non-diabetes subjects. **Results:** Ip et al., 2016.

3. Publications:

Immune regulators of inflammation in obesity-associated type 2 diabetes and coronary artery disease. Strissel KJ, Denis GV, **Nikolajczyk** BS. Curr Opin Endocrinol Diabetes Obes. 2014 Oct;21(5):330-8.

Ip BC, Hogan AE, **Nikolajczyk BS.** 2015. Lymphocyte roles in metabolic dysfunction: of men and mice. *Trends Endocrinol Metab.* 26:91-100. PMID: 25573740.

Bucur O, Almasan A, Zubarev R, Friedman M, Nicolson GL, Sumazin P, Leabu M, **Nikolajczyk** BS, Avram D, Kunej T, Calin GA, Godwin AK, Adami HO, Zaphiropoulos PG, Richardson DR, Schmitt-Ulms G, Westerblad H, Keniry M, Grau GE, Carbonetto S, Stan RV, Popa-Wagner A, Takhar K, Baron BW, Galardy PJ, Yang F, Data D, Fadare O, Yeo KJ, Gabreanu GR, Andrei S, Soare GR, Nelson MA, Liehn EA. An updated h-index measures both the primary and total scientific output of a researcher. Discoveries (Craiova). 2015 pii: e50. Epub 2015 Sep 30. PMID: 26504901.

Ip, B, Cilfone, N, Belkina, AC, DeFuria, J, Jagannathan-Bogdan, M, Zhu, M, Kuchibhatla, R, McDonnell, ME, Xiao, Q, Kepler, TB, Apovian, CM, Lauffenburger, DA and **Nikolajczyk, BS**. 2016. Th17 cytokines differentiate obesity from obesity-associated type 2 diabetes and promote TNFα production. *Obesity.* 24:102-112. PMID: 26576827.

Nicholas, D, **Nikolajczyk BS**. 2016. B Cells Shed Light on Diminished Vaccine Responses in Obesity. *Obesity* (In Press).