Personalized Gene Expression Profile Information Predicts Severity of Systemic Sclerosis Despite Heterogeneity of Disease

Zariel J. Johnson¹, Thomas Medsger², Tongbin Li³, Carol Feghali-Bostwick⁴, Yvette Conley¹, Cecelia C Yates¹, ¹School of Nursing, ²Department of Medicine, University of Pittsburgh, Pittsburgh, PA, ³AccuraScience, Johnson, IA, ⁴Department of Medicine, Medical University of South Carolina, Charleston, SC

Background: Systemic sclerosis (scleroderma, SSc) is an autoimmune disease that shows considerable heterogeneity in progression rate and clinical presentation amongst patients. Along with vascular damage and aberrant autoantibody production, SSc causes fibrosis of skin and internal organs. SSc is classified into two clinical subgroups: diffuse and limited, based on amount of skin involvement. Fibrosis of vital organs, mainly lung and heart, causes morbidity and mortality as a result of SSc. The modified Rodnan skin score (mRSS) is currently used to measure severity and disease progression, but is limited by variable sensitivity across disease progression. Thus, the objective of our study was to improve understanding of SSc by developing a method to predict SSc severity based on unbiased, personalized information (gene expression profiles) and evaluate heterogeneity of fibroblast activity between patients.

Methods: We used gene expression data from skin biopsies from 93 donors (mRSS 0-43) to train and test performance of several candidate prediction models. We used the Database for Annotation, Visualization, and Integrated Discovery (DAVID) to identify pathways associated with the genes that defined low and high severity SSc patient groups. We performed qRT-PCR on fibroblasts derived from multiple SSc patients to examine heterogeneity between donors.

Results: We developed the first classification model to accurately predict SSc severity based on gene signature and the clinical measurement of mRSS. DAVID analysis identified several pathways that were enriched with genes from the high and low severity profiles and relevance of several of these pathways were supported by the current literature. Overall, patients with more severe SSc expressed higher levels of genes associated with JAK/STAT signaling and innate immunity. We are currently investigating these other pathways for their role in disease. qRT-PCR analysis of fibroblasts demonstrated a heterogeneous response to fibrotic and anti-fibrotic factors, underscoring the need for a personalized medicine approach to this disease. Treatment with TGF-beta elicited variable levels of expression of pro-fibrotic genes including Fibronecin, Tenascin C, and Collagen I. Likewise, pro-fibrotic chemokines had variable effects across fibroblast samples.

Conclusions: Our study represents the first time that an independently validated classification model has been used to predict SSc severity based on personalized, patient-specific information. This model yields gene signatures of high and low severity groups and may inform treatment of this highly variable disease. Our methodology can be applied to other datasets to build prognostic models for SSc and other fibrotic diseases.

Support or Funding Information
This work was supported by grants from NIAMS (AR68317 CCY) and the University of Pittsburgh School of Nursing.