Application of a Novel Computational Approach to Identify New Targets and Pathways for Therapeutic Intervention in Scleroderma

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INTRODUCTION

Systemic Sclerosis (SSc) is a complex autoimmune disease with chronic progressive course and high patient variability. It is characterized by inflammation, vascular dysfunction and ultimately fibrosis. Fibrosis of the skin and outras organs results in reversible scarring, damage and ultimately organ failure, affecting for mortality and high morbidity. Current organ manifestations are organ-specific and are variably associated with clinical outcomes, including survival. While major advances have been made in understanding SSc, the vast majority of patients experience a progressive course marked by significant organ damage and poor outcomes. The exact cause of the disease remains elusive although the effect of environmental factors is generally understood. Individuals with SSc can be classified according to the extent of skin fibrosis (limited) or high-resolution cutaneous SSc (scleroderma)

OVERVIEW

Currently there is no approved target therapy with disease-modifying potential. Several translational studies were published, which focused on the expression of a panel of drug targets from SSc patients in order to understand the heterogeneity of underlying disease. We interrogated these datasets using a novel data analysis methodology and accepted the knowledge of complex disease model to identify perturbations in well-associated proteins (WAPs) that represents potentially unique targets for therapeutic intervention in Scc. SSc is unique as they were reproducibly related across isobaric variable SSc datasets. Additional patient subpopulations that may benefit from targeted therapies against selected WAPs were identified.

METHODS

Figure 1: SSc Emerging Therapies were Discovered using Model Systems, not Human Bioassays

Most drugs discovered using model systems

- Human bioassays are challenging

- Few quality assessments

- Sample quality, robust number, collection

- Investigator experience and design

- Lack of technology standards

- Biase quality data

- Lack of reproducibility

SSc Therapy Development Process

Finding validated therapeutic targets

- Complex disease processes

- High interpatient variability

- Currently, there is limited evidence for emerging therapies

- Patients are classified according to the extent of skin fibrosis, into limited (lSSc) or diffuse cutaneous (dcSSc) sclerosis.

- There is a high need for identification of patients at risk for specific organ complications and rapid progression.

Figure 2: Top Approach to Human Bioassays Addressed the Challenges

- Both approaches validated therapeutic targets with high reproducibility

- Application to the largest SSc data set: restricted to high MRSS

- Over 1,000 DEGs (green + red)

- Only 49 are also WAPs (black)

- 166 WAPs are not DEGs (blue): these can only be identified by analyzing the protein network

- Not only top WAPs are more robust than top DEGs across the two largest SSc data sets, but they also more enriched in known druggable targets (versus proteins)

- Combining the two largest SSc data sets does not improve Citeline representation for DEGs but it does for WAPs

- Typical Approach: Identify individual DEGs with significant change in SSc vs. healthy skin

- Large gene-expression data sets on SSc skin samples

- Sourced > 20 published human disease high-quality dataset

- Novel in-house Pathway Kit

- Biologically relevant

- Key biology pathway

- With disease identified

- 300 potential targets identified

- Known targets

- Novel pathways

- MNTA Approach: Well-associated proteins, WAP

- Contain DEGs with the knowledge of their networks

- STRING analysis

- Analyze double positive WAPs (DAPs) with significant change in mRNA

- Not all WAPs are DAPs

- WAP analysis led to a prioritized list of targets for SSc, including existing clinical agents and novel targets

- Permutation testing is utilized to identify which regulators have significant contributions to the disease

- Figure 5: Top 100 WAPs have Frequent Annotation in Citeline

- World’s largest databases of drugs in development

- Efficacy

- Human Testing

- > 100 potential targets

- Citeline: 13,718 in 2016

- Novel in-house screens

- Optimization of clinical development

- 424 with high MRSS

- - Prioritize clinical opportunities?

- - Improve the robustness of human sample bioassays to result in better target selection and optimization of clinical development.

- - 424 with high MRSS

- - Significantly enhanced robustness across human sample studies, by combining gene expression with prior biological knowledge of disease

- - MNTA analysis led to prioritized set of targets for SSc, including existing clinical agents and novel targets.

- - This approach can be applied to any disease with robust human datasets.

Figure 6: DEGs are More Enriched than Egs across Data Sets

- The two largest SSc data sets peak GEMP, WAP and MRSS, and it’s about 424 with high MRSS

- When ranking proteins across different experiments using WAPs, the DEG score is more enriched across different disease than DEG scores. This is illustrated on 17 datasets using STRING of WAPs across different disease

- C. WAP scores obtained with narrowly defined protein datasets

- GEMP and MRSS are significantly better ranked than DEG scores, meaning that enhanced reproducibility of WAPs relies on the prior biological knowledge encoded in STRING

- Figure 7: WAPs Correlated with Measureable Clinical Factors in rSSc (skin score)

- Because GEMP signature and MRSS contains unique subjects with high MRSS who might predict a population of patients now susceptible to a compound selected through traditional modeling

- Figure 8: WAPs and Clinical Factors

- Promising the robustness of human sample bioassays to result in better target selection and optimization of clinical development.

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- Increased robustness across human sample studies, by combining gene expression with prior biological knowledge of disease

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- This approach can be applied to any disease with robust human datasets.