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Veronica Anania, J Proteomics Bioinform 2016, 9:11(Suppl)
http://dx.doi.org/10.4172/0974-276X.C1.091

Quantitative proteomic approaches for identifying urinary biomarkers in Lupus nephritis

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Lupus nephritis (LN) is a severe clinical manifestation of systemic lupus erythematosus (SLE) associated with significant morbidity and mortality. Assessment of severity and activity of renal involvement in SLE requires a kidney biopsy, an invasive procedure with limited prognostic value. Despite years of research, a need remains for proximal, non-invasive biomarkers to help inform treatment decisions and to monitor disease activity and progression. Although proteinuria is highly correlated with disease progression in LN, the composition of the urinary proteome of LN patients remains poorly characterized. To better characterize the urinary LN proteome, we performed a preliminary proteomics study comprised of complimentary discovery proteomic methods to identify urinary biomarkers of LN. Urine samples from 3 female patients with biopsy confirmed LN, high proteinuria were compared to age- and gender- matched healthy controls. These samples were profiled using 3 mass spectrometry-based methods: 2D SDS-PAGE fractionation, a chemical labeling approach using tandem mass tags, and a label free data-independent acquisition (DIA) method. Using these combined approaches >2300 proteins were identified, 236 of which are up-regulated >2-fold in LN samples compared to healthy controls. While the chemical labeling approach enabled identification of more total proteins (2,598 with chemical labeling vs. 1,117 with DIA), the DIA approach outperformed the chemical labeling approach in identification of proteins significantly up-regulated in LN samples (52 with chemical labeling vs. 197 with DIA). These results suggest that DIA-based approaches are less biased towards high abundance analytes and therefore potentially more suitable for proteomic profiling of biological matrices with a broad dynamic range like urine. Furthermore, candidate biomarkers identified using the DIA method are easily adapted into a targeted, multiplexed mass spectrometry assay suitable for absolute quantitation of candidate biomarkers in a clinical trial. Results from this study will be used to inform longitudinal and interventional studies focused on understanding the biological implications of these candidate biomarkers and to direct development of novel tools to evaluate disease progression and treatment efficacy of current and future LN therapeutics.

Biography

Veronica Anania received a PhD in Molecular and Cell Biology from UC Berkeley and is currently a Scientist in Biomarker Development at Genentech. Her research is focused on implementing targeted and discovery mass spectrometric approaches to develop multiplexed biomarker panels to monitor pharmacodynamic changes in autoimmune disorders. Additionally, she is developing targeted methods to quantify changes in bioactive lipids from a variety of biological matrices to support respiratory disease programs.

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