Researchers Apply Mass Spec to Single-Cell Proteomics

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Premium

NEW YORK (GenomeWeb) – Researchers at Northeastern and Harvard Universities have developed a technique that enables mass spectrometry-based proteomics at the single-cell level.

Called Single Cell Proteomics by Mass Spectrometry (SCOPE-MS), the approach uses tandem mass tagging (TMT) to quantify thousands of proteins in single mammalian cells, and is one of the first techniques to bring large-scale mass spec analysis to the single-cell level.

The method was detailed in a paper that was published last week on the preprint server bioRxiv. According the study authors, Harvard researcher Bogdan Budnik and Northeastern researchers Ezra Levy and Nikolai Slavov, it could significantly increase the depth of single-cell proteomic analyses, which to date have relied on antibody-based methods, and aid investigations of phenomena like tumor heterogeneity where the ability to characterize and distinguish between small cell populations is crucial.

The study has not yet undergone peer review, but Ian Pike, chief scientific officer of Proteome Sciences, which invented the TMT technology used in the SCOPE-MS method, called the work "very exciting," adding that "it will be interesting to see if the results can be replicated by other groups."

Pike, who was not involved in the research, noted that the approach is somewhat similar to Proteome Sciences' TMT Calibrator product, which works by combining TMT-labeled peptides from both the sample of interest and another sample source (such as tissue) where the target proteins are produced in higher abundance. By including the second supplementary sample source at a higher concentration than the sample of interest, researchers are able to ensure that even analytes present as only low abundance in the

sample of interest are present at high abundance in the overall sample, making them more likely to be fragmented and detected by the mass spec.

SCOPE-MS similarly uses TMT labeling to include in the analysis several hundred cells in addition to the single cell that is the target of the mass spec run. As the authors note, "TMT allows quantifying the level of each TMT-labeled peptide in each sample while identifying its sequence from the total peptide amount pooled across all samples. SCOPE-MS capitalizes on this capability by augmenting each single-cell set with a sample comprised of around 100 to 200 carrier cells that provide enough ions for peptide sequence identification."

The authors noted that also key was the ability to deliver their samples to the mass spectrometer with minimal loss of material. To this end, they manually picked live cells and lysed them mechanically, which, they said, eliminated the need for reagents that might cause losses during "peptide separation and ionization or sample cleanup."

In the study, the researchers used the SCOPE-MS method to distinguish between single Jurkat and U-937 cells, quantifying 583 proteins at the single-cell level and then using principal component analysis to identify the two cell types.

They also combined their proteomic data with single-cell transcriptomic data to investigate whether genes co-expressed at the mRNA level are also co-expressed at the protein level, finding that the former was predictive of the latter.

The findings, the authors wrote, suggest that SCOPE-MS "is broadly applicable to measuring proteome configurations of single cells and linking them to functional phenotypes, such as cell type and differentiation potentials."

"Considering the very low protein amounts used, they still get moderate numbers of peptides and proteins, suggesting the technique is viable for a wide range of studies," Pike said, adding that "improvements in mass spec sensitivity and speed will further enhance [the method's] performance."

He noted, though, that "it is likely to be some time before the method could be extended into more challenging studies such as tumor heterogeneity."

"For now, the biggest advantage will be to compare the transcriptome and proteome of single cells to further explore the translation of the genome to the proteome," he said, adding that he believed that "extending this to studying post-translational modifications would be a next logical step."

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