Comprehensive evaluation of phosphoproteomic-based kinase activity inference

Info

PUBLIZIERT AM
2025-05-22

JOURNAL
Nature Communications

LINK
https://doi.org/10.1038/s41467-025-59779-y

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Abstract

Kinases regulate cellular processes and are essential for understanding cellular function and disease. To investigate the regulatory state of a kinase, numerous methods have been developed to infer kinase activities from phosphoproteomics data using kinase-substrate libraries. However, few phosphorylation sites can be attributed to an upstream kinase in these libraries, limiting the scope of kinase activity inference. Moreover, inferred activities vary across methods, necessitating evaluation for accurate interpretation. Here, we present benchmarKIN, an R package enabling comprehensive evaluation of kinase activity inference methods. Alongside classical perturbation experiments, benchmarKIN introduces a tumor-based benchmarking approach utilizing multi-omics data to identify highly active or inactive kinases. We used benchmarKIN to evaluate kinase-substrate libraries, inference algorithms and the potential of adding predicted kinase-substrate interactions to overcome the coverage limitations. Our evaluation shows most computational methods perform similarly, but the choice of library impacts the inferred activities with a combination of manually curated libraries demonstrating superior performance in recapitulating kinase activities. Additionally, in the tumor-based evaluation, adding predicted targets from NetworKIN further boosts the performance. We then demonstrate how kinase activity inference aids characterize kinase inhibitor responses in cell lines. Overall, benchmarKIN helps researchers to select reliable methods for identifying deregulated kinases.