A Novel Method to Efficiently Identify Functional Pathways by Building an Increasingly Complex Interactome of Directly Interacting Proteins

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Interactomes provide a framework for understanding the interactions that dictate biological processes. A well-constructed interactome allows for better disease understanding; however, traditional construction methods are slow and limited in scale. Thus, I developed a more efficient, cost-effective method to build interactomes of direct protein-protein interactions (PPIs). Using p53 as an initial seed, I performed hierarchical clustering to identify genes co-expressed with p53. A matrix of potential PPIs between p53 and its co-expressed genes was built. Using AlphaFold3, the direct PPIs in this matrix were identified. This process was repeated for each subsequent generation of direct PPIs, resulting in the screening of 10,172 potential PPIs to identify 124 direct PPIs that formed my interactome. The most likely functional pathways were mapped by identifying shared functions using GO terms and published literature. This interactome became increasingly complex and orderly with each generation. The functional pathways mapped (DNA damage response, apoptosis, cell cycle control, and metabolism) included proteins associated with p53 and those not associated with it. The proteins in the interactome represented 13 functional categories, all of which have been shown to be involved with p53. Trimeric complexes that overlap multiple pathways were also identified, suggesting possible molecular switches that may regulate convergence or divergence within pathways. My novel process enables researchers to build interactomes for any protein of interest in a significantly shorter time frame, accelerating our understanding of cellular processes and disease states. An interactome has not been built in this manner before, nor have functional biological pathways been identified this rapidly.

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