PROSynMOGN: Enhancing Molecular Graph Neural Networks Toward Predicting Synergistic Cancer Drug Combinations Driven by Protein Expression

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Cancer's molecular heterogeneity and complexity pose significant treatment challenges. Drug combinations have recently been employed to enhance cancer therapy due to their synergistic effects, which improve efficacy, reduce drug resistance, and minimize toxicity. Nowadays, deep learning (DL) has revolutionized the traditional drug combination discovery process to overcome time-consuming and costly laboratory obstacles. However, most existing DL models mainly focus on the drugs' molecular structure and cancer cells' gene expression, neglecting the impact of protein expression. Since drugs typically interact with proteins, which affect biological processes and characterize cell phenotypes, exploring protein expression is crucial. Therefore, we developed PROSynMOGN, an explainable DL model to predict synergistic effects of cancer drug combinations by leveraging graph neural networks for the drugs' molecular structure and deep neural networks (DNN) for gene and protein expressions. Our findings show that PROSynMOGN-GATFP integrating the molecular graph and fingerprints through graph attention network and DNN, achieves high predictive performances in the ONEIL, FRIEDMAN, and ASTRAZENECA studies. It also outperforms state-of-the-art models across cancer tissue datasets, significantly improving accuracy by 1.2–6.0%. Notably, integrating protein expression features improves prediction accuracy by 0.5–4.4% compared to using only gene expression features. Furthermore, our model reveals cancer-associated proteins related to molecular mechanisms and provides molecular substructures for real-world cancer drug design. Our strategy benefits unveiling cancer drug combinations and enhances understanding of biological mechanisms of synergistic effects between drugs and cancer cells.

Awards Won:
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