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Application status of traditional computational methods and machine learning in cancer drug repositioning

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ABSTRACT

The escalating global burden of cancer has spurred extensive research and development efforts aimed at discovering effective anti-cancer agents. However, the prohibitively high costs associated with developing novel drugs remain a formidable challenge. This paper describes a cost-effective approach, drug repositioning, which repurposes approved drugs for novel therapeutic indications, offering a promising solution to this dilemma. We present a comprehensive review of computational strategies employed in cancer drug repositioning, with a particular focus on machine learning. In recent years, the integration of bioinformatics technologies with multi-omics data has significantly advanced the field of cancer drug repurposing. In particular, machine learning and deep learning techniques have been instrumental in driving substantial progress in this area. This review summarizes the current application of traditional computational methods alongside machine learning in drug repositioning, highlighting the great potential of machine learning, both independently and in synergy with other bioinformatics-based approaches. The insights provided here offer valuable reference for further integration of computational strategies into the research and development of cancer therapies.

Introduction

Characterized by complexity and heterogeneity, cancer poses a severe public health challenge. A wide array of commonly utilized anticancer drugs, particularly chemotherapeutic agents, often exhibit suboptimal efficacy, primarily due to factors such as limited bioavailability, nonspecificity, toxicity, and drug resistance.[1] Therefore, there is an urgent need to develop cancer drugs with better efficacy and lower toxicity. The de novo discovery of antitumor drugs demands extensive preclinical and clinical studies, a process that is both time-consuming and costly, with considerable inherent risks.[2] Statistical data indicate that the typical drug development timeline spans 10–15 years, with costs reaching upwards of 800 million to 1 billion USD, and a success rate of less than 10 %.[3]

In response to these challenges, drug repositioning has emerged as a promising strategy. This approach leverages approved drugs for new therapeutic indications through methods such as rescreening, combination therapies, or modifications to existing drugs. Approved drugs have already undergone rigorous clinical testing, ensuring a certain degree of safety. If new clinical indications for these drugs are identified, they can be rapidly reintroduced into Phase II clinical trials, thereby accelerating the drug development process and significantly reducing both the risks and costs associated with research and development.[4,5] Although often overlooked by pharmaceutical companies due to marketing challenges, drug repositioning has, in recent years, greatly benefited from the systematic application of computational methods, including structure-based, feature-based, network-based, and machine learning (ML)-based approaches(Fig. 1).[2] This paper provides a comprehensive review of the computational strategies utilized in cancer drug repositioning, with a particular focus on the role of machine learning.

Traditional computational methods for drug repositioning

Structure-based methods

Structure-based methods rank molecules in a database based on their structural and electronic complementarity with the target, which

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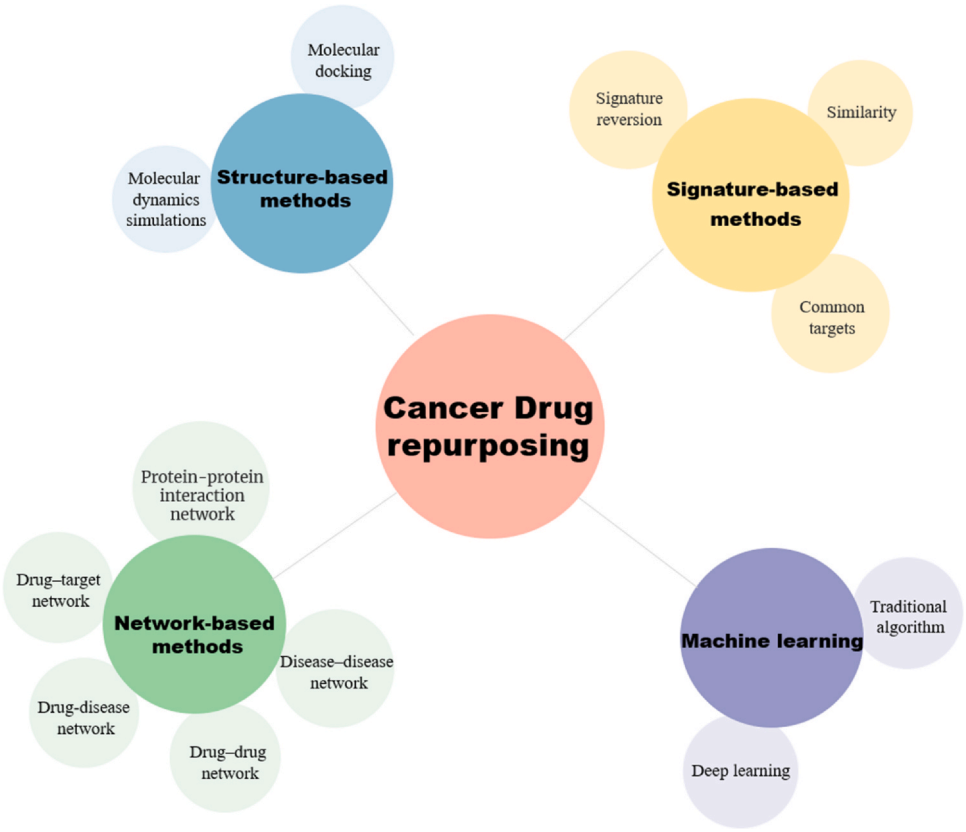

Fig. 1. Computational methods for cancer drug repositioning.

heavily rely on the three-dimensional structures of drug targets.[6,7] One commonly utilized approach is molecular docking, which facilitates drug repositioning by predicting the conformation of ligands within the target binding site, as well as assessing the binding affinity and binding mode.[8] More specifically, molecular docking simulates the conformation of ligands located within the target binding site, calculates physicochemical parameters, and generates docking scores. Molecules with high docking scores are considered promising drug candidates.[9] Molecular dynamics simulations are often used to validate the results of molecular docking. This technique, based on Newton's equations of motion, simulates molecular motion at the atomic scale by calculating the forces acting on each atom.[10] Molecular docking typically involves three main steps: identifying the target and ligand, searching for binding sites and conformations, and evaluating the quality of poses.[11] Identifying the target is the primary task, usually focusing on nucleic acids or proteins. The subsequent steps can be supported by databases such as the Protein Data Bank[12] and ZINC15,[13] as well as software such as AutoDock[14]and AutoDock Vina.[15] The proto-oncogene c-MYC, known for its close association with tumorigenesis, has been the focus of several drug repositioning studies. Boulos et al.[16] virtually screened FDA-approved drugs targeting c-MYC from the ZINC15 database and conducted molecular docking studies using AutoDock 4.2.6 on the top 117 compounds with the best binding affinity to c-MYC. Among these, adapalene, a drug commonly used in acne treatment, was identified as an effective c-MYC inhibitor due to its strong binding affinity. This finding was further supported by both in vitro and in vivo experimental results, revealing the potential of adapalene as a novel therapy for multiple myeloma. Molecular docking has also been applied in identifying potential therapeutic agents for Non-small Cell Lung Cancer (NSCLC), where deregulation and conformational alterations of Akt, a serine/threonine kinase, have been widely reported. Baby et al.[17] employed molecular docking and molecular dynamics simulations to screen for potential allosteric inhibitors of Akt-1 from an FDA-approved drug library. Their predictions indicate that valganciclovir, dasatinib, indacaterol, novobiocin, ezetimibe, delerozepam, pitavastatin and nebivolol can bind to the allosteric site of Akt-1, suggesting their potential as therapeutic agents for NSCLC.

Moreover, molecular docking can also be used to identify multi-target drugs. Peroxisome proliferator activated receptors (PPARs), which are lipid-sensing nuclear receptors, include three isoforms: α, β/δ, and γ. Mandal et al.[18] screened novel PPAR pan-agonists from the ZINC database targeting these three PPAR isoforms. Eprosartan, identified through molecular docking and dynamics analyses, showed excellent protein-ligand interactions and holds promise as a potential anticancer agent.

Signature-based methods

Compared to structure-based approaches, drug repositioning based on cancer characteristics represents a relatively novel methodology.[19] The signatures associated with a drug or disease can be derived from three primary types of data: transcriptomic, proteomic, or metabolomic data. Additionally, non-omics data, such as chemical structures, adverse event profiles, and electronic medical records, can also be utilized. The characteristic-based approach treats features as independent, focusing solely on their overlaps without considering their interrelations.[20] From a computational perspective, this methodology can be further classified into three distinct categories: signature-reversion-based, similarity-based, and target-based approaches.

(1) Based on signature reversion

Transcriptome signature reversion has been extensively utilized in drug repositioning for various cancers, based on the premise that drugs capable of reverting gene expression associated with a diseased state to its healthy state may as potential therapeutic candidates for that disease.[21] A prominent example of this approach is drug repositioning using the Connectivity Map (CMap).[22] For instance, Katharine Yu et al.[23] extracted drug resistance profiles from a neoadjuvant trial for

early stage breast cancer, then searched for compounds that could reverse these signatures in a breast cancer cell line using CMap.[22] This process ultimately identified fulvestrant as a potential therapeutic agent to sensitize drug resistant breast cancers. Additionally, based on gene expression signatures related to tumorigenesis, patient survival, and proliferation, Qing Ye et al.[24] identified BX-912, daunorubicin, and midostaurin as potential repositioning drugs for treating NSCLC using CMap.[22]

(2) Based on similarity

The similarity-based methodology assumes that compounds with similar signatures exhibit similar biological behaviors. One example of this approach is the Computational Analysis of Novel Drug Opportunities (CANDO), a platform for shotgun multiscale therapeutic discovery, repurposing, and design. CANDO integrates features such as drug side effects, protein pathways, protein-protein interactions, protein-disease associations, and computes the similarity of characteristics between all compound-compound pairs in the database to predict potential associations between drugs and indications.[25] Another platform, DrugSimDB,[26] aggregates and evaluates structure-, pathway-, target- and function-based similarities between pairs of drugs, ultimately prioritizing repositioning candidates based on the overall degree of similarity. These platforms hold considerable promise in facilitating the repositioning of cancer drugs.

(3) Based on targets

Advancements in genomic and proteomic technologies have significantly enhanced the evaluation of cancer-specific biological pathways, opening up numerous opportunities for identifying novel drug targets. This progress is particularly relevant to drug repositioning, as drugs targeting common pathways with cancer-related targets may have therapeutic potential in treating other cancers. For example, histone deacetylases (HDACs), which are dysregulated in refractory cancers, are promising therapeutic targets for circumventing chemoresistance. Kenneth K. W. To et al.[27] used an open-source computational tool, "DRUGSURV[28]", to search for putative HDAC inhibitors among clinically approved drugs. After considering bioavailability and side effect profiles, twelve drug candidates were shortlisted. The ability of triamterene to circumvent cisplatin resistance was further verified in a patient-derived tumor xenograft (PDX) model from a cisplatin-refractory NSCLC patient. In another study, Rawikant Kamolphiwong et al.[29] re-analyzed gene expression profiles, selected candidate gene targets, and matched them with drug targets from the Drug Repurposing Hub[30]. The results provided a list of current anti-cancer drugs with potential for repositioning in osteosarcoma treatment.

Network-based methods

Cancer is a heterogeneous disease mainly driven by abnormal gene perturbations within complex regulatory networks. Therefore, identifying common and specific perturbed genes across multiple cancer networks is a promising strategy for drug repositioning.[31] While molecular docking is limited in identifying drugs that influence biological networks, network-based methods have been successful in prioritizing such drugs.[32]

The development of most cancers cannot be solely attributed to defects in single genes or proteins but rather involves the disruption of coordinated functions across distinct biological networks. Network-based approaches possess a natural capability to integrate and interpret human genomics and interactomics data, rendering them far more powerful than methods that focus solely on individual features for drug repositioning. Xianbin Li et al.[33] proposed a novel Drug Repurposing method based on the Inhibition Effect on gene regulatory network (DRIE) to identify potential cancer therapeutics. DRIE integrates gene expression profiles with gene regulatory networks to calculate inhibition score by using the shortest path in a disease-specific network. This approach clearly identified potential agents for colorectal, breast, and lung cancers, and demonstrated superior performance over signature-based methods when validated across 11 datasets. Furthermore, drug-target, drug-disease, drug-drug, disease-disease, protein-protein interaction (PPI), and gene co-expression networks can be used to identify therapeutic biomarkers and drug targets, thereby providing new opportunities for drug repositioning.[2] Zhang et al.[31] utilized protein-protein and gene regulatory interactions, enzyme-substrate relationships, protein complexes, and intercellular communication to reconstruct cancer-specific networks. They developed a network proximity approach to systematically screen FDA-approved or clinically investigational drugs, and identified 19 drugs with the potential to affect cancer genes in seven cancer types. Similarly, Occam Graves et al.[34] used gene co-expression network analysis to identify hub genes driving tumor development. They repositioned one clinically used drug mitoxantrone, and two pre-clinical drug candidates, CGP-60474 and wortmannin. Upon testing with the A549 cell line, these drugs emerged as promising candidates for the treatment of lung adenocarcinoma. While network-based methods offer a broader spectrum of candidate drugs, signature-based methods are more stringent. Federica Torricelli et al.[35] integrated signature-matching and network-based methods for drug repositioning in endometrial cancer (EC), combining the strengths of both approaches while minimizing their weaknesses. This hybrid approach predicted five drugs that were highly efficient in reducing EC metastasis.

Existing drug-drug network-based approaches typically consider only the target, side effects and structure of the drug, often overlooking the clinical therapeutic effects. However, it cannot be denied that the clinical efficacy of drugs is of great significance in constructing networks. By integrating the functional and clinical treatment similarities of drugs, Qin et al.[36]constructed a cancer-related drug similarity network and quantified the correlation score of each drug with a specific cancer. Of the 11 potentially repurposable drugs for NSCLC, 10 were confirmed by clinical trial articles and databases.

Drug repositioning methods based on machine learning

A vast amount of data has been generated from numerous research endeavors in biology, medicine, and chemistry. Traditional data analysis methods, such as manual inspection and statistical approaches, are labor-intensive and time-consuming. In contrast, machine learning (ML) has emerged as a powerful tool capable of rapidly and efficiently analyzing large datasets, identifying patterns, and making judgments or predictions on new data, which significantly accelerates the process of drug repositioning.[37] Rather than relying on manually coded routines with a predefined set of instructions, ML algorithms are trained using large amounts of data, enabling the machine to autonomously perform tasks.[38] ML is often combined with the aforementioned methods to enhance predictive accuracy.

ML combined with structure-based methods

ML is frequently employed in conjunction with structure-based methods, where ML plays a pivotal role in prediction, while molecular docking and molecular dynamics simulations are utilized for validation. For example, PredictONCO 1.0 utilizes the XGBoost classification model to assess the impact of mutations on the sequential and structural properties of proteins. It also integrates molecular docking and virtual screening to identify potential inhibitors. This model repositioned Lumacaftor as a CDK4 inhibitor, predicting its potential application in melanoma treatment. Notably, this model consists of a collection of small decision trees, which, despite their individual weak predictive power (each decision tree typically uses one to three features only), collectively demonstrate state-of-the-art performance, comparable to advanced deep learning methods.[39] Cyclophosphamide (CP), a widely

used anticancer drug, is often associated with long-term use-induced ALDH1A1-mediated inactivation and subsequent resistance. Gera Narendra et al.[40] employed ML models to virtually screen FDA-approved drugs from the ZINC database. The resulting hits were further analyzed using structure-based drug-designing approaches, including molecular docking, molecular dynamics, and waterswap analysis. The in-silico and in vitro studies indicated that raloxifene and bazedoxifene could act as promising adjuvants with CP, potentially enhancing treatment efficacy for cancer patients while minimizing toxicity.

ML combined with signature-based methods

ML is closely integrated with feature-based approaches in drug repositioning, as it learns from data features to identify potential drug candidates. One such example is the Deep Learning-based Efficacy Prediction System (DLEPS), which uses changes in gene expression profiles associated with disease states as input to predict potential drug candidates. DLEPS has successfully predicted drugs with potential disease-relevant impacts on obesity, hyperuricemia and nonalcoholic steatohepatitis.[41] Although it has not yet been applied specifically for cancer drug repositioning, it holds promise as a powerful tool for cancer drug repositioning if trained using transcriptional profile changes associated with cancer.

ML is capable of addressing some challenges encountered by signature-based methods. For instance, while normal control tissue samples are commonly accessible, certain tissue samples, such as normal brain tissue, are rarely available from the same patient. Zhao et al.[42] combined disease signatures from two bulk RNA-seq samples and employed unsupervised ML models to identify reference controls from other studies. This approach led to the prediction of three drugs, triptolide, mycophenolate mofetil, and triamterene, that had not previously been studied in diffuse intrinsic pontine glioma (DIPG). The antitumor activity of these drugs was evaluated in DIPG cell lines, and the efficacy of mycophenolate mofetil was further validated in a mouse model of DIPG.

ML combined with network-based methods

ML possesses the capability to extract valuable features from complex biological networks. One such model, VGAEDR, established a drug-disease heterogeneous network and learned low-dimensional feature representations for heterogeneous networks. These features were then input into a fully connected layer and a Softmax layer to predict new drug-disease associations. VGAEDR accurately predicted the top ten potential anti-COVID-19 drugs, six of which were subsequently validated by other studies, underscoring its reliability.[43] Another example is DRONet, which employs network embedding methods to acquire deep features of drugs from a heterogeneous drug-disease network. This model also integrates a drug-indication dataset that includes effectiveness comparative relationships (ECR) among drugs. DRONet successfully combines the embedding features with ECR using a tailored ranking learning model to prioritize candidate drugs for repositioning.[44]The representation of biological networks as knowledge graphs, which can utilize graph theory and powerful graph machine learning methods, is well suited for target-based drug retargeting methods in systems biology.[45] Additionally, DREAMwalk (Drug Repurposing through Exploring Associations using Multi-layer random walk) employs a multi-layer random walk guided by semantic information. It applies the XGBoost classifier to learn from biomedical knowledge graphs and predict drug-disease associations. The effectiveness of the model is demonstrated through a case study on drug repositioning for breast cancer. Furthermore, DREAMwalk's use of biomedical knowledge graphs not only enhances prediction accuracy but also provides interpretability to the results.[46] Although these models have not yet achieved successful cancer drug repositioning, their potential application in this area warrants further exploration.

Deep learning

Deep learning (DL) is a subgroup of ML that focuses on making predictions using multi-layered neural network algorithms inspired by the neurological architecture of the brain.[47] Compared to other ML methods, the neural network architecture of DL enables the model to scale exponentially with increasing data volume and dimensionality, indicating its efficiency in handling large-scale datasets.[48] DeepCancerMap, for example, utilizes the FP-GNN deep learning method to predict the inhibitory activity of compounds against targets and tumor cell lines. Compared to the classical ML and other DL methods, the FP-GNN models demonstrate significant improvements in predictive performance.[49] Convolutional Neural Networks (CNNs), a prominent type of DL, have shown exceptional performance, especially in image processing. BG-DTI, a new framework based on biological feature and graph representation learning for predicting drug-target interactions (DTI), combines graph convolutional network (GCN) and graph attention network (GAT) to learn feature representation of drugs and targets. A random forest classifier is employed to predict drug-target interactions. BG-DTI, by integrating both ML and DL, outperforms existing state-of-the-art methods, making it a powerful tool for cancer drug repositioning.[50]

Challenges of ML in drug repositioning

Despite the widespread application of ML in cancer drug repositioning, several challenges persist. One of these challenges is the lack of interpretability.[51] Data quality poses another obstacle. To bolster the overall performance of the model, newcomers in the field of drug repurposing frequently prioritize the deployment of the latest ML methods. However, it is crucial to initially focus on the training data as it serves as the cornerstone for subsequent advancements. Regardless of the specific model employed, the abundance of high-quality data consistently contributes to better generalization performance.[52] Data-related challenges can be categorized into the following three aspects. First, the scarcity of gold-standard datasets remains a prominent concern. The incorporation of data from diverse trial methodologies, batches, and human cell lines introduces noise and will engender a model highly reliant on the specific dataset.[53] Second, drug repurposing is susceptible to publication bias, as much of the accessible data is derived from published studies. Celebrated drugs typically feature a greater volume of publications, potentially resulting in a biased weighting of evidence compared to less-studied drugs.[54] Thirdly, many data types utilized in drug repositioning are incomplete. For instance, the understanding of all protein folds and structures remains incomplete, and dose-dependent profile data is also incomplete, making it difficult to predict adverse reactions.

Discussion

Cancer poses significant challenges in the development of effective pharmacological treatments. Drug repositioning has emerged as an effective strategy to accelerate the discovery of cancer therapies by repurposing existing, approved drugs. This approach circumvents many of the obstacles associated with novel drug discovery. Recent advancements and successful cases have demonstrated the potential of computational strategies, particularly machine learning (ML), in cancer drug repositioning. However, ML encounters two major challenges: interpretability and data quality. In recent years, considerable efforts have been made to address these challenges. For instance, the incorporation of biomedical knowledge graphs[55] and the adoption of attention mechanisms[56] into models can enhance interpretability. Furthermore, ML can also be employed to predict missing data. Given the ever-expanding volume of pharmacological and biological data, the application of ML, either used independently or in combination with other bioinformatics-based methods, holds great promise for advancing cancer drug repositioning.

Several critical points merit special consideration. Firstly, understanding both the commonalities and differences across various cancer types is important for advancing research in drug repositioning. The commonalities reside in the shared molecular and cellular mechanisms. For instance, numerous cancer types exhibit dysregulation in cell metabolism[57,58] and impaired apoptotic pathways.[59] This suggests that specific drugs targeting these shared mechanisms may demonstrate efficacy across multiple cancer types. Conversely, the diversity among cancers is equally crucial. Each cancer type has unique genetic profiles, biomarkers, and microenvironment interactions, resulting in varied responses to the same drug. Hence, it is crucial to consider the distinct characteristics and therapeutic needs of each cancer type when pursuing drug repositioning. On the other hand, while experimental oncology continuously validates novel targets and drugs, therapeutic resistance remains a significant issue that hampers the effectiveness of drug discovery. Therefore, computational approaches that test existing approved drugs for their combinatorial potential hold promise for overcoming therapeutic resistance and enhancing the effectiveness of current anticancer therapies.

Furthermore, drug repositioning represents merely the first step in cancer drug development. Rigorous and well-designed clinical trials remain indispensable. This entails not only the traditional assessment of drug safety and efficacy but also an in-depth understanding of the mechanism of the drug in specific cancer types. By designing clinical trials that include various cancer types and patient groups, we can more comprehensively evaluate the therapeutic potential of repurposed drugs.[60]

Declarations

Not applicable.

Authors' contributions

Yixin Cao: Conceptualization, Methodology, Writing - Original draft preparation. Yongzhi Li: Supervision, Writing - Reviewing and Editing. Lingxi Wei, Yan Zhou, Fei Gao: Data curation, Resources, Investigation. Qi Yu: Writing - Reviewing and Editing, Validation.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' other information

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