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Concatenate Omics with Drug Repurposing: A Proposed Workflow

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About the Study

Continuous development of new anti-cancer drugs is a challenging but necessary process for various cancer types, especially for those considered incurable like multiple myeloma. There are two approaches on developing a new drug, *de novo* drug discovery and drug repurposing. Recently, drug repurposing has gained a lot of interest since the cost, risk and production timeline of finding new indications for existing drugs are significantly shorter compared to traditional drug discovery. Here, we focus on drug repurposing and with a flow paradigm on multiple myeloma transcriptomic data we show how the rigorous analysis of omics data may assist repurposing approaches.

Multiple Myeloma (MM) is the second most common hematologic malignancy, characterized by the infiltration of clonal plasma cells in the bone marrow compartment. It mainly affects the elderly with an estimated incidence of 5/100,000 in Europe [1]. Despite significant progress in the therapeutic landscape of MM, it remains an incurable disease. Current goal remains the achievement of deep and durable remissions through different therapeutic combinations which result in prolonged survival of MM patients [2]. Nevertheless, patients inevitably experience serial relapses and eventually become refractory to all available regimens. Further research of MM's complex biology is needed to identify new targets which will enable the development of novel therapeutic molecules.

Traditional drug development aims to produce therapeutic molecules from scratch, based on the available information of a biological target [3]. Despite significant progress in the growth algorithms, *de novo* drug design is still an expensive and time-consuming procedure, with high failure rates. It is estimated that only a small fraction of the initial candidate compounds (5 in 5000) makes it through testing and reach the patient's bedside [3]. These limitations have highlighted the importance of drug repurposing, an alternative to traditional drug design, whose basic principle is to identify new uses for existing drugs [4]. Key benefits of drug repositioning are the shorter production time, the reduced development risk, the reduced costs and the availability of plethora of toxicological and other data of the existing drug.

There are several repurposing approaches that can be categorized into experimental or computational approaches [5]. Experimental repurposing approaches, like binding assays, enable the direct identification of previously unknown interactions between known ligands and known compounds. In contrast, computational repurposing approaches utilize known information from drugs, targets and biology to indirectly establish potential new interactions between drugs and targets that would later need to be further validated with experimental assays. Both approaches are promising but rely on information from already known targets and compounds. Coupling primary research with repurposing approaches could enable the identification of new biological targets that can later serve as ligands for therapeutic intervention with known compounds.

Gene expression profiling has emerged as a powerful investigational tool in modern cancer research, allowing the identification of pathogenic patterns in gene expression. Concerning multiple myeloma, gene expression profiling studies have proven to be helpful in molecular classification, patient stratification, survival prediction and disease understanding [6-8]. Most importantly, owing to the open access culture of science, there is now an enormous amount of transcriptomic data from MM patients available in public domain. Processing these data can offer new perspectives in MM's biology and potentially identify new targets for therapeutic intervention.

On this basis, we recently mined the Gene Expression Omnibus (GEO) database for datasets with transcriptomic data from purified $CD138^+$ cells from Newly Diagnosed Multiple Myeloma (NDMM) patients and healthy donors [9]. After applying strict filtering criteria, we successfully encountered 7 relevant datasets. Two of them contained bulk RNA-seq data and the other 5 contained microarray-based transcriptomic data. Each dataset was analyzed separately and differentially expressed genes between patients and healthy donors were identified. We specifically applied a stringent threshold of absolute fold change equal or greater than 4 to ensure that we obtained only the genes with significant change.

We next integrated the lists of differentially expressed genes that we obtained from each dataset and selected positively those genes that were observed to be differentially expressed in at least 3 of the 7

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datasets. By applying this strict criterion, we ensured that false positive results were excluded from our downstream analyses. Additionally, in order to further filter our results, we excluded genes with no biological significance and genes with inadequate bibliographic evidence of involvement in multiple myeloma pathogenesis. After all these filtering steps, we identified 28 differentially expressed genes with 22 of them being over-expressed in the NDMM group, thus serving as potential targets for intervention.

We, then mined drug repositories and examined whether existing compounds target any of the 22 gene products. For genes encoding soluble molecules, we also evaluated the existence of drugs inhibiting their binding receptors. Our initial search resulted in more than 150 candidate compounds. To narrow down the results, we excluded the drugs that are not yet FDA-approved, the drugs that target any of the 22 molecules with an off-target mechanism of action, the drugs that have already been evaluated for the treatment of MM in previous clinical trials and failed to show effectiveness and the drugs that are currently used in MM treatment. We resulted in 11 FDA-approved drugs (not for MM) that target 4 of the 22 previously identified gene products. It should be stated that these 11 drugs can enter the clinical testing for MM patients from phase II trials since they have already received FDA-approval and successfully passed safety barriers. Thus, these drugs represent potentially important therapeutic options and future studies should test their efficacy [10].

Conclusion

In conclusion, therapeutic advances of the past decades have significantly extended survival and quality of life of MM patients. Age-standardized five-year survival has increased from 41% to 69% for patients under 69 years old. Despite significant progress, the need for new regiments for refractory patients is urgent. Repurposing existing drugs for the treatment of multiple myeloma is a promising approach to accelerate the lab to bedside timeline. Coupling repurposing approaches with omics, as described with our paradigm, can increase the number of druggable targets and potentially widen our therapeutic options.

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