Using Prognosis-Related Gene Expression Signature and Connectivity Map for Personalized Drug Repositioning in Multiple Myeloma

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Background: Multiple myeloma (MM) is the second most common hematologic cancer with poor prognosis. Novel therapeutic strategies are needed to decrease the high mortality rate. The aim of this study was to identify prospective agents for MM.

Material/Methods: A microarray dataset was mined, which contains the transcriptome profiles of 588 MM patients. Univariate Cox analysis was performed to analyze the relationships between genes and clinical outcome. Gene Ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) were determined. Protective and risky genes were uploaded to Connectivity Map (CMAP) database to identify the potentially unknown effects of existing drugs. An example was selected to be docked on the known molecules.

Results: A total of 1445 genes significantly correlated with the event free survival (EFS) of MM patients were identified and included 676 protective and 769 risky indicators. KEGG pathway analysis revealed that these prognosis-associated genes were enriched in the “cell cycle,” “DNA replication,” and “P53 signaling pathway”. The top 3 most significant potential molecules were vorinostat, trifluoperazine, and thioridazine. CDK1 (cyclin-dependent kinase-1) ranked as the core in the class of prognosis-related genes in MM based on protein-protein interaction (PPI) network analysis. With Sybyl-X 2.0, the majority of the top 10 molecules aforementioned displayed high binding forces with CDK1. Among these molecules, trichostatin A had the greatest ability in combining with CDK1.

Conclusions: Genes that mainly accumulate in the cell cycle pathway play an essential role in the prognosis of MM, and these prognosis-related genes also have great value in drug development.

MeSH Keywords: Drug Repositioning • Multiple Myeloma • Prognosis • Transcriptome

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/913970

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Source of support: This work was supported in part by Program of Scientific and Technology Project, Guilin Science Research and Technology Development (2016012706-2); National Natural Science Foundation of China (No. 81460038); Guangxi Natural Science Foundation of China (No. 2017GXNSFAA198178)
Background

Multiple myeloma (MM) is a malignant tumor of progressive plasma cells, which is the second most common hematologic cancer [1]. MM accounts for roughly 1.8% of all malignancies and slightly over 17% of hematologic malignancies in the United States [2]. The American Cancer Society has estimated that 30,280 new MM cases would take place in the United States in 2017 and result in an estimated 12,590 deaths [2]. MM is characterized by the abnormal expansion of malignant plasma cells in the bone marrow, leading to the overproduction of monoclonal immunoglobulin in the blood and urine, defective renal function, anemia, osteolytic bone lesions, and recurring infections in patients. Furthermore, MM patients may have an immunodeficiency that compromises both longevity and quality of life [2–6].

Over the past 10 years, significant advances have been made in integrating the cellular and molecular mechanisms of MM, prompting the development of new treatment approaches. A few types of agents are currently used for MM treatments: proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), histone deacetylase inhibitors, monoclonal antibodies, alkylators, and steroids. These drugs are combined as doublets, triplets, and/or multiple drug regimens for MM treatments, and this makes the decisions about optimal therapy at diagnosis and relapse quite challenging [7]. Hence, novel therapeutic strategies are needed in order to decrease the mortality rate.

The effect of a drug may rely on the genetic and epigenetic processes of the disease. Recently, high throughput data have been pledged to public databases. The data extracted from microarray and RNA-sequencing analysis have been arranged as a database in Gene Expression Omnibus (GEO) or ArrayExpress. Previously, the differentially expressed genes from a microarray (GSE36474) were input into the Connectivity Map (CMAP) database to search potential markers and new agents for MM. However, only 4 cases of MM and 3 cases of normal controls were included [8]. Moreover, the prognostic value of those biomarkers was not examined.

As the clinical efficiency of a certain drug is judged by the patients’ survival status, the prognosis-related genes may be closely related to the potential agents. Thus, in the current study, we first determined prognosis-related genes of MM from the microarray data. We then identified the prospective agents for MM and verified the relationship between an agent and a target by molecular docking.

Material and Methods

Informative genes of multiple myeloma selection

By acquiring the GEO database, the microarray dataset GSE24080 that contains the transcriptome profiles of 588 newly diagnosed MM patients was used for further survival analysis. For a plurality of probes corresponding to 1 gene, the average value is expressed as the gene. Only mRNA expression profiles were extracted and used in the research. For survival analysis, given that event free survival (EFS) could provide more information about the progression and survival, we chose EFS as the endpoint of survival analysis. Univariate Cox analysis was performed to analyze the relationships between genes and clinical outcome by using the “survival” package of R software. Genes were considered as prognosis-related genes when the P-value was less than 0.005.

Functional enrichment analysis

We used the clusterProfiler package in R software to examine the Gene Ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) to determine the pathways for survival-associated genes. The clusterProfiler package proposes a gene classification technique to identify the biological processes which are enriched by prognostic molecules. A protein-protein interaction (PPI) network was developed to explore the relationships between each other using the online database STRING (https://string-db.org/). We chose 0.9 as the threshold and did not display nodes that were disconnected with each other. Then, visualization of the PPI network was conducted with Cytoscape software ver. 3.6.1.

CMAP analysis

CMAP is an online database that has comprehensively profiled the transcriptomic response of several types of tumor cells treating by 1309 molecules. By acquiring the datasets, we can repurpose small molecules that possess the potential for reversing the progression of tumors. Protective genes and risky genes were uploaded to CMAP to identify the potentially unknown effects of existing drugs. Chemical molecular structures were downloaded from PubChem Compound.

Molecular docking analysis

To explore the relationships between small molecules and hub genes in the development of MM, cyclin-dependent kinase-1 (CDK1), the hub genes in the process of MM prognosis, docked on each one of the molecules using the Surflex-Dock module of the Sybyl-X 2.0 program (Tripos, St. Louis, MO, USA). The structure of CDK1 was downloaded from a protein data bank (PDB).
Results

Informative genes of multiple myeloma

A total of 1445 genes significantly correlated with the EFS of MM patients ($P < 0.005$) were identified by the univariate Cox regression model and included 676 protective and 769 risky indicators. The top 20 most significant protective and risky genes are displayed in Figure 1.

Functional enrichment analysis

To determine the biological functions of prognosis-related genes, GO function and KEGG pathway enrichment were analyzed, and the functions of these 1445 genes were classified into 3 groups: biological process (BP), cellular component (CC), and molecular function (MF). For the BP level, prognosis-related mRNAs were mainly enriched in “sister chromatid segregation,” “chromosome segregation,” and “nuclear chromosome segregation”; for the CC level, the terms “chromosome, centromeric region,” “chromosomal region,” and “condensed chromosome” were the 3 most significant categories. For the MF level, the prognosis-related genes were mainly enriched in “microtubule binding,” “tubulin binding,” and “catalytic activity, acting on DNA.” Specifically, the top 10 ranked most significant terms of each group are shown in Figure 2. Notably, KEGG pathway analysis revealed that these prognosis-associated genes were enriched in the “cell cycle”, “DNA replication”, and “PS3 signaling pathway” (Figure 3, Table 1). These pathways suggested that these genes are significantly involved in tumor progression and survival status.

PPI network and module analysis

Next, the PPI networks obtained from the STRING database and visualized by Cytoscape software helped us to identify the hub genes in this batch of prognosis-related genes (Figure 4A). The core genes (degrees >20) were further submitted to PPI network analysis which indicated that CDC20, CDK1, and CCNB1 were clearly at the center of the network (Figure 4B).

Potential drugs for MM

Protective genes and risky genes were uploaded to CMAP to determine potential drugs for reversing the poor clinical outcome of MM patients. The top 10 most significant potential molecules were vorinostat, trifluoperazine, thioridazine, prochlorperazine, trichostatin A, LY-294002, sirolimus, resveratrol, sulconazole, and norcyclobenzaprine (Figure 5). The chemical structures of these molecules were also downloaded (Figure 6).

Potential binding force between molecules and targets

Given that molecular docking analysis could provide the potential binding relationships between molecules and target genes, we exploited it to observe whether the aforementioned molecules were screened out could target prognosis-related genes directly or not, especially the hub genes. CDK1 ranked as the core in the class of prognosis-related genes in MM based on PPI network analysis. Therefore, the relationships between potential anti-MM molecules and CDK1 were explored to identify the plasticity of developing anti-MM inhibitors. With Sybyl-X 2.0, the majority of the top 10 molecules mentioned above displayed high binding forces with CDK1 (Table 2). These findings
suggest these molecules have the potential to inhibit CDK1 directly. Among these molecules, trichostatin A had the greatest ability in combining with CDK1 (Figure 7).

Discussion

Over the last 2 decades, the establishment of autologous stem cell transplantation and the accessibility of new drugs with diverse mechanisms of action, including proteasome inhibitors and immunomodulatory agents, have enabled the development of therapeutic tactics for MM treatment and apparently extended the survival of MM patients. Nevertheless, a cure is hardly attained because of resistance to the drugs and the persistence of minimal residual disease. Therefore, there is an unmet need for pioneering therapeutic methods to prevent MM relapses and prolong the patients’ survival. In this study, potential drugs were screened based on the prognosis-related genes in MM. It was found that 1445 prognosis-related genes were concentrated in the cell cycle pathway and closely related to the effects of some known drugs. Finally, we also used molecular docking technology, taking trichostatin A as an example, and determined that trichostatin A had a clear docking relationship with the prognosis-related gene CDK1. This study is the first to explore novel MM treatment options from MM prognosis-related genes.

The driver genes and pathways related to the pathogenesis of MM have been studied. For instance, the common alteration of the mitogen-activated protein kinase pathway plays a critical role in the subclonality of MM, which was found to consist of subclonal mutations of hypothetical driver genes KRAS, NRAS,
Table 1. Gene ontology and Kyoto Encyclopedia of genes and genomes enrichment analysis of prognostic genes in multiple myeloma.

| GO                  | Description                                      | P.adjust | Gene ID                                                                 | Count |
|---------------------|--------------------------------------------------|----------|-------------------------------------------------------------------------|-------|
| GO: 0000819         | Sister chromatid segregation                      | 2.08E-28 | KIF14/CENPL/NEK2/NUF2/SMC4/RACGAP1/ZWILCH/CENPE/TOP2A/UBE2C etc.         | 75    |
| GO: 0007059         | Chromosome segregation                            | 8.67E-26 | KIF14/CENPL/NEK2/NUF2/SMC4/RACGAP1/ZWILCH/HJURP/CENPE/TOP2A etc.         | 89    |
| GO: 0098813         | Nuclear chromosome segregation                     | 2.67E-25 | KIF14/CENPL/NEK2/NUF2/SMC4/RACGAP1/ZWILCH/CENPE/TOP2A/UBE2C etc.         | 81    |
| GO: 0140014         | Mitotic nuclear division                          | 2.38E-21 | KIF14/NEK2/SMC4/TPX2/AURKA/RACGAP1/CENPE/UBE2C/KIF23/ZWINT etc.          | 69    |
| GO: 0000070         | Mitotic sister chromatid segregation              | 1.33E-19 | KIF14/SMC4/RACGAP1/CENPE/UBE2C/KIF23/ZWINT/ESPL1/TACC3 etc.             | 49    |
| GO: 0000280         | Nuclear division                                  | 1.15E-17 | KIF14/NEK2/SMC4/TPX2/MSH2/AURKA/RACGAP1/CENPE/ASPM/TOP2A etc.            | 82    |
| GO: 0007062         | Sister chromatid cohesion                         | 6.63E-16 | CENPE/ASPM/ZWILCH/CENPE/UBE2C/ZWINT/ESPL1/ESPL1/UBE2C/ASPM/TOP2A etc.   | 43    |
| GO: 0048285         | Organelle fission                                 | 8.88E-16 | KIF14/NEK2/SMC4/TPX2/MSH2/AURKA/RACGAP1/CENPE/ASPM/TOP2A etc.            | 84    |
| GO: 0051783         | Regulation of nuclear division                    | 7.97E-15 | NEK2/MSH2/AURKA/CENPE/UBE2C/MKI67/ESPL1/TACC3/DLGAPS/KIF11 etc.          | 49    |
| GO: 0007088         | Regulation of mitotic nuclear division            | 1.39E-14 | NEK2/AURKA/CENPE/UBE2C/MKI67/ESPL1/TACC3/DLGAPS/KIF11/BUB1 etc.          | 45    |
| GO: 0000775         | Chromosome, centromeric region                    | 6.12E-25 | CENPL/NEK2/NUF2/AURKA/ZWILCH/HJURP/CENPE/HELLS/ZWINT/BIRC5 etc.           | 63    |
| GO: 0098687         | Chromosomal region                                | 6.12E-25 | CENPL/NEK2/NUF2/MSH2/MCM2/AURKA/MCM3/MCM6/CDK1/ZWILCH etc.               | 87    |
| GO: 0000793         | Condensed chromosome                              | 5.78E-19 | NEK2/NUF2/SMC4/TOPBP1/AURKA/ZWILCH/HJURP/CENPE/TOP2A/ZWINT etc.           | 59    |
| GO: 0055819         | Spindle                                           | 5.89E-19 | KIF14/NEK2/TPX2/TOPBP1/AURKA/RACGAP1/CENPE/LATS2/ASPM etc.               | 73    |
| GO: 0000776         | Kinetochore                                       | 1.36E-18 | NEK2/NUF2/ZWILCH/HJURP/CENPE/ZWINT/BIRC5/SKA1/XPO1/BUB1 etc.             | 45    |
| GO: 0000779         | Condensed chromosome, centromeric region          | 1.36E-18 | NEK2/NUF2/AURKA/ZWILCH/HJURP/CENPE/ZWINT/BIRC5/SKA1/XPO1/BUB1 etc.       | 42    |
| GO: 0000777         | Condensed chromosome, centromeric region          | 3.73E-17 | NEK2/NUF2/ZWILCH/HJURP/CENPE/ZWINT/BIRC5/SKA1/BUB1/BUB1B etc.            | 38    |
| GO: 000922          | Spindle pole                                      | 8.34E-10 | NEK2/TPX2/TOPBP1/AURKA/LATS2/ASPM/TACC3/DLGAPS/KIF11/RASSF1 etc.         | 36    |
| GO: 0072686         | Mitotic spindle                                   | 3.16E-09 | TPX2/AURKA/RACGAP1/CENPE/ASPM/KIF23/ESPL1/TPR/KIF18A etc.               | 25    |
| GO: 0005874         | Microtubule                                       | 4.44E-09 | KIF14/NEK2/TPX2/AURKA/RACGAP1/CENPE/LATS2/ASPM etc.                     | 63    |
| GO: 0008017         | Microtubule binding                               | 0.000893388 | KIF14/RACGAP1/KIF21B/CENPE/KIF23/KIF20A/BIRC5/SKA1/KIF11/NUSAP1 etc. | 36    |
| GO: 0015631         | Tubulin binding                                   | 0.001492616 | KIF14/RACGAP1/KIF21B/CENPE/KIF23/KIF20A/BIRC5/SKA1/KIF11/TPR etc. | 43    |
| GO: 0140097         | Catalytic activity, acting on DNA                 | 0.003621655 | KIF14/ABC210/MSH2/MCM6/KIF21B/CENPE/DNA1/TOP2A/GINS1/CHD1L/MCM6/CDK1/| 30    |
| GO: 0016887         | ATPase activity                                   | 0.024082711 | KIF14/ABC210/MSH2/MCM6/KIF21B/CENPE/DNA1/TOP2A/RF4/RFK23 etc.         | 51    |
Table 1 continued. Gene ontology and Kyoto Encyclopedia of genes and genomes enrichment analysis of prognostic genes in multiple myeloma.

| ID        | Description               | P.adjust | Gene ID                                                                 | Count |
|-----------|---------------------------|----------|-------------------------------------------------------------------------|-------|
| hsa04110  | Cell cycle                | 4.32E-14 | MCM2/MCM3/MCM6/CDK1/WEI1/ESPL1/BUB1/BUB1B/MCM4/CCNA2 etc.               | 39    |
| hsa03030  | DNA replication           | 5.53E-05 | MCM2/MCM3/MCM6/DNA2/RFC4/MCM4/PCNA/RFC5/POLA1/FEN1 etc.                | 13    |
| hsa04115  | p53 signaling pathway     | 0.033703246 | CDK1/RRM2/CDKN1A/CCNB1/CCNB2/GORAB/GADD45A/RFWD2/IGF1/SIAH1 etc.     | 14    |

Figure 4. Protein-protein interaction (PPI) network of prognosis-related genes in multiple myeloma. (A) PPI network was constructed based on all survival-associated genes. (B) PPI network was constructed based on core genes (degrees >20).

Figure 5. Top 10 most significant molecules based on CMAP for multiple myeloma.

and BRAF [9]. The phosphatidylinositol-3-kinase (PI3K) pathway also plays a vital part in regulating the bone marrow microenvironment of MM, as it enhances a plethora of signaling cascades inside the MM cells [10]. Some other essential pathways include the receptor activator of nuclear factor-kappa B ligand/osteoprotegerin pathway, the macrophage inflammatory proteins, and activin-A that play a vital role in osteoclast stimulation in MM, while the wingless-type (Wnt) signaling inhibitors (sclerostin and dickkopf-1) along with the growth factor independence-1 are regarded as the central players in the osteoblast dysfunction of MM [11,12]. As treatment efficiency is widely judged by the patients’ survival, we focused on the survival-related genes and pathways in the current study of MM. Based on the microarray technique, we collected the survival-related genes based on 558 MM patients and found that several pathways were closely related to patients’ survival, including the cell cycle, DNA replication, and P53 signaling pathway, which have also been documented previously as factors that start the process of MM [13–15]. Thus, these key pathways could play pivotal roles in both the genesis and development of MM leading to a new rationale for their clinical assessment.

The important survival-related genes and pathways can hint at being potential clinical agents as they act as the direct targets of these drugs. Several bioinformatics tools and public data sources, including CMAP, provide the targeting relationships between genes and known drugs, thus making drug
repositioning possible. A previous study based on four MM cases and three cases of normal controls used the differentially expressed genes from GSE36474 to search for potential new agents for MM [8] and identified vinblastine for MM. However, no prospective drugs related to survival-related genes have been identified so far. In the current study, our survival-related genes in MM brought a series of unknown drugs, which could supplement the choices of research for novel pharmacotherapies. To further verify the bioinformatics findings from CMAP, we performed molecular docking between some drugs and a hub gene, CDK1. Interestingly, trichostatin A was the number one drug that could target CDK1 directly.

CDK1, as a cell proliferation-associated gene, has been reported to be an important driver for MM disease progression [16,17], which made it a favorable target for drug design in MM treatment. A study synthesized an aryl-guanidino compound, DCZ3301, which had strong cytotoxicity against MM by targeting CDK1 [16]. As a T prostanoid receptor antagonist, SQ29548 could inhibit cell proliferation in MM. This SQ29548 facilitated cell G2/M phase delay in MM cells in addition to decreasing cyclin B1/CDK1 mRNA and protein expression [17]. Moreover, P276-00 and dinaciclib (SCH727965) are also small molecule inhibitors of CDK1 [18,19]. However, CDK1 has never been observed to be targeted by trichostatin A; this remains to be verified in the future. However, trichostatin A, as

Table 2. Molecular docking results.

| Drug                  | Total score | Crash  | Polar   | Similarity |
|-----------------------|-------------|--------|---------|------------|
| Trichostatin A        | 8.2838      | –1.4224 | 3.43    | 0.392      |
| Vorinostat            | 7.8655      | –0.8206 | 2.1131  | 0.576      |
| Prochlorperazine       | 7.0049      | –1.0189 | 0.1404  | 0.656      |
| LY-294002             | 6.6988      | –1.1875 | 1.1792  | 0.546      |
| Trifluoperazine        | 6.6117      | –3.1285 | 0       | 0.554      |
| Resveratrol           | 6.4726      | –2.0157 | 3.4143  | 0.477      |
| Thioridazine          | 6.1874      | –1.6763 | 0.3284  | 0.502      |
| Norcyclobenzaprine    | 5.7653      | –1.8963 | 0       | 0.512      |
| Sulconazole           | 5.2691      | –1.9808 | 0.7293  | 0.469      |
| Sirolimus             | 1.2118      | –2.8722 | 1.1689  | 0.23       |

Figure 6. Chemical structures of the top ten most significant molecules for multiple myeloma. (A) Vorinostat. (B) Trifluoperazine. (C) Thioridazine. (D) Prochlorperazine. (E) Trichostatin A. (F) LY-294002. (G) Sirolimus. (H) Resveratrol. (I) Sulconazole. (J) Norcyclobenzaprine.
a histone deacetylase (HDAC) inhibitor [20], has been tested in MM. The treatment of trichostatin A in MM cells led to alterations in H3K4 methylation [21]. After treatment with trichostatin A, the proliferation inhibition of MM cells was found via GLI1 degradation and P21 overexpression, and this proliferation inhibitory effect had a time- and dose-dependent character [22]. The result of the molecular docking between trichostatin A and CDK1 may reveal a new mechanism for the action of trichostatin A in MM.

Since trichostatin A has already been investigated in the treatment of MM, other drugs which have never been tested in MM will be more interesting and valuable. Among the several candidates for targeting CDK1, prochlorperazine is new in the treatment of MM. It is a phenothiazine antipsychotic used primarily in the treatment of nausea, vomiting, and vertigo. It has been used clinically for cancer patients to treat nausea and vomiting [23]. Surprisingly, according to the CMAP and molecular docking findings, prochlorperazine has the potential to treat cancer, including MM, by targeting CDK1. However, despite the results of molecular docking, the role and mechanism of prochlorperazine in MM require further study in the future.

Even if the current findings have proposed new drug candidates for augmenting our present management of MM, there are several limitations that need to be resolved for future improvements. First, our survival-related genes were derived from a single cohort. Although more than 500 cases were included, it is best if the prognosis-related genes can be verified by other studies. Second, the direct target of drug activity should be protein. Currently, we used prognosis-related mRNA for targeted drug selection, which had certain biases. Third, there were no direct reacting genes of MM in the CMAP database, so the predictive drugs in this study were based on indirect evidence. It needs to be determined if these drugs play a similar role in MM as in other tumors. Fourth, the study was in silico research. Whether the known drugs found in the current study can be used requires further in vitro cell experiments and in vivo animal experiments for verification. Fifth, the exact mechanism for different subgroup of MM patients has not been explored fully, which need to be further explored in the future.

**Conclusions**

Genes that mainly accumulate in the cell cycle pathway play an essential role in the prognosis of MM, and these prognosis-related genes also have great value in drug development. For example, trichostatin A may exert anticancer effects by targeting the prognosis-related gene CDK1. The use of CMAP and molecular docking approaches can provide new evidence for the clinical treatment options of MM, but the findings of these in silico methods need to be further studied. Since MM is an incurable disease for most of the patients, there continues to be a need to find new MM target molecules and explore selective therapeutic strategies.
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