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Screening of traditional Chinese medicine monomers as ribonucleotide reductase M2 inhibitors for tumor treatment

Ya-ya Qin, Song Feng, Xiao-dong Zhang, Bin Peng

Abstract

BACKGROUND

Ribonucleotide reductase (RR) is a key enzyme in tumor proliferation, especially its subunit-RRM2. Although there are multiple therapeutics for tumors, they all have certain limitations. Given their advantages, traditional Chinese medicine (TCM) monomers have become an important source of anti-tumor drugs. Therefore, screening and analysis of TCM monomers with RRM2 inhibition can provide a reference for further anti-tumor drug development.

AIM

To screen and analyze potential anti-tumor TCM monomers with a good binding capacity to RRM2.

METHODS

The Gene Expression Profiling Interactive Analysis database was used to analyze the level of RRM2 gene expression in normal and tumor tissues as well as RRM2's effect on the overall survival rate of tumor patients. TCM monomers that potentially act on RRM2 were screened *via* literature mining. Using AutoDock software, the screened monomers were docked with the RRM2 protein.

RESULTS

The expression of RRM2 mRNA in multiple tumor tissues was significantly higher than that in normal tissues, and it was negatively correlated with the overall survival rate of patients with the majority of tumor types. Through literature mining, we discovered that berberine, ursolic acid, gambogic acid, cinobufagin, quercetin, daphnetin, and osalmide have inhibitory effects on RRM2. The results of molecular docking identified that the above TCM monomers have a strong binding capacity with RRM2 protein, which mainly interacted through hydrogen bonds and hydrophobic force. The main binding sites were Arg330, Tyr323, Ser263, and Met350.

CONCLUSION

RRM2 is an important tumor therapeutic target. The TCM monomers screened have a good binding capacity with the RRM2 protein.

INTRODUCTION

The tumor is a major contributor to endangering human health. In terms of disability-adjusted life years, it is only second to cardiovascular disease. The World Health Organization predicts that there will be a global increase in new tumor cases of more than 50%, from 18 million in 2018 to 27 million in 2040 [1]. In addition to conventional surgical resection, drug adjuvant therapy still occupies a considerable part in the treatment of tumors. Although numerous chemotherapy medications have been developed, the majority of them have more or less side effects and some are rather pricey. Since natural chemicals are safer, cheaper, and more effective than synthetic ones, there has been an increasing interest in finding medications to prevent and cure tumors from natural compounds [2].

Ribonucleotide reductase (RR), the only multi-subunit enzyme existing in all biological cells that can catalyze the reduction of ribonucleotides to corresponding deoxyribonucleotides, is the rate-limiting enzyme of DNA synthesis. By regulating and

balancing the content of different deoxyribonucleic acids (dNTPs) in the cell cycle, RR is mainly involved in DNA replication and repair, which is crucial for controlling cell proliferation and preserving genomic stability [3, 4]. Human RR is composed of two large subunits M1 (RRM1) and two small subunits M2 (RRM2) [5]. Since RRM2 has the ability to regulate and catalyze substrates, the enzymatic activity of RR is primarily controlled by RRM2 [6]. The tumor is a highly invasive disease, the tumor cell proliferation requires the participation of a large number of dNTPs [3]. Studies have found that most tumor cells express more ribonucleotide reductase (RR) than normal cells do. The overexpression of RRM2 is related to tumor malignancy, invasion, metastasis, drug resistance, and autophagy [7-9]. Inhibiting or reducing the expression of RRM2 may improve tumor patients' disease progression and prognosis, and lengthen their survival [10].

According to the target and mechanism of action, RRM2 inhibitors are roughly divided into gene expression regulators and protein inactivators. The gene expression regulators include R2 antisense inhibitors and siRNA inhibitors, whereas free radical scavengers, iron chelators, and iron mimics fall under the category of protein inactivators [11]. Due to a wide range of pharmacological properties, some TCM monomers have also been used as RRM2 inhibitors for research. Through literature mining, we found multiple TCM monomers that have inhibitory effects against RRM2 in tumors. However, there are few studies on their interaction sites. This paper aims to elucidate the relationship between RRM2 and malignant tumors and the prognosis of tumor patients, and then to screen out potential anti-tumor TCM monomers with good binding ability to RRM2. Through the analysis of their main binding sites, some thoughts for the development of new anti-tumor drugs with RRM2 inhibition are provided.

MATERIALS AND METHODS

Tumor patients' data acquisition

Through the Expression Profiling Interactive Analysis database (GEPIA) (<http://gepia.cancer-pku.cn>), we analyzed and obtained the mRNA level of the RRM2 gene in normal tissues and tumor tissues, as well as its effect on the overall survival rate of tumor patients. All tumor abbreviations were listed in **Table 1**.

Literature mining

PubMed database (<http://www.ncbi.nlm.nih.gov/pubmed/>) and the China National Knowledge Infrastructure database (CNKI, <https://www.cnki.net>) were used to retrieve and download the articles related to TCM monomers acting on RRM2 targets. Subsequently, the application of TCM monomers in tumors was summarized and analyzed one by one.

Molecular docking

According to the small molecule CAS number from the PubChem database, we downloaded the 3D structure of TCM monomers with small molecule SDF format, then imported them into chembio3d ultra 14.0 for energy minimization respectively. The three-dimensional structure of the RRM2 protein was obtained from the PDB (<http://www.rcsb.org>). AutoDock vina1.1.2 was used to complete the molecular docking between RRM2 protein and TCM monomers. The relevant parameters of RRM2 protein were set to center_x = -4.715, center_y = -3.6 and 33, center_Z = 15.668; The size of the grid box was set to 50×50×50 (the spacing of each grid point is 0.375 Å), and the other parameters were the default settings. Finally, analyzation of the interaction mode of the docking results was performed by Pymol 2.3.0 and ligplot V2.1.

RESULTS

RRM2 was identified as the tumor therapeutic target

In the GEPIA database, we found 31 types of tumor tissues with RRM2 differential expression and their paired normal samples. The findings revealed that, except for LAML, the mRNA expression of RRM2 in 30 types of tumor tissues was considerably

higher than that in normal tissues (**Figure 1**). The investigation of the overall survival rate of 33 tumor patients revealed that the RRM2 gene expression of 23 types of tumor patients was negatively correlated with the overall survival rate (**Figure 2**), while it was positively correlated in 10 types of tumor patients (**Figure 3**). Among them, the reason for the small number of positive correlation results that have been seen may be that there are other issues having an impact on the overall survival rate.

Seven TCM monomers with inhibitory effect on RRM2 in tumors were screened

Through the literature search in the PubMed database and CNKI database, we found seven TCM monomers that may be used as RRM2 inhibitors in tumors (**Table 2**). They all will be described in subsequent sections separately.

1. Berberine Berberine is a quaternary ammonium alkaloid extracted from medicinal plants such as *Coptis chinensis*, *Berberis aristata*, *Hydrastis canadensis*, and *Coptis japonica* [12]. Berberine and its derivatives have been identified to have pharmacological properties against multiple diseases, including digestive diseases, metabolic diseases, cardiovascular diseases, and neurological diseases [13]. Recent studies have discovered that berberine can also inhibit the invasion and metastasis of many kinds of tumors, such as oral squamous cell carcinoma, lung cancer, liver cancer, glioblastoma, breast cancer, and so on [12]. Through binding to P53, NF- κ B, matrix metalloproteinase (MMP), Bcl-2, and receptors e.g. estrogen receptor, berberine could promote the cell cycle arrest and death of tumor cell lines, and induce the expression of pro-apoptotic factors [14-16]. In addition, some other information indicates that RRM2 may also be a potential target of berberine in the treatment of tumors. A bioinformatic analysis showed that RRM2 is the hub-gene for berberine to act on breast cancer [17]. After berberine treatment *in vitro*, the expression level of the RRM2 gene and protein in non-small cell lung cancer cell lines (A549, H1299, and H1975) was significantly reduced [18].

2. Ursolic acid Ursolic acid, a natural pentacyclic triterpene compound, is widely found in fruits and vegetables. It has been demonstrated to have multiple biological functions, including anti-inflammatory, antioxidant, anti-apoptotic, and anti-allergic

activities ^[19]. At present, ursolic acid has also been reported to have anti-tumor pharmacological properties, acting as an active therapeutic agent for several malignancies such as breast cancer, colon cancer, pancreatic cancer, and liver cancer ^[20]. By regulating a variety of enzymes (ATPase, GST, COX-2), transcription factors (AP-1, NF- κ B, STAT-3), growth factors (EGF, PDGF, HGF), receptors (EGFR, ER- α , HER-2, ESR), as well as inflammatory factors (MAP-K, PKA, PTK, IL-6, IL-1, IL-8, MIP), it could inhibit tumor proliferation, metastasis, and angiogenesis ^[21, 22]. Recently, a network pharmacology analysis detected that RRM2 may be also the potential target of ursolic acid in tumors ^[23], but still needs to be further confirmed in clinical and experimental studies.

3. Gambogic acid Gambogic acid, a kind of caged xanthone extracted from dry resin secreted by *Garcinia hanburyi* tree, has the functions of promoting blood circulation, anti-cancer, detoxification, and hemostasis ^[24]. According to numerous studies, multiple carcinomas, including breast cancer, lung cancer, liver cancer, colon cancer, and pancreatic cancer, were inhibited by gambogic acid ^[25]. Through the combination of several major targets such as VEGF, Bcl-2, MDM2, MMP-9, MMP-2, EGFR, and P53, gambogic acid promotes tumor cell apoptosis, autophagy, and arrests cell cycle, thereby inhibiting tumor invasion, metastasis, and angiogenesis ^[26]. An investigation in pancreatic cancer demonstrated that following treatment with gambogic acid *in vivo* and *in vitro*, the expression of RRM2 protein and mRNA was significantly decreased ^[6], suggesting that RRM2 may also be the target of gambogic acid in tumor treatment.

4. Cinobufagin Bufadienolide cinobufagin, which is extracted from the Asiatic toad *Bufo gargarizans*, has analgesic, detoxifying, and detumescent properties ^[27]. Some investigations conducted recently have revealed that it has potent anti-tumor effects as well. In non-small cell lung cancer, cinobufagin could suppress proliferation, migration, and invasion of cancer cells by inhibiting the expression of G9a ^[27]. By interfering with the cell cycle, cinobufagin also inhibits the survival of cancer cells and promotes apoptosis ^[28]. It also exerts anti-tumor effects through multiple pathways, such as the Notch signaling pathway^[29], AURKA/mTOR/eIF4E axis ^[30], c-Myc pathway^[31],

ROS/JNK/p38 signaling pathway^[32]. After cinobufagin treatment, the expression of RRM2 in endometrial carcinoma (Ishikawa cell line) decreased significantly at gene and protein levels, inhibiting cell proliferation and reducing invasiveness^[33]. *In vivo* studies likewise produced the same results^[34]. Cinobufacin is expected to be an RRM2 inhibitor with multiple anti-tumor effects.

After cinobufagin treatment, the expression of RRM2 in endometrial carcinoma (Ishikawa cell line) decreased significantly at gene and protein levels, so as to inhibit cell proliferation and reduce invasiveness

5. Quercetin Quercetin, a flavonol compound widely existing in many plants, has been reported to have multiple pharmacological effects on preventing osteoporosis, cardiovascular disease, aging, and tumors^[35]. In terms of anti-tumor properties, the main mechanisms are to regulate the viability, apoptosis, and autophagy of tumor cells through ³PI3K/Akt/mTOR, Wnt/ β -Catenin, and MAPK/ERK1/2 pathways^[36], and then exhibits inhibitory activities against a variety of tumors, such as colon cancer (Caco-2 cell line), lung cancer (NCI-H446, A549 cell line), and gastric cancer (MGC-803, SGC-7901 cell line)^[37]. A comprehensive analysis based on differential genes and drug targets found that quercetin was closely related to RRM2^[23]. After treatment with quercetin, the activity of *Leishmania donovani* was inhibited by targeting RR^[38]. Therefore, we speculate that the anti-tumor effect of quercetin may be partially attributed to the inhibition of RRM2.

6. Daphnetin Daphnetin is a coumarin derivative with rich pharmacological activity, extracted from *Daphne odora*. It is often used in the treatment and research of neurological diseases, malaria, parasites, and arthritis^[39]. Currently, some studies suggest that daphnetin also has an inhibitory effect on tumor growth, with the mechanisms of action including downregulating Cyclin D1 expression in breast cancer (MCF-7 cell line), inducing G2/M and S phase arrest in hepatoma cells (SMMC-7721 cell line), suppressing the Akt/NF- κ B signaling pathway in lung adenocarcinoma (A549 cell line), and inhibiting the AMPK/Akt/mTOR pathway in ovarian cancer (A2780 cell line)^[40]. In addition, a study on malaria found that daphnetin could also inhibit the

expression and activity of RR by binding to the iron-containing group (RRM2) [41]. However, as an indispensable key enzyme for tumor growth, whether daphnetin can inhibit RRM2 in human tumor cells needs further research to confirm.

7. Osalmid In clinical practice, osalmid has been used to treat biliary tract inflammation, cholecystitis, and post cholecystectomy syndrome. By decreasing RRM2 activity and activating P53, it was found that osalmid also inhibits the progression of human hepatocellular carcinoma [42]. The expression of RRM2 in esophageal cancer was similarly inhibited by osalmid. In addition to promoting apoptosis, blocking cell cycle and DNA damage, and inhibiting the proliferation and migration of tumor cells, the radiosensitivity was enhanced [43]. Due to their powerful anti-tumor activities, Osalmid and its derivatives have been used in numerous investigations as new RRM2 inhibitors [44-46].

The screened TCM monomers have a good binding capacity with RRM2 protein

Molecular docking presented interaction between the aforementioned seven TCM monomers and RRM2 protein, and the results showed that they all had a strong binding capacity. The specific results are described in detail in the following sections (**Table 3**).

1. Berberine binds to the RRM2 protein with a binding energy of -7.3 kcal/mol, mostly made up of one hydrogen bond and eight hydrophobic bonds (**Figure 3A**). The hydrogen bond is mainly localized at Ser263(A) of RRM2, with a length of 3.73 Å, and the hydrophobic sites are situated at Glu260(A), Arg264(A), Tyr323(A), Arg330(A), Gly233(A), Val327(A), Ser237(A) and Gly267(A) of RRM2.

2. Ursolic acid and RRM2 protein have a binding energy of -8.6 kcal/mol (**Figure 3B**). There is just hydrophobic force between them. Arg264(A), Gly267(A), Cys270(A), Gly233(A), Arg330(A), Val327(A), and Ser263(A) of RRM2 are the primary hydrophobic action sites.

3. Gambogic acid and RRM2 protein bond with a -8.6 kcal/mol binding energy (**Figure 3C**). Their interaction is achieved through the formation of hydrogen bonds and hydrophobic forces. The hydrogen bonds in RRM2 are at positions Arg330(A) and

Tyr323(A), with lengths of 3.24 Å and 2.74 Å, respectively. The hydrophobic action sites in RRM2 are found at Gly267(A), Leu268(A), Ser100(A), Lys96(A), Arg264(A), Met350(A), and Ser263(A).

4. The binding energy between cinobufagin and RRM2 protein is -7.6kcal/mol (**Figure 3D**). They interact with each other through the formation of hydrogen bonds and hydrophobic force. The hydrogen bond lengths are 3.88 Å and 2.82 Å, respectively, which are located at Asp271 (A) and Arg330 (A) of RRM2. The hydrophobic effect was generated on Glu334 (A), Leu331 (A), Cys270 (A), Gly267 (A), Glu266 (A), Ser263 (A), Phe244 (A), and Met350 (A) of RRM2 and cinobufagin.

5. Quercetin and RRM2 protein have a binding energy of -7.4 kcal/mol (**Figure 4A**). Quercetin mainly forms three hydrogen bonds and nine hydrophobic forces with RRM2. The hydrogen bond lengths are 3.16 Å, 3.05 Å, and 2.77 Å, respectively, which are mainly formed in Arg330 (A) and Tyr323 (A) of RRM2. The hydrophobic sites were found in the following positions in RRM2: Met350 (A), Arg264 (A), Glu260 (A), Phe244 (A), Ser263 (A), Glu232 (A), Gly233 (A), Phe240 (A) and Val327 (A).

6. The binding energy between daphnetin and RRM2 protein is -6.7kcal/mol (**Figure 4B**). Tyr323 (A) and Arg330 (A) of RRM2 make four hydrogen bonds with daphnetin, whereas Val327 (A), Ser263 (A), Phe240 (A), Met350 (A), Gly267 (A), Gly233 (A), and Gys270 (A) of RRM2 form seven hydrophobic forces with daphnetin. whose hydrogen bonds have lengths of 2.87 Å, 3.19 Å, 2.80 Å, and 3.24 Å, respectively.

7. Osalmide and RRM2 protein have a -6.8kcal/mol binding energy (**Figure 4C**). They only interact hydrophobically, and their hydrophobic interaction sites were found in Phe244 (A), Arg264 (A), Tyr323 (A), Phe240 (A), Ser237 (A), Met350 (A), Gly233 (A), and Ser263 (A) of RRM2.

DISCUSSION

Nowadays, the acknowledged tumor treatment strategies include surgical resection, chemotherapy, and radiotherapy, as well as biotherapy, immunotherapy, and targeted therapy developed in recent decades. Due to some limitations and defects,

monotherapy does not seem to be able to fully achieve the ideal effect [47]. Therefore, combination therapy and adjuvant therapy are often required. As a natural medicine, some active ingredients of TCM have been proven to have excellent anti-tumor activity. TCM can not only inhibit the proliferation of tumor cells through multiple targets, improve the cancer microenvironment, and strengthen the function of anti-tumor immunity, but also enhance the efficacy of chemotherapy, radiotherapy, targeted therapy, and immunotherapy, and reduce the damage caused by these therapies, to prolong the survival time of tumor patients and improve the quality of life to a certain extent [48]. Because of their advantages of broad spectrum, high efficacy, low toxicity, and strong specificity, TCMs and extracts are widely used as adjuvant therapy for tumors in clinics [49]. Paclitaxel, vinblastine, and hydroxycamptothecin are three examples of commonly used clinical chemotherapeutic medicines [50-52]. Compared with traditional synthetic medications, the anti-tumor mechanisms of TCMs are more complex and extensive. They involve multiple signaling pathways and biological targets related to cancer. Despite the long history of TCM study, part of the mechanism of action and molecular targets are not completely clear [53]. TCM monomers, as the active compound of TCM, including their functions still need to be further explored and studied.

Deoxyribonucleotide triphosphate (dNTP), the building block for DNA synthesis, is in high demand in tumors. As the key enzyme of DNA synthesis, RR not only participates in DNA synthesis and repair *via* producing dNTP but is also involved in cell cycle regulation [5, 54]. RRM2 is an important subunit of RR, which also play a regulatory role in multiple biological processes, including the survival, proliferation, apoptosis, and chemoresistance of various cancer cells [7]. According to GEPIA database analysis, we found that RRM2 is highly expressed in more than 30 types of tumor tissues, and negatively correlated with the overall survival rate of patients with the majority of tumor types. A study in prostate cancer has found that RRM2 is a driver of aggressive subtypes, and elevated RRM2 contributes to tumor cell immune escape [55]. The overexpression of RRM2 in breast cancer cells activated NF- κ B and MMP-9 to alter

the tumor microenvironment, thereby enhancing the migratory abilities of tumor cells [56]. Increased RRM2 expression is also associated with tamoxifen resistance, inhibition of RRM2 not only reduced migration and invasion characteristics of cancer cells *in vitro* but also reversed tamoxifen resistance of breast cancer cells, which may be mediated by NF- κ B, HIF-1 α , and MAPK/JNK pathway [57]. GW8510 acts as an RRM2 inhibitor, improving acquired tamoxifen resistance in breast cancer cells by autophagy induction, a similar effect was seen in lung squamous cell carcinoma cells [58, 59]. Besides, knockdown of RRM2 enhanced the drug sensitivity of chronic myeloid leukemia to imatinib treatment by activating the Bcl-2/caspase apoptosis pathway and inhibiting the Akt cell signaling pathway [60]. These results indicate that RRM2 is an independent predictor of poor prognosis in a variety of tumors and could be a good target for tumor therapy.

RRM2 has two important drug binding targets: tyrosine free radical and divalent iron radical, most of the currently developed RRM2 inhibitors act on these two targets [61]. Hydroxyurea is a common anti-tumor chemotherapy drug as well as an RRM2 inhibitor, which can inhibit RRM2 activity by scavenging tyrosine free radicals, and then inhibit DNA synthesis [62]. Gallium, an iron analog, has chemical characteristics similar to iron. Though interacting with iron-binding protein, gallium interferes with cellular iron uptake and damages iron homeostasis in cells, resulting in the inhibition of RRM2 function [63]. Triapine also inhibits RRM2 activity by forming iron chelates with iron groups [64]. However, some RRM2 inhibitors may lead to different degrees of side effects such as blood and lymphatic system metabolic disorders, liver and kidney dysfunction, gastrointestinal reactions, and reproductive toxicity [65, 66]. Therefore, it is urgent to develop or find new RRM2 inhibitors that are safer, more effective, and more specific.

Through literature mining, we retrieved seven TCM monomers with an inhibitory effect on RRM2 in tumors. They all have good binding capacities with RRM2, according to molecular docking analysis, with binding energies ranging from -8.6 to -6.8 kcal/mol. The hydrogen bonds and/or hydrophobic forces are the main contributors to these

binding energies, their major active sites are Arg330, Tyr323, Ser263, and Met350 of RRM2. Among them, Arg330 is the site where the most hydrogen bonds are formed between TCM monomer and RRM2, followed by Tyr323. The locations with the highest frequency of hydrophobic action are Ser263 and Met350, the next are Gly267 and Arg264. These findings imply that Arg330, Tyr323, Ser263 and Met350 may be important binding sites of RRM2 inhibitors with RRM2, which will provide some thoughts for the development of new anti-tumor drugs with RRM2 inhibition based on these sites.

CONCLUSION

RRM2 is a crucial tumor therapeutic target. It is highly expressed in almost all tumors and negatively correlated with the overall survival rate of patients with the majority of tumor types. The seven screened TCM monomers have a good binding capacity to RRM2, and their binding sites are mainly concentrated in Arg330, Tyr323, Ser263, and Met350 of RRM2. This will provide theoretical support and a point for the development of anti-tumor medications with RRM2 inhibition based on these binding sites. Meanwhile, natural drugs with abundant structures are an important source for the development of anti-tumor drugs, it is anticipated that more effective RRM2 inhibitors will be developed through in-depth research.

ARTICLE HIGHLIGHTS

Research background

1. The tumor is a major contributor to endangering human health, traditional Chinese medicine (TCM) monomer is an important source of anti-tumor drugs.
2. Ribonucleotide reductase (RR) is a key enzyme in tumor proliferation, especially its subunit-RRM2.
3. Screening and analysis of TCM monomers with RRM2 inhibition can provide a reference for further anti-tumor drug development.

Research motivation

To screen and analyze potential anti-tumor TCM monomers with a good binding capacity to RRM2, and provide some thoughts for the development of anti-tumor drugs with RRM2 inhibition in the future.

Research objectives

1. To clarify the relationship between RRM2 and malignant tumors.
2. To clarify the relationship between RRM2 and the prognosis of tumor patients.
3. To screen and analyze potential anti-tumor TCM monomers with a good binding capacity to RRM2, and provide some thoughts for the development of anti-tumor drugs with RRM2 inhibition in the future.

Research methods

1. The GEPIA database was used to analyze the level of RRM2 gene expression in normal and tumor tissues as well as RRM2's effect on the overall survival rate of tumor patients.
2. TCM monomers that potentially act on RRM2 were screened *via* literature mining.
3. Using AutoDock software, the screened monomers were docked with the RRM2 protein.

Research results

1. The expression of RRM2 mRNA in multiple tumor tissues was significantly higher than that in normal tissues,
2. RRM2 was negatively correlated with the overall survival rate of patients with the majority of tumor types.
3. Berberine, ursolic acid, gambogic acid, cinobufagin, quercetin, daphnetin, and osalmide have inhibitory effects on RRM2.
4. The screened TCM monomers had a strong binding capacity with RRM2 protein.

Research conclusions

1. RRM2 is an important tumor therapeutic target.
2. The screened TCM monomers have a good binding ability with the RRM2.

Research perspectives

Their main binding sites could provide new thoughts for the development of anti-tumor drugs with RRM2 inhibition.

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