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Gene Signatures to Therapeutics: Assessing the Potential of Ivermectin Against t(4;14) Multiple Myeloma

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Abstract

BACKGROUND

Multiple myeloma (MM) is a terminal differentiated B-cell tumor disease characterized by clonal proliferation of malignant plasma cells and excessive levels of monoclonal immunoglobulins in the bone marrow. The translocation, t(4;14), results in high-risk MM with limited treatment alternatives. Thus, there is an urgent need for identification and validation of potential treatments for this MM subtype. Microarray data and sequencing information from public databases could offer opportunities for the discovery of new diagnostic or therapeutic targets.

AIM

To elucidate the molecular basis and search for potential effective drugs of t(4;14) MM subtype by employing a comprehensive approach.

METHODS

The transcriptional signature of t(4;14) MM was sourced from the Gene Expression Omnibus. Two datasets, GSE16558 and GSE116294, which included 17 and 15 t(4;14) MM bone marrow samples, and five and four normal bone marrow samples,

respectively. After the differentially expressed genes were identified, the Cutohuba tool was used to screen for hub genes. Then, the hub genes were analyzed using Gene Ontology and Kyoto Encyclopedia of Genes and Genomes analysis. Using the STRING database and Cytoscape, protein-protein interaction networks and core targets were identified. Potential small-molecule drugs were identified and validated using the Connectivity Map database and molecular docking analysis, respectively.

RESULTS

In this study, a total of 258 differentially expressed genes with enriched functions in cancer pathways, namely cytokine receptor interactions, nuclear factor (NF)- κ B signaling pathway, lipid metabolism, atherosclerosis, and Hippo signaling pathway, were identified. Ten hub genes (*cd45*, *vcam1*, *ccl3*, *cd56*, *app*, *cd48*, *ltk*, *ccr2*, *cybb*, and *cxcl12*) were identified. Nine drugs, including ivermectin, deforolimus, and isoliquiritigenin, were predicted by the Connectivity Map database to have potential therapeutic effects on t (4;14) MM. In molecular docking, ivermectin showed strong binding affinity to all 10 identified targets, especially *cd45* and *cybb*. Ivermectin inhibited t(4;14) MM cell growth *via* the NF- κ B pathway and induced MM cell apoptosis *in vitro*. Furthermore, ivermectin increased reactive oxygen species accumulation and altered the mitochondrial membrane potential in t(4;14) MM cells.

CONCLUSION

Collectively, the findings offer valuable molecular insights for biomarker validation and potential drug development in t(4;14) MM diagnosis and treatment, with ivermectin emerging as a potential therapeutic alternative.

INTRODUCTION

Multiple myeloma (MM) represents a severe hematological malignancy, affecting 176,404 individuals and resulting in 117,077 fatalities annually [1]. MM is characterized by uncontrolled plasma cell proliferation in the bone marrow, leading to

severe complications, such as bone and kidney damage, anemia, and hypercalcemia [2]. Of particular concern is the t(4;14) subtype, comprising up to 15% of new MM cases, with notably low survival rates and strong resistance to existing therapies [3]. Thus, effectively addressing this subtype remains an important medical challenge. Although the seminal research of Steven *et al* [4] and Cody *et al* [5] have provided insights into the pivotal facets of t(4;14) MM (Table S1), which have advanced our understanding of this malignancy, certain aspects remain elusive.

Translational medicine is increasingly considering drug repurposing as a potential strategy to develop efficient, safe, cost-effective, and readily available anticancer treatments [6]. Advances in high-throughput sequencing technology have expanded biomedical and computational resources, facilitating a deeper understanding of cancer etiology and drug-target interactions, thus enabling drug repurposing [7]. Notably, the Connectivity Map (CMap) tool, housing a comprehensive dataset of 7,000 microarrays from various cancer cells treated with 1,309 molecular compounds, has been instrumental in identifying potential treatments for various cancers [8]. Notably, Shi *et al* used CMap to identify eugenol as a potential treatment for triple-negative breast cancer [9], and Qiu *et al* computationally identified small-molecule drugs with the potential to treat cervical cancer [10].

There is an urgent need for identification and validation of potential treatments for this MM subtype, therefore, we aim to elucidate the molecular basis and search for potential effective drugs by employing a comprehensive approach. We hope to contribute to advancing early MM diagnosis and tailoring its treatment.

MATERIALS AND METHODS

Differential expression analysis

The Gene Expression Omnibus (GEO) database (<https://www.ncbi.nlm.nih.gov/gds>) is a key public repository housing high-throughput gene expression data, microarray data, and gene chip information. For this study, we sourced the t(4;14) MM-related expression dataset from GEO. Our search parameters were tailored to t(4;14) MM across

all fields, combined with filters for "Homo sapiens" as the organism and "dataset." Two datasets, GSE16558 and GSE116294, which included 17 and 15 t(4;14) MM bone marrow samples, and five and four normal bone marrow samples, respectively (Table S2), were further considered for our analysis. To identify DEGs between the t(4;14) MM samples and normal samples, we used the "limma" package in R software (version 4.2.2, [<http://www.R-project.org/>]). Our selection criteria were a p-value <0.05 and absolute log2 fold change (FC) >1.

PPI network analysis

To construct a functional PPI network for the identified DEGs, we used the STRING online database tool (<https://string-db.org/>)^[11]. Our selected threshold required a credibility score of >0.4 for inclusion within the network. The Cytoscape software (version 3.10.1, [<https://cytoscape.org/>]) was used to visually map the PPI, offering a clear understanding of protein interactions.

Hub gene mapping

Using Cytoscape, the molecular complex detection (MCODE) plugin was activated to highlight prominent clusters, abiding by criteria, such as an MCODE score >6 and a node count >4. The CytoHubba plugin ^[12] within Cytoscape, paired with the **Maximal Clique Centrality (MCC)** method, was used to filter and identify the top-ranking genes. A combination of results drawn from the MCODE, MCC, and degree scores led to the identification of 10 key hub genes.

Functional enrichment analysis

The enrichment analysis was performed using the "GSEAPy" package within Python (v.3.11.4, [<https://www.python.org/>]), using the Kyoto Encyclopedia of Genes and Genomes (KEGG) and **Gene Ontology**. Subsequently, statistical significance was evaluated using the p-value, whereas the visualization of data was achieved using the "ggplot2" package in R. Gene Set Enrichment Analysis (GSEA) was performed using its

dedicated software, sourcing gene sets from the Molecular Signature Database (<http://software.broadinstitute.org/gsea/index.jsp>).

Drug screening using CMap

The CMap database (<https://clue.io>)^[13], a key tool in systems biology, was used to identify potential therapeutic candidates. Our criteria were rigorous, with a cutoff score of <-80.

Molecular docking

For our molecular docking investigations, 3D structural models of the proteins encoded by target genes were retrieved from UniProt^[14] and Protein Data Bank databases and augmented with AlphaFold data. Focusing on structures determined *via* X-ray diffraction with a co-crystal resolution <2.5 Å, we downloaded the 2D structural model of ivermectin from PubChem^[15] and converted it into a 3D structure using the LigPrep module in Maestro. AutoDockTools were used to preprocess the ligands. Optimization included water removal, hydrogenation, charge determination, and torsion centers and bond selection, yielding a pdbqt file suitable for docking studies. Macromolecular docking calculations were performed using Vina software (version 1.1.2, <http://vina.scripps.edu/>). To illustrate the post-docking ligand-receptor interactions, we used Ligplot+^[16] for 2D mapping and PyMOL^[17] for in-depth 3D analysis.

Reagents and antibodies

Ivermectin was purchased from Aladdin Biological Technology (Shanghai, China). The following primary antibodies were purchased from CST (Danvers, MA, USA): anti-poly(ADP-ribose) polymerase (PARP) (9532; 1:1000), anti-cleaved PARP (5625; 1:1000), anti-cleaved caspase 3 (9661; 1:500), anti-cleaved caspase 9 (20750; 1:1000), and β-actin (3700; 1:1000). The following primary antibodies were purchased from Abcam (Cambridge, UK): anti-B-cell lymphoma 2 (Bcl2; ab182858; 1:1000), anti-Bcl-2-associated X protein (Bax; ab32503; 1:1000), anti-NF-κB p65 (ab32536; 1:1000), anti-NF-κB p65

(phospho S536) (ab86299; 1:1000), anti-inhibitor of NF- κ B (I κ B) alpha (ab32518; 1:1000), and anti-I κ B alpha (phospho-S36) (ab133462; 1:1000). The following secondary antibodies were purchased from Beyotime Biotechnology (Shanghai, China): anti-rabbit IgG (A0208; 1:5000) and anti-mouse IgG (A0216; 1:5000).

Cell culture

NCI-H929, a t(4;14) MM cell line, was obtained from the Cell Bank of the Type Culture Collection of the Chinese Academy of Sciences (Shanghai, China). The cells were cultured in RPMI-1640 medium (Gibco, Billings, MO, USA) with 10% fetal bovine serum (Gibco) and 1% penicillin/streptomycin (Gibco) at 37 °C with 5% CO₂. Preliminary tests confirmed that the cell lines were *Mycoplasma*-free.

Cytotoxic activity assay

To assess cytotoxic activity, 5,000 cells were seeded per well into a 96-well plate and exposed to ivermectin concentrations ranging from 0–20 μ M for 24–48 h. After incubation, cell viability was evaluated using Cell Counting Kit-8 (CCK8) (DojinDo, Shanghai, China), which required an additional 2-h incubation with 10 μ L of CCK8 solution at 37 °C. The absorbance of the reaction mixture was measured at 450 nm using a microplate reader (Thermo Fisher Scientific, California, USA). The inhibitory concentration 50% (IC₅₀) of ivermectin for each cell type was determined from the viability data using GraphPad Prism v.10 and the following equation:

$$[(As - Ab) / (Ac - Ab)] \times 100\%,$$

Where “As,” “Ac,” and “Ab” are the absorbance values in the experimental, control, and blank wells, respectively.

Apoptosis assay

Cells were seeded into 6-well plates and treated with ivermectin for 24 h. After treatment, the cells were collected by centrifugation. They were then stained using the FITC Annexin V Apoptosis Detection Kit with 7-aminoactinomycin D (7-AAD; 640922;

BioLegend, San Diego, CA, USA) by adding 5 μ L of fluorescein isothiocyanate (FITC) conjugated with annexin V and 5 μ L of 7-AAD solution. This was followed by 15 min incubation in the dark at 25 °C. Subsequently, the stained cells were analyzed using a flow cytometer (LSRFortessa; BD, Franklin Lakes, NJ, USA), and the data obtained were processed and interpreted using FlowJo software (v.10.4).

ROS assay

The cells were cultured in 6-well plates overnight. Fresh RPMI-1640 medium containing the indicated concentrations of ivermectin was added, and the cells were cultured for 24 h. A reactive oxygen species (ROS) assay kit (S0033S; Beyotime) was used to detect intracellular ROS levels using the following protocol: treated cells were incubated with 2',7'-dichlorodihydrofluorescein diacetate for 20 min at 37 °C. Cells were washed thrice with serum-free medium, and images were acquired using a fluorescent inverted microscope (Olympus, Tokyo, Japan).

Mitochondrial membrane potential assay

Cells were first allowed to settle in 6-well plates, after which they were treated with ivermectin for 24 h. A JC-1 assay kit (M34152; Thermo Fisher Scientific) was used to evaluate the mitochondrial membrane potential within these cells. The assessment was performed in strict accordance with the manufacturer's guidelines. Readings from this assessment were captured using a flow cytometer (LSRFortessa; BD).

Western blot analysis

After 48 h of ivermectin treatment, the cells were harvested and lysed using Cell Lysis Buffer (P0013; Beyotime), which included a protease inhibitor. The subsequent lysate was subjected to a 30-min ice bath before centrifugation at 12,000 rpm for 20 min at 4 °C. Proteins were quantified using a BCA assay kit (P0010; Beyotime), separated by sodium dodecyl-sulfate polyacrylamide gel electrophoresis, and transferred onto polyvinylidene fluoride membranes. Subsequently, these membranes were blocked

with 5% skim milk for 2 h and incubated with primary antibodies overnight at 4 °C. After thorough washing, the membranes were incubated with horseradish peroxidase-conjugated secondary antibodies for 1 h at 25 °C. The proteins were visualized using an electrochemiluminescence kit (NCM Biotech, Suzhou, China).

Statistical analysis

All statistical evaluations were performed using both the R package and GraphPad Prism v.9.0 (GraphPad Software Inc., San Diego, CA, USA). Student's t-test was used to compare the means between two groups. Comparisons across multiple groups were conducted using one- and two-way ANOVA. All results are presented as the mean \pm standard deviation. Statistical significance was set at p-levels < 0.05 .

RESULTS

Identification of DEGs

We identified 1,100 DEGs (270 upregulated and 830 downregulated) and 1746 DEGs (808 upregulated and 938 downregulated) in the GSE16558 and GSE116294 datasets, respectively. These microarray findings have been presented using heat maps and volcano graphs, applying a threshold of $p < 0.05$, $\log_{2}FC < 1$ for downregulated genes, and $\log_{2}FC > 1$ for upregulated genes (Figure S1).

Potential targets involved in t(4;14) MM and PPI network

To better understand the therapeutic pathways involved in t(4;14) MM, we constructed a Venn diagram and identified 258 probable targets related to t(4;14) MM (Figure 1A). Subsequently, a PPI network containing these targets was constructed to elucidate the target interrelations. The PPI network comprised 175 nodes and 697 edges (Figure 1B). Three targets that lacked interactions with other targets were excluded from the assessment. The top five identified nodes were cd45, btk, ccl3, cdh1, and cxcl12, highlighting their pivotal roles in the network.

Identification of clusters and hub targets in the PPI network

Using the Cytoscape MCODE plugin, we identified two clusters with scores >6 (Figure 1D). The first group, with 57 nodes and 343 edges, was centered on the seed gene, *CD45*, and was predominantly related to altered transcriptional regulation in cancer. The second smaller cluster, which included 15 nodes and 66 edges, had *TLR1* as its seed gene and was primarily related to the negative regulation of apoptosis and signal transduction. Subsequently, the CytoHubba score was used to identify the top 15 genes (Figure 1C). Each of these 15 genes had a degree score >15, indicating comprehensive interactions among them. Combining insights from MCODE, MCC, and degree scores, we identified 10 central hub genes: *cd45*, *vcam1*, *ccl3*, *cd56*, *app*, *cd48*, *btik*, *ccr2*, *cybb*, and *cxcl12* (Figure 1E).

Functional enrichment analysis

To better understand the potential therapeutic targets of t(4;14) MM, we performed functional enrichment analysis of the 255 shared targets. Using the KEGG database, we identified 232 enriched signal pathway terms through enrichment analysis. With an adjusted p-value of <0.05, the top 20 pathways, including those related to cancer, cytokine-cytokine receptor interaction, NF- κ B signaling, and the Hippo signaling pathway, were identified (Figure 1F). The GSEA for the NF- κ B signaling pathway is illustrated in Figure 1G. Based on these findings, we focused on the NF- κ B signaling pathway to elucidate the potential mechanisms related to t(4;14) MM.

Ivermectin identified as a potential drug using CMap

We used 258 DEGs as potential drug targets for t(4; 14) MM and assessed the CMap database to identify small compounds that could serve as prospective drugs. Table 1 Lists the top nine small-molecule drugs believed to hold therapeutic potential in countering the gene expression pattern of t(4;14) MM (with a cut-off score of <-80). Notably, ivermectin, which was listed among the identified small molecules, was considered for further investigation, as it is a high-ranking approved non-

chemotherapeutic drug. Thus, we evaluated the potential inhibitory effects of ivermectin on t(4;14) MM cells.

Molecular docking

Molecular docking is a pivotal technique for the design of structure-based drugs. It facilitates the assessment of molecular interactions by determining the most favorable conformation between small-molecule targets and compounds. In molecular docking simulations, ivermectin displayed strong binding affinity to all 10 identified targets, with docking energy scores below -7 kcal/mol (Figure 2B). Notably, CD45 and CYBB demonstrated the most potent binding, with binding energies of -10.2 kcal/mol and -9.9 kcal/mol, respectively. The 3D structural analysis revealed favorable binding sites for ivermectin in both CD45 (Figure 2E) and CYBB (Figure 2F). Additionally, 2D interaction diagrams indicated hydrogen bond formation between ivermectin and specific amino acid residues in CD45 (Glu1030 and Glu1003) and CYBB (Art73), along with hydrophobic interactions in CD45 and water-mediated interactions in CYBB (Figure 2D). These findings shed light on the binding mechanisms underlying the strong affinity between ivermectin and its targets, providing valuable insights for future drug design.

Ivermectin inhibits the proliferation of t(4;14) MM cells

We evaluated the impact of ivermectin on t(4;14) MM cell proliferation by subjecting cells to varying concentrations (0, 4, 6, 8, 10, and 20 μ M) of ivermectin and time intervals (24 and 48 h) of exposure. Cell viability, determined using CCK8, demonstrated a significant, concentration- and time-dependent decrease in cancer cell viability (Figure 3A, B). The half-maximum inhibitory concentration (IC_{50}) of ivermectin was approximately 9.4 μ M in NCI-H929 cells.

Ivermectin induces apoptosis in t(4;14) MM cells

Drug-induced apoptosis is the primary mechanism underlying cancer cell death [18]. To assess this, we analyzed the expression of the pro- and anti-apoptotic proteins BAX and BCL2, respectively, after treatment and further inspected the BAX/BCL2 ratio. We observed that ivermectin induced apoptosis in t(4;14) MM cells, as evidenced by the upregulation of pro-apoptotic protein BAX and a decrease in anti-apoptotic protein BCL2 levels (Figure 3C). The BAX/BCL2 ratio significantly increased (Figure 3D), and the intrinsic mitochondrial apoptotic pathway was activated, as indicated by elevated caspase-9, caspase-3, downstream effector caspase-3, and PARP expression levels (Figure 3E, F). Annexin V-FITC/propidium iodide staining revealed a substantial increase in the proportion of apoptotic t(4;14) MM cells after ivermectin treatment compared with that of the control (Figure 3G, H), highlighting that the suppressive effect of ivermectin on t(4;14) MM cells was associated with apoptosis.

Ivermectin increases ROS accumulation and alters the mitochondrial membrane potential in t(4;14) MM cells

Mitochondria are widely known to be the intracellular source of ROS. These species can trigger oxidative damage, leading to a series of mitochondria-related events, including apoptosis [19]. We detected a significant accumulation of ROS in t(4;14) MM cells treated with ivermectin compared with that in untreated controls (Figure 4A). We also observed a notable reduction in the mitochondrial membrane potential (Figure 4B and C), suggesting that ivermectin-induced apoptosis in t(4;14) MM cells was related to mitochondrial function. Collectively, these findings suggest a relationship between ivermectin-induced apoptosis in t(4;14) MM cells and altered mitochondrial dynamics.

Ivermectin triggers apoptosis in t(4;14) MM cells via NF- κ B signaling pathway

The NF- κ B signaling pathway plays a crucial role in the onset and progression of the disease in t(4;14) MM, often exhibiting overactivation in these cells and promoting their survival [20]. Our results revealed that ivermectin treatment substantially reduced both the protein expression and phosphorylation levels of NF- κ B p65 in a dose-dependent

manner (Figure 4D and E). Furthermore, the protein expression and phosphorylation levels of I κ B α , a regulator upstream of NF- κ B, were also suppressed in t(4;14) MM cells post-ivermectin treatment.

DISCUSSION

MM is a multifaceted and incurable disease that displays vast heterogeneity in its clinical manifestations, genetic changes, therapeutic responses, and overall prognosis [2]. Guidelines from bodies, such as the International Myeloma Working Group, recognize t(4;14) MM as a high-risk cytogenetic abnormality [21]. The t(4;14) MM subtype continues to present a challenging prognosis despite advances in drug therapies [22]. Therefore, there is an urgent need to develop new therapeutic drugs to treat t(4;14) MM. Recent studies have highlighted the potential of identifying molecular targets and therapeutic drugs for MM through expression profiling and functional enrichment analyses. Meo *et al* identified ILT3 as an immunotherapeutic target for MM [23], whereas Mereu *et al* revealed that UNC0642 increased carfilzomib sensitivity and counteracted drug resistance in MM cell lines [24]. In this study, we identified the key genes and prospective therapeutic agents for t(4;14) MM using gene expression profile analysis.

The regulation of the immune response is fundamental for the development and progression of MM [25]. We identified CD45, CD48, and CD56 as the key genes in t(4;14) MM. Compared with healthy bone marrow controls, patients with t(4;14) MM exhibited decreased CD45 expression levels, whereas CD48 and CD56 Levels were notably increased. CD45, also known as protein tyrosine phosphatase receptor type C, was previously called the common leukocyte antigen. This protein is essential for modulating antigen receptor signaling, which is crucial for lymphocyte development, survival, and function [26]. However, the role of CD45 in MM remains elusive. Evidence suggests that CD45 expression decreases during MM progression [27]. As mature MM cells are predominantly CD45-negative and have inactive SRC family kinases, they remain unaffected by elotuzumab [28]. Moreover, MM cells in high-risk genetic

categories tend to express reduced CD45 levels [29]. CD48 [30], a member of the signaling lymphocytic activation molecule family, plays a role in immune cell adhesion and activation. Although it is present in almost all MM plasma cells, it is absent from non-hematopoietic tissues. Van Acker *et al* identified CD48 as a promising molecular target for the therapy of MM antibody therapy. CD56 [31], a neural cell adhesion molecule, is a glycoprotein present in neural and muscle tissues, as well as in myeloma cells. Cottini *et al* observed its high expression levels in the t(4;14) MM cell line NCI-H929. CD56 boosts MM cell growth and influences adhesion to stromal cells [32]. Collectively, these findings highlight the potential for a deeper evaluation of immune phenotypes for both diagnosis and treatment of t(4;14) MM.

In this study, we also utilized the CMap database to identify potential small-molecule drugs targeting t(4;14) MM. Our primary focus was on molecular docking and subsequent experimental validation of the predicted drug, ivermectin. Traditionally, ivermectin is a macrocyclic lactone antibiotic used to treat parasitic diseases [33]. Recent studies have revealed its potential antitumor capabilities in various cancers, including breast [34] and pancreatic [35] cancer. Emerging evidence also suggests its synergistic lethal effects on MM cells when combined with proteasome inhibitors [36]. However, a comprehensive understanding of the specific action mechanisms of ivermectin against MM, especially the t(4;14) subtype, remains elusive. Our findings demonstrate that ivermectin suppresses the growth of t(4;14) MM cells, as well as triggers apoptosis.

The NF- κ B signaling pathway is crucial for driving cancer progression, angiogenesis, and shaping the tumor microenvironment [37]. It orchestrates the production of pro-inflammatory cytokines, inflammatory mediators, and cell adhesion molecules, creating a favorable microenvironment for MM initiation and progression [38]. Consequently, many leading anti-MM drugs indirectly target the NF- κ B signaling pathway [39]. Bortezomib hinders the proteasomal degradation of NF- κ B and I κ B proteins, inhibiting gene transcription activation [40]. Our findings revealed a pronounced suppression of the NF- κ B signaling pathway in ivermectin-treated t(4;14)

MM cells (Figure 5). This suggests that ivermectin, by acting as an external signaling agent, inhibits the activation of this pathway, reducing anti-apoptotic effects and thereby enhancing cell apoptosis.

Mitochondria are essential for cell survival, functioning as the primary source of ROS and producing adenosine triphosphate (ATP) through oxidative phosphorylation [41]. In a pathological state, mitochondrial dysfunction results in ATP depletion [42]. In the current study, treatment of t(4;14) MM with ivermectin led to elevated ROS levels and decreased cell membrane potential. These findings, along with previous reports, suggest that ivermectin exposure can induce oxidative stress and disrupt the mitochondrial balance, facilitating the apoptosis of t(4;14) MM cells.

There are also some limitations of the present study. Firstly, the sample size may be insufficient, potentially leading to selection bias. Secondly, regarding the experiments on ivermectin against t(4;14) MM, this study has only completed a portion of the *in vitro* experiments, and further validation of its effectiveness and safety is still required in *in vivo* experiments. Furthermore, additional genetic and experimental studies are needed to elucidate the mechanisms and functions of these key genes in the occurrence and development of t(4;14) translocated multiple myeloma.

CONCLUSION

In conclusion, we utilized bioinformatics tools, molecular docking, and experimental validation to identify key genes and potential treatments for t(4;14) MM. Notably, we confirmed that ivermectin induced apoptosis in t(4;14) MM cells via the NF- κ B signaling pathway. However, these insights require additional exploration and robust validation in further studies.

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