Network and Computational Drug Repurposing Analysis for c-Myc Inhibition in Burkitt Lymphoma

YONGMIN LEE and SEUNGYOON NAM

1Department of Health Sciences and Technology, Gachon Advanced Institute for Health Sciences and Technology (GAIHST), Gachon University, Incheon, Republic of Korea; 2Department of Genome Medicine and Science, AI Convergence Center for Medical Science, Gachon Institute of Genome Medicine and Science, Gachon University Gil Medical Center, Gachon University College of Medicine, Incheon, Republic of Korea

Abstract. Background/Aim: The treatment rate of Burkitt lymphoma (BL) is still low in low-income countries and among elderly patients. The c-Myc dysregulation induced by mutations is one of the characteristics of BL. However, studies on the downstream signaling pathways of c-Myc are still lacking. This study aimed to identify the signaling pathways regulated by c-Myc. Materials and Methods: Network and gene set analyses using c-Myc inhibition (i.e., c-Myc knock-down and c-Myc inhibitor treatment) transcriptome datasets for BL cell lines were performed to determine the pathways regulated by c-Myc. In addition, computational drug repurposing was used to identify drugs that can regulate c-Myc downstream signaling pathway. Results: Computational drug repurposing revealed that the ERK/MAPK signaling pathway is regulated by c-Myc in BL and that this pathway can be modulated by vorinostat. Furthermore, in the pharmacogenomics database, vorinostat showed a cell viability half-maximal inhibitory concentration of less than 2 μM in the BL cell lines. Conclusion: The downstream signaling pathway regulated by c-Myc and the drug that can modulate this pathway is presented for the first time.

Correspondence to: Seungyoon Nam, Ph.D., Gachon University College of Medicine, Dokjeom-ro 3 Beon-gil, 38-13, Namdong-gu, Incheon 21565, Republic of Korea. Tel: +82 324582737, Fax: +82 324582875, e-mail: nams@gachon.ac.kr

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Burkitt lymphoma (BL) is a lymphoma associated with Epstein-Barr virus (EBV) infection and has a chromosomal translocation by activation of the proto-oncogene, c-Myc (1). It is also a highly aggressive, B cell, non-Hodgkin lymphoma (2). A treatment rate of 90% is reported for BL in developed countries (1). However, treatment rates in low-income countries are very low, so BL is still important (1). Chemotherapy treatment in adult patients with BL results in a good response rate, but the response rate is still low in patients over 60 years of age and in patients with central nervous system diseases (2, 3). Therefore, there is a need to understand the pathogenesis of BL.

Recently, several studies have been conducted to address the limitations of BL treatment, and direct or indirect drugs targeting c-Myc have emerged (4-6). Artesunate, a therapeutic agent for malaria, is known to be an effective growth inhibitory agent for BL and induces ferroptosis in BL cells (i.e., DAUDI and CA-46) to induce an endoplasmic reticulum (ER) stress response and activate the ATF4-CHOP-CHAC1 pathway (7). It was also reported to inhibit the proliferation of BL in a mouse-transplanted tumor model for BL cells (i.e., Daudi and CA-46) (7). As a transcription factor, c-Myc forms a heterodimer with the MAX protein and acts by directly binding to the DNA sequence of a specific gene (8). Omomyc is an inhibitor that degrades c-Myc by inhibiting the binding of c-Myc to MAX (9). In addition, JQ1 is a small-molecule bromodomain inhibitor that blocks the binding of BRD4 to acetylated histones within the c-Myc gene locus and reduces the expression of the entire c-Myc superfamily (10). Due to the promising intervention of c-Myc in BL, diverse inhibitors of c-Myc are also under clinical evaluation (5). Despite the emphasis on BL-vulnerable patient groups (2, 3), detailed downstream pathway changes of c-Myc inhibition have not been revealed.

In this study, we investigated downstream signaling affected by c-Myc inhibition in BL cell lines. For this purpose, we
performed network analysis (11) and gene set enrichment analysis (12) by using c-Myc inhibition transcriptome datasets for BL cell lines (JQ1, c-Myc-inhibitor-treated dataset, and c-Myc-shRNA-treated dataset) (13, 14). To determine possible drug repurposing in BL, we found compounds enriched in transcriptional networks for the downstream signaling of c-Myc.

Materials and Methods

Collection of transcriptome related to c-Myc inhibition in BL cell lines. To find transcriptome datasets related to c-Myc inhibition in BL cell lines, we searched with the keyword “c-Myc” in the Gene Expression Omnibus (GEO) (15) until April 28, 2022. Three transcriptome datasets treated with c-Myc gene knock-down or c-Myc inhibition in BL cell lines were identified: 1) the GSE76188 (13), GSE106869 (14), GSE119925 (16), and GSE76188 (13) datasets compared JQ1-treated vs. untreated Raji cell lines; 2) the GSE106869 (14) dataset compared c-Myc knock-down vs. shControl Daudi cell lines; and 3) the GSE119925 (16) dataset compared c-Myc knock-down vs. shControl ST486 cell lines.

Network analysis of c-Myc inhibition transcriptome datasets. To identify the transcriptional networks associated with the inhibition of c-Myc (i.e., c-Myc knock-down and c-Myc inhibitor treatment) in the three transcriptome datasets, PATHOME-Drug (11) was applied to individual datasets, and the networks were merged into a single network. PATHOME-Drug reported that the network contained the genes belonging to the KEGG pathway database (17). As a result, four pathways (i.e., “MAPK signaling pathway”, “pathway in cancer”, “JAK-STAT signaling pathway”, and “regulation of actin cytoskeleton”) in the network were considered.

Gene set analysis of down-regulated genes in the network for c-Myc inhibition transcriptome datasets. From the aforementioned network analysis, genes that were consistently down-regulated by c-Myc inhibition compared to the control in the three BL datasets (GSE76188, GSE106869, GSE119925) were determined among the genes in the four pathways (i.e., “MAPK signaling pathway”, “pathways in cancer”, “JAK-STAT signaling pathway”, and “regulation of actin cytoskeleton”). Consequently, we assumed that the down-regulated genes in c-Myc inhibition were positively correlated with c-Myc-inducing oncogenic functions. Gene set analysis was performed using these genes. Using the Hallmark gene sets of the MIT Molecular Signatures Database (12) as the reference gene sets, the statistically significant gene sets (i.e., false discovery rate (FDR) <0.05) were obtained. These significant gene sets indicate biological functions.

Inspection of compounds enriched in the aforementioned networks. Again, we assumed that the down-regulated genes in c-Myc inhibition were positively correlated with c-Myc-inducing oncogenic functions. PATHOME-Drug presented the compounds known to regulate proteins that belong to the aforementioned networks. Specifically, among the genes down-regulated by c-Myc inhibition from two or more datasets of the aforementioned “integrated network”, PATHOME-Drug indicated that proteins from the three genes (FGFR1, MAP2K1, MAPK3) belonging to the extracellular signal-regulated protein kinase/mitogen-activated protein kinase (ERK/MAPK) signaling pathway were regulated by the drugs.

To verify the results of the computational drug repurposing presented by PATHOME-Drug (11), the cell viability IC_{50} data from the Genomics of Drug Sensitivity in Cancer (GDSC) database (18) were reanalyzed. From the three BL datasets (GSE76188, GSE106869, GSE119925), drug sensitivity IC_{50} data were analyzed for three genes (FGFR1, MAP2K1, MAPK3). It should be noted that, in GDSC, the screening concentration ranged from 0.001 μM to 10.0 μM for drugs (19).

Results

Overview. In this study, we investigated signaling pathways regulated by c-Myc in BL. We collected three BL transcriptome datasets of c-Myc inhibition in BL cell lines from the GEO (15): (i) c-Myc knock-down in the Daudi cell line (GSE106869) (14), (ii) c-Myc knock-down in the ST486 cell line (GSE119925) (16), and (iii) JQ-1 (c-Myc inhibitor) treatment in the Raji cell line (GSE76188) (13). Using the three datasets perturbed by c-Myc inhibition, PATHOME-Drug (11) was used to perform network analysis by taking the transcriptome as input to generate a dysregulated pathway network as a result of the inhibition. The gene set analysis took selected pathways in the PATHOME-Drug-generating network as input to reveal biological functions. For this purpose, gene set analysis was performed on the selected pathways. Computational drug repurposing using PATHOME-Drug indicated that several existing drugs could target the proteins of the genes in the network and also suggested compounds enriched in the networks, potentially indicating drug repurposing. These drugs were validated using the cell viability IC_{50} experimental data included in the GDSC database (18) for BL cell lines (Raji, Daudi, ST486) (Figure 1).

C-Myc inhibition in the BL cell lines showed down-regulation of MAPK, JAK-STAT, actin cytoskeleton, and cancer pathways. We performed the network analysis by using PATHOME-Drug (11) to obtain individual dysregulated pathway networks upon c-Myc inhibition in the three BL datasets (i.e., c-Myc inhibition vs. control in Daudi, ST486, and Raji cell lines; GEO accessions GSE76188, GSE106869, and GSE119925). Subsequently, the individual networks were combined to an integrated network where most genes belonged to the four Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways (17): “JAK-STAT signaling pathway”, “MAPK signaling pathway”, “pathways in cancer”, and “regulation of actin cytoskeleton” (Figure 2A and B). For the three datasets (GEO accessions GSE76188, GSE106869, GSE119925), the expression levels of the genes upon c-Myc inhibition compared to the control (log2 fold changes of c-Myc knock-down vs. shRNA; and JQ1-treated vs. untreated in the BL cell lines) were also marked (Figure 2B). The results showed a pattern of consistent down-regulation of seven genes (MAP2K1, MAPK3, HRAS, ELK1, KRAS,
RASGRP2, STMN1), belonging to the MAPK signaling pathway by c-Myc inhibition compared to the control from two or more BL datasets. In the “pathways in cancer”, GRB2 and CDK4 showed a pattern of consistent down-regulation by c-Myc inhibition compared to the control from all three BL datasets. Five genes that belong to the JAK-STAT signaling pathway (AKT1, AKT2, CRLF2, CBL, CBLC) showed a pattern of consistent down-regulation by c-Myc inhibition compared to the control from two or more BL datasets. Four genes that belong to the “regulation of...
Figure 2. Network analysis for c-Myc inhibition is relevant for cancer-related signaling pathways. (A) Network analysis for c-Myc inhibition is relevant for various pathways. Many genes with expression level changes belong to four pathways (i.e., “MAPK signaling pathway”, “pathway in cancer”, “JAK-STAT signaling pathway”, and “regulation of actin cytoskeleton”). (B) Changes in gene expression level for the four pathways (i.e., “MAPK signaling pathway”, “pathway in cancer”, “JAK-STAT signaling pathway”, and “regulation of actin cytoskeleton”).
actin cytoskeleton” pathway (FGFR1, ARHGEF6, ROCK2, MYLK3) showed a pattern of consistent down-regulation by c-Myc inhibition compared to the control from two or more BL datasets. Overall, c-Myc inhibition consistently reduced the expression levels of the genes that belong to the “JAK-STAT signaling pathway”, “MAPK signaling pathway”, “pathways in cancer”, and “regulation of actin cytoskeleton pathway”. This led to the investigation of the biological functions of these genes.

**Genes that belong to the aforementioned four pathways affected by c-Myc inhibition were involved in immune, signaling, cellular component, and proliferation functions.** Gene set analysis (12) was conducted to find the gene sets functionally associated with the 177 genes that belong to the four pathways (“JAK-STAT signaling pathway”, “MAPK signaling pathway”, “pathway in cancer”, and “regulation of actin cytoskeleton pathway”). The results showed functional association with 10 statistically significant Hallmark gene sets (Figure 3A). The 10 identified Hallmark gene sets (20) belonged to the four Hallmark gene set groups (immunity, signaling, cellular components, and proliferation). In these gene set groups, 39 genes that showed a consistent up- or down-regulation pattern with c-Myc inhibition compared to the control, from at least two datasets, were selected (Figure 3B). A total of 19 genes (CDK4, FGFR1, GRB2, MAP2K1, MAPK1, MAPK3, HRAS, ROCK2, AKT1, AKT2, KRAS, MYLK3, CBL, ARHGEF6, CRLF2, RASGRP2, CBL, STMN1, ELK1) showed down-regulation with c-Myc inhibition compared to the control in two or more datasets (see Supplementary Table SII), and 20 genes (PIK3CB, JAK1, AKT3, TYK2, SOS1, MYL12B, FGFR2, STAT2, TPR, CACNA1H, RASGRP3, CCND1, CACNG5, STAT1, SOCS7, PIK3CA, PIA51, FGF11, PIP5K1C, RRAS2) showed up-regulation with c-Myc inhibition compared to the control in two or more datasets (see Supplementary Table SII). The genes that were down-regulated by c-Myc inhibition could potentially be the downstream genes of c-Myc. Among these genes down-regulated by c-Myc inhibition, four genes associated with immunity (GRB2, AKT1, CRLF2, CBL); seven genes associated with signaling (CDK4, GRB2, MAPK1, HRAS, AKT1, AKT2, CBL); and three genes associated with cellular components (HRAS, AKT2, ARHGEF7) were identified. Among the 39 genes, eight genes (FGFR1, GRB2, KRAS, HRAS, MAP2K1, MAPK1, MAPK3, CDK4) showed a consistent down-regulation pattern with c-Myc inhibition compared to the control and belonged to the ERK/MAPK signaling pathway in the “pathways in cancer” of the KEGG pathways. Hence, as these eight genes were affected by c-Myc inhibition, the ERK/MAPK signaling pathway was likely inhibited. Therefore, controlling these pathways had potential as a new therapeutic approach in BL (21).

**Proteins whose genes belong to the ERK/MAPK signaling pathway have potential for drug repurposing.** As mentioned previously, eight genes (FGFR1, GRB2, KRAS, HRAS, MAP2K1, MAPK1, and CDK4) showed consistent down-regulation with c-Myc inhibition compared to the control and belonged to the ERK/MAPK signaling pathway (Figure 4A). PATHOME-Drug also reported the results of computational drug repurposing for these genes and the adjacent genes in the aforementioned integrated network (Figure 4B and C, and Supplementary Table SIII). Finally, the compounds targeting the proteins whose genes were down-regulated by c-Myc inhibition compared to the control (FGFR1, MAP2K1, MAPK3) in two or more datasets were selected. Consequently, four drugs associated with FGFR1 (palifermin, ponatinib, regorafenib, sorafenib) were identified (Figure 4B). Two compounds (bosutinib and trametinib) associated with MAP2K1, and two compounds associated with MAPK3 (sulindac and vorinostat) were identified (Figure 4C).

**Ponatinib, sorafenib, and vorinostat showed potent cell viability in BL cell lines.** To validate the drugs associated with the three genes (i.e., FGFR1, MAP2K1, MAPK3), the drug sensitivity (i.e., cell viability IC$_{50}$) data of GDSC (18) were reanalyzed. Of the drugs associated with FGFR1, MAP2K1, and MAPK3, the cell viability IC$_{50}$ data were analyzed for five drugs (ponatinib, sorafenib, bosutinib, trametinib, and vorinostat) that could be verified in the GDSC data. Cell viability IC$_{50}$ of 2 μM or less indicated reactivity of the drug (19).

Ponatinib had a cell viability IC$_{50}$ of 2 μM or less, with 0.028 μM in the Daudi cell line and 0.538 μM in the ST486 cell line (Table I). Bosutinib had a cell viability IC$_{50}$ of 2 μM or less, with 1.769 μM in the ST486 cell line. Vorinostat had a cell viability IC$_{50}$ of 2 μM or less, with 1.892 μM in the Daudi cell line and 0.538 μM in the ST486 cell line (Table I). As ponatinib, bosutinib, and vorinostat all had cell viability IC$_{50}$ values of 2 μM or less, their drug repurposing potential was confirmed.

**Discussion**

Since c-Myc is involved in BL, downstream genes regulated by c-Myc might be candidates for BL pathogenesis. We performed network and computational drug repurposing for BL by utilizing c-Myc inhibition data (in the BL cell lines) from GEO. The computational drug repurposing result was supported by a pharmacogenomics database that included the cell viability IC$_{50}$ assays for compounds. As a result, the consistent down-regulation patterns of three ERK/MAPK signaling pathway genes (FGFR1, MAP2K1, MAPK3) were identified. In addition, five compounds (ponatinib, sorafenib,
Figure 3. Consistently up- or down-regulated genes during c-Myc inhibition compared to control in the four pathways (i.e., "MAPK signaling pathway," "pathway in cancer", "JAK-STAT signaling pathway", and "regulation of actin cytoskeleton") are involved in four biological functions (immune, signaling, cellular component, and proliferation). (A) Top 10 significant biological functions in c-Myc inhibition versus control in the Burkitt lymphoma (BL) cell lines. (B) Four biological functions and heatmaps for the four pathways of the genes (JQ1-treated vs. untreated and c-Myc knock-down vs. shControl) showing consistent up- or down-regulation patterns in c-Myc inhibition relative to control. The expression levels shown on the heatmap indicate a log2 fold change range based on 0. Purple and green colors mean that the corresponding genes are involved in the biological functions and four pathways.
Figure 4. ERK/MAPK signaling pathway can be a candidate for drug repurposing in Burkitt lymphoma (BL). (A) ERK/MAPK signaling pathway containing many genes with consistent down-regulation patterns in c-Myc inhibition relative to control (JQ1-treated vs. untreated and c-Myc knockdown vs. shControl) in the “integrated network”. Red stars indicate genes for proteins with computational drug repurposing results. (B) Genes with consistent up- or down-regulation patterns during c-Myc inhibition compared to control (i.e., FGFR1, FGFR2) and their adjacent genes. (C) Genes with consistent up- or down-regulation patterns during c-Myc inhibition compared to control (i.e., MAP2K1, MAPK1, MAPK3) and their adjacent genes. The boxes connected to genes indicate drugs related to the corresponding genes according to the computational drug repurposing results.
Table I. Experimental results of drug repurposing related to genes in the ERK/MAPK signaling pathway. Cell viability IC_{50} (μM) values of drugs related to genes with consistent down-regulation patterns during c-Myc inhibition compared to that in the control were obtained from the cell viability assay experiment database, GDSC. The cell viability values indicate the potential for drug repurposing (19).

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Cell lines</th>
<th>IC_{50} (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ponatinib</td>
<td>Daudi</td>
<td>0.028965</td>
</tr>
<tr>
<td></td>
<td>ST486</td>
<td>0.53875</td>
</tr>
<tr>
<td></td>
<td>Raji</td>
<td>2.611251</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Daudi</td>
<td>2.911831</td>
</tr>
<tr>
<td></td>
<td>ST486</td>
<td>7.143163</td>
</tr>
<tr>
<td></td>
<td>Raji</td>
<td>13.005439</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>Daudi</td>
<td>5.587349</td>
</tr>
<tr>
<td></td>
<td>ST486</td>
<td>1.769921</td>
</tr>
<tr>
<td></td>
<td>Raji</td>
<td>16.850243</td>
</tr>
<tr>
<td>Trametinib</td>
<td>Daudi</td>
<td>8.159071</td>
</tr>
<tr>
<td></td>
<td>ST486</td>
<td>9.026487</td>
</tr>
<tr>
<td></td>
<td>Raji</td>
<td>14.547296</td>
</tr>
<tr>
<td>Vorinostat</td>
<td>Daudi</td>
<td>1.892711</td>
</tr>
<tr>
<td></td>
<td>ST486</td>
<td>1.298119</td>
</tr>
<tr>
<td></td>
<td>Raji</td>
<td>2.195733</td>
</tr>
</tbody>
</table>

The proteins of the three genes. Of the five compounds, ponatinib, bosutinib, and vorinostat were confirmed in cell viability assays using BL cell lines.

In vivo studies have shown that inhibiting c-Myc causes antiproliferative effects and long-term tumor suppression, while changes in healthy tissue are reversible (5). As a result, the c-Myc gene has emerged as one of the most appealing therapeutic targets for cancer drug development (5). However, direct and indirect compounds targeting c-Myc are still lacking (22). In the case of elderly patients with BL, chemotherapy is ineffective (3), and the development of new compounds or compound repurposing is required.

In the network analysis (Figure 4), the ERK/MAPK signaling pathway was found to be involved in the oncogenesis of BL according to c-Myc inhibition. The preclinical data from a previous study indicated that the MAPK signaling pathway is critical for cancer biology (23). Furthermore, the MAPK signaling pathway is considered to be an interesting therapeutic target for various carcinomas (24). The ERK/MAPK signaling pathway is one of the most important pathways for cell proliferation among various functional aspects and is located downstream of numerous growth factor receptors, including epidermal growth factor (25). In addition, loss of function of Ksr1, an established positive regulator of RAS signaling, inhibits RAS/MAPK pathway signaling, leading to increased Myc-induced B cell apoptosis and decreased lymphoma development (26). Considering the consistent down-regulation of the three major genes (FGFR1, MAP2K1, MAPK3) of the ERK/MAPK signaling pathway by c-Myc inhibition in BL (Figure 4), they are potential therapeutic targets. This will be analyzed further in future studies (25).

Using gene expression and network analysis with c-Myc inhibition, therapeutic target candidates for BL were identified (FGFR1, MAP2K1, MAPK3) (Figure 4). Fibroblast growth factor (FGF) receptor 1 (FGFR1), which is a receptor for FGF, is involved in immunity, apoptosis, and angiogenesis (27). Although FGFR1 overexpression is considered as a therapeutic target applicable in non-small cell lung cancer, FGFR1 inhibitors have not produced clinical effects thus far (28). FGFR1 overexpression was also reported to affect endocrine resistance by regulating the transcription of specific genes in estrogen receptor positive breast cancer (29). However, studies on FGFR1 have not reported its association with BL or its potential as a therapeutic target for BL. This indicates that FGFR1 should be further examined as a new therapeutic target for BL.

Mitogen-activated protein kinase 1 (MAP2K1) activates MAPK1 and MAPK3. In addition, it regulates proliferation and apoptosis by activating the ERK/MAPK signaling pathway (30). Three mutations were identified for MAP2K1 in several cancers: Glu56Pro, Lys57Asn, and Asp67Asn (31, 32). Dysregulation of MAP2K1 by mutations is known to affect hairy-cell leukemia (33). Despite the importance of c-Myc in BL, studies of inhibitors that can modulate MAP2K1, a downstream signaling molecule of c-Myc, are still lacking. Hence, it needs to be investigated further as a therapeutic target (5, 34).

MAPK3 is a protein kinase involved in RAS-RAF-MEK-ERK MAP kinase signaling (35). It is also involved in other functions, such as cell proliferation and immune response (35). MAPK3 inhibitors developed so far have shown excellent antitumor effects (36). However, the majority of patients develop resistance to MEK inhibitors (37). Ulixertinib, an ERK1/2 inhibitor, is in early clinical trial for the treatment of various advanced/metastatic solid tumors (35, 37). However, MEK and ERK inhibitors have not been assessed for BL. Considering the current study results of MAPK3 down-regulation with c-Myc inhibition, MAPK3 inhibition in BL should be analyzed further.

Our study presented ponatinib, bosutinib, and vorinostat as drug repurposing candidates for BL. Ponatinib is a kinase inhibitor (38) developed to counteract T315I mutation and has a strong activity against BCR-ABL1 (39). It showed a consistent effect in patients with chronic-phase chronic myeloid leukemia (CP-CML) with resistance (39, 40). Bosutinib has been useful for improving the survival of patients with CML (41). However, the risk of high-grade B
cell lymphoma has been reported during treatment using bosutinib (41). Hence, bosutinib requires separate verification of safety (42). Vorinostat, a tyrosine kinase inhibitor, is a histone deacetylase inhibitor as well as an inhibitor that disrupts the latent period of EBV (43). Vorinostat is reported to be effective in rituximab-chemotherapy-resistant cell lines and can be used as a potential inhibitor to address the acquired resistance in aggressive B cell lymphoma (43).

Our study had certain limitations. The sample size of the c-Myc inhibition datasets for BL was not sufficient. Therefore, empirical verification is required for the drug repurposing results. However, independent validation was performed using the drug sensitivity (i.e., cell viability IC50) experimental data from the in vitro cell models of GDSC (18). Further verification with in vivo models will be needed.

Conclusion

In this study, genes and signaling pathways regulated by c-Myc inhibition in BL were identified. In addition, the drugs with potential for drug repurposing in BL cell lines were identified (ponatinib, bosutinib and vorinostat). Further verification of these drugs in in vivo models is needed in the future.

Supplementary Material

Supplementary Tables SI, SII, and SIII are available at: https://github.com/labnams/YongminLee2023

Conflicts of Interest

The Authors declare no competing interests.

Authors’ Contributions

Conceptualization: SN; Methodology: YL; Sample collection: YL; Data curation: YL; Formal Analysis: YL; Funding acquisition: SN; Investigation: YL; Supervision: SN; Validation: SN; Visualization: YL; Writing – original draft: YL, SN; Writing – review & editing: YL, SN. All authors have read and agreed to the published version of the manuscript.

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