Original Article

Potential biomarkers screening to predict side effects of dexamethasone in different cancers

Da Jiang | Hui Jin | Jing Zuo | Yan Kong | Xue Zhang | Qian Dong | Zhihong Xu | Ying Li

Department of Medical Oncology, the Fourth Hospital of Hebei Medical University, Shijiazhuang, China

Correspondence
Da Jiang, Department of Medical Oncology, the Fourth Hospital of Hebei Medical University, No.12 Health Road, Shijiazhuang 050000, Hebei, China.
Email: jiangda03@163.com

Abstract

Background: Excessive or prolonged usage of dexamethasone can cause serious side effects, but few studies reveal the related mechanism. Dexamethasone work differently in blood tumors and solid tumors, and the cause is still obscure. The aims of this study was to identify potential biomarkers associated with the side effects of dexamethasone in different tumors.

Methods: Gene Expression Omnibus database (GEO) datasets of blood tumors and solid tumors were retrieval to selected microarray data. The differentially expressed genes (DEGs) were identified. Gene ontology (GO) and pathway enrichment analyses, and protein–protein interaction (PPI) network analysis were performed.

Results: One hundred and eighty dexamethasone-specific DEGs (92 up and 88 downregulated) were obtained in lymphoma cell samples (named as DEGs-lymph), including APOD, TP53INP1, CLIC3, SERPINA9, and C3orf52. One hundred and four specific DEGs (100 up and 4 downregulated) were identified in prostate cancer cell samples (named as DEGs-prostate), including COL6A2, OSBPL5, OLAH, OGFRL1, and SLC39A14. The significantly enriched GO terms of DEGs-lymph contained cellular amino acid metabolic process and cell cycle. The most significantly enriched pathway of DEGs-lymph was cytosolic tRNA aminoacylation. The DEGs-prostate was enriched in 39 GO terms and two pathways, and the pathways were PPARA activates gene expression Homo sapiens, and insulin resistance. The PPI network of DEGs-lymph gathered into two major clusters, WARS1 and CDC25A were representatives for them, respectively. One cluster was mainly involved in cytosolic tRNA aminoacylation, aminoacyl-tRNA biosynthesis and the function of amino acid metabolism; another was associated with cell cycle and cell apoptosis. As for the PPI network of DEGs-prostate, HELZ2 was the top nodes involved in the most protein–protein pairs, which was related to the pathway of “PPARA activates gene expression Homo sapiens.”

Conclusions: WARS1 and CDC25A might be potential biomarkers for side effects of dexamethasone in lymphoma, and HELZ2 in prostate cancer.
1 | INTRODUCTION

Glucocorticoid receptor (GR) is important to signal conduction of tumor cell which plays its biologic role through binding to cortisol and other glucocorticoids (Machado, Rosado, & Isaias, 2016). GR transactivation is linked with metabolic side effects, whereas GR transrepression underlies glucocorticoid therapeutic action. However, severe dose-limiting side effects occur, including osteoporosis, muscle wasting, diabetes, and other metabolic complications. GR activity may play a crucial role in chemotherapy resistance in a wide variety of solid tumors. A recent study revealed that GR was expressed in 20 tumor types including renal cell carcinoma, sarcoma, cervical cancer, and melanoma (Block, Murphy, Munster, Nguyen, & Lynch, 2017). Another study showed that activated GR decreased aromatase expression and induced Leydig tumor (Panza et al., 2016). Thus, it was suggested that GR might be a potential target for the therapy of Leydig cell tumors. High GR expression or activation correlates with poor therapeutic response or prognosis in many solid tumors, such as breast cancer, prostate cancer, and ovarian cancer (Veneris et al., 2017; Voisin et al., 2017). These findings provide the basis for the study of GR in different cancers.

Dexamethasone and other corticosteroids are agonists of the GR, and mifepristone and ketoconazole are antagonists. Dexamethasone is a type of corticosteroid medication and produces the effects of anti-inflammation, antiangiogenesis, control of estrogen activity, etc (Mukwaya et al., 2017). People with cancer undergoing chemotherapy are often given dexamethasone to counteract certain side effects of their antitumor treatments (Wang, Lu, & Zhou, 2015). Dexamethasone is also used as a direct chemotherapeutic agent in certain hematological malignancies, especially in the treatment of multiple myeloma (Gosmanov, Goorha, Stelts, Peng, & Umpierrez, 2013). Excessive or long-term use of dexamethasone can cause a lot of serious side effects, including osteoporosis, muscle atrophy, diabetes, and other metabolic complications. At present, few studies reveal the related mechanism of the side effects of dexamethasone. Dexamethasone mainly regulates malignant cell apoptosis in hematological malignancies, suppresses nausea and vomiting in solid tumors. However, it

| Gene | LogFC | Ave Expr | p value | Gene | LogFC | Ave Expr | p value |
|------|-------|----------|--------|------|-------|----------|--------|
| APOD | 3.185273623 | 5.628389358 | 3.58E-08 | TMEM2 | 1.765467513 | 5.268372522 | 6.72E-06 |
| TP53INP1 | 2.675916694 | 7.6698158 | 1.15E-07 | IL1R2 | 1.61994409 | 6.470399154 | 6.72E-06 |
| CLIC3 | 2.681141648 | 7.543077799 | 3.16E-07 | LPIN1 | 1.478080815 | 9.099590438 | 7.29E-06 |
| SERPINA9 | 2.312639694 | 5.3421891 | 3.16E-07 | FKB5P | 2.04715541 | 9.975247827 | 7.44E-06 |
| C3orf52 | 2.073103446 | 6.021958169 | 5.85E-07 | CHAC1 | −2.082938108 | 6.946409758 | 7.89E-06 |
| DDIT3 | −2.017171393 | 7.978211299 | 7.74E-07 | SESN1 | 1.627206809 | 8.277299943 | 8.11E-06 |
| ZFP36L2 | 2.163042889 | 6.720630103 | 8.82E-07 | PK3IP1 | 1.478030162 | 8.764130339 | 8.50E-06 |
| SGK1 | −2.034781245 | 6.162132073 | 1.00E-06 | PNPLA7 | 1.525753877 | 7.070019115 | 9.31E-06 |
| TSC22D3 | 1.893569262 | 6.805833114 | 1.25E-06 | STMN3 | 1.444271052 | 6.416256288 | 9.40E-06 |
| CARMIL1 | 1.908410942 | 5.902524272 | 1.70E-06 | CTH | −1.487998874 | 6.772393378 | 9.50E-06 |
| RNASET2 | 1.80598794 | 10.28363369 | 1.72E-06 | PIM1 | −1.400996888 | 8.006606741 | 9.84E-06 |
| STS | −1.810979759 | 5.979462961 | 2.03E-06 | RELB | −1.441838193 | 7.543406756 | 9.92E-06 |
| GLIPR2 | 1.960144615 | 6.275641698 | 2.12E-06 | GDPD5 | 1.39484582 | 6.916121892 | 1.00E-05 |
| SPATA13 | 1.777107242 | 5.018675392 | 2.21E-06 | GPT2 | −1.431285506 | 10.38633659 | 1.07E-05 |
| MYB | −1.752394782 | 9.308276717 | 2.43E-06 | NEK8 | 1.428658647 | 5.501768703 | 1.11E-05 |
| ALPK2 | −1.749251802 | 7.407134453 | 2.74E-06 | PCK2 | −1.386308574 | 7.252804877 | 1.23E-05 |
| FGER1G | 1.612070575 | 7.11846032 | 4.43E-06 | KCNH4 | 1.500762164 | 4.826354791 | 1.28E-05 |
| PEL1 | −1.575237715 | 8.98381926 | 4.47E-06 | ZNF223 | 1.363697288 | 8.072786673 | 1.29E-05 |
| PLEK | −1.597512711 | 10.43496729 | 4.49E-06 | TMEM100 | 1.598156283 | 5.954715476 | 1.29E-05 |
| ESPNL | 1.500799492 | 6.365103052 | 5.69E-06 | NFE2L1 | −1.435235921 | 8.824460657 | 1.31E-05 |

Abbreviation: DEGs, differentially expressed genes.
is still obscure what causes of differences in dexamethasone in blood tumors and solid tumors. Novel selective GR agonist Compound A (CpdA) prevents GR dimerization and transactivation, specifically activates GR transrepression. Moreover, CpdA has fewer side effects compared to glucocorticoids. In this study, lymphoma and prostate cancer cell lines were, respectively, treated with dexamethasone and CpdA, and the gene microarray analyses of them were conducted. The aim was to identify potential biomarkers associated with the side effects of dexamethasone in different tumors.

2 MATERIALS AND METHODS

2.1 Expression profiles

The Gene Expression Omnibus database (GEO, http://www.ncbi.nlm.nih.gov/geo) of NCBI was used to selected relevant microarray datasets. The selection rules were as follows: the samples must be human cancer cells (including hematological malignancy cells); the samples should be simultaneously treated with dexamethasone and at least one GR agonist; the sample number must be more than 5; the datasets must be published in the recent 3 years; and the study type of dataset was expression profiles studies. Thus, the expression profiles of GSE71102 and GSE71099 were screened out, and the signal data and annotation data of them were downloaded. There were six B-cell mantle cell lymphoma cell samples in GSE71102, which were treated with dexamethasone, CpdA, or solvent for 16 hr, and two samples in each group. They were detected with the platform of Illumina HumanHT-12 V4.0 expression beadchip. There were 16 prostate cancer cell samples in GSE71099, which were treated with dexamethasone or CpdA for 8, 24, or 48 hr, respectively, and two samples in each group. They were detected with Illumina humanRef-8 V2.0 expression beadchip.

| Table 2 | The top 40 most significant dexamethasone-specific DEGs in prostate cancer cell according to the p value and their logFC and average expression values |

| Gene     | LogFC | Ave Expr | p value | Gene     | LogFC | Ave Expr | p value |
|----------|-------|----------|---------|----------|-------|----------|---------|
| COL6A2   | 1.743969656 | 8.109382808 | 1.79E-08 | CTGF     | 2.695309204 | 8.599605297 | 2.04E-06 |
| OSBPL5   | 1.521546631 | 9.618781716 | 5.14E-08 | TMEM43   | 1.237589011 | 10.85574997 | 2.07E-06 |
| OLH      | 1.945853091 | 8.26574808  | 1.54E-07 | CEMIP    | 1.231471868 | 8.658786653 | 2.21E-06 |
| OGFRL1   | 1.812991494 | 8.591279084 | 4.05E-07 | PHACTR3  | 1.212493348 | 7.766688868 | 2.40E-06 |
| SLC39A14 | 1.699993455 | 9.906608772 | 4.53E-07 | SCNN1A   | 1.29576372  | 12.8362568  | 2.46E-06 |
| TIPARP   | 2.86204472  | 10.323505   | 4.88E-07 | NET1     | 1.368242022 | 9.973973516 | 2.52E-06 |
| SRD5A1   | 2.347733735 | 9.710381661 | 5.40E-07 | Clorf116 | −1.074512694 | 11.21312958 | 2.53E-06 |
| CHST3    | 2.51242683 | 8.663169795 | 5.84E-07 | NSDHL    | 2.050492739 | 10.8431303  | 2.61E-06 |
| TAF5L    | 1.226743004 | 8.695460357 | 7.27E-07 | IL2RB    | 1.835307645 | 8.251317175 | 2.73E-06 |
| GPR1     | 1.349285309 | 8.363498953 | 7.46E-07 | ZFP36    | 1.290376007 | 9.350672655 | 2.94E-06 |
| IL20R    | 1.471263988 | 7.951547191 | 7.80E-07 | TDRD9    | 1.613410353 | 8.130339977 | 3.31E-06 |
| CRYAB    | 1.431639141 | 8.553134668 | 8.34E-07 | KRT80    | 1.132465659 | 8.276365952 | 3.57E-06 |
| PLIN2    | 1.171468796 | 7.809425344 | 1.13E-06 | FLVCR2   | 1.363748822 | 8.837545548 | 3.68E-06 |
| COL6A1   | 2.930934025 | 11.07511346 | 1.18E-06 | MIR600HG | 1.251010469 | 9.13334152  | 4.55E-06 |
| SLC39A11 | 1.003911248 | 9.904771281 | 1.21E-06 | ZNF18    | 1.527379892 | 9.365080812 | 4.58E-06 |
| HELZ2    | 1.395470506 | 9.974581535 | 1.24E-06 | PTGER4   | 1.566299147 | 8.829475739 | 4.66E-06 |
| PQLC1    | 1.808653932 | 11.71458702 | 1.24E-06 | SERPINA3 | 1.861508248 | 9.765803832 | 4.74E-06 |
| ABCCC8   | 1.467279288 | 8.348424813 | 3.93E-06 | ST3GAL4  | 1.763492264 | 9.667747986 | 4.75E-06 |
| SLC25A18 | 1.195957505 | 7.707604051 | 1.63E-06 | GNMT     | 1.565550552 | 8.730744309 | 5.18E-06 |
| CDH2     | 2.259356536 | 8.1347656   | 1.92E-06 | RASD1    | 2.482072201 | 10.2635577  | 5.66E-06 |

Abbreviation: DEGs, differentially expressed genes.
2.3 Functional and pathway enrichment analyses of DEGs

The functional and pathways analyses of DEGs were performed via the Database for Annotation, Visualization and Integrated Discovery (DAVID) V6.8 (http://david.abcc.ncifcrf.gov/), Kyoto Encyclopedia of Genes and Genomes (KEGG) PATHWAY (http://www.genome.jp/kegg), and Reactome (http://www.reactome.org). The gene ontology (GO) terms and pathway terms were selected out with \( p < 0.05 \).

2.4 Analysis of protein–protein interaction (PPI) network

To determine the function of the proteins that they encoded, the protein–protein pairs of DEGs were identified via Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) V10.5 (https://string-db.org/). The confidence score >0.5 was as the threshold value. The protein–protein interaction (PPI) network were further constructed and visualized by Cytoscape V3.5.1 software (http://www.cytoscape.org/download.php).

3 RESULTS

3.1 DEGs

In GSE71102, only three DEGs were identified in lymphoma cell samples treated with CpdA compared with solvent, namely EIF3CL (OMIM 603916), TSPAN14, and IFI44L (OMIM 613975), and all of them were downregulated. A total of 180 (92 up and 88 downregulated) DEGs were screened in lymphoma cell samples treated

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**FIGURE 1** All the 51 enriched biological process (BP) terms of the 180 dexamethasone-specific DEGs in lymphoma cell (DEGs-lymph)
with dexamethasone compared with solvent. Moreover, the above two sets of DEGs had no overlap and then the 180 DEGs were specific DEGs only for dexamethasone and they were named as DEGs-lymph. Besides, the top 40 most significant DEGs of them are shown in Table 1, including APOD (OMIM 107740), TP53INP1 (OMIM 606185), CLIC3 (OMIM 606533), SERPINA9 (OMIM 615677), and C3orf52 (OMIM 611956).

In GSE71099, a total of 27 (6 up and 21 downregulated), 13 (0 up and 13 downregulated), and 29 (1 up and 28 downregulated) DEGs were identified in prostate cancer cell treated with CpdA compared with solvent for 8, 24, and 48 hr, respectively. Sixty-three (56 up and 7 downregulated), 124 (120 up and 4 downregulated), and 87 (79 up and 8 downregulated) DEGs were identified in prostate cancer cell treated with dexamethasone compared with solvent for 8, 24, and 48 hr, respectively. After repeated removal among different time points and different drugs, 104 dexamethasone-specific DEGs were obtained and named as DEGs-prostate, including 100 upregulated and four downregulated. The top 40 most significant DEGs of them are shown in Table 2, including COL6A2 (OMIM 120240), OSBP1S (OMIM 606733), OLAL (OMIM 615677), OGFRL1 (OMIM 615677), and SLC39A14 (OMIM 608736).

### Table 3

| Category Term | Count | p value |
|---------------|-------|---------|
| GOTERM_BP_3 GO:0033554–cellular response to stress | 35 | 7.90E-05 |
| GOTERM_BP_3 GO:0016875–ligase activity, forming carbon-oxygen bonds | 6 | 9.20E-05 |
| GOTERM_BP_3 GO:0009968–negative regulation of signal transduction | 25 | 1.38E-04 |
| GOTERM_BP_3 GO:0007049–cell cycle | 31 | 6.94E-04 |
| GOTERM_BP_3 GO:0006520–cellular amino acid metabolic process | 10 | 7.69E-04 |
| GOTERM_BP_3 GO:0044249–cellular biosynthetic process | 80 | 0.01073952 |
| GOTERM_BP_3 GO:1901576–organic substance biosynthetic process | 81 | 0.01138515 |
| GOTERM_BP_3 GO:0051726–regulation of cell cycle | 21 | 0.01276764 |
| GOTERM_CC_3 GO:0005783–endoplasmic reticulum | 29 | 0.02003545 |

### Table 4

| Category Term | Count | p value |
|---------------|-------|---------|
| REACTOME_PATHWAY R-HAS-379716:Cytoplasmic tRNA aminoacylation | 5 | 1.11E-04 |
| REACTOME_PATHWAY R-HAS-352230:Amino acid transport across the plasma membrane | 5 | 3.09E-04 |
| KEGG_PATHWAY hsa00970:Aminoacyl-tRNA biosynthesis | 6 | 8.41E-04 |
| BIOCARTA_PATHWAY H_ccdc25Pathway:cdc25 and chk1 regulatory pathway in response to DNA damage | 3 | 0.00594937 |
| KEGG_PATHWAY hsa05166:HTLV-I infection | 9 | 0.007925779 |
| REACTOME_PATHWAY R-HAS-69202:Cyclin E-associated events during G1/S transition | 3 | 0.009464424 |
| REACTOME_PATHWAY R-HAS-156711:Polo-like kinase mediated events | 3 | 0.01230867 |
| BIOCARTA_PATHWAY h_rbPathway:RB tumor suppressor/checkpoint signaling in response to DNA damage | 3 | 0.012473973 |
| REACTOME_PATHWAY R-HAS-69273:Cyclin A/B1/B2-associated events during G2/M transition | 3 | 0.02273176 |
| BIOCARTA_PATHWAY h_g2Pathway:Cell cycle: G2/M checkpoint | 3 | 0.039586422 |

### Table 3

The top 10 most significant GO terms of DEGs-lymph according to p values and their enriched gene numbers

| Category Term | Count | p value |
|---------------|-------|---------|
| GOTERM_BP_3 GO:0033554–cellular response to stress | 35 | 7.90E-05 |
| GOTERM_BP_3 GO:0016875–ligase activity, forming carbon-oxygen bonds | 6 | 9.20E-05 |
| GOTERM_BP_3 GO:0009968–negative regulation of signal transduction | 25 | 1.38E-04 |
| GOTERM_BP_3 GO:0007049–cell cycle | 31 | 6.94E-04 |
| GOTERM_BP_3 GO:0006520–cellular amino acid metabolic process | 10 | 7.69E-04 |
| GOTERM_BP_3 GO:0044249–cellular biosynthetic process | 80 | 0.01073952 |
| GOTERM_BP_3 GO:1901576–organic substance biosynthetic process | 81 | 0.01138515 |
| GOTERM_BP_3 GO:0051726–regulation of cell cycle | 21 | 0.01276764 |
| GOTERM_CC_3 GO:0005783–endoplasmic reticulum | 29 | 0.02003545 |

### Table 4

The enriched KEGG and Reactome pathway terms of DEGs-lymph with p < .05, and the number of genes enriched in them

Abbreviation: BP, biological process; CC, cellular component; DEGs, differentially expressed genes; GO, gene ontology; MF, molecular function.

In addition, SESNI (OMIM 606103) was the only overlap between DEGs-lymph and DEGs-prostate.

### 3.2 Enriched GO terms and pathways

The DEGs-lymph was enriched 66 GO terms, which contained 51 biological process (BP) terms, 11 cellular component (CC) terms, and four molecular function (MF) terms.
The 51 BP terms were exhibited in Figure 1. The top 10 significantly enriched GO terms are shown in Table 3, including cellular response to stress, cellular amino acid metabolic process, cellular biosynthetic process, cell cycle, and regulation of cell cycle. Furthermore, the DEGs-lymph was enriched in 13 pathway terms, and they are shown in Table 4. We found the top three enriched pathway terms were cytosolic tRNA aminoacylation ($p = 1.11 \times 10^{-4}$), amino acid transport across the plasma membrane ($p = 3.09 \times 10^{-4}$), and aminoacyl-tRNA biosynthesis ($p = 8.41 \times 10^{-4}$).

The DEGs-prostate was enriched in 39 GO (31 BP, 6CC, and 2 MF) terms and two pathways. The 31 BP terms are exhibited in Figure 2. The top enriched BP terms were response to oxygen-containing compound ($p = 1.11E-04$), amino acid transport across the plasma membrane ($p = 3.09E-04$), and aminoacyl-tRNA biosynthesis ($p = 8.41E-04$).

The DEGs-prostate was enriched in 39 GO (31 BP, 6CC, and 2 MF) terms and two pathways. The 31 BP terms are exhibited in Figure 2. The top enriched BP terms were response to oxygen-containing compound ($p = 5.29E-06$), response to organic substance ($p = 4.44E-04$), and cellular response to chemical stimulus ($p = 0.0021$); CC terms were sarcolemma ($p = .0032$), and endomembrane system ($p = .012$); MF terms were growth factor binding ($p = .030$). Besides, the two enriched pathways were PPARA activates gene expression Homo sapiens ($p = .028$), and insulin resistance ($p = .031$).

3.3 The PPI network

The PPI network for the total of DEGs-lymph was composed with 78 nodes and 117 edges (Figure 3). As shown in Figure 3, these nodes mainly gathered in two different gene clusters, one was represented by WARS1 (OMIM 191050) (dark yellow), and another was represented by CDC25A (OMIM 116947) (dark yellow). The former gene cluster was majorly involved in the pathways of “cytosolic tRNA aminoacylation” and “aminoacyl-tRNA biosynthesis,” and the function of amino acid metabolism. The later chiefly...
participated in the cell cycle-related pathways, such as cyclin E associated events during G1/S transition, polo-like kinase-mediated events, RB tumor suppressor/checkpoint signaling in response to DNA damage and cyclin A/B1/B2-associated events during G2/M transition, and the primarily function of it was to promote cell apoptosis. Moreover,
the two genes of WARS1 and CDC25A were obviously downregulated in lymphoma cell sample treated with dexamethasone compared with solvent, with the logFC values of −1.359 and −1.003 and the p values of 1.36E-05 and 3.28E-04, respectively.

The PPI network of DEGs-prostate was established based on 28 nodes and 33 edges (Figure 4). HELZ2 (OMIM 611265) was the top nodes involved in the most protein–protein pairs, and it was associated with the pathway of “PPARA activates gene expression Homo sapiens.”

4 | DISCUSSION

In this study, a total of 180 and 104 dexamethasone-specific DEGs were identified, respectively, in lymphoma cell samples and prostate cancer cell samples (DEGs-lymph and DEGs-prostate). However, only one was overlapping (SERN1) between them, which indicated that the roles and related mechanism of dexamethasone might be very different in hematoma and solid tumors. However, few scholars have studied this difference in depth. In this article, we would study the side effects of dexamethasone in hematoma and solid tumors. After PPI network analyses, the PPI network of DEGs-lymph gathered in WARS1 cluster and CDC25A cluster, and HELZ2 was the top nodes involved in the most protein–protein pairs, and it was associated with the pathway of “PPARA activates gene expression Homo sapiens.”

WARS1 gene encodes tryptophanyl-tRNA synthetase (WARS), which catalyzes the aminoacylation of tRNA by their cognate amino acid. The immune microenvironment is a prognostic factor for various malignancies, including lymphoma, leukemia, and other hematologic malignancies, and WARS is one of the significant players of the immune microenvironment (Blakely et al., 2018). Blakely et al. (2018) reported that the WARS expression was correlated with tumor size, mitoses, and outcomes, and 60 of 127 gastrointestinal stromal tumors were positive for WARS (47.2%). Moreover, dexamethasone can increase the risk of infection complications in relapsed/refractory mantle cell lymphoma, and then it will affect the immune activation (Zaja et al., 2012). Therefore, we suspected that WARS1 might play some critical roles in the side effects of dexamethasone by regulating the immune activation. Furthermore, the WARS1 cluster was found to be majorly enriched in the pathways of “cytosolic tRNA aminoacylation” and “aminoacyl-tRNA biosynthesis” in this study. Over the past decade, the identification of cancer-associated biomarkers has been a subject both in the tumorigenesis and therapeutic targets. However, aminoacyl-tRNA synthetases (ARSs) have been overlooked for a long time, mostly because many assumed that they were simply “housekeepers” that were involved in protein synthesis (Kim, You, & Hwang, 2011). Upon to this day, some evidences have been confirmed that ARSs is more than housekeeping. A study made integrative genome-wide analysis of ARSs to show cancer-associated activities in glioblastoma multiforme (GBM), and ARSs and ARS-interacting multifunctional proteins (AIMPs) showed a biology-dominant contribution in the biology of GBM (Kim, Kwon, Liu, Kim, & Kim, 2012). ARS complex-interacting multifunctional protein 2 (AIMP2) works as potent tumor suppressor, and its splicing variant lacking exon 2 (AIMP2-DX2) is related to poor clinical outcome of lung cancer (Jung et al., 2017). In this article, we found that some ARSs might be the target of dexamethasone in the treatment of hematological malignancies. CDC25A encodes cell division cycle 25 homolog A (CDC25A), which is a family of phosphatases that activate the cyclin-dependent kinases at different points of the cell cycle. Some studies have verified that CDC25A takes part in the pathogenesis and progression of lymphoma. A previous study suggested that CDC25A was over-expressed in a relatively large number of malignant lymphomas and might participate in the pathogenesis of aggressive variants (Hernandez et al., 2000). Another study suggested that CDC25A played a role in the early phase of thyroid lymphoma possibly including the malignant transformation from chronic thyroiditis, and CDC25A might contribute to the progression of lymphoma (Ito et al., 2004). We also found CDC25A mainly enriched in cell cycle-related pathways, and function of cell apoptosis promoting. It is well known that dexamethasone can regulate the cell cycle and cell apoptosis.

| Direct target gene | Significant datasets (p < .01) | Direct target gene | Significant datasets (p < .01) |
|-------------------|-----------------------------|-------------------|-----------------------------|
| NR3C1             | 13                          | CYP2A6            | 2                           |
| CYP2B6            | 7                           | NR3C2             | 2                           |
| CYP1B1            | 7                           | CYP11A1           | 2                           |
| CYP2C9            | 6                           | CYP3A5            | 1                           |
| CFTR              | 5                           | CYP2D6            | 1                           |
| AR                | 4                           | CYP2C8            | 1                           |
| CYP2B7P1          | 3                           | NR0B1             | 1                           |
| ANXA1             | 3                           | CYP3A4            | 1                           |
| NFE2L2            | 3                           | NOS2              | 1                           |
| CYP2E1            | 3                           | CYP3A7            | 1                           |
| CYP19A1           | 3                           | CYP17A1           | 0                           |
| CYP2C19           | 2                           | CYP1A1            | 0                           |
### TABLE 6  Survival profile of WARS1, CDC25A, and HELZ2 with $p < .05$ across available datasets

| Gene     | GEO dataset                                                                 | Cancer type               | p value  | Effect sign |
|----------|----------------------------------------------------------------------------|---------------------------|----------|-------------|
| WARS1    | Strong time dependence of the 76-gene prognostic signature                 | Breast cancer             | .0114    | Negative    |
|          | Downregulation of ecrg4, a candidate tumor suppressor gene in human breast cancer | Breast cancer             | .0184    | Positive    |
|          | 183 breast tumors from the helsinki univerisity central hospital with survival information | Breast cancer             | .0253    | Negative    |
|          | Discovery cohort for genomic predictor of response and survival following neoadjuvant taxane-anthracycline chemotherapy in breast cancer | Breast cancer             | .0341    | Negative    |
|          | A gene signature predicting for survival in suboptimally debulked patients with ovarian cancer | Ovarian cancer            | .0387    | Positive    |
|          | Experimentally derived metastasis gene expression profile predicts recurrence and death in colon cancer patients | Colon cancer              | .0446    | Negative    |
| CDC25A   | An expression signature for p53 in breast cancer predicts mutation status, transcriptional effects, and patient survival | Breast cancer             | 2.38E-05 | Negative    |
|          | Gene expression profiling in breast cancer: understanding the molecular basis of histologic grade to improve prognosis | Breast cancer             | 8.14E-04 | Negative    |
|          | Experimentally derived metastasis gene expression profile predicts recurrence and death in colon cancer patients | Colon cancer              | .00105   | Positive    |
|          | 183 breast tumors from the helsinki univerisity central hospital with survival information | Breast cancer             | .00114   | Negative    |
|          | Whole-transcript expression data for liposarcoma                          | Liposarcoma               | .00143   | Negative    |
|          | Breast cancer relapse free survival                                        | Breast cancer             | .00199   | Negative    |
|          | The humoral immune system has a key prognostic impact in node-negative breast cancer | Breast cancer             | .00299   | Negative    |
|          | Metastasis gene expression profile predicts recurrence and death in colon cancer patients (moffitt samples) | Colon cancer              | .00618   | Positive    |
|          | Gene expression data for pathological stage i-ii lung adenocarcinomas       | Lung cancer               | .0081    | Negative    |
|          | maqc-ii project: multiple myeloma (mm) dataset                             | Multiple myeloma          | .0133    | Negative    |
|          | Molecular subclasses of high-grade glioma: prognosis, disease progression, and neurogenesis | High-grade glioma         | .0142    | Negative    |
|          | Expression data from untreated cll patients                                | Chronic lymphocytic leukemia | .0162 | Positive    |
|          | Human lung adenocarcinoma                                                  | Lung cancer               | .021     | Negative    |
|          | Heterogeneity of response to chemotherapy and recurrence-free survival in neoadjuvant breast cancer: results from the i-spy 1 trial | Breast cancer             | .0258    | Negative    |
|          | Prediction of survival in diffuse large b cell lymphoma treated with chemotherapy plus rituximab | Diffuse large b cell lymphoma | .0277    | Negative    |
|          | Relapse-related molecular signature in lung adenocarcinomas identifies patients with dismal prognosis | Lung cancer               | .0325    | Negative    |
|          | Search for a gene-expression signature of breast cancer local recurrence in young women | Breast cancer             | .0466    | Negative    |
| HELZ2    | Prediction of survival in diffuse large b cell lymphoma treated with chemotherapy plus rituximab | Diffuse large b cell lymphoma | 3.25E-04 | Negative    |
|          | An eight-gene expression signature for the prediction of survival and time to treatment in chronic lymphocytic leukemia | Chronic lymphocytic leukemia | 3.65E-04 | Positive    |
|          | Gene expression data for pathological stage i-ii lung adenocarcinomas       | Lung cancer               | 5.92E-04 | Positive    |
|          | Molecular subclasses of high-grade glioma: prognosis, disease progression, and neurogenesis | High-grade glioma         | .013     | Positive    |
Bernardi et al. (2001) reported that combination of 1-alpha, 25-dihydroxyvitamin D with dexamethasone enhanced cell cycle arrest and apoptosis. Li et al. (2012) revealed that GR and sequential P53 activation by dexamethasone-mediated apoptosis and cell cycle arrest of osteoblastic MC3T3-E1 cells. Arafa, Abdel-Hamid, El-Khouly, Elmazar, and Osman (2006) demonstrated that dexamethasone regulated tumor angiogenesis and cell cycle kinetics in a murine tumor paradigm. Nevertheless, our results suggested that CDC25A might affect the side effects of dexamethasone by regulating the cell cycle and cell apoptosis.

HELZ2 is a lipid metabolic gene, and closely associated with adipocyte differentiation and primary biliary cirrhosis (Katano-Toki et al., 2013; Li et al., 2016). However, few reports to study the effect of HELZ2 on tumors. A recent study found that HELZ2 was an IFN effector molecules, which was involved in viral infections (Fusco et al., 2017). Here, we found that HELZ2 might be associated with the side effect of dexamethasone, and it enriched in the pathway of “PPARA activates gene expression Homo sapiens.” However, more direct evidences needed to be excavated to confirm the relationship between them.

5 | CONCLUSION

In conclusion, WARS1 and CDC25A might be potential biomarkers for the side effect of dexamethasone in lymphoma, and HELZ2 might be a potential biomarker for that in prostate cancer. Furthermore, pathways of cytosolic tRNA aminoacylation, aminoacyl-tRNA biosynthesis and cell cycle, functions of amino acid metabolism and cell apoptosis might be associated with the side effect of dexamethasone in blood tumors. The pathway of “PPARA activates gene expression Homo sapiens” might play some roles in the side effect of dexamethasone in solid tumors. However, it was worth mentioning that the sample size was small in this study, and only the bioinformatics analysis was carried out. Thus, these conclusions only provided some clues for the study of the side effect of dexamethasone, and further experimental verifications and clinical studies were needed.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Da Jiang https://orcid.org/0000-0003-4945-7493

REFERENCES

Arafa, H. M., Abdel-Hamid, M. A., El-Khouly, A. A., Elmazar, M. M., & Osman, A. M. (2006). Enhancement by dexamethasone of the therapeutic benefits of cisplatin via regulation of tumor angiogenesis and cell cycle kinetics in a murine tumor paradigm. *Toxicology*, 222(1–2), 103–113. https://doi.org/10.1016/j.tox.2006.02.007

Bernardi, R. J., Trump, D. L., Yu, W. D., McGuire, T. F., Hershberger, P. A., & Johnson, C. S. (2001). Combination of 1alpha,25-dihydroxyvitamin D(3) with dexamethasone enhances cell cycle arrest and apoptosis: Role of nuclear receptor cross-talk and Erk/Akt signaling. *Clinical Cancer Research*, 7(12), 4164–4173.

Blakely, A. M., Matoso, A., Patil, P. A., Taliano, R., Machan, J. T., Miner, T. J., … Wang, L.-J. (2018). Role of immune microenvironment in gastrointestinal stromal tumours. *Histopathology*, 72(3), 405–413. https://doi.org/10.1111/his.13382

Block, T. S., Murphy, T. I., Munster, P. N., Nguyen, D. P., & Lynch, F. J. (2017). Glucocorticoid receptor expression in 20 solid tumor types using immunohistochemistry assay. *Cancer Management and Research*, 9, 65–72. https://doi.org/10.2147/CMAR.S124475

Fusco, D. N., Pratt, H., Kandilas, S., Cheon, S. Y. S., Lin, W., Cronkite, D. A., … Chung, R. T. (2017). HELZ2 is an IFN effector mediating suppression of dengue virus. *Frontiers in Microbiology*, 8, 240. https://doi.org/10.3389/fmicb.2017.00240

Gosmanov, A. R., Goorha, S., Stelts, S., Peng, L., & Umpierrez, G. E. (2013). Management of hyperglycemia in diabetic patients with hematologic malignancies during dexamethasone therapy. *Endocrine Practice*, 19(2), 231–235. https://doi.org/10.4158/EP12256.OR

Hernández, S., Hernández, L., Bea, S., Pinyl, M., Nayach, I., Bellosillo, B., … Campo, E. (2000). cdc25a and the splicing variant cdc25b2, but not cdc25b1, -B3 or -C, are over-expressed in aggressive human non-Hodgkin’s lymphomas. *International Journal of Cancer*, 89(2), 148–152. https://doi.org/10.1002/(SICI)1097-0215(20000320)89:2<148:AIID-IICS>3.0.CO;2-R

Ito, Y., Yoshida, H., Matsuoka, F., Matsuura, N., Nakamura, Y., Nakamine, H., … Miyauchi, A. (2004). Cdc25A and cdc25B expression in malignant lymphoma of the thyroid: Correlation with histological subtypes and cell proliferation. *International Journal of Molecular Medicine*, 13(3), 431–435. https://doi.org/10.3892/ijmm.13.3.431

Jung, J. Y., Kim, E. Y., Kim, A., Chang, J., Kwon, N. H., Moon, Y., … Chang, Y. S. (2017). Ratio of autoantibodies of tumor suppressor AIMP2 and its oncogenic variant is associated with clinical outcome in lung cancer. *Journal of Cancer*, 8(8), 1347–1354. https://doi.org/10.7150/jca.18450

Katano-Toki, A., Satoh, T., Tomaru, T., Yoshino, S., Ishizuka, T., Ishii, S., … Mori, M. (2013). THRAP3 interacts with HELZ2 and plays a novel role in adipocyte differentiation. *Molecular Endocrinology*, 27(5), 769–780. https://doi.org/10.1210/me.2012-1332

Kim, S., You, S., & Hwang, D. (2011). Aminoacyl-tRNA synthetases and tumorigenesis: More than housekeeping. *Nature Reviews Cancer*, 11(10), 708–718. https://doi.org/10.1038/nrc3124

Kim, Y. W., Kwon, C., Liu, J. L., Kim, S. H., & Kim, S. (2012). Cancer association study of aminoacyl-tRNA synthetase signaling network in glioblastoma. *PLoS ONE*, 7(8), e40960. https://doi.org/10.1371/journal.pone.0040960

Li, H., Qian, W., Weng, X., Wu, Z., Li, H., Zhuang, Q., … Bian, Y. (2012). Glucocorticoid receptor and sequential P53 activation by dexamethasone mediates apoptosis and cell cycle arrest of osteoblastic MC3T3-E1 cells. *PLoS ONE*, 7(6), e37030. https://doi.org/10.1371/journal.pone.0037030

Li, P., Lu, G., Wang, L., Cui, Y., Wu, Z., Chen, S. I., … Li, Y. (2016). A rare nonsynonymous variant in the lipid metabolic gene HELZ2 related to primary biliary cirrhosis in Chinese Han. *Allergy, Asthma and Clinical Immunology*, 12, 14. https://doi.org/10.1186/s13223-016-0120-6
Machado, X. A., Rosado, R. T., & Isaías, G. (2016). Gene expression control by glucocorticoid receptors during innate immune responses. *Frontiers in Endocrinology, 7*, 31. https://doi.org/10.3389/fendo.2016.00031

Mukwaya, A., Mirabelli, P., Lennikov, A., Xeroudaki, M., Schaupper, M., Peebo, B., & Lagali, N. (2017). Genome-wide expression datasets of anti-vegf and dexamethasone treatment of angiogenesis in the rat cornea. *Scientific Data, 4*, 170111. https://doi.org/10.1038/sdata.2017.111

Panza, S., Malivindi, R., Chemi, F., Rago, V., Giordano, C., Barone, I., … Catalano, S. (2016). Glucocorticoid receptor as a potential target to decrease aromatase expression and inhibit Leydig tumor growth. *American Journal of Pathology, 186*(5), 1328–1339. https://doi.org/10.1016/j.ajpath.2015.12.024

Veneris, J. T., Darcy, K. M., Mhawech-Fauceglia, P., Tian, C., Lengyel, E., Lastra, R. R., … Fleming, G. F. (2017). High glucocorticoid receptor expression predicts short progression-free survival in ovarian cancer. *Gynecologic Oncology, 146*(1), 153–160. https://doi.org/10.1016/j.ygyno.2017.04.012

Voisin, M., de Medina, P., Mallinger, A., Dalenc, F., Huc-Claustre, E., Leignadier, J., … Silvente-Poirot, S. (2017). Identification of a tumor-promoter cholesterol metabolite in human breast cancers acting through the glucocorticoid receptor. *Proceedings of the National Academy of Sciences of the United States of America, 114*(44), E9346–E9355. https://doi.org/10.1073/pnas.1707965114

Wang, L. J., Lu, W., & Zhou, T. Y. (2015). Current applications of dexamethasone for cancer treatment. *Yao Xue Xue Bao, 50*(10), 217–224.

Zaja, F., De Luca, S., Vitolo, U., Orsucci, L., Levis, A., Salvi, F., … Fanin, R. (2012). Salvage treatment with lenalidomide and dexamethasone in relapsed/refractory mantle cell lymphoma: Clinical results and effects on microenvironment and neo-angiogenic biomarkers. *Haematologica, 97*(3), 416–422. https://doi.org/10.3324/haematol.2011.051813

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