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

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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.

KEYWORDS
biomarkers, dexamethasone, gene expression, glucocorticoid receptor, side effects

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

TABLE 1 The top 40 most significant DEGs of in lymphoma cell samples treated with dexamethasone compared with solvent according to the *p* value and their logFC and average expression values

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	5.243037779	3.16E-07	LPIN1	1.478080815	9.099590438	7.29E-06
SERPINA9	2.312639694	5.3421891	3.44E-07	FKBP5	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	7.978211929	7.74E-07	SESN1	1.627206809	8.277299943	8.11E-06
ZFP36L2	2.163042889	6.720630103	8.82E-07	PIK3IP1	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	−1.400999688	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
FCER1G	1.612070575	7.11846032	4.43E-06	KCNH4	1.500762164	4.826354791	1.28E-05
PELI1	−1.575237715	8.98381926	4.47E-06	ZNF223	1.363697288	8.072766376	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 agonists; 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.

2.2 | Data preprocessing and differential expression analysis

The raw data were normalized using Robust Multiarray Analysis (RMA) algorithm in *R* Affy package. The probe symbols were converted into gene symbols. If multiple probes corresponded to one gene, the average expression values of them were considered as the expression value of the gene. Afterward, the differentially expressed genes (DEGs) were identified with limma V3.32.2 (http://www.bioconductor.org/packages/3.5/bioc/html/limma.html) according to the criteria: $p < .05$ and $|\log_2 (\text{fold change})| > 1$.

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
OLAH	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	7.766668886	2.40E-06
SLC39A14	1.699993455	9.906608772	4.53E-07	SCNN1A	1.29576372	12.8362568	2.46E-06
TIPARP	2.86204172	10.323505	4.88E-07	NET1	1.368242022	9.973973516	2.52E-06
SRD5A1	2.347733735	9.710381661	5.40E-07	C1orf116	−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	8.363449853	7.46E-07	ZFP36	1.290376007	9.350672655	2.94E-06
IL20RB	1.471263988	7.951547191	7.80E-07	TDRD9	1.613410353	8.130333977	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	9.133334152	4.55E-06
SLC39A11	1.003911248	9.094771281	1.21E-06	ZNF18	1.527378982	9.365080812	4.58E-06
HELZ2	1.395475056	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
ABCC8	1.467279288	8.348424813	1.39E-06	ST3GAL4	1.763492264	9.667747986	4.75E-06
SLC25A18	1.195957503	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 $p < .05$.

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

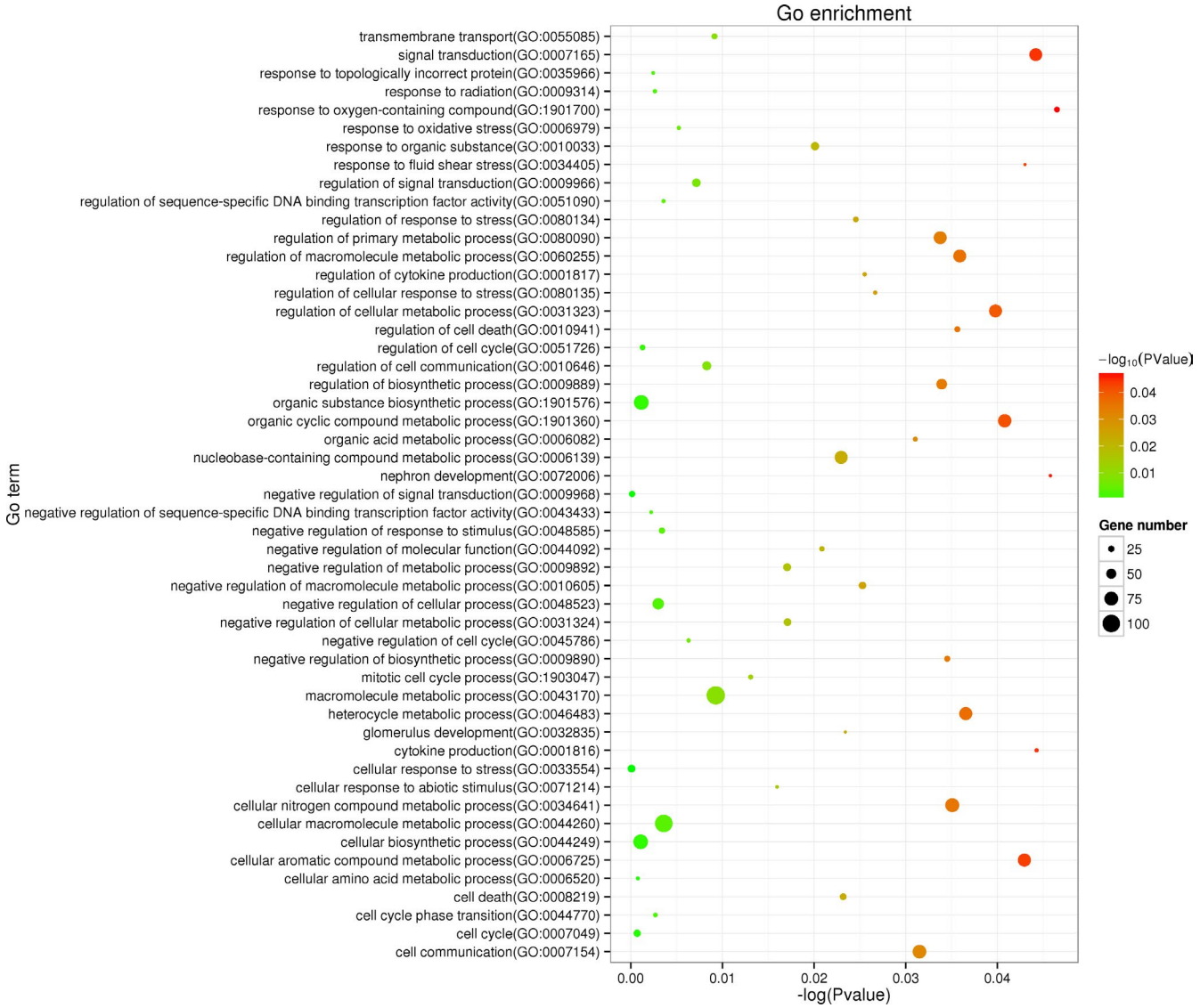


FIGURE 1 All the 51 enriched biological process (BP) terms of the 180 dexamethasone-specific DEGs in lymphoma cell (DEGs-lymph)

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_MF_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	.001073952
GOTERM_BP_3	GO:1901576~organic substance biosynthetic process	81	.001138515
GOTERM_BP_3	GO:0051726~regulation of cell cycle	21	.001276764
GOTERM_CC_3	GO:0005783~endoplasmic reticulum	29	.002003545

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

TABLE 4 The enriched KEGG and Reactome pathway terms of DEGs-lymph with $p < .05$, and the number of genes enriched in them

Category	Term	Count	*p* value
REACTOME_PATHWAY	R-HAS-379716:Cytosolic 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_cdc25Pathway:cdc25 and chk1 regulatory pathway in response to DNA damage	3	.00594937
KEGG_PATHWAY	hsa05166:HTLV-I infection	9	.007925779
REACTOME_PATHWAY	R-HAS-69202:Cyclin E-associated events during G1/S transition	3	.009464424
REACTOME_PATHWAY	R-HAS-156711:Polo-like kinase mediated events	3	.01230867
BIOCARTA_PATHWAY	h_rbPathway:RB tumor suppressor/checkpoint signaling in response to DNA damage	3	.012473973
REACTOME_PATHWAY	R-HAS-69273:Cyclin A/B1/B2-associated events during G2/M transition	3	.02273176
REACTOME_PATHWAY	R-HAS-210991:Basigin interactions	3	.028918242
KEGG_PATHWAY	hsa04115:p53 signaling pathway	4	.039586422
KEGG_PATHWAY	hsa04141:Protein processing in endoplasmic reticulum	6	.041635918
BIOCARTA_PATHWAY	h_g2Pathway:Cell cycle: G2/M checkpoint	3	.043498145

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), *OSBPL5* (OMIM 606733), *OLAH* (OMIM 615677), *OGFRL1* (OMIM 615677), and *SLC39A14* (OMIM 608736).

In addition, *SESN1* (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.

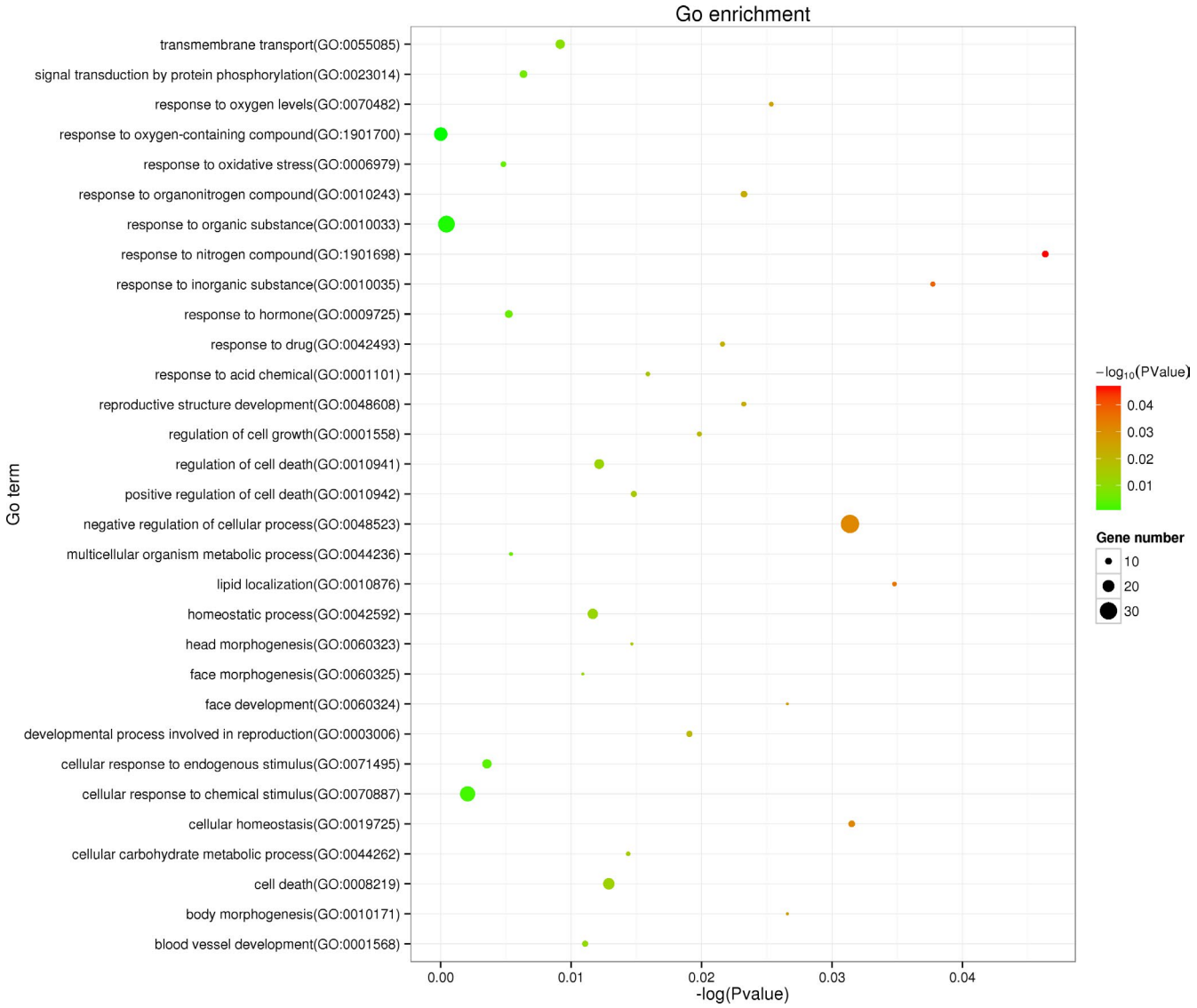


FIGURE 2 All of the 31 enriched biological process (BP) terms of dexamethasone-specific DEGs in prostate cancer cell (DEGs-prostate)

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 = 1.11E-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 = .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

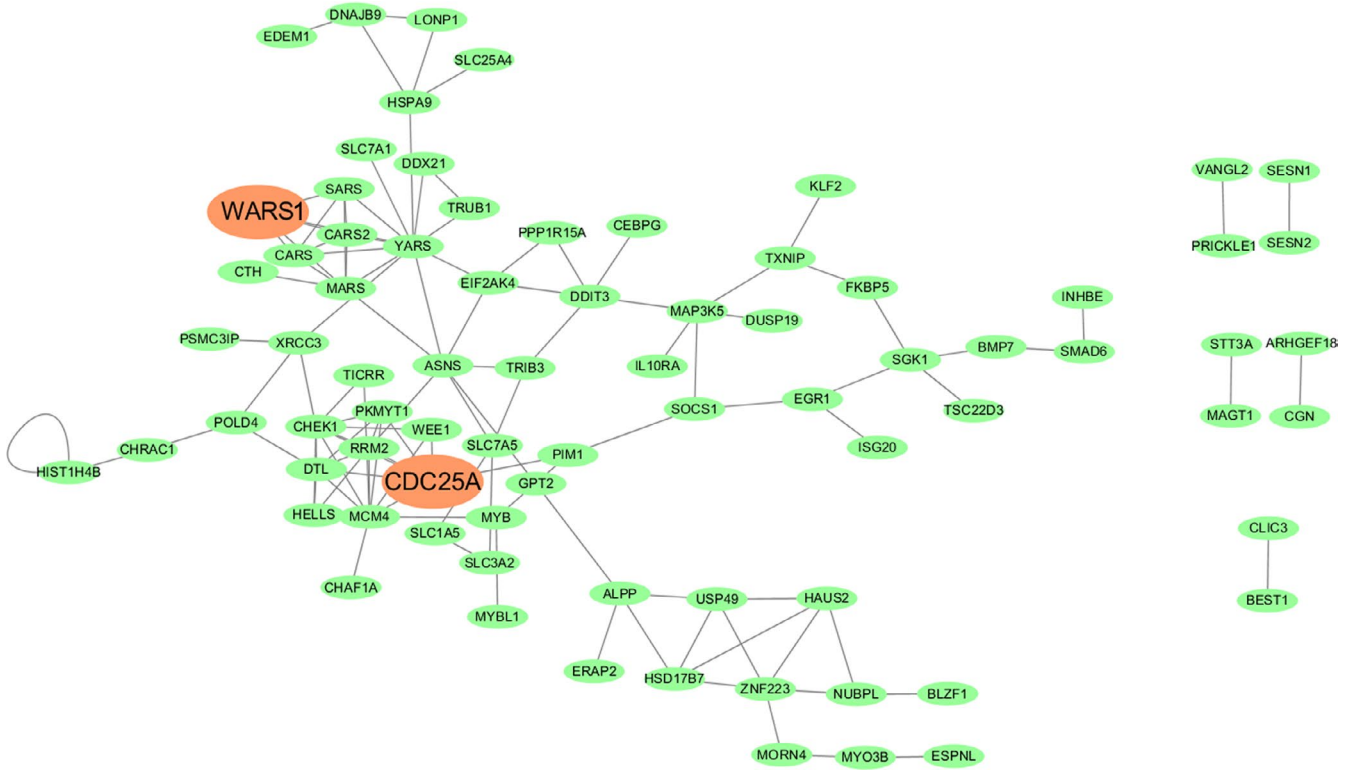
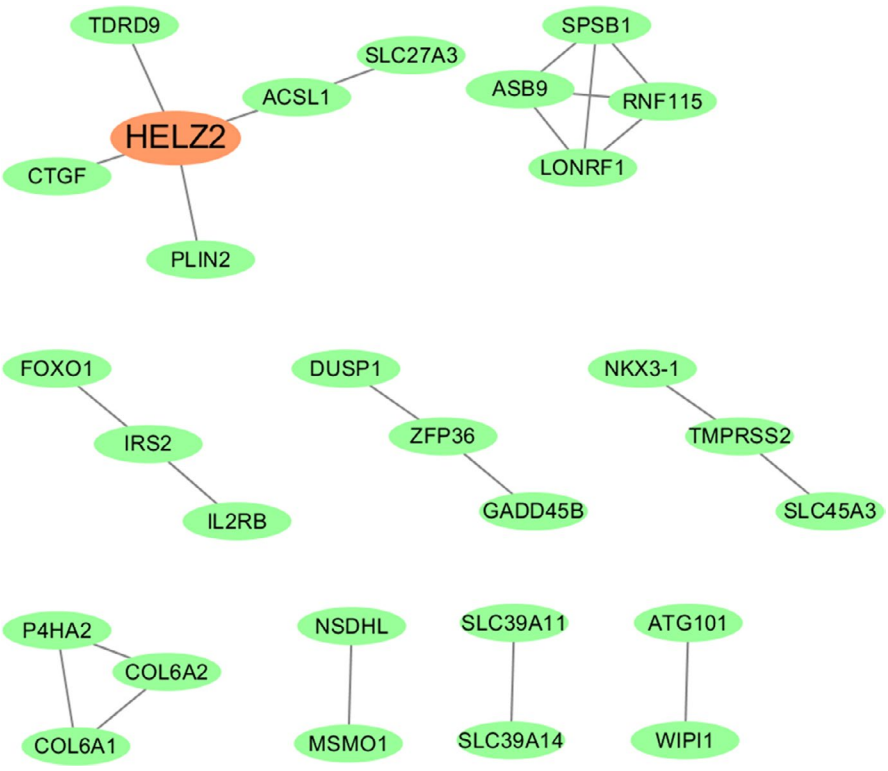


FIGURE 3 The PPI network of DEGs-lymph consisted 78 nodes and 117 edges, and formed two gene clusters represented, respectively, by *WARS1* and *CDC25A*

FIGURE 4 The PPI network of DEGs-prostate composed with 28 nodes and 33 edges, in which *HELZ2* was the node with the highest degree



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 (*SESN1*) 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 node in the PPI network of DEGs-prostate. To find evidence for our results, we further searched the target genes of dexamethasone (Table 5) and survival profile of *WARS1*, *CDC25A,* and *HELZ2* in different cancers with $p < .05$ across available datasets (Table 6). However, we did not find one of the above three genes contained in the target gene of dexamethasone, illustrated that they might be novel potential biomarkers for, respectively, lymphoma and prostate cancer, which needs further experimental and clinical studies.

TABLE 5 The direct targets of dexamethasone

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

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 studied 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.

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.

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