Prognostic values, ceRNA network, and immune regulation function of SDPR in KRAS-mutant lung cancer

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Abstract

**Background:** Serum Deprivation Protein Response (SDPR) plays an important role in formation of pulmonary alveoli. However, the function and values of SDPR in lung cancer remain unknown. We explored prognostic value, expression pattern, and biological function of SDPR in non-small cell lung cancer (NSCLC) and KRAS-mutant lung cancers.

**Methods:** SDPR expression was evaluated by quantitative real-time PCR (RT-qPCR), immunohistochemistry (IHC), and Western blot on human NSCLC cells, lung adenocarcinoma tissue array, KRAS-mutant transgenic mice, TCGA, and GEO datasets. Prognostic values of SDPR were evaluated by Kaplan–Meier and Cox regression analysis. Bioinformatics implications of SDPR including SDPR-combined transcription factors (TFs) and microRNAs were predicted. In addition, correlations between SDPR, immune checkpoint molecules, and tumor infiltration models were illustrated.

**Results:** SDPR expression was downregulated in tumor cells and tissues. Low SDPR expression was an independent factor that correlated with shorter overall survival of patients both in lung cancer and KRAS-mutant subgroups. Meanwhile, ceRNA network was constructed to clarify the regulatory and biological functions of SDPR. Negative correlations were found between SDPR and immune checkpoint molecules (PD-L1, TNFRSF18, TNFRSF9, and TDO2). Moreover, diversity immune infiltration models were observed in NSCLC with different SDPR expression and copy number variation (CNV) patterns.

**Conclusions:** This study elucidated regulation network of SDPR in KRAS-mutant NSCLC, and illustrated correlations between low SDPR expression and suppressed immune system, unfolding a prognostic factor and potential target for the treatment of lung cancer, especially for KRAS-mutant NSCLC.

**Background**

Lung cancer is the most common and lethal cancer among all cancer types (1). With the conception of individualized therapy (2), significant progress has been made based on specific pathologic subtype and molecular aberrations (e.g., epidermal growth factor receptor [EGFR], anaplastic lymphoma kinase [ALK] (3). Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation is frequently detected in lung adenocarcinoma and closely related with smoking status (4-6). KRAS mutation is the most common genetic alteration type, and it occurs in approximately 10%-25% of lung cancer in Western and Asia countries (7-9). The effective clinical strategies of EGFR (10), ALK (11), and rearranged during transfection [RET] (12) aberrations remains to be explored for tumors with KRAS mutations (2). The RAS gene family encodes a small hydrolyzed guanosine triphosphate GTPase membrane-bound protein,
which interacts with downstream effectors to activate transduction of cellular survival signals, such as RAF-MEK-ERK, PI3K-AKT-mTOR, and RALGDS-RA (13-15). Frequent mutant RAS subtypes include KRAS (86%), neuroblastoma rat sarcoma viral oncogene homolog (NRAS) (11%), and Harvey rat sarcoma viral oncogene homolog (HRAS) (3%) (16). In case of NSCLC, KRAS mutations occur predominantly in codons 12 and 13, and most frequent variants include G12C, G12V, and G12D (9, 17). Recently, a series of compounds targeting KRAS-G12C variant have been developed and achieved promising effects in preclinical experiments and phase I clinical trials (18-20). However, it is not clear whether KRAS mutation, especially G-12V and G-12D variant, can have any clinical benefits. Meanwhile, Dong found that patients with co-occurring TP53/KRAS mutations showed remarkable clinical response to immune checkpoint inhibitors (CPI) (21). Liu found that patients with KRAS mutation had favorable clinical benefits of anti-PD-1/PD-L1 immunotherapy (22), and Falk found that high PD-L1 expression in tumor cells was associated with improved overall survival in KRAS mutant patients (23). However, Skoulidis found that Stk11/Lkb1 loss promoted programmed PD-1/PD-L1 inhibitor resistance (24). These studies indicated that the presence of co-occurring genetic events and the mutant KRAS allelic content increase biological heterogeneities of KRAS-mutant NSCLC, which complicates the treatment of KRAS-mutant lung cancers.

To investigate the gene expression signature in KRAS oncogene-driven lung cancer, we compared the differences between KRAS-mutant tumors and normal lung tissue derived from a genetically engineered mouse model (GEMM), based on expression profiling and comprehensive bioinformatics analysis. Several differentially expressed genes (DEG) were screened according to the gene expression profile, but SDPR was the only DEG that decreased in both GEMM tumors.

SDPR (also known as CAVIN2, NC_000002.12, gene ID 8436), a key substrate for protein kinase C, was found to play a critical role in inducing membrane curvature and participating in the formation of caveolae (25). It has been reported that SDPR is a potential diagnostic indicator in cancers such as hepatocellular carcinoma and gastric cancer (26-28). However, it remains unknown whether SDPR could be a predictor or target for lung cancer, especially in KRAS-mutant group. Moreover, although SDPR is considered a suppressor gene in papillary thyroid cancer (29), the regulatory mechanism of SDPR remains to be illustrated. Meanwhile, the connection between SDPR and tumor microenvironment (TME) has rarely been explored. Our study explored the gene signature, regulation, and effect of SDPR on tumor and immune infiltration, based on comprehensive bioinformatics analysis, evaluation of lung cancer specimens, and preclinical experiments.

**Methods**

**Cell lines and Reagents**

Human non-small cell lung cancer cells (HCC4006, H23, SK-LU-1 and H1299) were purchased from American Type Culture Collection (ATCC), Virginia., America. Human embryonal lung cell (MRC-5) was purchased from the Type Culture Collection of the Chinese Academy of Sciences, Shanghai, China (30). HCC4006, H23 and H1299 cells were maintained in RPMI 1640 supplemented medium, MRC-5 cells were...
maintained in Dulbecco's Modified Eagle's Medium (DMEM), and SK-LU-1 cell lines was maintained in Minimum Essential Medium (MEM), respectively. All cells were cultured in standard environment as described previously (31).

**Transgenetic mouse and establishment of KRAS-mutant lung cancer models**

The LSL-KRAS mice (B6.129S4-KRAS<sup>tm4Tyj/JNju</sup>) were purchased from Nanjing biomedical institution of Nanjing University, Nanjing, China, and housed in specific pathogen-free (SPF) institution of Experimental animal center in Southern Medical University, Guangzhou, China. Cre recombinase induced Adeno-associated viruses (AAV-CMV-bGloin-Cre) were purchase from Shanghai genechem Co., Ltd., China. AAV-CMV-bGloin-Cre virus was tracheally instilled into LSL-KRAS mice to induce KRAS-oncogene expression (32). After further 4-6 months, visible tumor nodules were observed in lung tissue. Finally, tumor-bearing mice were sacrificed, and tumor tissue and normal lung tissue were collected.

**Reverse transcription, quantitative real-time PCR and Western blot**

Reverse transcription, quantitative real-time PCR and Western blot were performed as described previously (33). Oligonucleotide primers used for SDPR and GAPDH (internal control) were as follows: SDPR: 5'-CTCCGACGCAACCATT-3' (sense); 5'-CTTTCTTGAGGCTATCCACTT-3' (antisense); GAPDH: 5'-AGAAGGTGGGGCTCATTTG-3' (sense); 5'-AGGGGCCATCCACAGTCTTC-3' (antisense); human-DACH1: 5'-GGAATGGATTGTGGCTGAAC-3' (sense); 5'-GGTATTGGACTGGTGACATCAAG-3' (antisense); mouse-DACH1: 5'-AGTGGTGGTTCTTGGGATAAGG-3' (sense); 5'-TGAGAGGATGGCTAACTGGAA-3' (antisense) (34). All the reactions were performed in triplicate for each sample. Cycle threshold (Ct) values of SDPR cDNA were normalized to GAPDH using the -2 ΔΔCt method. Western blot was performed according to standard protocols. These antibodies were used: SDPR (Proteintech, #12339-1-AP; RRID:2183305), β-Actin (CST, #8457; RRID:10950489). All the experiments were repeated three times.

**Clinical Specimens and Immunohistochemistry (IHC) staining**

Tissue microarray with clinical pathological data of lung cancer (HLugA180Su06) was purchased from Shanghai Outdo Biotech Biotechnology Co., Ltd., China. This lung cancer microarray (HLugA180Su06) contains 94 tumors and 86 paired adjacent normal tissues. All the tissues were collected from lung adenocarcinoma patients who underwent surgical resection from July 2004 to June 2009. The follow-up was from August 2014 and ranged from five to ten years. IHC staining were performed as described in Supplementary file S3 (31). Antibody: “Sections were stained with a rabbit polyclonal antibody against SDPR (Proteintech, #12339-1-AP; RRID:2183305).

**Screening of differentially expressed genes (DEGs) and identification of the abundance of tumor immune infiltration**

In this study, GSE18784, GSE49200, GSE72094 and GSE48414 were downloaded from GEO dataset, dataset (PanCancer Atlas) contained lung adenocarcinoma expression profiles and paired normal tissues were downloaded from TCGA database through cBioPortal and sangerbox download tools. “EdgeR” R
package in R version 3.6.2 (The R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/) was used to screen out the DEGs between normal murine tissues and tumor tissues. “CIBERSORT.R” R package were used to explore the abundance of tumor immune infiltrations in KRAS-mutant lung adenocarcinomas, and TIMER 1.0 and 2.0 (Tumor Immune Estimation Resource, https://cistrome.shinyapps.io/timer/) were used to identify the abundance of immune cells, such as B cells, CD4⁺ T cells, CD8⁺ T cells, Neutrophils, Macrophages and Dendritic cells, in lung adenocarcinoma with different SDPR copy number variation (CNV) patterns. The description of the above datasets and analysis processing method were described in Supplementary file S1.

Phylogenetic analysis of SDPR

SDPR (NC_000002.12, gene ID 8436), also known as CAVIN2 is located in Chromosome 2. Homo sapiens amino acid sequences of CAV and CAVIN family members were downloaded from Uniprot database. Subsequently MEGA–X (https://www.megasoftware.net/) was used to conduct sequence alignment and infer phylogenetic trees. The phylogeny was inferred using the Neighbor-Joining method, and the tree is created and conducted using Interactive Tree Of Life (iTOL, https://itol.embl.de/).

Bioinformatics mining of SDPR

The information of chromosome location site and gene structure of SDPR gene were analyzed through GeneCards (https://www.genecards.org/). Protein sequences among CAVIN and CAV family members were downloaded from Uniprot database (https://www.uniprot.org/), and the sequence alignment were performed to analyze the identity between Homo sapiens, Mus Mus musculus, Rattus norvegicus, Pan troglodytes, Macaca mulatta, Sus scrofa and Felis catus.

GEO dataset (GSE72094) and TCGA datasets (lung adenocarcinoma, PanCancer Atlas) and Gene Expression Profiling Interactive Analysis (GEPIA) database (http://gepia.cancer-pku.cn/) were used to calculate the correlations between SDPR and Transcription factors (TFs), and evaluate overall survival (OS) of lung adenocarcinoma patients, under different SDPR expression levels and KRAS mutation status. TFs of SDPR were predicted using GeneCards (https://www.genecards.org/) and Promo (http://alggen.lsi.upc.es/cgi-bin/promo_v3/promo/promoinit.cgi?dirDB=TF_8.3), and microRNAs were predicted using miRanda (http://www.microma.org/), miRDB (http://www.mirdb.org/) and TargetScan (http://www.targetscan.org/vert_72/). The potential ceRNA network of SDPR in KRAS-mutant lung cancer was constructed using Cytoskype software. DAVID (https://david.ncifcrf.gov/) and Gene Set Enrichment Analysis (GSEA,http://software.broadinstitute.org/gsea/register.jsp) were used to perform the Gene Ontology (GO) enrichment analysis for biological process (BP), cellular component (CC), molecule function (MF) and pathways. “pheatmap” and “ggplot2” packages were used to visualize heatmaps and bubble charts.

Statistical analysis
All the data were analyzed by SPSS, version 20, IBM Corp., Armonk, USA. SDPR or DACH1 expression was presented as the mean ± standard deviation (SD), and differences between the means were examined by student's t test or one-way analysis of variance (ANOVA). Multiple comparisons among the groups were performed using LSD method. Nonparametric test was used to analyze the SDPR scores in lung and tumor tissues, and correlation analysis was assessed by Pearson or Spearman correlation method. Kaplan-Meier method and Cox proportional hazard regression model were used to evaluate the prognostic value of SDPR in lung adenocarcinoma. Differences with a value of P < 0.05 were considered statistically significant. All of the experiments were performed at least thrice.

Results

The discovery of gene expression signature in KRAS-oncogene-driven lung cancer

To uncover specific gene expression signature of KRAS-oncogene-driven lung cancer, we analyzed transcriptional expression profiles of normal lung tissues and KRAS-mutant lung tumor tissues based on GEO datasets (GSE18784, GSE49200), respectively, and identified differentially expressed genes (DEGs) with statistical difference (p < 0.05) between normal and tumor tissues. As shown in Figure 1a-b, 155 upregulated DEGs and 120 downregulated DEGs were screened out based on GSE18784 dataset, using “EdgeR” R package. Using the same method, 25 upregulated DEGs and 45 downregulated DEGs were screened out based on GSE49200 dataset. The signatures between the two DEGs sets were different, indicating the heterogeneity of KRAS-driven tumors. Interestingly, SDPR was the only DEG that decreased in KRAS-mutant tumor tissues based on GEO datasets (GSE18784, GSE49200), which suggested that the downregulation of SDPR might be a specific signature during the development of KRAS-mutant lung cancer.

Structure and phylogenetic conservative analysis of SDPR

SDPR, also named CAVIN2, is a member of CAVIN family, which is located at chromosome 2, q32.3 (Fig. 1c). The structures of SDPR gene include 5’UTR exon, two exons, 3’UTR exon, and one intron. Protein sequences were compared to explore conservation of SDPR during molecule and species evolution, and the alignment results showed that Homo sapiens SDPR shared 82.82%, 81.88%, 99.53%, 96%, 87.29% and 89.18% identity with Mus musculus, Rattus norvegicus, Pan troglodytes, Macaca mulatta, Sus scrofa, and Felis catus, respectively, which indicates that SDPR is highly conserved in mammals (Fig. 1d).

CAV and CAVIN family members play important roles in the formation and stability of pulmonary alveoli (35). Moreover, CAVIN members could regulate the expression of CAV members. Thus, we analyzed the phylogenetic conservation of CAV and CAVIN family members. As shown in Figure 1e, CAV and CAVIN family members are divided into two major clusters, and CAVIN2 shares a closer evolutionary relationship with CAVIN3, compared with CAVIN1 and CAVIN4.

SDPR is downregulated in human lung adenocarcinoma, including KRAS-mutant group
To identify the SDPR expression level in mouse and human lung tissues and tumors, we established *KRAS*-oncogene-driven lung cancer models (32) and detected SDPR expression using RT-qPCR. As shown in Fig. 2a, higher SDPR expression was detected in pulmonary than in bronchial tissue. Moreover, lower SDPR expression was observed in *KRAS*-mutant tumor tissues (P < 0.05). We further confirmed SDPR expression in human tissues and found a similar result in *KRAS*-mutant tumors. As shown in Fig. 2b-e, SDPR expression significantly decreased in *KRAS*-mutant specimens as well as all lung tumors compared with normal tissue (P < 0.05). In addition, low SDPR expression was detected in *KRAS*-mutant and *KRAS*-wild type NSCLC cell lines compared with immortalized normal lung cells, MRC-5 (Fig. 2f-g).

**Low expression of SDPR is associated with a poor prognosis in NSCLC patients**

As shown in Fig. 3a-c, low expression of SDPR was associated with shorter OS in NSCLC patients as well as in *KRAS*-mutant group, based on GEO dataset and lung cancer microarray (GSE72094, HLugA180Su06, P < 0.05). Similar results were found in NSCLC patients using GEPIA (Fig. 3d, P < 0.05). Meanwhile, univariate survival analysis indicated that low SDPR expression was associated with the shorter OS in NSCLC patients as well as in *KRAS*-mutant group (*KRAS*-mutant lung adenocarcinoma, P < 0.05, hazard ratio [HR] = 0.7; lung adenocarcinoma, P < 0.05, hazard ratio [HR] = 0.7; Table 1). Moreover, multivariate survival analysis showed that SDPR expression and stage were independent predictors of prognosis in lung adenocarcinoma patients as well as in *KRAS*-mutant group (Table 1). These data highlight the prognostic value of SDPR in human lung adenocarcinoma, especially in *KRAS*-mutant subgroup.

**Construction of competing endogenous RNA (ceRNA) network of SDPR in *KRAS*-mutant lung adenocarcinoma pathway**

To identify the upstream regulatory structure of SDPR in *KRAS*-mutant lung cancer, DEGs based on GSE72094 and three public predicted websites (TargetScan, miRDB and miranda) were used (Fig. 4a). Briefly, 139 expression profiles of *KRAS*-mutant patients with complete clinical information were collected (GSE72074), and DEGs sets between low and high SDPR group were screened out using “EdgeR” R package. Three public websites, TargetScan, miRDB and miranda, were used to predict potential combinations between SDPR and transcription factors. As shown in Fig. 4a, two transcription factors (DACH1, WT-1) were identified based on DEGs and TargetScan websites. Moreover, SDPR correlated positively with DACH1 ($R^2=0.509, P < 0.01$; Fig. 4b) and negatively with WT-1 ($R^2=-0.218, P < 0.05$; Fig. 4c). We detected the expression of DACH1 in NSCLC cell lines, MRC5 cells and the *KRAS*-oncogene-driven lung cancer mice. The DACH1 expression in bronchial tissue was lower than that in normal lung tissue based on *KRAS*-oncogenic mice models. Meanwhile, DACH1 expression was lower in tumor tissue than in normal lung tissue. Moreover, The DACH1 expression in NSCLC cells was lower than that in MRC5 cells (Supplementary Figure S1).

Similar to the above screening method of transcription factors, a set of miRNAs was predicted, and five miRNAs (hsa-miR-1, hsa-miR-204, hsa-miR-144, hsa-miR-105 and hsa-miR-363) were ultimately screened
out, which were observed in the above 4 miRNA sets (Fig. 4d). All of them were downregulated in KRAS-mutant lung adenocarcinoma compared with normal lung tissues (Fig. 4e). Interestingly, we found some potential complementary sequences between hsa-miR-1 and DACH-1 (Fig. 4f), indicating that the above miRNAs and TFs may form a complex network to regulate SDPR expression. Thus, we screened a series of miRNAs with potential combination sequence with SDPR-related TFs, and constructed a competing endogenous RNA (ceRNA) network of SDPR in KRAS-mutant lung adenocarcinoma (Fig. 4g).

**Biological enrichment analysis of SDPR downstream pathway**

To explore the downstream pathway of SDPR, DEGs based on GSE72094 were explored to identify biological differences between tissues with low and high SDPR expression in KRAS-mutant lung cancer. Gene ontology analysis was performed using DAVID online software to unfold the biological function of biological process, cellular component and molecule function among the above DEGs. As shown in Figure 5a-c, biological processes were mainly associated with cell mitosis and cell cycle, and the differences of cellular components were mainly located in the extracellular space, exosomes, and matrix. In addition, there were a series of members related to redox balance and energy transfer, indicating the close interaction between SDPR expression and metabolism. Moreover, GSEA analysis results showed that G2 pathway and TGF-beta pathway were most likely associated with the above DEGs (Fig. 5d-e).

**Correlation between SDPR, immune negative regulatory molecules and immune infiltration models**

Recently, SDPR was reported to play a vital role in cancer progression and metastasis via epithelial mesenchymal transition (EMT) in gastric and breast cancers (27, 36). However, the function of SDPR in lung cancer, especially in KRAS-mutant group, remains unclear. Since different SDPR expression levels are accompanied with changes in extracellular components (Fig. 5c), we hypothesized that SDPR expression may be closely related with tumor environment. Thus, we explored the correlation between SDPR and immune checkpoint molecules and immune infiltration models.

As shown in Figure 6a, SDPR expression level negatively correlated with PD-L1(CD274), GITR(TNFRSF18), 4-1BBR(TNFRSF9) and TDO2 ($R^2 = -0.247, -0.327, -0.183, -0.233$, respectively; $P < 0.05$). Since the role of SDPR in immune infiltration is unclear, we analyzed the abundance of immune cells in lung cancers at different SDPR expression levels and copy number variation (CNVs) patterns. In KRAS-mutant subgroups, cancer tissue with lower expression of SDPR was accompanied with less infiltration of γ T cells and resting mast cells but higher abundance of plasma cells, CD4+ memory activated T cells and M1 macrophages (Fig. 6b). Meanwhile, SDPR expression in lung adenocarcinoma positively correlated with infiltration of memory B cells, endothelial cells, M1 and M2 macrophages, myeloid dendritic cells, neutrophils, memory resting CD4+ T cells, CD8+ T cells, but negatively correlated with M0 macrophages, plasma B cells, and CD4+ memory activated T cells based on TIMER 2.0 website (Table 2). In addition, lung adenocarcinoma with SDPR arm-level deletion showed less infiltration of CD4+ T cells, macrophages and neutrophils in TME (Fig. 6c).
These results illustrated close relationship between SDPR, PD-L1(CD274), GITR(TNFRSF18), 4-1BBR(TNFRSF9), TDO2, and abundance of immune cells in human lung adenocarcinoma, especially in KRAS-mutant subgroups.

**Discussion**

Over eight different variants of KRAS mutation have been identified at codons 12, 13 and 61 in NSCLC (37). Several studies explored the therapeutic vulnerability and prognostic differences between the KRAS mutation subtypes (38-40). However, KRAS mutant status may not be recommended to select NSCLC patients for specific treatment such as adjuvant chemotherapy. Meanwhile, there were no significant differences in the phosphorylation level of MEK/ERK kinase among the above variants, despite phosphorylation of AKT and activation of RAL seem to differ between KRASG12C and KRASG12V cells (4, 38). In summary, no specific KRAS variants were validated as ideal prognostic factors of survival or vulnerability indicators for treatment of KRAS-mutant tumors. In our study, we found that SDPR expression was not only decreased in KRAS-mutant NSCLC cells, and KRAS-driven murine tumor from GEMMs, but also downregulated in human NSCLC specimens based on GEO datasets, TCGA datasets, and lung adenocarcinoma tissue array (Fig. 2a-g). Moreover, SDPR expression was suggested to be an independent prognostic factor in lung cancer (Fig. 3a-d, Table. 1). Our research provides a potential target for the prognosis and treatment of NSCLC independent of KRAS variants. More biological experiments and clinical trials are needed to validate and complement our conclusions.

Co-occurring genetic events were frequently observed in KRAS-mutant lung tumors, unlike other oncogene-driven lung cancers (40, 41). STK11 co-mutations (KL), TP53 co-mutations (KP), and CDKN2A/B inactivation plus low thyroid transcription factor-1 (TTF-1) expression (KC) were considered as classical models among KRAS-mutant tumors, and may induce different biological behaviors and characteristics of tumors (40, 42). Co-occurring STK11 or KEAP1 mutations were associated with worse OS in KRAS-mutant NSCLCs (9, 40). Moreover, the lowest levels of PD-L1 and deficient inflammatory immune cells infiltration were found in the KL group. In contrast, the KP group with the highest PD-L1 expression was infiltrated with active inflammation (mainly T-cell inflammation) (24). Our research found negative correlations between SDPR, PD-L1, and immune cells in KRAS-mutant lung cancers (Fig6. a-c). More studies should explore the influence of co-occurring genetic events on SDPR expression and malignant biological behaviors of tumors.

Previous research explored the prognostic and diagnostic significance of SDPR in gastric cancer (27), hepatocellular carcinoma (28), and papillary thyroid cancer (PTC) (29). Our research originally found downregulation of SDPR in lung cancers as well as in KRAS-mutant subgroup (Fig. 2a-g), and innovatively explored the immune checkpoint molecules and abundance of immune infiltrations at different SDPR expression and CNVs models (Fig 6a-c, Table. 2). Those results provide a novel theory for the immune regulatory functions of SDPR in tumorigenesis, progression and metastasis.
In terms of the regulation and function of SDPR in lung cancer, the reason leads to the decline of SDPR is unclear. Liao (27) found that miR-577 regulates TGF-β in gastric cancer through a SDPR-modulated positive-feedback loop. Thiagalingam (36) found that overexpression of SDPR inhibited the activity of ERK and NF-κB pathways in breast cancer. In our study, a series of pathways, including the TGF-β pathway, were enriched between SDPR-low and SDPR-high specimens in KRAS mutant lung cancers (Fig. 5d). In addition, results of GO analysis indicated different distribution of extracellular components depending on SDPR expression (Fig. 5c). Our study screened out a series of TFs and miRNAs as promising candidates for the upstream targets of SDPR in KRAS-mutant cancers, and we constructed a ceRNA regulation network of SDPR in KRAS mutant lung cancers, which provided useful information for the molecule regulatory network of SDPR in KRAS-mutant lung cancers.

**Conclusions**

In our study, a decrease of SDPR was found in lung cancers as well as in KRAS-mutant subgroup, and which may be a promising prognostic marker for the survival of patients with lung cancer. Moreover, systematic exploration of SDPR in gene location, species conservation, function, and potential regulatory network was illustrated in lung cancer, especially in KRAS-mutant tumors. In addition, our research originally unfolded the correlation between SDPR, immune checkpoint molecules, and abundance of immune infiltrations. In summary, SDPR could be a promising prognostic factor and potential target for the treatment of lung cancer, especially for KRAS-mutant adenocarcinomas.

**Declarations**

**Ethics approval and consent to participate**

The research presented here has been performed in accordance with the Declaration of Helsinki and has been approved by the ethics committee of Nanfang hospital, Southern Medical University, China.

**Consent for publication**

All of the authors of this article have participated in the planning and drafting and all of the authors listed have read and approved the final version including details and images. Written informed consent for the publication has been obtained from all of the authors.

**Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

**Competing interests**

The authors declare that they have no competing interests.

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Data collection (provided animals, acquired and managed patients, provided facilities, etc.): Xiaoqing Luo, Shunli Peng, Rong Wang, Yueyun Ma, Shiyu Chen, Yanxia Wang

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Shunli Peng, Xiaoqing Luo, Wei Wang

Writing, review, and/or revision of the manuscript: Xiaoqing Luo, Shunli Peng, Wei Wang

Literature search and organization of figure and table: (i.e., reporting or organizing data, constructing databases): Shunli Peng, Xiaoqing Luo, Sijie Ding, Qin Zeng

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Abbreviations

SDPR, Serum Deprivation Protein Response; NSCLC, Non-Small Cell Lung Cancer; IHC, Immunohistochemistry; TCGA, The Cancer Genome Atlas; TFs, Transcription factors; TNFRSF18, Tumor Necrosis Factor Receptor Superfamily Member 18; TNFRSF9, Tumor Necrosis Factor Receptor Superfamily Member 9; TDO2, Tryptophan 2,3-Dioxygenase 2; TME, Tumor Microenvironment; CNV, Copy Number Variation; EGFR, Epidermal Growth Factor Receptor; ALK, Anaplastic Lymphoma Kinase; ATCC, American Type Culture Collection; GEMM, Genetically Engineered Mouse Model; GSEA, Gene Set Enrichment Analysis; GEO, GENE EXPRESSION OMNIBUS; DEG, Differentially Expressed Gene.

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Tables

Due to technical limitations, table 1 & 2 is only available as a download in the Supplemental Files section.