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DUSP1 regulates the JAK2/STAT3 signaling pathway through targeting miR-21 in cervical cancer cells

Hailin Chen[1#], Songsen Ren[2#], Hui Wan[3], Wengong Wei[1], Yi Luo[1], Meiling Cai[1*]

[1] Department of Obstetrics and Gynecology, Qingpu Branch, Zhongshan Hospital Affiliated to Fudan University, Shanghai 201700, China
[2] Department of Obstetrics and Gynecology, Taihe Hospital of Shiyan City, Shiyan 442000, Hubei Province, China
[3] Department of Nursing, Qingpu Branch, Zhongshan Hospital Affiliated to Fudan University, Shanghai 201700, China

[#]These authors contributed equally to this work as co-first author

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ABSTRACT

This study was to investigate the effect of DUSP1 on cervical cancer (CC) cells by targeting the miR-21 regulatory JAK2/STAT3 signaling pathway. For this purpose, fifteen CC patients treated at our hospital from January 2021 to February 2023 were selected. CC tissues and para-cancerous (PC) tissues were collected from the patients, and DUSP1 protein and mRNA expression levels were detected by Western blot and qPCR. The C33a control group (COG) and DUSP1 overexpression group (OVG) were set up: human cervical squamous carcinoma cells (CSCC) in the C33a COG were cultured without any treatment, while the DUSP1 OVG was cultured using DUSP1 gene overexpression lentivirus infection progeny. The proliferation ability of the three groups of cells was measured by CCK8, protein and mRNA expression by Western blot and qPCR, and cell migration and invasion ability by Transwell. It was found that DUSP1 protein and mRNA in CC tissues were reduced compared with those in PC tissues ($P<0.05$). The miR-21 in the DUSP1 OVG was reduced than those in the C33a COG ($P<0.05$). The expression of JAK2, STAT3 mRNA and protein in the DUSP1 OVG were reduced compared with those in the C33a COG ($P<0.05$). In conclusion, overexpression of DUSP1 can target and reduce the expression of miR-21, block the JAK2/STAT3 signaling pathway, reduce the viability of CC cells, inhibit the proliferation and migration and invasion ability of CC cells, and induce apoptosis of CC cells, thus providing a theoretical basis for the targeted treatment of clinical CC.

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Introduction

Cervical cancer(CC) is a commonly seen clinical gynaecological malignancy. As the second most common cancer in women worldwide, CC has emerged as the second most common malignancy of the reproductive system causing death in women, seriously threatening the life and safety health of women in China (1). The development of CC is a long-term process, from cervical precancerous lesions to cervical intraepithelial neoplasia takes a long time, usually 5-10 years, so early diagnosis and treatment of CC are important to improve its prognosis (2). At present, the clinical treatment of CC patients lacks radical means and mainly adopts radiotherapy treatment and surgical resection treatment. In recent years, with the advancement of targeted therapy, more and more clinical treatments for malignant tumors have gradually adopted targeted therapy. Therefore, in-depth research on the pathogenesis and causes of CC and the search for new therapeutic targets is of great clinical significance in improving patients' clinical symptoms, slowing down the progression of cancer and improving their quality of life (3). Dual specificity phosphatase 1 (DUSP1) belongs to the protein complex phosphatase gene superfamily that is a regulator of tumor suppressors and cancer-related inflammation (4). MicroRNAs (miRNAs) are small non-coding RNAs with highly conserved properties that have a key part to play in regulating cellular biological functions, of which miR-21 has been shown to be aberrantly expressed in patients with CC (5). Janus kinase/signal transducer and activator of transcription (JAK2/STAT3) signaling pathway is widely involved in cell proliferation, migration and apoptosis It has been found that miR-21 has a regulatory role in the JAK2/STAT3 signaling pathway (6). In our research, we investigated DUSP1 on CC cells by targeting miR-21 to regulate the JAK2/STAT3 signaling pathway, with a view to providing a promising target for the treatment of CC.

Materials and Methods

General information

Fifteen CC patients treated at our hospital from January 2021 to February 2023 were selected, and CC tissue, paracancerous (PC) tissue and clinical data were collected from the patients. The age of the patients ranged from 35 to 58 years. All were reviewed and approved by the hospital ethics committee and all signed an informed consent form. Inclusion criteria: ① pathological examination confirmed the diagnosis of CC (7); ② no previous history of pelvic radiation; ③ patients with complete clinical history. Ex-

* Corresponding author. Email: Shmiky001@126.com

clusion criteria: ① those who had already received pharmacological or surgical treatment for the cervical disease; ② those with a combination of other known tumors; ③ those with severe cardiac, hepatic or renal insufficiency; ④ those with a history of previous uterine surgery.

Materials and reagents

CSCC line C33a was purchased from ATCC Cell Bank, USA. DUSP1, miR-21, JAK2, and STAT3 mRNA primers were purchased from Thermo Fisher Scientific, USA. DUSP1, miR-21, JAK2, STAT3 mRNA primers and β-actin primers (Sigma, USA). DUSP1, miR21, JAK2, STAT3 mRNA primers and β-actin primers (Sigma, USA); qPCR assay kit, immunohistochemistry sheep anti-rabbit secondary antibody, CCK-8 assay kit (Shanghai Biyuntian Co. (Shanghai Biyuntian); Transwell (Corning, USA); artificially reconstituted basement membrane gel (Matrigel) (Abcam Biotechnology Ltd., UK); DUSP1, JAK2 and STAT3 primary antibodies (BD, USA). Ltd.); cellular DUSP1 gene overexpression lentivirus (Shanghai Gikai Genetics Co., Ltd.) for this study.

Methods

Cell culture and treatment

After recovery, the cells were inoculated in T25 flasks and incubated in a constant temperature incubator (37°C, 5% CO2), and trypsin digestion, passaging and freezing were performed according to cell growth. C33a control and DUSP1 overexpression groups (OVG) were set up: the C33a control group (COG) was cultured without any treatment and the DUSP1 OVG was cultured using the DUSP1 gene overexpression lentivirus to infect the progeny. Each experiment was repeated 15 times.

Detection of protein level by Western blot

Take 1×10^6 cells/well and inoculated in 6-well plates, incubated in a constant temperature incubator (37℃, 5% CO2), and the cells in the DUSP1 OVG were stably infected with the DUSP1 gene by lentivirus. The supernatant was centrifuged after homogenization at 4℃ to make 10% homogenate; the CC tissue and PC tissue were homogenized at 4℃ to make 10% homogenate after the addition of tissue protein lysis solution. The protein concentration was determined by BCA, gel preparation, electrophoresis for 90 min, gel cutting, membrane transfer for 90 min, milk containment, washing, incubation with primary and secondary antibodies, development and analysis of the results using Bio-Rad Image Lab software.

qPCR to detect mRNA

Take 1×10^6 cells/well and inoculated in 6-well plates in a constant temperature incubator (37℃, 5% CO_2). After the cells in the DUSP1 OVG were infected by DUSP1 gene overexpression lentivirus for stable transmission, RNA extraction using RNA extraction kit, reverse transcription using One Step Prime Script miRNA cDNA synthesis kit and real-time quantitative PCR using PCR detection kit, and the cycle was completed according to the kit instructions. After the reaction was completed, the relative mRNA expression was calculated in the software.

The proliferation of cells was detected by CCK8

After the cells in the DUSP1 OVG were infected by DUSP1 gene overexpression lentivirus and stably passaged, 10μl CCK8 solution was added to each well of each group of cells and incubated in a constant temperature incubator (37℃, 5% CO_2) for 4 h. The proliferative capacity of each group of cells was determined on an enzyme marker (OD 450 nm).

Detection of cell migration and invasion by the Transwell method

After the cells in the DUSP1 OVG were stably passaged by DUSP1 gene overexpression lentivirus infection, inoculate 5×10^5 cells/well in the Transwell upper chamber and complete medium in the lower chamber, and the low and high dose groups were treated with propofol for 48 h. The COG was given equal amounts of DMEM medium, fixed, stained and then microscopically. The purple-stained membrane penetrating cells were counted and cell migration capacity was calculated. For the invasion experiments, the upper chamber of the Transwell was first covered with Matrigel in the ultra-clean bench and the subsequent steps were the same as for cell migration.

Statistical method

SPSS 22.0 was used for statistical data processing and measurements were expressed in (x±s) and t-tests were used for comparison, with $P<0.05$ being a statistically significant difference.

Results

Expression of DUSP1 in CC tissues and PC tissues

The relative expression levels of DUSP1 protein, as well as mRNA, were significantly lower in CC tissues than in PC tissues ($P<0.05$), as shown in Table 1.

Establishment of a DUSP1 overexpression cell line

The relative expression levels of DUSP1 protein, as well as mRNA, were significantly higher in the DUSP1 OVG compared with the C33a COG ($P<0.05$), as shown in Table 2.

Effect of overexpression of DUSP1 on proliferation, migration and invasion of CC cells

The cell proliferation activity, number of cell migrations and number of cell invasions were lower in the DUSP1 OVG compared with the C33a COG ($P<0.05$), as shown in Table 3.

Table 1. DUSP1expression levels in CC tissues and PC tissues.

Group	Number	DUSP1protein	DUSP1 mRNA
CC	15	0.40±0.14	3.05±1.26
PC	15	0.98±0.24	7.12±2.35
t		-8.085	-5.917
P		0.000	0.000

Table 2. Establishment of a DUSP1 overexpression cell line.

Group	Number	DUSP1protein	DUSP1 mRNA
COG	15	0.41±0.13	1.59±0.57
OVG	15	0.94±0.25	3.36±1.03
t		-7.285	-5.823
P		0.000	0.001

Table 3. Effect of overexpression of DUSP1 on proliferation, migration and invasion of CC cells.

Group	Number	Proliferation	Migration	Invasion
COG	15	0.28±0.04	142.74±24.34	121.05±20.26
OVG	15	0.18±0.03	106.48±17.44	93.12±16.35
t		7.746	4.690	4.155
P		0.000	0.000	0.000

Effect of overexpression of DUSP1 on miR-21 expression in CC cells

The miR-21 expression level of CC cells in the DUSP1 OVG was lower compared with that of the C33a COG (P<0.05), as shown in Table 4.

Effect of overexpression of DUSP1 on the relative expression of JAK2 and STAT3 mRNA in CC cells

The relative expression levels of JAK2 and STAT3 mRNA in the DUSP1 OVG of CC cells were reduced compared with those in the C33a COG (P<0.05), as shown in Table 5.

Effect of overexpression of DUSP1 on the expression levels of JAK2 and STAT3 proteins in CC cells

The JAK2 and STAT protein were significantly lower in the DUSP1 OVG of CC cells than in the C33a COG (P<0.05), see Table 6.

Discussion

Over the past years, as people's habits, diets and working environment, the incidence of CC has been on the rise year by year, becoming a more common malignant tumor of the reproductive system (8). Patients with CC were mainly present with clinical symptoms, such as thin, watery fluid, leucorrhoea, irregular vaginal bleeding, anaemia and painful sexual intercourse, which seriously affect the reproductive function and life of the patient (9). CC is also called "cervical invasive cancer", and cervical intraepithelial neoplasia is a pre-cancerous phase of the cervix. The pathogenesis and causes of CC are not yet fully understood, but recent studies have found that age, genetic susceptibility, inflammatory response, immune disorders and physicochemical radiation are all associated with the development of CC (10). Currently, radiotherapy and surgical excision are mainly used to treat patients with CC. Although this can help some patients to cure their cancer, some patients are diagnosed late, lose the opportunity of surgical excision of tumor treatment at a late stage, and are not sensitive to radiotherapy treatment, resulting in limited clinical treatment effects (11). CC is characterized by high incidence, aggressiveness, metastatic potential and recurrence rates, and radical treatment targeting cancer cells in patients with CC has greater clinical significance. Therefore, an in-depth study of the pathogenesis and etiology of CC, identification of the molecular mechanisms of proliferation, invasion and migration of CC cells, and search for new therapeutic targets are of great clinical significance to improve patients' clinical symptoms, slow down the pathological progression of CC and improve their quality of life.

Table 4. Effect of overexpression of DUSP1 on miR-21 expression in CC cells.

Group	Number	miR-21
COG	15	2.47±0.54
OVG	15	1.24±0.52
t		6.355
P		0.000

Table 5. Effect of overexpression of DUSP1 on JAK2 and STAT3 mRNA in CC cells.

Group	Number	JAK2 mRNA	STAT3 mRNA
COG	15	2.71±0.72	2.34±0.76
OVG	15	1.63±0.41	1.28±0.34
t		5.048	4.931
P		0.000	0.000

Table 6. Effect of overexpression of DUSP1 on JAK2 and STAT3 proteins in CC cells.

Group	Number	JAK2	STAT3
COG	15	1.25±0.37	0.83±0.35
OVG	15	0.84±0.21	0.59±0.17
t		3.732	2.389
P		0.001	0.024

DUSP1 is the first and most important phosphatase to be identified in a large family of phosphatases that dephosphorylate certain proteins (12). It has a key role in the regulation of tumor suppressors and the inflammatory and immune responses associated with cancer (13). DUSP1 has been found to be an important negative regulator of the MAPK signaling pathway and has a key function in the treatment of various malignancies, inflammation-related diseases such as asthma, rheumatoid arthritis and osteolytic diseases (14). In this study, the DUSP1 protein and mRNA in CC tissues were reduced compared with those in the PC tissues. The proliferation activity, cell migration number and cell invasion number of DUSP1 OVG were significantly lower than those of C33a COG. It was suggested that overexpression of DUSP1 could reduce the viability of CC cells and inhibit the proliferation, migration and invasion ability of CC cells.

Recently, there has been increasing interest in the study of miRNAs in malignancies, which are a group of small non-coding RNAs that are involved in the regulation of biological functions such as cell proliferation, differentiation, migration and apoptosis by binding to target genes (15). miR-21 is a class of miRNAs implicated in the regulation of cancer-associated inflammatory responses, and this specific regulatory action in cancer-associated inflammatory responses has not been fully elucidated, but it has been found that miRNAs can exert anti-inflammatory effects by targeting and regulating JNK as well as TSG4 (16). Confirmation that miR-21 is highly expressed in CC tissues and the degree of cervical intraepithelial lesions was closely and positively correlated with miR-21 expression levels, suggesting that miR-21 expression levels are

closely related to the severity of CC disease (17). In addition, it was found that miR-21 could promote the invasion and migration ability of CC cells, and inhibit the apoptosis of cancer cells, suggesting that miR-21 could be a significant target for CC (18). This research found that the miR-21 level of CC cells in the DUSP1 OVG was reduced compared with that of the C33a COG. It was suggested that the miR-21 level in CC cells was highly expressed, and DUSP1 could target to reduce the miR-21 expression level, decrease the viability of CC cells, and inhibit the proliferation and migration and invasion ability of CC cells.

The JAK2/STAT3 signaling pathway, as a signaling channel with a very broad role in the human body, is an important signaling system that mediates the response from extracellular stimuli to intracellular cells, regulating cell proliferation, differentiation, migration, apoptosis, etc. It has a major influence in the development and infiltration of malignant cells and is involved in regulating other processes such as cell growth and development (19). Numerous researches showed that the JAK2/STAT3 signaling pathway has a major influence in tumor progression and anti-tumor therapy (20). It has been found that the JAK2/STAT3 signaling pathway is promoted in CC, ovarian cancer and other malignant diseases. STAT3, an important protein molecule in the JAK2/STAT3 signaling pathway, is highly expressed and activated by phosphorylation in CC tissues, leading to the formation of JAK/STAT dimers, which activate the transcription and expression of the corresponding downstream genes (21). It was demonstrated that expression levels of STAT3 and JAK2 proteins were reduced in miR-21-transfected cancer cells compared to blank controls and that cells overexpressing miR-21 were able to target and inhibit the activation of the JAK/STAT signaling pathway (22). Another study found that miR-21 could promote STAT3 by binding to the STAT3 promoter. All those studies suggest that miR-21 is closely related to the activation of the JAK2/STAT3 signaling pathway (23). In our study, the levels of JAK2 and STAT3 mRNA in the DUSP1 OVG of CC cells were significantly reduced compared with those in the C33a COG. This suggests that DUSP1 can target to increase the expression level of miR-21 and block the JAK2/STAT3 signaling pathway, providing a theoretical basis for clinical tumor metastasis and invasion.

In conclusion, overexpression of DUSP1 can target and reduce the expression level of miR-21, block the JAK2/STAT3 signaling pathway, reduce the viability of CC cells, inhibit the proliferation, migration and invasion ability of CC cells, and induce apoptosis of CC cells that provides the basis for research into the targeted treatment of clinical CC.

References

1. Hamada M, Ebihara Y, Yoshida S, Saito N, Enoki Y, Inoue H, Matsumura S, Nakahira M, Yasuda M, Sugasawa M. Prediction Formula for Pathological Depth of Invasion From Clinical Depth of Invasion in Tongue Squamous Cell Carcinoma (SCC) Stage I/II Cases. Cureus 2023 Feb 1; 15(2): e34516. https://doi.org/10.7759/cureus.34516
2. Wang Y, Zhang Y, Du Q, Cao D, Lu X, Meng Z. Sensitive SERS detection of oral squamous cell carcinoma-related miRNAs in saliva via a gold nanohexagon array coupled with hybridization chain reaction amplification. Analytical Methods 2022; 14(44): 4563-4575. https://doi.org/10.1039/D2AY01180H
3. Zhang S, Han X, Wang M, Shen X. Comment on letters to the editor in oral oncology referring to microRNAs as therapeutic molecules for oral squamous cell carcinoma. Oral Oncol 2023 Feb; 137: 106298. https://doi.org/10.1016/j.oraloncology.2022.106298
4. Chen S, Guan X, Xie L, Liu C, Li C, He M, Hu J, Fan H, Li Q, Xie L, Yang M, Zhang X, Xiao S, Tang J. Aloe-emodin targets multiple signaling pathways by blocking ubiquitin-mediated degradation of DUSP1 in nasopharyngeal carcinoma cells. Phytother Res 2023 Mar 3. https://doi.org/10.1002/ptr.7793
5. Jiamin D, Yifeng X, Zuoliang C, Wanlu C, Zhongxiong MA, Yunde X, Lin Z. Qilan preparation inhibits proliferation and induces apoptosis by down-regulating microRNA-21 in human Tca8113 tongue squamous cell carcinoma cells. J Tradit Chin Med 2022 Oct; 42(5): 693-700. https://doi.org/10.19852/j.cnki.jtcm.2022.05.003
6. Xiao L, Li X, Cao P, Fei W, Zhou H, Tang N, Liu Y. Interleukin-6 mediated inflammasome activation promotes oral squamous cell carcinoma progression via JAK2/STAT3/Sox4/NLRP3 signaling pathway. J Exp Clin Cancer Res 2022 May 5; 41(1): 166. https://doi.org/10.1186/s13046-022-02376-4
7. Liu Z, Gao J, Yang Y, Zhao H, Ma C, Yu T. Potential targets identified in adenoid cystic carcinoma point out new directions for further research. Am J Transl Res 2021 Mar 15; 13(3): 1085-1108.
8. Li Z, Zhang L, Liu FY, Li P, He J, Kirkwood CL, Sohn J, Chan JM, Magner WJ, Kirkwood KL. MKP-1 is required to limit myeloid-cell mediated oral squamous cell carcinoma progression and regional extension. Oral Oncol 2021 Sep; 120: 105401. https://doi.org/10.1016/j.oraloncology.2021.105401
9. Shaw AK, Garcha V, Shetty V, Vinay V, Bhor K, Ambildhok K, Karande P. Diagnostic Accuracy of Salivary Biomarkers in Detecting Early Oral Squamous Cell Carcinoma: A Systematic Review and Meta-Analysis. Asian Pac J Cancer Prev. 2022 May 1; 23(5): 1483-1495. https://doi.org/10.31557/APJCP.2022.23.5.1483
10. Su PH, Lai HC, Huang RL, Chen LY, Wang YC, Wu TI, Chan MWY, Liao CC, Chen CW, Lin WY, Chang CC. Paired Box-1 (PAX1) Activates Multiple Phosphatases and Inhibits Kinase Cascades in Cervical Cancer. Sci Rep 2019 Jun 24; 9(1): 9195. https://doi.org/10.1038/s41598-019-45477-5
11. Soni S, Saroch MK, Chander B, Tirpude NV, Padwad YS. MAPKAPK2 plays a crucial role in the progression of head and neck squamous cell carcinoma by regulating transcript stability. J Exp Clin Cancer Res 2019 Apr 25; 38(1): 175. https://doi.org/10.1186/s13046-019-1167-2
12. Liu Z, Wang J, Dai F, Zhang D, Li W. DUSP1 mediates BCG induced apoptosis and inflammatory response in THP-1 cells via MAPKs/NF-κB signaling pathway. Sci Rep 2023 Feb 14; 13(1): 2606. https://doi.org/10.1038/s41598-023-29900-6
13. Gaba FI, Sheth CC, Veses V. Salivary biomarkers and their efficacies as diagnostic tools for Oral Squamous Cell Carcinoma: Systematic review and meta-analysis. J Oral Pathol Med 2021 Mar; 50(3): 299-307. https://doi.org/10.1111/jop.12791
14. Benito-León M, Gil-Redondo JC, Perez-Sen R, Delicado EG, Ortega F, Gomez-Villafuertes R. BCI, an inhibitor of the DUSP1 and DUSP6 dual specificity phosphatases, enhances P2X7 receptor expression in neuroblastoma cells. Front Cell Dev Biol 2022 Dec 15; 10: 1049566. https://doi.org/10.3389/fcell.2022.1049566
15. Abdolrahmani A, Kardouni Khoozestani N, Azmoudeh-Ardalan F, Shamshiri AR. Prognostic impact of MUC1 and potential regulatory miR-145 and miR-21 expression in salivary mucoepidermoid carcinoma. Head Neck Pathol 2022 Dec; 16(4): 1134-1145. https://doi.org/10.1007/s12105-022-01475-0
16. Yan G, Wan Z, Zhong Y, Chen M. LncRNA MCM3AP-AS1

Regulates miR-21/PTEN Axis to Affect Cervical Squamous Cell Carcinoma Cell Proliferation and Apoptosis. Crit Rev Eukaryot Gene Expr 2022; 32(4): 49-56. https://doi.org/10.1615/CritRevEukaryotGeneExpr.2022041014

17. Jadhav KB, Shah V, Chauhan N, Shah N, Parmar G. Expression of microRNA-21 in saliva and tumor tissue of patients with oral squamous cell carcinoma: a predictor of cervical lymph node metastasis. Oral Surg Oral Med Oral Pathol Oral Radiol 2022 Jan; 133(1): 60-69. https://doi.org/10.1016/j.oooo.2021.07.012
18. Irimie-Aghiorghiesei AI, Pop-Bica C, Pintea S, Braicu C, Cojocneanu R, Zimța AA, Gulei D, Slabý O, Berindan-Neagoe I. Prognostic Value of MiR-21: An Updated Meta-Analysis in Head and Neck Squamous Cell Carcinoma (HNSCC). J Clin Med 2019 Nov 21; 8(12): 2041. https://doi.org/10.3390/jcm8122041
19. Cao M, Tian K, Sun W, Xu J, Tang Y, Wu S. MicroRNA-141-3p inhibits the progression of oral squamous cell carcinoma via targeting PBX1 through the JAK2/STAT3 pathway. Exp Ther Med 2022 Jan; 23(1): 97. https://doi.org/10.3892/etm.2021.11020
20. Zhao C, Chen HY, Zhao F, Feng HJ, Su JP. Acylglycerol kinase promotes paclitaxel resistance in nasopharyngeal carcinoma cells by regulating FOXM1 via the JAK2/STAT3 pathway. Cytokine 2021 Dec; 148: 155595. https://doi.org/10.1016/j.cyto.2021.155595
21. Zhu X, Liu L, Wang Y, Cong J, Lin Z, Wang Y, Liu Q, Wang L, Yang B, Li T. lncRNA MIAT/HMGB1 Axis Is Involved in Cisplatin Resistance *via* Regulating IL6-Mediated Activation of the JAK2/STAT3 Pathway in Nasopharyngeal Carcinoma. Front Oncol 2021 May 20; 11: 651693. https://doi.org/10.3389/fonc.2021.651693
22. Du T, Jiang J, Chen Y, Zhang N, Chen G, Wang X, Long X, Feng X. MiR-138-1-3p alters the stemness and radiosensitivity of tumor cells by targeting CRIPTO and the JAK2/STAT3 pathway in nasopharyngeal carcinoma. Ann Transl Med 2021 Mar; 9(6): 485. https://doi.org/10.21037/atm-21-521
23. Luo H, Yang Z, Zhang Q, Shao L, Wei S, Liu R, Li Z, Geng Y, Li C, Wang X. Carbon Ion Therapy Inhibits Esophageal Squamous Cell Carcinoma Metastasis by Upregulating STAT3 Through the JAK2/STAT3 Signaling Pathway. Front Public Health 2020 Nov 20; 8: 579705. https://doi.org/10.3389/fpubh.2020.579705