Investigation on Post Translational Modification of GSK3 Beta Upon SIRT6 Silencing in Non-Small Cell Lung Cancer Cell Lines

R. K. Brindhadevi
Department of Biomedical Science
Alagappa University, Karaikudi, Tamil Nadu, India

OPEN ACCESS

Volume: 12

Special Issue: 1

Month: July

Year: 2024

P-ISSN: 2321-788X

E-ISSN: 2582-0397

Received: 27.05.2024

Accepted: 30.06.2024

Published: 10.07.2024

Citation:
Brindhadevi, RK. "Investigation on Post Translational Modification of GSK3 Beta Upon SIRT6 Silencing in Non-Small Cell Lung Cancer Cell Lines." *Shanlax International Journal of Arts, Science and Humanities*, vol. 12, no. S1, 2024, pp. 67–80.

DOI:
https://doi.org/10.34293/sijash.v12i1.8020

Abstract
SIRT6 aberration has been widely reported in a variety of serious human disorders during the past few decades.This work is to analyse the SIRT6 knockdown effect on the stability of a non-small cell lung cancer cell lines expressing GSK-3 Beta. The main objectives includes Silencing of SIRT6 in A549 and H460 cell lines by using (SIRT6 siRNA 1, SIRT6 siRNA 2) and investigation on the phosphorylation status of GSK-3beta.Methods used in this work are In vitro experiments with human NSCLC cells have been performed. Western Blot was performed to explore the key events in the regulation of GSK-3β by silencing SIRT6 in NSCLC. The findings of this study suggest that silencing of SIRT6 significantly promotes the phosphorylation status of GSK-3β and destabilizes it.
Keywords: SIRT6, Lung Cancer, GSK3 Beta

Introduction

The accumulation of genetic and epigenetic alterations in two genes results in cancer tumor suppressor genes (TSGs) and proto-oncogenes (Wang, L. H., et al., 2018). Cancer is a terrible disease that affects both men and women at all times, from newborn to adults (Selvarathinam, K., et al., 2021). Cancer results from a series of successive mutations in genes, and these mutations change the way cells functions. Chemical compound plays a clear role in the development of genetic mutations and cancer cells. Interestingly, carcinogenic environmental chemicals directly or indirectly affect the cytoplasm and nucleus, resulting in gene mutation and genetic diseases. Typically, cancer disrupts cellular communication and cause dysfunction of vital genes. This disruption affects the cell cycle and cause abnormal proliferation (Hassanpour, S. H., & Dehghani, M. 2017). Proto-oncogenes are responsible for cell division and growth under normal condition, but oncogenes with genetic mutations that are most dangerous for the existence of the cell. Moreover, the absence of tumor suppressor genes leads to uncontrolled cell division (Hassanpour, S. H., & Dehghani, M. 2017).

As the name suggests, glycogen synthase kinase 3 (GSK3) was first identified as the protein kinase that phosphorylates and inhibits glycogen synthase (1). It was then quickly discovered that this widely expressed serine/threonine kinase could link different extracellular stimuli to intracellular signals to maintain appropriate homeostasis

and phosphorylate more than a hundred protein substrates. Consequently, a wide range of illnesses, such as mental illnesses, neurological conditions, cardiovascular diseases, diabetes, and several malignancies, have been linked to GSK3 dysregulation. Two isoforms of GSK3, called GSK3α (51 kDa) and GSK3β (47 kDa), are expressed and are encoded by separate genes found in all mammalian cells. These isoforms exhibit an overall homology of more than 67%, with the catalytic domain showing a sequence similarity of more than 98%.

The downstream targets and the kinases and phosphatases that control GSK-3 activity are listed in Several signaling molecules have the ability to control GSK-3 activity. Akt is a well-researched GSK-3 regulator that is part of the PI3K/PTEN/Akt/mTORC1 pathway. According to Laurent et al. (2014), Akt is a serine/threonine kinase that also phosphorylates a number of important proteins that are involved in the control of cell development and death. Growth factor (GF) receptor ligand activation activates several pathways, including PI3K/PTEN/Akt/mTORC1, Ras/Raf/MEK/ERK, and others. GSK-3 can be phosphorylated by Akt activation, which in turn causes GSK-3 to become inactivated. TSC2 can be phosphorylated by GSK-3, increasing its activity and inhibiting mTORC1 activity (Inoki, K., et al., 2006).

GSK-3beta has the ability to phosphorylate Rictor at serine-1235 during cell stress, which prevents Akt from binding to mTORC2. Akt is not completely activated when mTORC2 is not functioning. Although Akt has the ability to adversely affect GSK-3 activity, GSK-3 occasionally has the ability to reciprocate by suppressing Akt activation.

The conserved 250 amino acid catalytic core of the SIRT family proteins is surrounded by varying lengths of N- and C-terminal extensions (NTE and CTE, respectively). With NTE residues 1–42, enzymatic core domain residues 43–276, and CTE residues 277–355, SIRT6 is 355 amino acids long overall. Not only is the NTE domain essential to SIRT6's intrinsic catalytic activity

Materials and Methods

Maintenance of Cells

Cell lines

- A549- Lung adenocarcinoma cell line
- NCI-H460- lung cancer cell line with large cells

Culture of Cells

The National Centre for Cell Sciences (NCCS), located in Pune, India, is where the lung cancer cell lines A549 and NCI-H460 were acquired. The cells were cultured in Dulbecco's Modified Eagle Medium (DMEM), which was enhanced with 10 % Fetal Bovine Serum (FBS) and 1 % antibiotics (penicillin, streptomycin, and amphotericin B). Every cell was grown in a CO2 incubator with 5 % CO2 at 37°C in a humid environment. Stock cultures were sub-cultured until all the cells reached 80 % confluency washed with phosphate buffered saline (PBS) and harvesting the cells using trypsin-EDTA and then seeding them in tissue culture flask to maintain them in exponential phase.

Cell Culture Reagents

Incomplete Medium

DMEM medium with HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) buffer, glucose, glutamine, sodium bicarbonate and sodium pyruvate were purchased from Himedia Laboratories, Mumbai, India.

Serum

10 % Fetal bovine serum (FBS) were purchased from Himedia Laboratories, Mumbai, India.

Antibiotics

Penicillin, streptomycin and amphotericin B were purchased from Himedia Laboratories, Mumbai, India.

Complete Medium (DMEM with 10 % FBS)

100 ml of growth medium/complete medium was prepared by adding 10 ml FBS in 90 ml DMEM and 1ml antibiotics. It was stored in a sterile container.

Chemicals

Trypsin, EDTA, disodium hydrogen phosphate, sodium chloride, potassium chloride and potassium dihydrogen phosphates were purchased from Hi- Media Laboratories, Mumbai, India. All other chemicals used in the present investigation were of cell culture and the analytical grade was purchased from Hi-Media Laboratories, Mumbai, India and SRL, Mumbai, India.

0.1% Trypsin-EDTA

0.1 g trypsin and 0.1 g EDTA were dissolved in 100 ml 1xPBS.

1X Phosphate Buffered Saline (PBS) pH 7.4

500 milliliters of sterile double-distilled water were used to dissolve 0.74 g of disodium hydrogen phosphate (Na_2HPO_4), 4 g of sodium chloride (NaCl), 0.1 g of potassium chloride (KCl), and 0.12 g of potassium dihydrogen phosphate (KH_2PO_4). After using 0.1 N NaOH to get the pH down to 7.4, the mixture was sterile filtered (0.22μm), and it was refrigerated.

Plastic-Wares

Tissue culture flasks, tissue culture plates, centrifuge tubes, serological pipettes, tips, etc., were purchased from Tarsons products, Kolkata, India.

Passaging the Cells

The cells were grown in culture flasks, upon reaching confluence; the cells were detached using the trypsin-EDTA solution as follows:

The cultural medium was aspired to. After swiftly aspirating again, the flask was cleaned with two milliliters of 1X PBS. After adding 1 ml of trypsin-EDTA solution, the mixture was incubated at 37°C for three to five minutes, or until the cells began to separate from the surface. As soon as the cells were loose, using a serological pipette the trypsinated medium containing cells were centrifuged at 1000 rpm for 3 minutes. With caution, the medium was aspirated. The pipette tip was carefully removed from the tube where the cells were pelleted.

The cells were gently suspended in fresh DMEM medium with 10% FBS by retro pipetting. A drop was applied to the edge of the Neuberger hemocytometer coverslip from the cell suspension. By capillary action, the drop was allowed to run under the coverslip. It was careful not to “force” the liquid and to prevent air bubbles from forming. Next, using a microscope, the cells from the E1, E2, E3, E4 and E5 squares were counted. After that, the cells were carefully resuspended in brand-new growth medium and put into sterile T-25 flasks. The medium’s volume was then increased to 5 ml using the growth medium/flask combination.

Transfection Efficiency of siRNA Oligonucleotides and Optimization of Transfection

One day before transfection, NSCLC cell lines were seeded in 1X106 per well of 6 well plates without antibiotics after reached 60 % of confluence. On the day of transfection, 25nM of negative control siRNA and SIRT6 siRNA oligos were used. In separate tubes, dilute siRNA (Tube A) and Lipofectamine 3000 (transfection reagent) (Tube B) were prepared in a serum- free medium. Tube A: 2 µl of 25nM of siRNA oligonucleotides diluted into 150 µl of OPTI- MEM serum-reduced medium. Tube B: 6 µl of Lipofectamine 3000 into 150 µl of OPTI-MEM serum- reduced medium. After 5 mins incubation of each tube, combined the diluted siRNA oligonucleotide with diluted Lipofectamine 3000 mixed gently and incubated for 25 mins at RT. After incubation, siRNA and Lipofectamine 3000 complexes were added drop-wise into 6 well plate containing cells and antibiotic-free medium. Incubated cells with the transfection complex under 5 % O2 at 37°C and 48 hours were spent maintaining the cells following transfection.

Transfection of SIRT6 siRNA and Negative Control

Lung cancer cells were seeded into six-well plate (1 X 106) after reaching 60 % confluency. For siRNA transfection, SIRT6 siRNA (sense: 5'-GAAUGUGCCAAGUGUAAGAtt-3', antisense: 5'-UCUUACACUUGGCACAUUCtt-3') and their negative control siRNA (AM4611) was purchased from Invitrogen, USA. The cells were transfected at a concentration of 25nM using Lipofectamine 3000 reagent (Invitrogen, USA) as per the manufacturer's instruction. Lipofectamine reagent alone is served as mock control and cells are maintained for 48hrs after transfection. Transfection efficiency was analyzed by RTPCR and western blotting.

Reverse Transcription PCR Analysis

Total RNA Isolation

Total RNA was isolated by using Takara RNAiso Plus reagent (Takara Bio Inc, Japan). Briefly, unsilenced A549 and NCI-H460 cells are silenced using siRNA transfected A549 and NCI-H460 cells washed with ice-cold PBS twice. 1 ml of TRIzol reagent was added into 6-well plates lysed the cells directly in a culture plate after lysed the cells collected into 2 ml centrifuge tubes and added 0.2 ml of chloroform then vortex vigorously for 5 mins and incubated 20 mins at RT. After incubation, The samples were centrifuged for 15 minutes at 4°C at 12,000 rpm. and carefully removed the upper aqueous phase which contains total RNA in a new 1.5 ml centrifuge tubes. Total RNA was precipitated from the aqueous phase by using isopropyl alcohol, 0.5 ml of isopropyl alcohol were added into the aqueous phase, mixed gently by inverting the tubes and incubated 10 mins at RT. After incubation, the samples were centrifuged at 10,000 rpm for 10 mins at 4ºC and after centrifugation, removed the supernatant carefully and washed the RNA pellet by adding 1 ml of 75 % ethanol, mixed gently by inverting the tubes again, centrifuged the tubes at 12,000 rpm 5 mins at 4°C after centrifugation, eliminated all leftover ethanol and invert the tubes allowed air dry RNA pellet for 10 mins. 50 µl of nuclease-free water was added to dissolve the RNA pellet, which was then kept in a freezer at -20°C for later research.

RNA Quantification cDNA Construction

Total RNA was quantified in the Eppendorf bio spectrophotometer. The samples A260/A280 ratio < 1.80 and the A260/A230 ratio < 0.5 only taken for cDNA synthesis. 2 µg of RNA was used for cDNA construction. cDNA was constructed by using prime script TM RT reagent kit (Catalog number: RR037A-Takara Bio Inc, Japan). For 20 µl of cDNA, 5X PrimeScript buffer - 4.0 µl; PrimeScript RT Enzyme- 1µl; 1.0 µl of 50 µM Oligo dT primer; Random 6 mers- 1 µl; RNA- 2 µg and Nuclease-free water up to 13 µl added all the reagents into 0.2 µl PCR tube vortex gently.

Incubated the RNA-primer mix under the following conditions: 15 minutes at 37˚C, 5 seconds at 85˚C and final hold in 4˚C in Takara PCR thermal cycler dice (Takara Bio Inc, Japan). Synthesized cDNA was stored at -20˚C for further experiments.

RT-PCR

The mRNA expression levels were quantified through RT-PCR using the Emerald Amp RT PCR master mix (Catalog number: RR310A - Takara Bio Inc, Japan) on the Takara PCR thermal cycler dice (Takara Bio Inc, Japan). For 10 µl RT-PCR reaction, 2X PCR master mix- 5 µl; cDNA - 1 µl; Forward Primer - 1 µl; Reverse Primer - 1 µl; Nuclease-free-water - 2 µl) were added to PCR tubes, and the mixture was gently mixed before the following conditions were met during incubation: 35 cycles of 30 seconds at 95°C, 60°C, and 72°C. Using 2 % agarose gel electrophoresis and Gelstan 1012 (Medicare Scientific), gene expression was measured for each gene of interest and normalized to a housekeeping gene (β-ACTIN)

The intensities of the bands were quantified utilizing the National Institutes of Health's ImageJ program (Bethesda, MD, USA).

Western Blotting

Total Protein Isolation

Unsilenced A549 and NCI-H460 cells and silenced using siRNA and their negative controls transfected in A549 and NCI-H460 1 ml was used to lyse the cells. of RIPA (Radio Immunoprecipitation Assay) lysis buffer (pH 7.4+ 0.1) containing 10 µl of (200 mM) PMSF, 10 µl of (100 mM) Sodium orthovanadate and 10 µl of protease inhibitor cocktail (Santa Cruz Biotechnology, Santa Cruz, CA, USA). The cells were collected from the plates by using cell scraper and added into micro centrifuge tubes, then kept in ice for 15 mins and vortexed for 5 mins. After incubation, the cells were centrifuged at 12,000 rpm for 20 mins at 4°C. The cleared supernatant was collected in a new tube and again centrifuged 12,000 rpm for 10 mins at 4°C. The cleared supernatant was collected and aliquoted for further use. Isolated protein samples were stored at -20°C freezer until further experiments.

Protein Estimation

Total protein concentration was measured by using Lowry's method (Lowry et al., 1951). BSA (Bovine Serum Albumin) was used as a standard and measured the absorbance of standards and samples at 660 nm.Separation of protein by SDS-Gel electrophoresis and detection

The quantified protein (50µg per lane) was resuspended in 6 X protein loading buffer and separated by using 12 % SDS-polyacrylamide gel electrophoresis (100V, 2.30h) and then were transferred onto a nitrocellulose membrane (150 V for a 1.30h) (Bio-Rad, Hercules, CA, USA) by using Towbin buffer (25mM Tris base, 20 % methanol, 190 mM glycine, and a pH of 8.3). The membranes were incubated at room temperature for 1 h with blocking buffer (freshly prepared To prevent nonspecific antibody binding, 5% skimmed milk powder in TBS-T (20 mM Tris, 136 mM NaCl, 0.1% Tween 20, pH 7.6) is added. Primary monoclonal antibodies against mice and rabbits were diluted 1:10,000 and incubated for an entire night at 4°C. Membranes were cleaned three times in five minutes using TBS-T and TBS. Following a further hour of incubation at room temperature, the membranes were rinsed three times for five minutes using TBS-T and TBS after being treated with a goat anti-rabbit or anti-mouse secondary antibody (Cell Signaling Technology, Danvers, MA, USA). The 200 µl BCIP/NBT solution (Merck Millipore, Bedford, MD, USA) was used to identify bands. Bio-Rad Gel doc XR plus (Bio-Rad, Hercules, CA, USA) was used to observe the bands, and ImageJ software (NIH) was used to quantify the band intensities.

Results and Discussion

Silencing of SIRT6 Increase Phosphorylation

SIRT6 was found to be overexpressed in NSCLC. Further, we intend to investigate whether the depletion of SIRT6 possesses an impact on the control of GSK3 BETA phosphorylation in NSCLC. Our results show that after the knockdown of SIRT6 the phospho- GSK3 BETA level was increased. This result indicates that SIRT6 alters GSK3 expression by posttranslational modification.

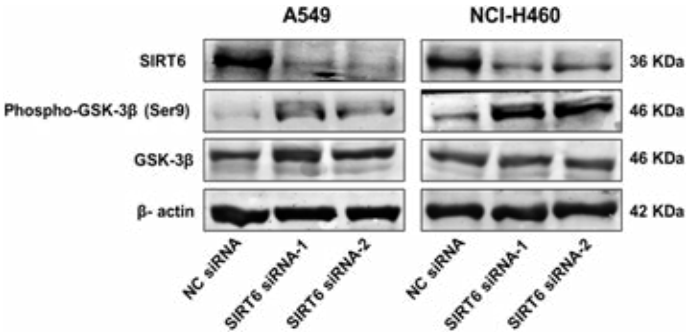

Figure 5.1 GSK-3Beta Expression

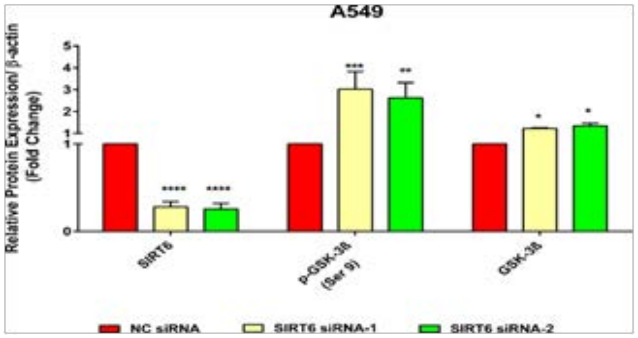

Figure 5.2 Effect of SIRT6 Knockdown by siRNA on GSK-3Beta in A549 Cell Line

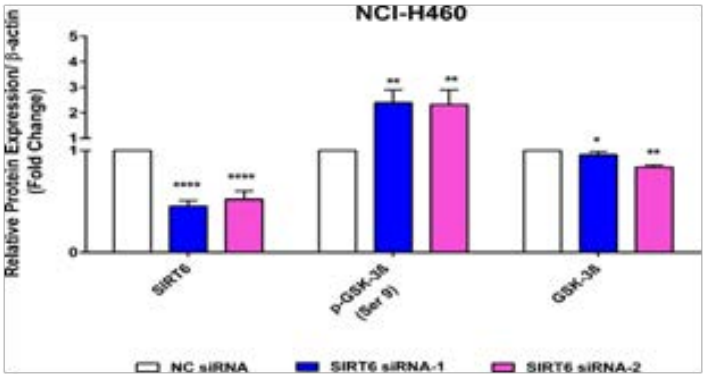

Figure 5.3 Effect of SIRT6 Knockdown by siRNA on GSK-3Beta in H460 Cell Line

Serine/threonine (S/T) protein kinase, GSK-3, is a kind of kinase. While the first identification of GSK-3's actions involved glycogen synthase control, more research revealed that GSK-3 is involved in numerous normal biochemical processes as well as a variety of pathological disorders.

Given its ability to regulate so many different substrates and processes, GSK-3 is sometimes referred to as a "moonlighting" protein. GSK-3 phosphorylates proteins, which often results in their destruction. Since AKT commonly phosphorylates GSK-3 and controls its inactivation, GSK-3 is frequently thought of as a part of the PI3K/PTEN/AKT/GSK-3/mTORC1 pathway. GSK-3 is frequently inactivated in human cancer because AKT is frequently active.

Furthermore, GSK-3 targets β-catenin and other proteins in the WNT/β-catenin signaling pathway and interacts with them. NF-κB activity, which is frequently expressed at high levels in cancer cells, can be altered by GSK-3. To reduce GSK-3 activity, several pharmaceutical companies created small molecule inhibitors. Furthermore, different natural compounds will alter the action of GSK-3. The impact of natural products and small chemical inhibitors on GSK-3 activity will be the main topic of this review, along with instances of how these substances have successfully stopped the spread of cancer.

According to recent research, SIRT6 overexpression inhibits the AKT/GSK3β/CRMP2 signaling pathway, which may lead to behaviors resembling depression. Conversely, in mice, downregulating hippocampus SIRT6 has an antidepressant-like effect.

According to our exact findings, GSK3β is phosphorylated more at the ser-09 location and is less active in NSCLC cell lines when SIRT6 is silenced.

Conclusions

The removal of the acetyl group from histone proteins is the primary function of the seven sirtuin proteins, which are class III histone deacetylase enzymes (HDAC) and nicotinamide adenine dinucleotide (NAD)-dependent deacetylases and ADP-ribosyl transferases. One of the sirtuins, SIRT6, is involved in the development of cancer in a variety of cancer types. As a result, suppressing SIRT6 in NSCLC cell lines causes apoptosis and reduces cell proliferation, as we recently revealed that SIRT6 functions as an oncogene in NSCLC. It has been observed that WNT signaling controls cell differentiation and proliferation in addition to being involved in cell survival. GSK-3, a serine/threonine protein kinase, is widely expressed and phosphorylates glycogen synthase, thereby rendering it inactive.

GSK-3 is an essential downstream component of the PI3K/Akt pathway that is phosphorylated at Ser9 of GSK-3β and Ser21 of GSK-3α by Akt, which inhibits GSK-3's function. GSK-3 is a part of the Wnt signaling pathway that is necessary for the development of Drosophila, Xenopus, and mammals. It has been linked to the control of cell destiny in Dictyostelium. The purpose of this work is to investigate the precise mechanism by which SIRT6 controls the posttranslational alteration GSK-3β in non-small cell lung cancer and how it is correlated with WNT signaling.

Main methods: Human NSCLC cells have been used in in vitro studies. By suppressing SIRT6 in NSCLC, Western blot was used to investigate the pivotal moments in the regulation of GSK-3β.

Key findings: The results of this investigation indicate that GSK-3β is markedly phosphorylated and destabilized when SIRT6 is silenced.

Acknowledgement

I gratefully acknowledged the Alagappa University for providing lab facilities to this work throughout my research period.

References

1. Aerts, H.J., Velazquez, E.R., Leijenaar, R.T., Parmar, C., Grossmann, P., Carvalho, S., Bussink, J., Monshouwer, R., Haibe-Kains, B., Rietveld, D. and Hoebers, F., 2014. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. Nature communications, 5(1), p. 4006.

2. Agrawal, N., Dasaradhi, P.V.N., Mohmmed, A., Malhotra, P., Bhatnagar, R.K. and Mukherjee, S.K., 2003. RNA interference: biology, mechanism, and applications. Microbiology and molecular biology reviews, 67(4), pp.657-685.
3. Ahringer, J., 2000. NuRD and SIN3: histone deacetylase complexes in development. Trends in Genetics, 16(8), pp.351-356.
4. Alberts, B., 2017. Molecular biology of the cell. Garland science.
5. Allis, C.D. and Jenuwein, T., 2016. The molecular hallmarks of epigenetic control. Nature Reviews Genetics, 17(8), pp.487-500.
6. Arab, A., Karimipoor, M., Irani, S., Kiani, A., Zeinali, S., Tafsiri, E. and Sheikhy, K., 2017. Potential circulating miRNA signature for early detection of NSCLC. Cancer Genetics, 216, pp.150-158.
7. Armitage, J.O., Gascoyne, R.D., Lunning, M.A. and Cavalli, F., 2017. Non-hodgkin lymphoma. The lancet, 390(10091), pp.298-310.
8. Avilkina, V., Chauveau, C. and Mhenni, O.G., 2022. Sirtuin function and metabolism: Role in pancreas, liver, and adipose tissue and their crosstalk impacting bone homeostasis. Bone, 154, p.116232.
9. B Uzdensky, A., V Demyanenko, S. and Y Bibov, M., 2013. Signal transduction in human cutaneous melanoma and target drugs. Current cancer drug targets, 13(8), pp.843-866.
10. Bauer, I., Grozio, A., Lasigliè, D., Basile, G., Sturla, L., Magnone, M., Sociali, G., Soncini, D., Caffa, I., Poggi, A. and Zoppoli, G., 2012. The NAD+-dependent histone deacetylase SIRT6 promotes cytokine production and migration in pancreatic cancer cells by regulating Ca2+ responses. Journal of Biological Chemistry, 287(49), pp.40924-40937.
11. B Bennecib, M., Gong, C.X., Grundke-Iqbal, I. and Iqbal, K., 2000. Role of protein phosphatase-2A and-1 in the regulation of GSK-3, cdk5 and cdc2 and the phosphorylation of tau in rat forebrain. FEBS letters, 485(1), pp.87-93.
12. Berdeaux, R., Goebel, N., Banaszynski, L., Takemori, H., Wandless, T., Shelton, G.D. and Montminy, M., 2007. SIK1 is a class II HDAC kinase that promotes survival of skeletal myocytes. Nature medicine, 13(5), pp.597-603.
13. Beurel, E. and Jope, R.S., 2006. The paradoxical pro-and anti-apoptotic actions of GSK3 in the intrinsic and extrinsic apoptosis signaling pathways. Progress in neurobiology, 79(4), pp.173-189.
14. Bharathi, J.K., Anandan, R., Benjamin, L.K., Muneer, S. and Prakash, M.A.S., 2023. Recent trends and advances of RNA interference (RNAi) to improve agricultural crops and enhance their resilience to biotic and abiotic stresses. Plant Physiology and Biochemistry, 194, pp.600-618.
15. Bian, C., Zhang, R., Wang, Y., Li, J., Song, Y., Guo, D., Gao, J. and Ren, H., 2022. Sirtuin 6 affects glucose reabsorption and gluconeogenesis in type 1 diabetes via FoxO1. Molecular and Cellular Endocrinology, 547, p.111597.
16. Bruscalupi, G., Di Micco, P., Failla, C.M., Pascarella, G., Morea, V., Saliola, M., De Paolis, A., Venditti, S. and Mauro, M.L., 2023. Arabidopsis thaliana sirtuins control proliferation and glutamate dehydrogenase activity. Plant Physiology and Biochemistry, 194, pp.236-245.
17. Buck-Koehntop, B.A. and Defossez, P.A., 2013. On how mammalian transcription factors recognize methylated DNA. Epigenetics, 8(2), pp.131-137.
18. Buechling, T. and Boutros, M., 2011. Wnt signaling: signaling at and above the receptor level. Current topics in developmental biology, 97, pp.21-53.
19. Burnett, C., Valentini, S., Cabreiro, F., Goss, M., Somogyvári, M., Piper, M.D., Hoddinott, M., Sutphin, G.L., Leko, V., McElwee, J.J. and Vazquez-Manrique, R.P., 2011. Absence of

effects of Sir2 overexpression on lifespan in C. elegans and Drosophila. nature, 477(7365), pp.482-485.
20. Burton, K.A., Ashack, K.A. and Khachemoune, A., 2016. Cutaneous squamous cell carcinoma: a review of high-risk and metastatic disease. American journal of clinical dermatology, 17, pp.491-508.
21. Cai, J., Liu, Z., Huang, X., Shu, S., Hu, X., Zheng, M., Tang, C., Liu, Y., Chen, G., Sun, L. and Liu, H., 2020. The deacetylase sirtuin 6 protects against kidney fibrosis by epigenetically blocking β-catenin target gene expression. Kidney international, 97(1), pp.106-118.
22. Cai, S., Fu, S., Zhang, W., Yuan, X., Cheng, Y. and Fang, J., 2021. SIRT6 silencing overcomes resistance to sorafenib by promoting ferroptosis in gastric cancer. Biochemical and biophysical research communications, 577, pp.158-164.
23. Cai, J., Wang, T., Zhou, Y., Tang, C., Liu, Y. and Dong, Z., 2022. Phosphorylation by GSK-3β increases the stability of SIRT6 to alleviate TGF-β-induced fibrotic response in renal tubular cells. Life sciences, 308, p.120914.
24. Carmon, K.S., Gong, X., Lin, Q., Thomas, A. and Liu, Q., 2011. R-spondins function as ligands of the orphan receptors LGR4 and LGR5 to regulate Wnt/β-catenin signaling. Proceedings of the National Academy of Sciences, 108(28), pp.11452-11457.
25. Chen, N., Wu, Q., Zhang, G., Fu, J., Geng, Q. and Zhang, Y., 2022. Deactivation of AKT/GSK-3β-mediated Wnt/β-catenin pathway by silencing of KIF26B weakens the malignant behaviors of non-small cell lung cancer. Tissue and Cell, 76, p.101750.
26. Clevers, H. and Nusse, R., 2012. Wnt/β-catenin signaling and disease. Cell, 149(6), pp.1192-1205.
27. Crooke, S.T., Witztum, J.L., Bennett, C.F. and Baker, B.F., 2018. RNA-targeted therapeutics. Cell metabolism, 27(4), pp.714-739.
28. Yi, D., Keng, S., Jing-he, L., Hui-fang, H., Ling-ya, P., Ming, W., Jia-xin, Y. and Ding-rong, Z., 2011. Primary sarcoma of the ovary: clinicopathological characteristics, prognostic factors and evaluation of therapy. Chinese medical journal, 124(9), pp.1316-1321.
29. De Lau, W., Barker, N., Low, T.Y., Koo, B.K., Li, V.S., Teunissen, H., Kujala, P., Haegebarth, A., Peters, P.J., Van De Wetering, M. and Stange, D.E., 2011. Lgr5 homologues associate with Wnt receptors and mediate R-spondin signalling. Nature, 476(7360), pp.293-297.
30. Ding, L., Lin, Y., Chen, X., Wang, R., Lu, H., Wang, H., Luo, W., Lu, Z., Xia, L., Zhou, X. and Li, G., 2023. circPHF16 suppresses prostate cancer metastasis via modulating miR-581/RNF128/Wnt/β-catenin pathway. Cellular Signalling, 102, p.110557.
31. Eastman, Q. and Grosschedl, R., 1999. Regulation of LEF-1/TCF transcription factors by Wnt and other signals. Current opinion in cell biology, 11(2), pp.233-240.
32. Egger, G., Liang, G., Aparicio, A. and Jones, P.A., 2004. Epigenetics in human disease and prospects for epigenetic therapy. Nature, 429(6990), pp.457-463.
33. Fiorentino, F., Carafa, V., Favale, G., Altucci, L., Mai, A. and Rotili, D., 2021. The two-faced role of SIRT6 in cancer. Cancers, 13(5), p.1156.
34. Fire, A., Xu, S., Montgomery, M.K., Kostas, S.A., Driver, S.E. and Mello, C.C., 1998. Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans. nature, 391(6669), pp.806-811.
35. Gao, T., Li, M., Mu, G., Hou, T., Zhu, W.G. and Yang, Y., 2019. PKCζ phosphorylates SIRT6 to mediate fatty acid β-oxidation in colon cancer cells. Neoplasia, 21(1), pp.61-73.
36. Germain, N.D., Chung, W.K. and Sarmiere, P.D., 2023. RNA interference (RNAi)-based therapeutics for treatment of rare neurologic diseases. Molecular Aspects of Medicine, 91, p.101148.

37. Giles, R.H., Van Es, J.H. and Clevers, H., 2003. Caught up in a Wnt storm: Wnt signaling in cancer. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer, 1653(1), pp.1-24.
38. Glinka, A., Dolde, C., Kirsch, N., Huang, Y.L., Kazanskaya, O., Ingelfinger, D., Boutros, M., Cruciat, C.M. and Niehrs, C., 2011. LGR4 and LGR5 are Rspondin receptors mediating Wnt/βcatenin and Wnt/PCP signalling. EMBO reports, 12(10), pp.1055-1061.
39. Gomig, T.H., Jucoski, T.S., Zambalde, E.P., Azevedo, A.L., Gradia, D.F. and Ribeiro, E.M., 2021. Sirtuins and the hallmarks of cancer. In Sirtuin Biology in Cancer and Metabolic Disease (pp. 129-152). Academic Press.
40. Gu, S., Liu, F., Xie, X., Ding, M., Wang, Z., Xing, X., Xiao, T. and Sun, X., 2023. β-Sitosterol blocks the LEF-1-mediated Wnt/β-catenin pathway to inhibit proliferation of human colon cancer cells. Cellular Signalling, 104, p.110585.
41. Gupta, R., Ambasta, R.K. and Kumar, P., 2022. Multifaced role of protein deacetylase sirtuins in neurodegenerative disease. Neuroscience & Biobehavioral Reviews, 132, pp.976-997.
42. Hai, R., Yang, D., Zheng, F., Wang, W., Han, X., Bode, A.M. and Luo, X., 2022. The emerging roles of HDACs and their therapeutic implications in cancer. European Journal of Pharmacology, p.175216.
43. Hammond, S.M., 2005. Dicing and slicing: the core machinery of the RNA interference pathway. FEBS letters, 579(26), pp.5822-5829.
44. Han, J.I. and Na, K.J., 2011. Wnt/β-Catenin signaling pathway in canine skin melanoma and a possibility as a cancer model for human skin melanoma. In Melanoma in the Clinic-Diagnosis, Management and Complications of Malignancy. IntechOpen.
45. Han, Z., Liu, L., Liu, Y. and Li, S., 2014. Sirtuin SIRT6 suppresses cell proliferation through inhibition of Twist1 expression in non-small cell lung cancer. International journal of clinical and experimental pathology, 7(8), p.4774.
46. Hashibe, M., Morgenstern, H., Cui, Y., Tashkin, D.P., Zhang, Z.F., Cozen, W., Mack, T.M. and Greenland, S., 2006. Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study. Cancer Epidemiology Biomarkers & Prevention, 15(10), pp.1829-1834.
47. Hassanpour, S.H. and Dehghani, M., 2017. Review of cancer from perspective of molecular. Journal of cancer research and practice, 4(4), pp.127-129.
48. Hassler, M.R., Turanov, A.A., Alterman, J.F., Haraszti, R.A., Coles, A.H., Osborn, M.F., Echeverria, D., Nikan, M., Salomon, W.E., Roux, L. and Godinho, B.M., 2018. Comparison of partially and fully chemically-modified siRNA in conjugate-mediated delivery in vivo. Nucleic acids research, 46(5), pp.2185-2196.
49. Hoerter, J.A. and Walter, N.G., 2007. Chemical modification resolves the asymmetry of siRNA strand degradation in human blood serum. Rna, 13(11), pp.1887-1893.
50. Hou, B., Qin, L. and Huang, L., 2023. Liver cancer cells as the model for developing liver-targeted RNAi therapeutics. Biochemical and Biophysical Research Communications, 644, pp.85-94.
51. Hu, B., Zhong, L., Weng, Y., Peng, L., Huang, Y., Zhao, Y. and Liang, X.J., 2020. Therapeutic siRNA: state of the art. Signal transduction and targeted therapy, 5(1), p.101.
52. Huang, M., Xiao, X., Ji, G. and Wu, Q., 2022. Histone modifications in neurodifferentiation of embryonic stem cells. Heliyon.
53. Huang, Z., Song, S., Zhang, X., Zeng, L., Sun, A. and Ge, J., 2023. Metabolic substrates, histone modifications, and heart failure. Biochimica et Biophysica Acta (BBA)-Gene Regulatory Mechanisms, 1866(1), p.194898.

54. Hur, E.M. and Zhou, F.Q., 2010. GSK3 signalling in neural development. Nature Reviews Neuroscience, 11(8), pp.539-551.
55. Ille, F. and Sommer, L., 2005. Wnt signaling: multiple functions in neural development. Cellular and Molecular Life Sciences CMLS, 62, pp.1100-1108.
56. Imran, A., Qamar, H.Y., Qurban, A.L.I., Naeem, H., Mariam, R.I.A.Z., Saima, A.M.I.N., Kanwal, N., Fawad, A.L.I., Sabar, M.F. and Nasir, I.A., 2017. Role of molecular biology in cancer treatment: a review article. Iranian journal of public health, 46(11), p.1475.
57. Inoki, K., Ouyang, H., Zhu, T., Lindvall, C., Wang, Y., Zhang, X., Yang, Q., Bennett, C., Harada, Y., Stankunas, K. and Wang, C.Y., 2006. TSC2 integrates Wnt and energy signals via a coordinated phosphorylation by AMPK and GSK3 to regulate cell growth. Cell, 126(5), pp. 955-968.
58. Jaeger, A., Baake, J., Weiss, D.G. and Kriehuber, R., 2013. Glycogen synthase kinase-3beta regulates differentiation-induced apoptosis of human neural progenitor cells. International Journal of Developmental Neuroscience, 31(1), pp.61-68.
59. Jin, Z., Wang, B., Ren, L., Yang, J., Zheng, Z., Yao, F., Ding, R., Wang, J., He, J., Wang, W. and Nan, G., 2023. 20-Hydroxyecdysone inhibits inflammation via SIRT6-mediated NF-κB signaling in endothelial cells. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 1870(5), p.119460..
60. Kahn, M., 2014. Can we safely target the WNT pathway?. Nature reviews Drug discovery, 13(7), pp.513-532.
61. Kasteng, F., Sobocki, P., Svedman, C. and Lundkvist, J., 2007. Economic evaluations of leukemia: a review of the literature. International journal of technology assessment in health care, 23(1), pp.43-53.
62. Kim, S.E., Huang, H., Zhao, M., Zhang, X., Zhang, A., Semonov, M.V., MacDonald, B.T., Zhang, X., Abreu, J.G., Peng, L. and He, X., 2013. Wnt stabilization of β-catenin reveals principles for morphogen receptor-scaffold assemblies. Science, 340(6134), pp.867-870.
63. Kimelman, D. and Xu, W., 2006. β-Catenin destruction complex: insights and questions from a structural perspective. Oncogene, 25(57), pp.7482-7491.
64. Komiya, Y. and Habas, R., 2008. Wnt signal transduction pathways. Organogenesis, 4(2), pp.68-75.
65. Kouzarides, T., 2007. Chromatin modifications and their function. Cell, 128(4), pp.693-705.
66. Krishnamoorthy, V. and Vilwanathan, R., 2020. Silencing Sirtuin 6 induces cell cycle arrest and apoptosis in non-small cell lung cancer cell lines. Genomics, 112(5), pp.3703-3712.
67. Kugel, S., Feldman, J.L., Klein, M.A., Silberman, D.M., Sebastián, C., Mermel, C., Dobersch, S., Clark, A.R., Getz, G., Denu, J.M. and Mostoslavsky, R., 2015. Identification of and molecular basis for SIRT6 loss-of-function point mutations in cancer. Cell reports, 13(3), pp.479-488.
68. Laurent, P.A., Severin, S., Gratacap, M.P. and Payrastre, B., 2014. Class I PI 3-kinases signaling in platelet activation and thrombosis: PDK1/Akt/GSK3 axis and impact of PTEN and SHIP1. Advances in biological regulation, 54, pp.162-174.
69. Lerrer, B., Gertler, A.A. and Cohen, H.Y., 2016. The complex role of SIRT6 in carcinogenesis. Carcinogenesis, 37(2), pp.108-118.
70. Li, V.S., Ng, S.S., Boersema, P.J., Low, T.Y., Karthaus, W.R., Gerlach, J.P., Mohammed, S., Heck, A.J., Maurice, M.M., Mahmoudi, T. and Clevers, H., 2012. Wnt signaling through inhibition of β-catenin degradation in an intact Axin1 complex. Cell, 149(6), pp.1245-1256.
71. Lin, Z., Yang, H., Tan, C., Li, J., Liu, Z., Quan, Q., Kong, S., Ye, J., Gao, B. and Fang, D., 2013. USP10 antagonizes c-Myc transcriptional activation through SIRT6 stabilization to suppress tumor formation. Cell reports, 5(6), pp.1639-1649.

72. Liu, C., Li, Y., Semenov, M., Han, C., Baeg, G.H., Tan, Y., Zhang, Z., Lin, X. and He, X., 2002. Control of β-catenin phosphorylation/degradation by a dual-kinase mechanism. Cell, 108(6), pp.837-847.
73. Liu, S., Wu, J., Lu, X., Guo, C., Zheng, Q., Wang, Y., Hu, Q., Bian, S., Luo, L., Cheng, Q. and Liu, Z., 2023. Targeting CDK12 obviates the malignant phenotypes of colorectal cancer through the Wnt/β-catenin signaling pathway. Experimental Cell Research, 428(1), p.113613.
74. Liu, T., Yang, L., Mao, H., Ma, F., Wang, Y., Li, S., Li, P. and Zhan, Y., 2022. Sirtuins as novel pharmacological targets in podocyte injury and related glomerular diseases. Biomedicine & Pharmacotherapy, 155, p.113620..
75. Liu, Y., Xie, Q.R., Wang, B., Shao, J., Zhang, T., Liu, T., Huang, G. and Xia, W., 2013. Inhibition of SIRT6 in prostate cancer reduces cell viability and increases sensitivity to chemotherapeutics. Protein & cell, 4, pp.702-710.
76. Logan, C.Y. and Nusse, R., 2004. The Wnt signaling pathway in development and disease. Annu. Rev. Cell Dev. Biol., 20, pp.781-810.
77. MacDonald, B.T., Tamai, K. and He, X., 2009. Wnt/β-catenin signaling: components, mechanisms, and diseases. Developmental cell, 17(1), pp.9-26.
78. Mao, J., Wang, J., Liu, B., Pan, W., Farr, G.H., Flynn, C., Yuan, H., Takada, S., Kimelman, D., Li, L. and Wu, D., 2001. Low-density lipoprotein receptor-related protein-5 binds to Axin and regulates the canonical Wnt signaling pathway. Molecular cell, 7(4), pp.801-809.
79. Marmorstein, R. and Roth, S.Y., 2001. Histone acetyltransferases: function, structure, and catalysis. Current opinion in genetics & development, 11(2), pp.155-161.
80. Maurer, M.H., Brömme, J.O., Feldmann, R.E., Järve, A., Sabouri, F., Bürgers, H.F., Schelshorn, D.W., Krüger, C., Schneider, A. and Kuschinsky, W., 2007. Glycogen synthase kinase 3β (GSK3β) regulates differentiation and proliferation in neural stem cells from the rat subventricular zone. Journal of proteome research, 6(3), pp.1198-1208.
81. McCubrey, J.A., Rakus, D., Gizak, A., Steelman, L.S., Abrams, S.L., Lertpiriyapong, K., Fitzgerald, T.L., Yang, L.V., Montalto, G., Cervello, M. and Libra, M., 2016. Effects of mutations in Wnt/β-catenin, hedgehog, Notch and PI3K pathways on GSK-3 activity—Diverse effects on cell growth, metabolism and cancer. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 1863(12), pp.2942-2976.
82. Meng, Y., Mao, Y., Tang, Z., Qiu, X., Bajinka, O., Tan, Y. and Song, Z., 2023. Crosstalk between the lung microbiome and lung cancer. Microbial Pathogenesis, p.106062.
83. Ming, M., Han, W., Zhao, B., Sundaresan, N.R., Deng, C.X., Gupta, M.P. and He, Y.Y., 2014. SIRT6 promotes COX-2 expression and acts as an oncogene in skin cancer. Cancer research, 74(20), pp.5925-5933.
84. Moore, L.D., Le, T. and Fan, G., 2013. DNA methylation and its basic function. Neuropsychopharmacology, 38(1), pp.23-38.
85. Nicholson, G., Smith, A.V., Jónsson, F., Gústafsson, Ó., Stefánsson, K. and Donnelly, P., 2002. Assessing population differentiation and isolation from single-nucleotide polymorphism data. Journal of the Royal Statistical Society Series B: Statistical Methodology, 64(4), pp.695-715.
86. Nusse, R. and Clevers, H., 2017. Wnt/β-catenin signaling, disease, and emerging therapeutic modalities. Cell, 169(6), pp.985-999.
87. Pai, S.G., Carneiro, B.A., Mota, J.M., Costa, R., Leite, C.A., Barroso-Sousa, R., Kaplan, J.B., Chae, Y.K. and Giles, F.J., 2017. Wnt/beta-catenin pathway: modulating anticancer immune response. Journal of hematology & oncology, 10, pp.1-12.
88. Ramakrishnan, A.B., Burby, P.E., Adiga, K. and Cadigan, K.M., 2023. SOX9 and TCF transcription factors associate to mediate Wnt/β-catenin target gene activation in colorectal cancer. Journal of Biological Chemistry, 299(1).

89. Ran, L.K., Chen, Y., Zhang, Z.Z., Tao, N.N., Ren, J.H., Zhou, L., Tang, H., Chen, X., Chen, K., Li, W.Y. and Huang, A.L., 2016. SIRT6 overexpression potentiates apoptosis evasion in hepatocellular carcinoma via BCL2-associated X protein–dependent apoptotic pathway. Clinical Cancer Research, 22(13), pp.3372-3382..
90. Rossetto, D., Avvakumov, N. and Côté, J., 2012. Histone phosphorylation: a chromatin modification involved in diverse nuclear events. Epigenetics, 7(10), pp.1098-1108.
91. Sebastián, C., Zwaans, B.M., Silberman, D.M., Gymrek, M., Goren, A., Zhong, L., Ram, O., Truelove, J., Guimaraes, A.R., Toiber, D. and Cosentino, C., 2012. The histone deacetylase SIRT6 is a tumor suppressor that controls cancer metabolism. Cell, 151(6), pp.1185-1199..
92. Selvarathinam, K., Thekkumalai, M., Perumalsamy, B. and Vilwanathan, R., 2021. Design and synthesis of a novel antimicrobial peptide targeting β-catenin in human breast cancer cell lines. International Journal of Peptide Research and Therapeutics, 27, pp.1849-1860.
93. Shanbhag, S. and Ambinder, R.F., 2018. Hodgkin lymphoma: A review and update on recent progress. CA: a cancer journal for clinicians, 68(2), pp.116-132.
94. Sharma, S., Kelly, T.K. and Jones, P.A., 2010. Epigenetics in cancer. Carcinogenesis, 31(1), pp.27-36.
95. Song, J.J., Yang, M., Liu, Y., Song, J.W., Wang, J., Chi, H.J., Liu, X.Y., Zuo, K., Yang, X.C. and Zhong, J.C., 2020. MicroRNA-122 aggravates angiotensin II-mediated apoptosis and autophagy imbalance in rat aortic adventitial fibroblasts via the modulation of SIRT6-elabela-ACE2 signaling. European journal of pharmacology, 883, p.173374.
96. Song, J.J., Yang, M., Liu, Y., Song, J.W., Wang, J., Chi, H.J., Liu, X.Y., Zuo, K., Yang, X.C. and Zhong, J.C., 2020. MicroRNA-122 aggravates angiotensin II-mediated apoptosis and autophagy imbalance in rat aortic adventitial fibroblasts via the modulation of SIRT6-elabela-ACE2 signaling. European journal of pharmacology, 883, p.173374.
97. Su, Y., Fu, C., Ishikawa, S., Stella, A., Kojima, M., Shitoh, K., Schreiber, E.M., Day, B.W. and Liu, B., 2008. APC is essential for targeting phosphorylated β-catenin to the SCFβ-TrCP ubiquitin ligase. Molecular cell, 32(5), pp.652-661.
98. Subramani, P., Nagarajan, N., Mariaraj, S. and Vilwanathan, R., 2023. Knockdown of sirtuin6 positively regulates acetylation of DNMT1 to inhibit NOTCH signaling pathway in non-small cell lung cancer cell lines. Cellular Signalling, 105, p.110629.
99. Tan, Z., Zhao, L., Huang, S., Jiang, Q., Wei, Y., Wu, J.L., Zhang, Z. and Li, Y., 2023. Small peptide LINC00511-133aa encoded by LINC00511 regulates breast cancer cell invasion and stemness through the Wnt/β-catenin pathway. Molecular and Cellular Probes, 69, p.101913.
100. Ungurianu, A., Zanfirescu, A. and Margină, D., 2023. Sirtuins, resveratrol and the intertwining cellular pathways connecting them. Ageing Research Reviews, 88, p.101936.
101. Van Dyke, T. and Merlino, G., 2012. β-catenin in metastatic melanoma–the smoking gun reloaded. Pigment cell & melanoma research, 25(2), p.125.
102. Van Meter, M., Mao, Z., Gorbunova, V. and Seluanov, A., 2011. SIRT6 overexpression induces massive apoptosis in cancer cells but not in normal cells. Cell cycle, 10(18), pp.3153-3158.
103. Varunkumar, K., Anusha, C., Saranya, T., Ramalingam, V., Raja, S. and Ravikumar, V., 2020. Avicennia marina engineered nanoparticles induce apoptosis in adenocarcinoma lung cancer cell line through p53 mediated signaling pathways. Process Biochemistry, 94, pp.349-358.
104. Wang, C., Liu, L., Cheng, Y. and Shi, H., 2023. Combined GSK-3β and MEK inhibitors modulate the stemness and radiotherapy sensitivity of cervical cancer stem cells through the Wnt signaling pathway. Chemico-Biological Interactions, 380, p.110515.
105. Wang, H.U., Diao, D., Shi, Z., Zhu, X., Gao, Y., Gao, S., Liu, X., Wu, Y., Rudolph, K.L., Liu, G. and Li, T., 2016. SIRT6 controls hematopoietic stem cell homeostasis through epigenetic regulation of Wnt signaling. Cell stem cell, 18(4), pp.495-507.

106. Wang, L.H., Wu, C.F., Rajasekaran, N. and Shin, Y.K., 2019. Loss of tumor suppressor gene function in human cancer: an overview. Cellular Physiology and Biochemistry, 51(6), pp.2647-2693.
107. Wang, M., Lan, L., Yang, F., Jiang, S., Xu, H., Zhang, C., Zhou, G., Xia, H. and Xia, J., 2022. Hepatic SIRT6 deficit promotes liver tumorigenesis in the mice models. Genes & Diseases, 9(3), pp.789-796.
108. Wang, X., Shi, Z., Lu, H.Y., Kim, J.J., Bu, W., Villalobos, J.A., Perera, D.N., Jung, S.Y., Wang, T., Grimm, S.L. and Taylor, B.C., 2022. High-throughput profiling of histone post-translational modifications and chromatin modifying proteins by reverse phase protein array. Journal of Proteomics, 262, p.104596.
109. Wang, Y.P. and Lei, Q.Y., 2018. Metabolic recoding of epigenetics in cancer. Cancer Communications, 38(1), pp.1-8.
110. Willert, K., Shibamoto, S. and Nusse, R., 1999. Wnt-induced dephosphorylation of axin releases β-catenin from the axin complex. Genes & development, 13(14), pp.1768-1773.
111. Witt, O., Deubzer, H.E., Milde, T. and Oehme, I., 2009. HDAC family: What are the cancer relevant targets?. Cancer letters, 277(1), pp.8-21.
112. Yang, Q., Qin, T., An, T., Wu, H., Xu, G., Xiang, J., Lei, K., Zhang, S., Xia, J., Su, G. and Wang, D., 2023. Novel PORCN inhibitor WHN-88 targets Wnt/β-catenin pathway and prevents the growth of Wnt-driven cancers . European Journal of Pharmacology, 945, p.175628.
113. Yang, Y., Zhang, M. and Wang, Y., 2022. The roles of histone modifications in tumorigenesis and associated inhibitors in cancer therapy. Journal of the National Cancer Center..
114. Ye, X., Li, M., Hou, T., Gao, T., Zhu, W.G. and Yang, Y., 2017. Sirtuins in glucose and lipid metabolism. Oncotarget, 8(1), p.1845.
115. Zhan, T., Rindtorff, N. and Boutros, M., 2017. Wnt signaling in cancer. Oncogene, 36(11), pp.1461-1473.
116. Zhang, Q., Chen, Y., Ni, D., Huang, Z., Wei, J., Feng, L., Su, J.C., Wei, Y., Ning, S., Yang, X. and Zhao, M., 2022. Targeting a cryptic allosteric site of SIRT6 with small-molecule inhibitors that inhibit the migration of pancreatic cancer cells. Acta Pharmaceutica Sinica B, 12(2), pp.876-889.
117. Zhang, X., Chen, R., Song, L.D., Zhu,L.F. and Zhan, J.F., 2022. SIRT6 Promotes the Progression of Prostate Cancer via Regulating the Wnt/β-Catenin Signaling Pathway. Journal of Oncology, 2022.
118. Zhang, X., Li, C., Wu, Y. and Cui, P., 2023. The research progress of Wnt/β-catenin signaling pathway in colorectal cancer. Clinics and Research in Hepatology and Gastroenterology, p.102086.
119. Zhaohui, C. and Shuihua, W., 2020. Protective effects of SIRT6 against inflammation, oxidative stress, and cell apoptosis in spinal cord injury. Inflammation, 43(5), pp.1751-1758.