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ROLE OF GSK3 (GLYCOGEN SYNTHASE KINASE 3) AS TUMOR PROMOTER AND TUMOR SUPPRESSOR – A REVIEW

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Abstract

GSK3 comes under the family of protein kinase that facilitates transfer of phosphate group either onto serine or threonine amino acid residue. It exists as two isoforms in eukaryotic cells namely GSK3*α* and GSK3*β*. Deviant activity of GSK3 has been found in much human pathology which includes Diabetes mellitus, Parkinson's disease, Alzheimer's disease, bipolar depression and cancer etc. Glycogen Synthase Kinase 3 exhibit very important role in cell proliferation and its aberrant behavior act as tumor promoter. In many tumors like colon, ovarian and liver tumors GSK3 has been found over expressed. GSK3 also act as tumor suppressor by suppressing Wnt/beta-catenin pathway which ultimately leads to inactivation of oncogenes. Exhaustive literature survey indicates that GSK3 play role to treat cancer which are resistant to chemotherapy and radiotherapy. It is very important to understand the role of signaling pathways related with GSK3 to develop a lead compound for the treatment of various type of cancer.

***Keywords*:** Glycogen Synthase Kinase 3 (GSK3), Tumor, Tumor suppressor, Tumor promoter

Introduction

GSK3 was first isolated and discovered in 1980 from rabbit skeletal muscles as a regulatory kinase for the eponym; Glycogen Synthase (Embi *et al.,* 1980) (A key enzyme for the conversion of glucose into glycogen in glycogenesis). Thus GSK3 was initially found to be very important role in metabolism. GSK3 is found in almost all eukaryotic cells and it exists in two isoforms: GSK3*α* (molecular weight 51 kilodalton) and GSK3*β* (molecular weight 47 kilodalton) encoded by different genes. GSK3*α* exhibit at less number in nerves, ovary and skin and exhibit at higher level in whole blood, immature red blood cells and in glands. While GSK3 *β* exhibit at less number in immature red blood cells, dura matter and lymph node and it appears at higher level in bone marrow granulocytes (Romina *et al.*, 2017) GSK3 is a member of protein kinase family that helps in transfer of phosphate group from adenosine triphosphate either to serine or threonine amino acid residue (Mukesh *et al.*, 2016). It is also called serine/threonine protein kinase. The process of phosphorylation helps in regulation of various biological processes which includes cell signaling (Watkins *et al.*, 2014; Maurer *et al.* 2014) apoptosis (Kuemmerle *et al.*, 2002, 2005) proliferation, and cellular transport (Singh *et al.*, 2014; Song *et al.,* 2014; Yucel *et al.,* 2011) GSK3 is reported as important regulatory enzyme in various types of disorders and diseases like: metabolic disorders (Grimes *et al.*, 2001; Frame *et al.*, 2001; Cross *et al.*, 1994 (diabetes, heart diseases, and atherosclerosis), neurological disorders (Eldar *et al.,* 2011; Li *et al.,* 2014; Llorens-Maritin *et al.,* 2014) (Alzheimer's, bipolar disorder, schizophrenia, mood disorder). GSK3 also play an important role in cancer progression (McCubrey *et al.*, 2014) In some cancer cells, GSK3 show tumor suppressor function while in other cancer cells GSK3 involved in tumor progression by stabilizing the beta-catenin pathway. Shimura T. in 2011 concluded that targeting GSK3 to treat cancer cell play a important role to those cancerous cells which are resistant to chemotherapy, radiotherapy and small molecules inhibitors (Shimura *et al.*, 2011)

GSK3 alpha and GSK3 beta: GSK3 comes under the family of protein kinase and its gene family consists of two highly conserved kinases GSK3*α* and GSK3*β*. Both these kinases are similar in structure and these are not identical in their function. Moreover both of these have different specific nature regarding substrate. Both have different role in cell and the loss of one cannot be compensate by the other (James *et al.*, 2014) Presence of both isoforms of GSK are important in cell, if there is deficiency of GSK3 beta during embryogenesis may be lethal due to liver degeneration. GSK3*α* has higher molecular weight than GSK3*β*. GSK3 alpha at its amino terminus has glycine rich amino acids. Both GSK3*α* and GSK3*β* exhibit 98% identical in their kinase domain and only 36% identical in their carboxyl terminus (Doble and Woodgett, 2003) They both are found to be active in non-stimulated cells. GSK3 alpha and beta are expressed its preferences to those substrate which are already phosphorylated by some another kinase. GSK3 kinase phoshorylate more than 40 proteins which also include transcription factors (Sutherland *et al.*, 2011). Most biochemical studies reveal that GSK3 alpha act as important target in acute myeloid leukemia. These studies also express role of GSK3 alpha in drug resistant and cancer stem cells (Banerji *et al.*, 2012).

Structure of GSK3: All eukaryotic cells have two isoforms of Glycogen Synthase Kinase -3. One isoform of it (GSK3*α*) is slightly heavier than another isoform (GSK3*β*). This is due to presence of extra 63 amino acids at its N-terminal in GSK3 alpha. GSK3 beta has two major domains: at its N terminus there is β strand domain which contain 25-138 amino acid residue and at its C terminus there is α helical domain which contain 139-343 amino acid residue. (Figure 1) (ter Haar *et al.,* 2001) ATP binding site exist at the boundary of two domains (α helical and β strand) and joined with glycine rich loop and hinge portion. A activation loop also present which consist 200-226 amino acid residue. 39 amino acid residue (344-382) on the C-terminal side are present outward from the core kinase which pack itself against α helical domain while β strand domain contain seven anti parallel β strands pack itself against β-domain. This type of helix preserve in all type of kinases.

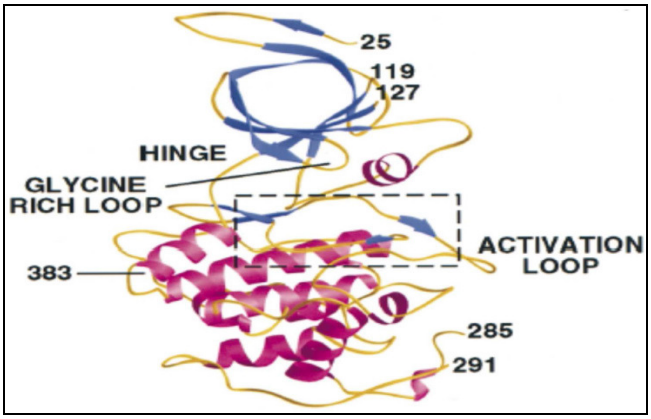


Fig 1 : Structure of GSK3 (different regions) Reproduced from ter Haar *et al.*, 2001

Studies reveal that GSK3 is a protein which is present in cytosol in active form, and it may also be found in nuclei and mitochondria. Inhibition of Serine/Threonine kinase by heavy metal results in the decreased level of active form of GSK3 in cytosol, nuclei and mitochondria (Bijur *et al.*, 2003). Apoptotic signal leads to increase the level of GSK3 several fold in mitochondria and nucleus (Bijur *et al.,* 2003)

Function of GSK3: Arg 96, Glu 97 and Lys 85 residue are important for structure alignment and functioning of GSK3. Phosphorylation at Ser 9 and at Ser 21 inactivates GSK3 beta (Woodgett *et al.*, 2001). And phosphorylation at Tyr 216 activates GSK3 beta. These two residues Ser 9 and Tyr 216 are important for catalytic activity of Glycogen Synthase Kinase 3 beta. Beta strand domain and α helical domain should be aligned into active conformation catalytically before phosphorylation. Arginines and lysines from β strand and α helical bind with phosphate group on activation loop which are necessary for proper alignment of both domains. Phosphorylation of these residues permits the substrate to bind by opening the binding groove. Serine/Threonine kinase phosphoylates different substrate with different mechanism. In some conditions, substrate phosphorylated directly and in some cases substrate requires priming by some another kinase before phosphorylation. Priming processing for phosphorylation is more efficient (100 to 1000 time) than without priming. It is supposed that mechanism of GSK3 for phosphorylation affects by two different processes. Firstly, phosphorylation at Ser 9 making a protein complex with GSK3 β. Bijur *et al.* in 2003 explain an another mechanism for GSK3 β activity via compartmentalization subcellularly (Bijur *et al.,* 2003, Davis *et al.,* 2011).

Molecular mechanism of GSK3 as tumor promoter: Cancerous cells which are resistant to chemotherapy, radiotherapy and target therapy, abnormal expression of GSK3 has been found in that cells (Shimura, 2011). It has been reported that GSK3 has very important role in cell proliferation and it's abnormal behavior in cells may produce tumor (Luo *et al.,* 2009). So, it act as tumor promoter. In colon, pancreas, liver and ovary cancer, aberrant expression of GSK3 has been noticed (Shakoori *et al.*, 2005; Ougolkov *et al.*, 2005). Current studies shows that GSK3 activity has been involved in cancer stem cells and it is called as cancer initiating cells (CICs) (McCubrey *et al.*, 2013). As CICs are normally drug resistant that's why these cells share various properties with drug resistant cells and proliferate slowly. If level of GSK3 in pancreatic cancer cells get suppress it may lead to inhibition of pancreatic cancer growth (Zhou *et al.* 2012). Over expression of GSK3 may activate oncogenes which lead to growth of cancerous cells. We can cure these cancerous cells by suppressing the level of GSK3 in these cells with the help of GSK3 inhibitors and can treat those cells in which GSK3 act as tumor promoter (McCubrey *et al.* 2014).

Molecular mechanism of GSK3 as tumor suppressor: GSK3 also act as tumor suppressor. The Wnt protein family responsible for Wnt pathway (A pathway that helps in transfer of signals from outside to inside of the cell with the help of cell surface receptor). There are some Wnt protein family members in human are present who are responsible for stimulation of growth in cells and some are responsible for inhibition of proliferation. Wnt protein also responsible for Wnt/ β-catenin pathway which leads to activation of T cell factor / Lymphoid enhancer factor-I (TCF)/LEF-I genes. Mutation in β-catenin at certain residue acts as oncogenes and suppresses the phosphorylation process by GSK3 and CKI. β-catenin is transactivator which binds with (TCF)/LEFs and help in transcription of gene. Wnt/β-catenin pathway can be suppressed by GSK3 by phosphorylation of beta-catenin which results into degradation of beta-catenin which is dependent on ubiquitin/proteasome (Farago *et al.* 2005). GSK3 beta mutant is introduced as kinase-inactive (KI) which act as inhibitor of GSK3 beta protein who is responsible for stimulation of tumorgenesis and signaling of Wnt. Increased level of kinase dead (KD) GSK3 beta, supposed to act as inhibitor of Wnt signaling, results into promotion of tumor of breast and skin (Ma C, Wang *et al.,* 2007). In some cases it is found that increased level of GSK3 beta mutant may lead to increased sensitivity of cancerous cells toward chemotherapy and cell cycle arrest also increased and ultimately reduction in growth of breast cancer (Dong *et al.,* 2005; Dolcetti *et al.*, 2008; Wang Y *et al.,* 2006). Here we come to know the opposing behavior of GSK3 on tumor growth. There may be a fine balance in the nature of GSK3 to act as tumor promoter or suppressor. Presence of KI GSK3 beta in breast cells stabilizes the beta-catenin protein complex and act as promoter of breast cancer development.

Patent Mapping on GSK3 inhibitor as anti cancer agents: Table 1 shows GSK3 inhibitor as anti cancer agents patented from 2016-2019 (from 2016 through present date). Data is collected from united state patent site and European Union patent site.

Heterocyclic compounds as GSK3 inhibitors: Heterocyclic compounds have been reported as anti cancer agents by inhibiting GSK3. Table 2 represents reported heterocyclic compounds as GSK3 inhibitor.

Clinical investigation of GSK3 inhibitors: Out of many synthesized GSK3 inhibitors, very few reached for clinical trials studies. Here, we have a table for GSK3 inhibitor as anti cancer agents listed on clinicaltrials.gov which include 9-ING-41 and LY2090314. Table 3 summarized it.

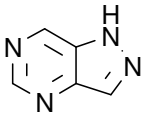
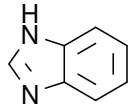
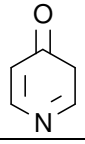
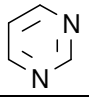
Conclusion

GSK3 is responsible for various types of activities in cell and have specific role in proliferation of cells. So, by understanding the cellular pathway and with the help of modulation in GSK3 activity may lead to effective approach for cancer therapy.

Table 1 : Patent Mapping on GSK3 inhibitor as anti cancer in last three years (2016-2019):

S. No.	Year	Title	Patent No. /Patent Office	Inventors
1.	April 23, 2019	Compositions and methods for treating cancers	10,266,505/ USPTO	Edderkaoui; Mouad (Los Angeles, CA), Murali; Ramachandran (Swarthmore, PA), Pandol; Stephen (Los Angeles, CA)
2.	February 12, 2019	Solubilized compositions for controlled proliferation of stem cells / generating inner ear hair cells using GSK3 inhibitors: I	10,201,540/ USPTO	Loose; Christopher (Winchester, MA), McLean; Will (North Haven, CT), Harrison; Megan (Middletown, CT), Jirousek; Michael R. (Chardon, OH)
3.	November 27, 2018	Kinase inhibitors and methods of use thereof	10,137,122/ USPTO	Wagner; Florence Fevrier (Ashland, MA), Pan; Jennifer Q. (Acton, MA), Dandapani; Sivaraman (Wakefield, MA), Germain; Andrew (Somerville, MA), Holson; Edward(Newton, MA), Munoz; Benito (Newtonville, MA), Nag; Partha P. (Somerville, MA), Lewis; Michael C. (Dedham, MA), Haggarty; Stephen J. (Gloucester, MA), Bishop; Joshua A. (Southborough, MA), Stegmaier; Kimberly (Jamaica Plain, MA), Weiwer; Michel (Cambridge, MA), Banerji; Versha (Winnipeg, CA)
4.	October 23, 2018	Directed differentiation and maturation of pluripotent cells into hepatocyte like cells by modulation of Wnt-signalling pathway	10,106,777/ USPTO	Brolen; Gabriella (Gothenburg, SE), Edsbagge; Josefina (Torslanda, SE)
5.	July 10, 2018	Solubilized compositions for controlled proliferation of stem cells / generating inner ear hair cells using GSK3 inhibitors: III	10,016,507/ USPTO	Loose; Christopher (Winchester, MA), McLean; Will (North Haven, CT), Harrison; Megan (Middletown, CT), Jirousek; Michael R. (Chardon, OH)
6.	February 23, 2016	Uses of chemicals to modulate GSK-3 signaling for treatment of bipolar disorder and other brain disorders	9,265,764/ USPTO	Haggarty; Stephen J. (Dorchester, MA), Fass; Daniel (Winchester, MA), Pan; Jennifer (Acton, MA), Ketterman; Josh (Cambridge, MA), Holson; Edward (Newton Highlands, MA), Petryshen; Tracey Lynn (Cambridge, MA), Lewis; Michael C. (Boston, MA)
7.	September, 07, 2017	Solubilized compositions for controlled proliferation of stem cells / generating inner ear hair cells using a gsk3 inhibitor: iv	US2017252450 (A1)/EPO	[Us]; Harrison [Us]; Jirousek Michael R [Us] Loose Christopher [Us]; Mclean Will Megan

Table 2 : Heterocyclic compounds reported as GSK3 inhibitors :

ATP-Competitive GSK3 Inhibitor	Pyrazolopyrimidine	
	Benzimidazole	
	Pyridinones	
	Pyrimidine	

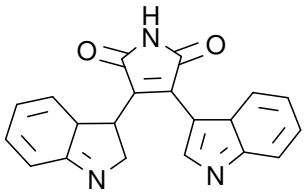
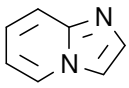
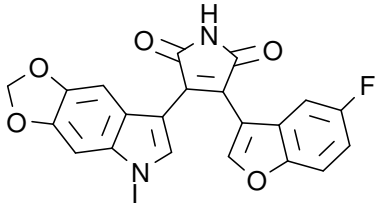
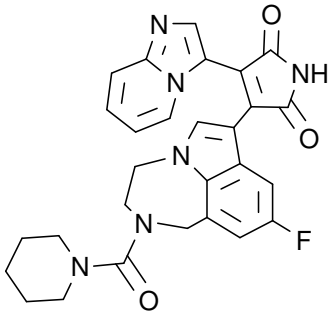
	Indolylmaleimide	
	Imidazopyrimidine	
	Oxadiazoles	
	Pyrazines	
Non-ATP-Competitive GSK3 Inhibitor	Thiadiazoles	

Table 3 : GSK3 inhibitors as anti cancer agents under Clinical Investigation:

Compound	Structure of GSK3 inhibitor clinically tested	Type of disease(s)	Actual study start date	Last update posted
9-ING-41		Malignancies, Lymphoma, Pancreatic cancer and solid tumor	January 4, 2019	May 21, 2019 (Recruiting)
LY2090314		Pancreatic cancer, Leukemia	March,2013	January,15,2019 (Terminated)

References

Banerji, V.; Frumm, S.M.; Ross, K.N.; Li, L.S.; Schinzel, A.C. and Hahn, C.K. (2012). The intersection of genetic and chemical genomic screens identifies GSK-3α as a target in human acute myeloid leukemia. The Journal of clinical investigation, 122(3): 935-947.

Bijur, G.N. and Jope, R.S. (2003). Glycogen synthase kinase-3β is highly activated in nuclei and mitochondria. Neuroreport, 14(18): 2415-2419.

Bijur, G.N. and Jope, R.S. (2001). Proapoptotic stimuli induce nuclear accumulation of glycogen synthase kinase-3β. Journal of Biological Chemistry, 276(40): 37436-37442.

Cross, D.A.; Alessi, D.R.; Vandenheede, J.R.; McDowell, H.E.; Hundal, H.S. and Cohen, P. (1994). The inhibition of glycogen synthase kinase-3 by insulin or insulin-like growth factor 1 in the rat skeletal muscle cell line L6 is blocked by wortmannin, but not by rapamycin: evidence that wortmannin blocks activation of the mitogen-activated protein kinase pathway in L6 cells between Ras and Raf. Biochemical Journal, 303(1): 21-26.

Dal Col, J. and Dolcetti, R. (2008). GSK-3b inhibition: At the crossroad between Akt and mTOR constitutive activation to enhance cyclin D1 protein stability in mantle cell lymphoma. Cell Cycle, 7(18): 2813-2816.

Davis, M.I.; Hunt, J.P.; Herrgard, S.; Ciceri, P.; Wodicka, L.M.; Pallares, G. and Zarrinkar, P.P. (2011). Comprehensive analysis of kinase inhibitor selectivity. Nature biotechnology, 29(11):1046.

Diehl, J.A.; Cheng, M.; Roussel, M.F. and Sherr, C.J. (1998). Glycogen synthase kinase-3β regulates cyclin D1 proteolysis and subcellular localization. Genes & development, 12(22): 3499-3511.

Doble, B.W. and Woodgett, J.R. (2003). GSK-3: tricks of the trade for a multi-tasking kinase. Journal of cell science, 116(7): 1175-1186.

Dong, J.; Peng, J.; Zhang, H.; Mondesire, W.H.; Jian, W.; Mills, G.B. and Meric-Bernstam, F. (2005). Role of glycogen synthase kinase 3β in rapamycin-mediated cell cycle regulation and chemosensitivity. Cancer research, 65(5): 1961-1972.

Eldar-Finkelman, H. and Martinez, A. (2011). GSK-3 inhibitors: preclinical and clinical focus on CNS. Frontiers in molecular neuroscience, 4: 32-37.

Embi, N.; Rylatt, D.B. and Cohen, P. (1980). Glycogen Synthase Kinase-3from Rabbit Skeletal Muscle: Separation from Cyclic‐AMP‐Dependent Protein Kinase and Phosphorylase Kinase. European Journal of biochemistry, 107(2): 519-527.

Farago, M.; Dominguez, I.; Landesman-Bollag; Xu, E.X.; Rosner, A.; Cardiff, R.D. and Seldin, D.C. (2005). Kinase-inactive glycogen synthase kinase 3β promotes Wnt signaling and mammary tumorigenesis. Cancer research, 65(13): 5792-5801.

Frame, S. and Cohen, P. (2001). GSK3 takes centre stage more than 20 years after its discovery. Biochemical Journal, 359(1): 1-16.

Grimes, C.A. and Jope, R.S. (2001). The multifaceted roles of glycogen synthase kinase 3β in cellular signaling. Progress in neurobiology, 65(4): 391-426.

Hoshi, M.; Takashima, A.; Noguchi, K.; Murayama, M.; Sato, M.; Kondo, S. and Imahori, K. (1996). Regulation of mitochondrial pyruvate dehydrogenase activity by tau protein kinase I/glycogen synthase kinase 3beta in brain. Proceedings of the National Academy of Sciences, 93(7): 2719-2723.

McCubrey, J.A.; Steelman, L.S.; Bertrand, F.E.; Davis, N.M.; Sokolosky, M.; Abrams, S.L.; Maestro, R. (2014). GSK-3 as potential target for therapeutic intervention in cancer. Oncotarget, 5(10): 2881.

Kuemmerle, J. (2002). Endogenous IGF-I promotes survival of human intestinal smooth muscle cells by Akt-dependent inhibition of GSK-3 beta activity. In Molecular Biology Of The Cell, 13: 165A-165A.

Kuemmerle, J.F. (2002). Endogenous IGF-I inhibits GSK-3 beta activity and promotes cell survival. In Gastroenterology 122, 4: A380-A380.

Kuemmerle, J.F. (2005). Endogenous IGF-I protects human intestinal smooth muscle cells from apoptosis by regulation of GSK-3β activity. American Journal of Physiology-Gastrointestinal and Liver Physiology, 288(1): G101-G110.

Li, D.W.; Liu, Z.Q.; Chen, W.; Yao, M. and Li, G.R. (2014). Association of glycogen synthase kinase-3β with Parkinson's disease. Molecular medicine reports, 9(6): 2043-2050.

Llorens-Marítin, M.; Jurado, J.; Hernández, F. and Ávila, J. (2014). GSK-3β, a pivotal kinase in Alzheimer disease. Frontiers in molecular neuroscience, 7: 46-53

Llorens-Martín, M.; Blazquez-Llorca, L.; Benavides-Piccione, R.; Rabano, A.; Hernandez, F.; Avila, J. and DeFelipe, J. (2014). Selective alterations of neurons and circuits related to early memory loss in Alzheimer's disease. Frontiers in neuroanatomy, 8: 38-42

Luo, J. (2009). Glycogen synthase kinase 3β (GSK3β) in tumorigenesis and cancer chemotherapy. Cancer letters, 273(2): 194-200.

Ma, C.; Wang, J.; Gao, Y.; Gao, T.W.; Chen, G.; Bower, K.A. and Luo, J. (2007). The role of glycogen synthase kinase 3β in the transformation of epidermal cells. Cancer research, 67(16): 7756-7764.

Maurer, U.; Preiss, F.; Brauns-Schubert, P.; Schlicher, L. and Charvet, C. (2014). GSK-3–at the crossroads of cell death and survival. J Cell Sci, 127(7): 1369-1378.

McCubrey, J.A.; Steelman, L.S.; Bertrand, F.E.; Davis, N.M.; Sokolosky, M.; Abrams, S.L.; Maestro, R. (2014). GSK-3 as potential target for therapeutic intervention in cancer. Oncotarget, 5(10): 2881.

McCubrey, J.A.; Steelman, L.S.; Bertrand, F.E.; Davis, N.M.; Abrams, S.L.; Montalto, G.; Basecke, J. (2014). Multifaceted roles of GSK-3 and Wnt/β-catenin in hematopoiesis and leukemogenesis: opportunities for therapeutic intervention. Leukemia, 28(1): 15-23

Pandey, M.K. and DeGrado, T.R. (2016). Glycogen synthase kinase-3 (GSK-3)-targeted therapy and imaging. Theranostics, 6(4): 571.

Ougolkov, A.V.; Fernandez-Zapico, M.E.; Savoy, D.N.; Urrutia, R.A. and Billadeau, D.D. (2005). Glycogen synthase kinase-3β participates in nuclear factor κB–mediated gene transcription and cell survival in pancreatic cancer cells. Cancer research, 65(6): 2076-2081.

Mancinelli, R.; Carpino, G.; Petrungaro, S.; Mammola, C.L.; Tomaipitinca, L.; Filippini, A.; Giampietri, C. (2017). Multifaceted roles of GSK-3 in cancer and autophagy-related diseases. Oxidative medicine and cellular longevity.

Mai, W.; Miyashita, K.; Shakoori, A.; Zhang, B.; Yu, Z.W.; Takahashi, Y. and Minamoto, T. (2006). Detection of active fraction of glycogen synthase kinase 3β in cancer cells by nonradioisotopic in vitro kinase assay. Oncology, 71(3-4): 297-305.

Shimura, T. (2011). Acquired radioresistance of cancer and the AKT/GSK3β/cyclin D1 overexpression cycle. Journal of radiation research, 52(5): 539-544.

Singh, V.; Lin, R.; Yang, J.; Cha, B.; Sarker, R.; Tse, C.M. and Donowitz, M. (2014). AKT and GSK-3 Are Necessary for Direct Ezrin Binding to NHE3 as Part of a C-terminal Stimulatory Complex Role Of A Novel Ser-Rich Nhe3 C-Terminal Motif In Nhe3 Activity and Trafficking. Journal of Biological Chemistry, 289(9): 5449-5461.

Song, J.; McColl, J.; Camp, E.; Kennerley, N.; Mok, G.F.; McCormick, D. and Münsterberg, A.E. (2014). Smad1 transcription factor integrates BMP2 and Wnt3a signals in migrating cardiac progenitor cells. Proceedings of the National Academy of Sciences, 111(20): 7337-7342.

Sutherland, C. (2011). What are the bona fide GSK3 substrates? International journal of Alzheimer's Disease, 2011(5): 56-62

ter Haar, E.; Coll, J.T.; Austen, D.A.; Hsiao, H.M.; Swenson, L. and Jain, J. (2001). Structure of GSK3β reveals a

primed phosphorylation mechanism. Nature Structural & Molecular Biology, 8(7): 593.

Thomas, G.M.; Frame, S.; Goedert, M.; Nathke, I.; Polakis, P. and Cohen, P. (1999). A GSK3 ‐ binding peptide from FRAT1 selectively inhibits the GSK3 ‐ catalysed phosphorylation of Axin and β ‐ catenin. FEBS letters, 458(2): 247-251.

Watkins, C.C.; Sawa, A. and Pomper, M.G. (2014). Glia and immune cell signaling in bipolar disorder: insights from neuropharmacology and molecular imaging to clinical application. Translational psychiatry, 4(1): e350.

Woodgett, J.R. (2001). Judging a protein by more than its name: GSK-3. Sci. STKE, 2001(100): re12-re12.

Yucel, G. and Oro, A.E. (2011). Cell Migration: GSK3β Steers the Cytoskeleton's Tip. Cell, 144(3): 319-321.

Zhou, W.; Wang, L.; Gou, S.M.; Wang, T.L.; Zhang, M.; Liu, T. and Wang, C.Y. (2012). ShRNA silencing glycogen synthase kinase-3 beta inhibits tumor growth and angiogenesis in pancreatic cancer. Cancer letters, 316(2): 178-186.