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The Role of Glycogen Synthase Kinase 3 β (GSK3 β) in Tumorigenesis and Cancer Chemotherapy

Jia Luo

Department of Microbiology, Immunology & Cell Biology, West Virginia University School of Medicine, Robert C. Byrd Health Sciences Center, Morgantown, WV 26506. Tel: 304-293-7208; Fax: 304-293-7823

Jia Luo: jluo@hsc.wvu.edu

Abstract

Glycogen synthase kinase 3 β (GSK3 β), a multifunctional serine/threonine kinase found in all eukaryotes, had been initially identified as a key regulator of insulin-dependent glycogen synthesis. It is now known that GSK3 β functions in diverse cellular processes including proliferation, differentiation, motility and survival. Aberrant regulation of GSK3 β has been implicated in a range of human pathologies including non-insulin-dependent diabetes mellitus, cardiovascular disease, some neurodegenerative diseases, and bipolar disorder. As a consequence, the therapeutic potential of GSK3 β inhibitors has become an important area of investigation. However, GSK3 β also participates in neoplastic transformation and tumor development. The role of GSK3 β in tumorigenesis and cancer progression remains controversial; it may function as a “tumor suppressor” for certain types of tumors, but promotes growth and development for some others. GSK3 β also mediates drug sensitivity/resistance in cancer chemotherapy. Therefore, although GSK3 β is an attractive therapeutic target for a number of human diseases, its potential impact on tumorigenesis and cancer chemotherapy needs to be carefully evaluated. This mini-review discusses the role of GSK3 β in tumorigenesis/cancer progression as well as its modulation of cancer chemotherapy.

Keywords

Apoptosis; carcinogenesis; cell cycle; chemotherapy; neoplastic transformation

Introduction

Glycogen synthase kinase 3 (GSK3) has become one of the most attractive therapeutic targets for the treatment of diabetes, inflammation, and multiple neurological diseases, including Alzheimer's, stroke and bipolar disorders [1,2]. GSK3 is a multifunctional serine/threonine kinase, originally found in mammals, and homologues have been found in all eukaryotes [3,4]. GSK3 was first identified as a critical mediator in glycogen metabolism

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and insulin signaling. It is now known that GSK3 is an important component of diverse signaling pathways involved in the regulation of cell fate, protein synthesis, glycogen metabolism, cell mobility, proliferation and survival [3,4]. There are two mammalian GSK3 isoforms encoded by distinct genes: *GSK3 α* and *GSK3 β* . The α and β isoforms share 85% identity [3]. The two genes map to human chromosomes 19q13.2 (*GSK3 α*) and 3q13.3 (*GSK3 β*). An elegant historical synopsis of the cloning and characterization of GSK3 genes has been reviewed by Plyte et al. [5]. Despite a high degree of similarity and functional overlap, these isoforms are not functionally identical and redundant. The signaling pathway and protein function of GSK3 β are much better investigated. This review will focus on the action of GSK3 β . Due to its diverse cellular functions, the pathways in which GSK3 β acts as a key regulator, when dysregulated, have been implicated in the development of a number of human diseases such as diabetes, cardiovascular disease, some neurodegenerative diseases and bipolar disorder [3,4,6]. The dysregulation of GSK3 β has also been implicated in tumorigenesis and cancer progression [7–10]. However, the mechanisms underlying GSK3 β regulation of neoplastic transformation and tumor development are unclear; it remains controversial whether GSK3 β is a “tumor suppressor” or “tumor promoter.” This review will discuss the evidence that supports GSK3 β as both “tumor suppressor” and “tumor promoter,” and the underlying mechanisms. In addition, the role of GSK3 β in cancer chemotherapy will be briefly reviewed.

1. Regulation of GSK3 β and its substrates

Unlike most protein kinases, GSK3 β is constitutively active in resting cells and undergoes a rapid and transient inhibition in response to a number of external signals [3,4]. GSK3 β activity is regulated by site-specific phosphorylation. Full activity of GSK3 β generally requires phosphorylation at tyrosine (Tyr216), and conversely, phosphorylation at serine (Ser9) inhibits GSK3 β activity. GSK3 β is subjected to multiple regulatory mechanisms and phosphorylation of Ser9 is probably the most important regulatory mechanism. Several kinases are capable of mediating this modification, including p70 S6 kinase, extracellular signal-regulated kinases (ERKs), p90Rsk (also called MAPKAP kinase-1), protein kinase B (also called Akt), certain isoforms of protein kinase C (PKC), and cyclic AMP-dependent protein kinase (protein kinase A) [3,4]. In opposition to the inhibitory modulation of GSK3 β that occurs by serine phosphorylation, tyrosine phosphorylation of GSK3 β increases the enzyme's activity. Studies of tyrosine phosphorylation of GSK3 β are relatively sparse and information about this regulatory mechanism is fragmentary. Stimulation of pGSK3 β (Tyr216) is reported to be mediated by alterations in intracellular calcium levels and a calcium-dependent tyrosine kinase, proline-rich tyrosine kinase 2 (PYK2), or by Fyn, a member of the Src tyrosine family [11–13]. pGSK3 β (Tyr216) is also subject to the regulation of mitogen-activated protein kinase kinase (MEK1/2) [14].

Although phosphorylation of GSK3 β is the most widely studied mechanism of regulation, a recent study indicated GSK3 β can be activated without apparent changes in pGSK3 β (Tyr216) and pGSK3 β (Ser9) [15]. Protein complex formation and intracellular localization also have important regulatory influences on GSK3 β activity. Such complex regulatory mechanisms are necessary for an enzyme that modifies multiple and diverse

substrates, including metabolic, signaling, and structural proteins and transcription factors. These regulatory mechanisms have been elegantly reviewed [3,4].

GSK3 β is active in resting cells and is inactivated during cellular responses. Its substrates therefore tend to be dephosphorylated; most of these substrates are functionally inhibited by GSK3 β . GSK3 β appears to act as a general repressor, keeping its targets switched off or inaccessible under resting conditions. More than 40 proteins are substrates of GSK3 β , and these proteins have roles in a wide spectrum of cellular processes, including glycogen metabolism, transcription, translation, cytoskeletal regulation, cell differentiation, proliferation and apoptosis [4,8]. A number of substrates that have a close association with tumorigenesis and cancer development are briefly discussed here. One of the most well-known substrates of GSK3 β is β -catenin, and GSK3 β is an important regulator of the Wnt/ β -catenin signaling pathway. The Wnts are a family of secreted, cysteine-rich and glycosylated protein ligands. Wnt signal transduction ultimately results in the activation of genes regulated by the T-cell factor (TCF)/lymphoid enhancer factor (LEF) family of transcription factors and is implicated in tumorigenesis and malignancy [16]. In the absence of Wnt signals, free cytoplasmic β -catenin is incorporated into a cytoplasmic complex that includes Axin, GSK3 β and adenomatous polyposis coli (APC). This enables GSK3 β to phosphorylate β -catenin and results in ubiquitin-mediated degradation of β -catenin. Wnt signaling inactivates GSK3 β and prevents it from phosphorylating β -catenin, thus stabilizing β -catenin in the cytoplasm. As β -catenin accumulates, it translocates into the nucleus where it binds to TCF/LEF and dramatically increases their transcriptional activity. Genes up-regulated by TCF/LEF include proto-oncogenes, such as *c-myc* and *cyclin-D1*, and genes regulating cell invasion/migration, such as *MMP-7*.

In addition to β -catenin, many proto-oncogenic or tumor suppressing transcription and translation factors are substrates of GSK3 β . For example, tumor suppressor transcription factor p53 is a target of GSK3 β . GSK3 β regulates the levels as well as intracellular localization of p53 [6]. GSK3 β forms a complex with nuclear p53 to promote p53-induced apoptosis. GSK3 β directly modulates the activity of transcription factors, activator protein 1 (AP-1) and nuclear factor- κ B (NF- κ B) [4,8,9]. Both transcription factors play a critical role in neoplastic transformation and tumor development.

2. Involvement of GSK3 β in tumorigenesis and cancer progression

Since GSK3 β negatively regulates many proto-oncogenic proteins and cell cycle regulators, one would predict that GSK3 β may suppress tumorigenesis. Several studies indeed support that GSK3 β functions as a “tumor suppressor” and represses cellular neoplastic transformation and tumor development. GSK3 β has been reported to be a negative regulator of skin tumorigenesis. In a mouse epidermal multistage carcinogenesis model, a dramatic increase in pGSK3 β (Ser9) (inactive form of GSK3 β) is observed in late papillomas and squamous cell carcinomas, while a significant decrease in pGSK3 β (Tyr216) (active form of GSK3 β) is detected in squamous cell carcinoma samples compared to normal tissues; this indicates an inactivation of GSK3 β occurs during mouse skin carcinogenesis [17]. A recent study examining human skin cancer tissues reveals a strong pGSK3 β (Ser9) expression in squamous cell carcinoma cells [18].

We have observed a dramatic decrease of GSK3 β expression in human non-melanoma skin cancers (cutaneous squamous cell carcinomas and basal cell carcinomas) compared to adjacent normal keratinocytes [19]. In addition, the immunostaining for GSK3 β in keratinocytes of patients with cutaneous squamous cell carcinomas or basal cell carcinomas is generally weaker than keratinocytes of age and sex-matched normal subjects. The expression of pGSK3 β (Tyr216) in skin specimens of cancer patients and control subjects is negative. The tumor suppressive effect of GSK3 β is further established using an *in vitro* model of neoplastic transformation, mouse epidermal JB6 P+ cells. In response to epidermal growth factor (EGF) or 12-*O*-tetradecanoylphorbol 13-acetate (TPA), the promotion sensitive JB6 P+ cells initiate neoplastic transformation, whereas the promotion resistant JB6 P- cells do not. Consistent with the observations in human skin tissues, the expression levels of GSK3 β in JB6 cells are correlated to the stage or potential of cell transformation. Transformation-resistant JB6 P- cells express the highest levels of GSK3 β while the levels of GSK3 β in transformation-sensitive JB6 P+ cells are intermediate; on the other hand, JB7 cells, the transformed derivatives of JB6, have the least amount of GSK3 β [19]. Tumor promoters EGF and TPA inactivate GSK3 β by inducing strong phosphorylation of GSK3 β at Ser9 in transformation-sensitive JB6 P+ cells. Transformation-resistant JB6 P- cells are insensitive to this negative regulation of GSK3 β . The involvement of GSK3 β in skin tumorigenesis is further demonstrated by modulation of GSK3 β activity in JB6 P+ cells. Overexpression of wild type GSK3 β or constitutively active S9A mutant GSK3 β inhibits *in vitro* cell transformation, as well as *in vivo* tumorigenicity in nude mice. In contrast, overexpression of a kinase deficient K85R GSK3 β or treatment with GSK3 β inhibitors drastically promotes *in vitro* cell transformation and greatly enhances *in vivo* tumorigenicity. Together, these results indicate that GSK3 β participates in neoplastic transformation and tumor development during skin carcinogenesis, and down-regulation or inactivation of GSK3 β is oncogenic for epidermal cells.

The negative regulation of GSK3 β on tumorigenesis also appears true for mammary tumors. Farago et al. [20] show that antagonizing the endogenous activity of GSK3 β by tissue-specific expression of a kinase-inactive GSK3 β (dominant negative) in mouse mammary glands promotes mammary tumorigenesis. The promotion of mammary tumorigenesis by this kinase-inactive GSK3 β is accompanied by the accumulation of β -catenin and cyclin D1, suggesting that the promotion is mediated by the dysregulation of the Wnt/ β -catenin pathway. Conversely, activation of GSK3 β suppresses mammary tumorigenesis. Activation of GSK3 β by adiponectin induces apoptosis and cell cycle arrest in MDAMB-231 human breast cancer cells, which is accompanied by suppressed intracellular accumulation of β -catenin and its nuclear activities and reduced cyclin D1 levels [21]. Moreover, *in vivo* activation of GSK3 β by supplementation of recombinant adiponectin or adenovirus-mediated overexpression of adiponectin substantially reduces the mammary tumorigenicity of MDAMB-231 cells in nude mice [21]. Similarly, activation of GSK3 β by rapamycin also induces down-regulation of cyclin D1 expression, cell cycle arrest and the inhibition of anchorage-dependent growth in breast cancer cells [22]. Consistent with these findings, expression of constitutively active GSK3 β (S9A mutant) causes apoptosis of human breast cancer cells; moreover, injection of the liposome complex with GSK3 β to tumor-bearing mice significantly inhibits mammary tumor growth [23]. Taken together, GSK3 β may

function as a “tumor suppressor” for mammary tumors, whereas antagonism of GSK3 β activity is oncogenic for mammary epithelial cells.

In addition to participation in neoplastic transformation and tumor growth, GSK3 β is also proposed to be involved in cancer cell metastasis [24,25]. The increased motility and invasiveness of cancer cells in the first phase of metastasis are reminiscent of epithelial-mesenchymal transition (EMT) during embryonic development [24–26]. Epithelial cells usually exist as sheets of immotile, tightly packed, well-coupled, polarized cells with distinct apical, basal and lateral surfaces. These cells can dramatically alter their morphology to become motile, fibroblast-like mesenchymal cells in EMT. The essential features of EMT are the disruption of intercellular contacts and the enhancement of cell motility, thereby leading to the release of cells from the parent epithelial tissue. The resulting mesenchymal-like phenotype is suitable for migration and, thus, for tumor invasion and dissemination, allowing metastatic progression to proceed [25,26]. GSK3 β plays an important role in EMT most likely through the modulation of Wnt, Hedgehog and Snail (a zinc-finger transcriptional repressor) pathways; inhibition of GSK3 β promotes the development of EMT [24–26]. Cyclooxygenase-2 (COX-2) has been the best documented in the regulation of various aspects of tumor progression and metastasis. COX-2 is an independent prognostic factor in gastric cancer. Inhibition of GSK3 β stimulates COX-2 expression in gastric cancer cells through increasing COX-2 mRNA stability [27], indicating GSK3 β is a negative regulator of COX-2. GSK3 β regulation of COX-2 in tumor cells may affect tumor development and metastasis.

In contrast to its tumor suppressive role, some studies suggest that GSK3 β may actually promote tumorigenesis and cancer development. GSK3 β protein overexpression has been found in human ovarian, colon and pancreatic carcinomas [9]. Higher levels of GSK3 β are observed in liver tumors than in normal liver tissues in a mouse model of hepatic carcinogenesis [28]. Consistent with its high expression in ovarian tumors, GSK3 β is reported to positively regulate the proliferation and survival of human ovarian cancer cells both *in vitro* and *in vivo* [29]. Inhibition of GSK3 β activity by pharmacological inhibitors suppresses proliferation of the ovarian cancer cells *in vitro* and prevents the formation of tumors in nude mice generated by the inoculation of human ovarian cancer cells. Conversely, overexpressing a constitutively active form of GSK3 β increases cyclin D1 expression and induces cell cycle progression of ovarian cancer cells [29].

Levels of GSK3 β expression and amounts of its active form in colon cancer cell lines and colorectal cancer patients are higher than in their normal counterparts [2,30]. Depletion of GSK3 β by RNA interference or pharmacological inhibition of GSK3 β kinase activity results in decreased survival and proliferation of colon cancer cells *in vitro* and *in vivo* [30,31]. Higher expression of active GSK3 β is also observed in pancreatic cancer cells [32]. Nuclear accumulation of active GSK3 β is found in some pancreatic cancer cell lines and human pancreatic adenocarcinomas [33]. GSK3 β nuclear accumulation is significantly correlated with human pancreatic cancer dedifferentiation. Inhibition of GSK3 β decreases pancreatic cancer cell survival and proliferation, and arrests pancreatic tumor growth in established tumor xenografts [32,33]. Other studies indicate that GSK3 β activation enhances the proliferation and survival of hepatocellular, prostate and lymphocytic leukemia cancer cells

[34–37]. Additionally, inactivation of GSK3 β is associated with growth suppression in medullary thyroid cancer cells [38]. Therefore, GSK3 β may be a “tumor promoter” for certain types of tumors. For this reason, inhibition of GSK3 β has been proposed to be an attractive therapeutic approach for the treatment of colon and pancreatic cancers [9,39].

3. Involvement of GSK3 β in cancer chemotherapy

GSK3 β also regulates cellular sensitivity/resistance to cancer chemotherapy. Increased expression of pGSK3 β (Ser9) is observed in cisplatin-resistant ovarian cancer cell line (CP70) compared to its cisplatin-sensitive counterpart A2780 cells [40]. High pGSK3 β (Ser9) levels in CP70 cells suggest that suppressed GSK3 β activity may account for their resistance to cisplatin. Inhibition of GSK3 β by treatment with lithium significantly reduces cisplatin-induced apoptosis and raises the IC₅₀ of cisplatin for ovarian cancer cells. Conversely, reactivation of GSK3 β by expressing a constitutively active S9A GSK3 β mutant reverses cisplatin resistance and enhances sensitivity of ovarian cancer cells to cisplatin. Thus, GSK3 β inhibition may confer resistance to cisplatin in ovarian carcinomas. Similarly, treatment with lithium causes resistance of hepatoma cells to two chemotherapy drugs, etoposide and camptothecin [41]. GSK3 β reactivation by exogenous expression of S9A GSK3 β mutant or treatment with LY294002 sensitizes hepatoma cells to etoposide- and camptothecin-induced apoptosis [42].

Rapamycin is known to activate GSK3 β ; it enhances a chemotherapy drug paclitaxel-induced apoptosis in GSK3 β wild-type, but not in GSK3 β null breast cancer cells [22], indicating that GSK3 β mediates rapamycin-induced chemosensitivity. A similar report indicates that GSK3 β activation sensitizes human breast cancer cells to chemotherapy drugs, 5-fluorouracil, cisplatin, taxol or prodigiosin-induced apoptosis [23,43]. Overexpression/activation of brain-derived neurotrophic factor (BDNF) and its receptor TrkB in neuroblastoma tumors are associated with poor prognosis and resistance to chemotherapy. TrkB activation-induced resistance to chemotherapy is mediated via GSK3 β [44]. Treatment of neuroblastoma cells with inhibitors of GSK3 β or a GSK3 β -targeted small interfering RNA enhances resistance to chemotherapy drugs. Conversely, expression of a constitutively active S9A GSK3 β sensitizes neuroblastoma cells to chemotherapy agents [44]. However, in some cases, inhibition of GSK3 β may sensitize cells to chemotherapy; small-molecule GSK3 β inhibitor promotes a genotoxic agent, adriamycin-induced apoptosis in human colorectal cancer cells in a p53-dependent manner [45].

In summary, it appears that GSK3 β regulation of response or resistance to cancer chemotherapy is also tumor cell type-dependent. The GSK3 β -regulated differential responses to chemotherapy among tumor cell types, however, are not entirely consistent with its role as a tumor suppressor or tumor promoter. For example, GSK3 β functions as a tumor suppressor for mammary tumors; its activation sensitizes human breast cancer cells to chemotherapy drugs. On the other hand, GSK3 β acts as a tumor promoter for colon tumors and its inhibition enhances the response of colon cancer cells to chemotherapy. In ovarian tumors, however, the finding that GSK3 β inhibition confers resistance to cisplatin contradicts its tumor promoting role. Therefore, it is likely the mechanisms underlying GSK3 β regulation of tumorigenesis and drug response are different.

4. The mechanisms of GSK3 β action

Since GSK3 β regulates diverse substrates and signaling pathways, the mechanisms underlying its anti-tumor or pro-tumor action are complex. One of the most important impacts of GSK3 β on neoplastic transformation tumor development is likely mediated by its influence on Wnt/ β -catenin signaling. Phosphorylation of β -catenin by active GSK3 β targets β -catenin for ubiquitin-mediated proteasomal degradation and maintains a low level of cytoplasmic β -catenin. Activation of Wnt signaling inhibits GSK3 β and stabilizes cytoplasmic β -catenin, qualifying β -catenin as a proto-oncogene [46,47]. As β -catenin accumulates, it translocates into the nucleus where it binds to TCF and LEF transcription factors and increases their transcriptional activity. A number of TCF/LEF-targeted proto-oncogenes, such as *c-myc* and *cyclin-D1*, and genes involved in cell invasion/migration, such as *MMP-7*, are drastically up-regulated. In a mouse model of mammary tumorigenesis, inhibition of GSK3 β by overexpression of kinase-inactive GSK3 β in mouse mammary glands promotes mammary tumorigenesis; this is accompanied by the over-expression of β -catenin and cyclin D1 [20], supporting that GSK3 β inhibition causes dysregulation of the Wnt/ β -catenin pathway which results in tumor promotion. However, other evidence indicates that GSK3 β 's action is independent of perturbation of β -catenin. Hoefflich et al. [48] report that cyclin D1 levels and β -catenin accumulation are not perturbed in GSK3 β deficient mice. In colon cancer, where β -catenin dysregulation is involved in the pathogenesis of the tumor, GSK3 β remains active and is overexpressed in the cancer cells; active GSK3 β is required for the growth of colon cancer cells [9]. These findings suggest GSK3 β may also modulate tumor development through mechanisms other than Wnt/ β -catenin signaling.

Recent studies suggest that GSK3 β -induced suppression of mammary tumors is mediated by myeloid cell leukemia-1 (Mcl-1), an anti-apoptotic Bcl-2 family member. Mcl-1 is overexpressed in many types of human cancer and associates with cell immortalization, malignant transformation and chemoresistance. The expression of Mcl-1 is correlated with pGSK3 β (Ser9) (inactive form of GSK3 β) in multiple cancer cell lines and primary human cancer samples; the high level of Mcl-1 is related to high tumor grade and poor survival of breast cancer patients [18]. Activation of GSK3 β results in Mcl-1 degradation, while inactivation of GSK3 β causes accumulation of Mcl-1 [23]. More importantly, inactivation of GSK3 β promotes mammary tumor development and induces chemoresistance in a Mcl-1-dependent manner [18,23].

GSK3 β is a direct regulator of AP-1. AP-1 is a heterodimeric transcription factor complex composed of a Jun family member and a FOS family member that binds the TRE DNA sequence (5'-TGAGTCA-3'). It is involved in a variety of cellular processes, including growth, survival and tumorigenesis [49]. GSK3 β -induced c-Jun phosphorylation inhibits DNA binding activity and suppresses AP-1 activity [4]. AP-1 activation is required for the transformation of epidermal cells and skin carcinogenesis [50,51]. In an *in vitro* model of epidermal cell neoplastic transformation, activation of phosphoinositide 3-kinase (PI3K), PKC or ERK results in AP-1 activation and subsequent neoplastic transformation [52,53]. We demonstrate that activation of PI3K and PKC inhibits GSK3 β activity by stimulating

pGSK3 β (Ser9) [19]. Inactivation of GSK3 β drastically enhances AP-1 activity and promotes epidermal cell transformation (Fig. 1).

NF- κ B is a transcription factor that plays a crucial role in many physiological and pathophysiological processes, including control of the adaptive and innate immune responses, inflammation, cell proliferation, survival and differentiation [54,55]. In a resting state, NF- κ B, p65/p50 heterodimers are generally inactive and form a complex with its inhibitory proteins I κ B α in the cytoplasm. Activation of I κ B kinase (IKK) phosphorylates I κ B α and results in its proteasomal degradation; this leads to liberation and translocation of NF- κ B into the nucleus where it regulates gene expression. A role for NF- κ B as a tumor promoter is firmly established. However, recent findings suggest an inhibitory role for NF- κ B in carcinogenesis and tumorigenesis [54,55]. NF- κ B activity is subject to regulation of GSK3 β ; the regulation is either positive or negative depending on the cell types being investigated [4,7]. In colon and pancreatic cancer cells, GSK3 β positively regulates NF- κ B and inactivation of GSK3 β inhibits NF- κ B activity [9]. GSK3 β -induced increase in the growth of colon and pancreatic cancer cells is believed to be mediated by NF- κ B activation [7,9]. However, GSK3 β is reported to inhibit NF- κ B activity in neuronal cells and astrocytes [56–58]. The molecular mechanisms underlying GSK3 β /NF- κ B interaction remain to be further investigated. In addition to AP-1 and NF- κ B, several other transcription factors that may participate in the regulation of cell proliferation, survival and tumorigenesis are subject to regulation of GSK3 β ; these include cyclic AMP response element binding protein (CREB), p53, heat shock factor-1 (HSF-1) and nuclear factor of activated T cells (NFAT) [4,6].

The tumor promoting or suppressing effect of GSK3 β may be mediated by its modulation cell cycle and cell survival. In general, GSK3 β activation could cause cell cycle arrest by suppressing the expression of a number of critical cell cycle regulators, such as cyclin D1, cyclin E, c-Jun and c-Myc; these regulators are closely associated with cell transformation and tumor development [59].

GSK3 β is also an important regulator of cell survival, and activation of GSK3 β can be either anti-apoptotic or pro-apoptotic. It has been suggested that GSK3 β promotes cell death caused by the intrinsic apoptotic pathway, but inhibits the death receptor-mediated extrinsic apoptotic signaling pathway [6]. The intrinsic apoptotic signaling pathway causes the disruption of mitochondria, leading to cell destruction. The intrinsic apoptotic signaling cascade can be induced by numerous stimuli that cause cell damage, such as DNA damage, oxidative stress and endoplasmic reticulum (ER) stress; GSK3 β promotes this cascade by facilitating signals that cause disruption of mitochondria and by regulating transcription factors that control the expression of anti- or pro-apoptotic proteins.

The extrinsic apoptotic pathway, on the other hand, is mediated by the activation of cell-surface death domain-containing receptors (DRs) and initiates apoptosis by activating caspase-8 [6]. DRs belong to the tumor necrosis factor (TNF) family of receptors that contain conserved intracellular death domains that are critical for the initiation of extrinsic apoptotic signaling. Among the most well known death receptors are TNF receptor 1 (TNF-R1), Fas, death receptor 4 (DR4) and DR5. GSK3 β activation generally inhibits the extrinsic apoptotic pathway. Conversely, death receptor-induced extrinsic apoptotic signaling is

potentiated by GSK3 β inhibition caused by the treatment of lithium and other GSK3 β inhibitors [6]; these may be useful in cancer therapies in conjunction with agents that activate death receptors, for example, employing GSK3 β inhibitors in combination with the DR4/DR5 activating ligand TRAIL may be efficient in killing tumor cells since these death receptors are preferentially expressed in cancer cells.

Conclusion

GSK3 β has emerged as one of the most attractive therapeutic targets for the treatment of some neurological diseases, including Alzheimer's, stroke and bipolar disorders, as well as diabetes and inflammation. Recently, GSK3 β has been viewed as a viable target in the treatment of several human neoplasms due to its involvement in tumor development and chemoresistance. However, it remains controversial whether GSK3 β is a "tumor suppressor" or "tumor promoter." Available evidence indicates that GSK3 β may function as a "tumor suppressor" for certain types of tumors, such as skin and mammary tumors; GSK3 β overexpression/activation inhibits neoplastic transformation and development of these tumors. On the other hand, GSK3 β may act as a "tumor promoter" for other types of tumors, such as colon and pancreatic cancers, and enhance carcinogenesis. Under the circumstances, GSK3 β inhibitors may provide an effective therapeutic avenue for the treatment of these tumors. Although the mechanisms underlying the differential effects of GSK3 β remain to be elucidated, both anti-tumor and pro-tumor properties of GSK3 β need to be carefully evaluated when a therapeutic strategy is being developed to target GSK3 β .

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Figure 1.

Diagram of the role of GSK3 β in skin tumorigenesis. EGF and TPA activate PI3K/Akt and PKC signaling pathways which induce phosphorylation of GSK3 β (Ser9) and inactivate GSK3 β . Inactivation of GSK3 β stimulates oncogenic transcription factor AP-1.

Hyperactivity of AP-1 promotes skin tumorigenesis. EGF and TPA can also activate AP-1 through the MEK1/ERK pathway which is independent of GSK3 β .