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Gene Section
Review

GSK3B (glycogen synthase kinase 3 beta)

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Identity

Other names: EC 2.7.11.26
HGNC (Hugo): GS3KB
Location: 3q13.33
Local order:
Human: Nuclear receptor subfamily 1, group I, member 2 (NR1I2); GSK3B; G-protein coupled receptor 156 (GPR156).
Mouse: G-protein coupled receptor 156 (Gpr156); Gsk3b; Nuclear receptor subfamily 1, group I, member 2 (Nr1i2).

DNA/RNA

Description

According to Entrez-Gene, human GSK3B maps to locus NC_000003.11.

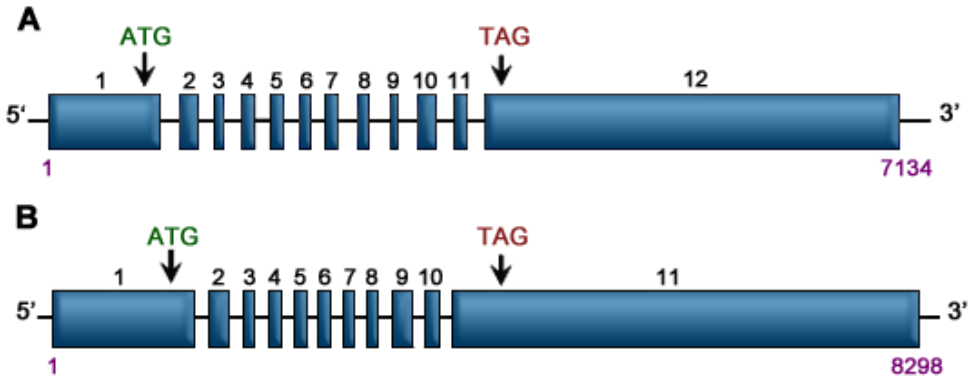
This gene contains 12 exons that encompass 266971 bp of genomic DNA. In mice, GSK3B maps to NC_000082.5 and contains 11 exons that span 157079 bp of DNA within the mouse genome.

Transcription

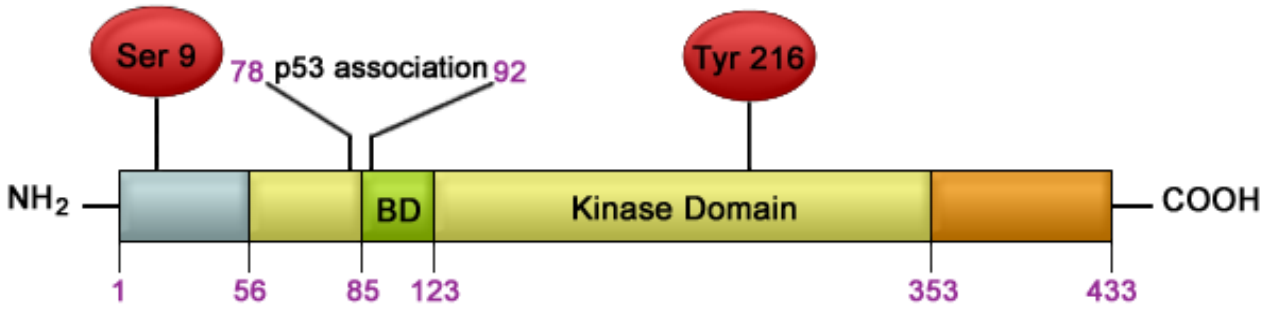
Human GSK3B mRNA (NM_002193.3) consists of 7134 bp, and murine GSK3B mRNA (NM_019827) contains 8298 bp. Alternatively spliced transcript variants encoding different isoforms (1 and 2) have been found for human gene. Transcript variant 2 is missing an in-frame coding exon (9) compared to variant 1, resulting in a shorter isoform 2 lacking a 13 aa segment compared to isoform 1.

Pseudogene

No pseudogene has been identified for GSK3B.



A) Human GSK3B gene, isoform 1. B) Mouse Gsk3b gene. GSK3B is comprised of 12 exons in human and 11 exons in mouse. The ATG start codon is located within exon 1 and the TAG stop codon is found in exon 12 (Human) and 11 (Mouse). The sizes of exons for human gene 1-12 are 1071 bp, 191 bp, 85 bp, 110 bp, 130 bp, 106 bp, 97 bp, 95 bp, 38 bp, 186 bp, 98 bp and 604 bp, respectively. The sizes of exons for mouse gene 1-11 are 1613 bp, 193 bp, 83 bp, 110 bp, 130 bp, 106 bp, 97 bp, 95 bp, 186 bp, 98 bp and 5577 bp, respectively.



GSK3B structure. GSK3B is a 46-47 kDa protein consisting of 433 and 420 amino acids in human and mouse respectively. The protein contains an N-terminal domain, a kinase domain and a C-terminal domain. Phosphorylation of Tyr216 located in the T-loop (activation site) facilitates substrate phosphorylation by GSK3B but is not strictly required for its kinase activity. Phosphorylation of GSK3B at Ser9 in N-terminal region leads to inhibition of its kinase activity. Binding domain (BD) includes GSK3B specific binding sites for substrates and protein complexes (e.g., p53).

Protein

Description

Glycogen synthase kinase-3 beta (GSK3B) was named due to its ability to phosphorylate and inactivate glycogen synthase. GSK3B is a multifunctional serine/threonine kinase which has been implicated in multiple biological processes including embryonic development, cell differentiation, apoptosis and insulin response. GSK3B is a key component in neuronal functions and has been implicated in major diseases involving the central nervous system.

Expression

GSK3B was originally isolated from the skeletal muscle but it is ubiquitously expressed in almost all the tissues. However, abundant expression is detected in brain tissue, especially in the neurons when compared to the astrocytes. The high level of expression in the brain is due to its vital role in the neuronal signaling. Dysregulation of GSK3B expression leads to various pathological conditions such as diabetes or insulin resistance, neuronal dysfunction and neuronal diseases.

Localisation

GSK3B is generally considered a cytosolic protein; however, it is reported to be present in the nucleus and mitochondria. Nuclear and mitochondrial localization of GSK3B correlates with its higher kinase activity compared to cytosolic protein. Translocation and specific cellular localization of GSK3B determine its involvement in signaling pathways, regulate its interaction with substrates and participation in protein complex formation, and influence gene expression and transcription.

Function

GSK3B is a multifunctional protein kinase which is implicated in a large number of cellular processes and diseases. GSK3B is regulated by serine (inhibitory) and tyrosine (activating) phosphorylation. More than 40 proteins have been reported to be phosphorylated by GSK3B. GSK3B substrates include metabolic and signaling proteins like glycogen synthase, Acetyl CoA carboxylase, Axin, Cyclin D1; structural proteins like Tau, neural cell adhesion protein (NCAM); transcription factors like beta-catenin, p53, Myc, NFkappaB, CREB and AP-1; apoptotic-related proteins like Bax and p53. GSK3B also regulates various cellular processes by binding to protein complexes.

Homology

The GSK3B gene is conserved in human, chimpanzee, dog, cow, rat, chicken, zebrafish, fruit fly, mosquito, C. elegans, A. thaliana, rice, and P. falciparum.

Mutations

Germinal

1. Several rare sequence variants in GSK3B were identified in the case-control study of patients with probable Alzheimer disease (AD), familial frontotemporal dementia (FTD), primary progressive aphasia, and aged healthy subjects. An intronic polymorphism (IVS2-68G>A) occurred at more than twice the frequency among patients with FTD (10.8%) and patients with AD (14.6%) than in aged healthy subjects (4.1%).
2. GSK3beta promoter single-nucleotide polymorphism (rs334558) influences transcriptional strength, and the less active form was associated with less detrimental clinical features of mood disorders. Effect of rs334558 was studied on grey matter volumes of patients affected by chronic schizophrenia. Carriers of the less active C allele variant showed significantly higher brain volumes in an area encompassing posterior regions of right middle and superior temporal gyrus, within the boundaries of Brodmann area 21. The temporal lobe is the brain parenchymal region with the most consistently documented morphometric abnormalities in schizophrenia, and neuropathological processes in these regions develop soon at the beginning of the illness.

Implicated in

Ovarian cancer

Note

Ovarian cancer is a leading cause of death from gynecological malignancies. GSK3B promotes ovarian cancer cell proliferation by regulating Cyclin D1. GSK3B-dependent increased Cyclin D1 expression in ovarian cancer cells supports a possibility that GSK3B is involved in ovarian tumor chemotherapy resistance. Therefore, it is possible that combination of traditional chemotherapy and GSK3B inhibitors would benefit ovarian cancer patient response.

Prostate cancer

Note

Androgen receptor (AR) regulates growth of normal and cancer prostate cells. AR phosphorylation status is associated with its transcriptional activation. GSK3B interacts directly with the AR, modulates AR signaling and plays important role in the control of the proliferation of normal and malignant androgen-regulated tissues. Therefore, pharmacological inhibitors designed to increase GSK3B activity could be useful in prostate cancer therapy.

Pancreatic cancer

Note

It was shown that pancreatic cancer cells contain a pool of active GSK3B, and that pharmacological inhibition of GSK3B kinase activity using small molecule inhibitors or genetic depletion of GSK3B by RNA interference leads to decreased cancer cell proliferation and survival. Hence GSK3B has potential as an important new target in the treatment of pancreatic cancer.

Colorectal cancer

Note

Colon cancer cell lines and colon cells from colorectal cancer patients have higher levels of GSK3B expression than their normal counterparts. Inhibition of GSK3B activity either by chemical inhibitors or by expression by RNA interference targeting GSK3B induced apoptosis and attenuation of proliferation of colon cancer cells in vitro. Hence GSK3B has a potential as therapeutic target in colorectal cancer.

Neuroblastoma

Note

Treatment of B65 neuroblastoma cell line with GSK3B inhibitors Lithium or SB415286 caused a decrease in cell proliferation that was associated with G2/M cell cycle arrest due to regulating the phosphorylation of Cdc2. Therefore, GSK3B and Cdc2 could be potential pharmacological targets in neuroblastoma.

Glioblastoma

Note

Glioblastoma is the most frequent malignant tumor of the brain and represents a subset of cancers that is mostly nonresponsive to currently available anticancer treatments.

The current standard therapy for newly diagnosed glioblastoma consists of surgical resection of the tumor to the extent that is safe and feasible, followed by chemotherapy and irradiation. There has been an emerging paradigm for the combination of chemotherapy and molecular targeted therapy to improve therapeutic efficiency. Glioblastoma cells depend on deregulated GSK3B to survive, proliferate, and resist chemotherapy and radiation. Pretreatment with low-dose GSK3B inhibitor enhanced the cytocidal effect of ionizing radiation in glioblastoma cells. At the same time, GSK3B inhibitors have been shown to protect normal hippocampal neurons from radiation-induced apoptosis. Therefore, GSK3B inhibition provides dual benefits for the glioblastoma patients treated with radiation: by attenuating tumor proliferation and by protecting host brain tissue from degradation and allowing its repair.

Insulin resistance and diabetes

Note

Insulin resistance is caused by the inability of insulin sensitive tissues to respond to insulin and efficiently clear blood glucose. Insulin signaling involves autophosphorylation of the insulin receptor leading to the activation of PI3K which activates PKB (Akt). The activated PKB phosphorylates and inactivates GSK3B. Dysregulation of GSK3B results in impaired insulin signaling leading to diabetes. Inhibitors of GSK3B improve insulin signaling and maintain proper glucose levels.

Alzheimer's disease

Note

Alzheimer's disease (AD) is a chronic disorder that slowly destroys neurons and causes serious cognitive disability. The two neuropathologiocal features of Alzheimer's disease are neurofibrillary tangles and amyloid plaques. GSK3B has been implicated in both neuropathologies. In addition, presenilin 1 (PS1) have been linked to Alzheimer's disease. Presenilin 1 binds to and regulates GSK3B activity. Presenilin 1 mutations might compromise neuronal function by increasing GSK3B activity.

Schizophrenia

Note

Schizophrenia is a severe brain illness in which the disrupted in schizophrenia 1 (DISC1) gene is disrupted by a balanced chromosomal translocation. DISC1 is

highly expressed in neural progenitor cells and required for embryonic brain development. DISC1 regulates beta-catenin turnover by inhibiting GSK3B activity. GSK3B inhibitors are able to normalize progenitor proliferation and behavioral defects caused by DISC1 loss of function.

Bipolar affective disorder

Note

Patients with bipolar affective disorder have a history of experiencing manic episodes that are often interspersed with depression, and major depression is commonly referred to as mood disorders. Lithium, a known GSK3B inhibitor, is one of the most widely used mood-stabilizing agents for the treatment of bipolar disorder.

References

Lau KF, Miller CC, Anderton BH, Shaw PC. Molecular cloning and characterization of the human glycogen synthase kinase-3beta promoter. Genomics. 1999 Sep 1;60(2):121-8

Dajani R, Fraser E, Roe SM, Young N, Good V, Dale TC, Pearl LH. Crystal structure of glycogen synthase kinase 3 beta: structural basis for phosphate-primed substrate specificity and autoinhibition. Cell. 2001 Jun 15;105(6):721-32

Martinez A, Castro A, Dorronsoro I, Alonso M. Glycogen synthase kinase 3 (GSK-3) inhibitors as new promising drugs for diabetes, neurodegeneration, cancer, and inflammation. Med Res Rev. 2002 Jul;22(4):373-84

Bhat RV, Budd Haeberlein SL, Avila J. Glycogen synthase kinase 3: a drug target for CNS therapies. J Neurochem. 2004 Jun;89(6):1313-7

Cohen P, Goedert M. GSK3 inhibitors: development and therapeutic potential. Nat Rev Drug Discov. 2004 Jun;3(6):479-87

Jope RS, Johnson GV. The glamour and gloom of glycogen synthase kinase-3. Trends Biochem Sci. 2004 Feb;29(2):95-102

Meijer L, Flajolet M, Greengard P. Pharmacological inhibitors of glycogen synthase kinase 3. Trends Pharmacol Sci. 2004 Sep;25(9):471-80

Wang L, Lin HK, Hu YC, Xie S, Yang L, Chang C. Suppression of androgen receptor-mediated transactivation and cell growth by the glycogen synthase kinase 3 beta in prostate cells. J Biol Chem. 2004 Jul 30;279(31):32444-52

Ougolkov AV, Fernandez-Zapico ME, Savoy DN, Urrutia RA, Billadeau DD. Glycogen synthase kinase-3beta participates in nuclear factor kappaB-mediated gene transcription and cell survival in pancreatic cancer cells. Cancer Res. 2005 Mar 15;65(6):2076-81

Shakoori A, Ougolkov A, Yu ZW, Zhang B, Modarressi MH, Billadeau DD, Mai M, Takahashi Y, Minamoto T. Deregulated GSK3beta activity in colorectal cancer: its association with tumor cell survival and proliferation. Biochem Biophys Res Commun. 2005 Sep 9;334(4):1365-73

Cao Q, Lu X, Feng YJ. Glycogen synthase kinase-3beta positively regulates the proliferation of human ovarian cancer cells. Cell Res. 2006 Jul;16(7):671-7

Yazlovitskaya EM, Edwards E, Thotala D, Fu A, Osusky KL, Whetsell WO Jr, Boone B, Shinohara ET, Hallahan DE. Lithium treatment prevents neurocognitive deficit resulting from cranial irradiation. Cancer Res. 2006 Dec 1;66(23):11179-86

Garcea G, Manson MM, Neal CP, Pattenden CJ, Sutton CD, Dennison AR, Berry DP. Glycogen synthase kinase-3 beta; a new target in pancreatic cancer? Curr Cancer Drug Targets. 2007 May;7(3):209-15

Schaffer BA, Bertram L, Miller BL, Mullin K, Weintraub S, Johnson N, Bigio EH, Mesulam M, Wiedau-Pazos M, Jackson GR, Cummings JL, Cantor RM, Levey AI, Tanzi RE, Geschwind DH. Association of GSK3B with Alzheimer disease and frontotemporal dementia. Arch Neurol. 2008 Oct;65(10):1368-74

Thotala DK, Hallahan DE, Yazlovitskaya EM. Inhibition of glycogen synthase kinase 3 beta attenuates neurocognitive dysfunction resulting from cranial irradiation. Cancer Res. 2008 Jul 15;68(14):5859-68

Eom TY, Jope RS. GSK3 beta N-terminus binding to p53 promotes its acetylation. Mol Cancer. 2009 Mar 5;8:14

Machado-Vieira R, Manji HK, Zarate CA Jr. The role of lithium in the treatment of bipolar disorder: convergent evidence for neurotrophic effects as a unifying hypothesis. Bipolar Disord. 2009 Jun;11 Suppl 2:92-109

Mao Y, Ge X, Frank CL, Madison JM, Koehler AN, Doud MK, Tassa C, Berry EM, Soda T, Singh KK, Biechele T, Petryshen TL, Moon RT, Haggarty SJ, Tsai LH. Disrupted in schizophrenia 1 regulates neuronal progenitor proliferation via modulation of GSK3beta/beta-catenin signaling. Cell. 2009 Mar 20;136(6):1017-31

Miyashita K, Kawakami K, Nakada M, Mai W, Shakoori A, Fujisawa H, Hayashi Y, Hamada J, Minamoto T. Potential therapeutic effect of glycogen synthase kinase 3beta inhibition against human glioblastoma. Clin Cancer Res. 2009 Feb 1;15(3):887-97

Pizarro JG, Folch J, Esparza JL, Jordan J, Pallàs M, Camins A. A molecular study of pathways involved in the inhibition of cell proliferation in neuroblastoma B65 cells by the GSK-3 inhibitors lithium and SB-415286. J Cell Mol Med. 2009 Sep;13(9B):3906-17

Takahashi-Yanaga F, Sasaguri T. Drug development targeting the glycogen synthase kinase-3beta (GSK-3beta)-mediated signal transduction pathway: inhibitors of the Wnt/beta-catenin signaling pathway as novel anticancer drugs. J Pharmacol Sci. 2009 Feb;109(2):179-83

Benedetti F, Poletti S, Radaelli D, Bernasconi A, Cavallaro R, Falini A, Lorenzi C, Pirovano A, Dallaspezia S, Locatelli C, Scotti G, Smeraldi E. Temporal lobe grey matter volume in schizophrenia is associated with a genetic polymorphism influencing glycogen synthase kinase 3-beta activity. Genes Brain Behav. 2010 Jun 1;9(4):365-71

Thotala DK, Geng L, Dickey AK, Hallahan DE, Yazlovitskaya EM. A new class of molecular targeted radioprotectors: GSK-3beta inhibitors. Int J Radiat Oncol Biol Phys. 2010 Feb 1;76(2):557-65

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