

More details on GSK-3

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Overview

Glycogen synthase kinase-3 (GSK-3) has recently emerged, in the field of medicinal chemistry, as one of the most attractive therapeutic targets for the development of selective inhibitors as promising new drugs for numerous serious pathologies, including Alzheimer's disease, stroke, bipolar disorders, chronic inflammatory processes, cancer, alopecia and Type II diabetes. The full potential of GSK-3 inhibitors is yet to be realised and the number of drug candidates being developed by both academic centres and pharmaceutical companies has increased exponentially in the last three years. This review discloses recent discoveries on peptides and small molecules targeting GSK-3. Antisense therapy for the modulation of GSK-3 expression is also discussed. Focusing attention on this exciting target could thus reap considerable clinical and economic rewards. [source](#)

Protein name: Glycogen synthase kinase-3 alpha

Synonyms: EC 2.7.11.26; GSK-3 alpha

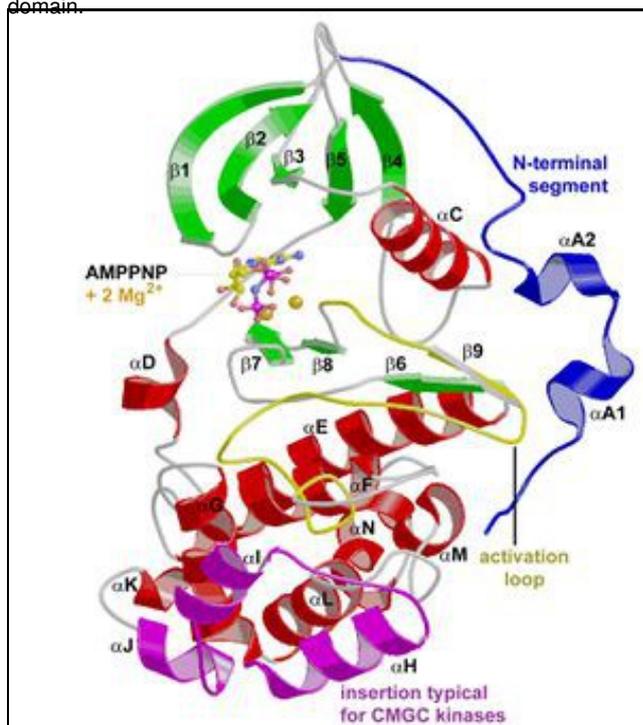
Gene name : Name: GSK3A

From : Homo sapiens (Human) [TaxID: 9606]

Function: Participates in the Wnt signaling pathway. Implicated in the hormonal control of several regulatory proteins including glycogen synthase, MYB and the transcription factor JUN. Phosphorylates JUN at sites proximal to its DNA-binding domain, thereby reducing its affinity for DNA.

Structural details

- GSK3 has the typical two-domain kinase fold with a beta-strand domain (residues 25?138) at the N-terminal end and an alpha-helical domain at the C-terminal end (residues 139?343).
- The ATP-binding site is at the interface of the alpha-helical and beta-strand domain and is bordered by the glycine-rich loop and the hinge.
- The activation loop (residues 200?226) runs along the surface of the substrate binding groove.
- The C-terminal 39 residues (residues 344?382) are outside the core kinase fold and form a small domain that packs against the alpha-helical domain.



- The beta-strand domain consists of seven antiparallel beta-strands: strands 2?6 form a -barrel that is interrupted between strand 4 and 5 by a short helix (residue 96?102) that packs against the beta-barrel.
- This helix is conserved in all kinases, and two of its residues play key roles in the catalytic activity of the enzyme. Arg 96 is involved in the alignment of the two domains. Glu 97 is positioned in the active site and forms a salt bridge with Lys 85, a key residue in catalysis.
- Molecular weight: 46744.3
- Theoretical pI: 8.98
- Total number of negatively charged residues (Asp + Glu): 41
- Total number of positively charged residues (Arg + Lys): 50

Atomic composition:

- - ◆ Carbon C 2085
 - ◆ Hydrogen H 3285
 - ◆ Nitrogen N 575

- ◆ Oxygen O 618
- ◆ Sulfur S 14
- Formula: C2085H3285N575O618S14
- Total number of atoms: 6577

Prediction search done on NetPhos 2.0 server for GSK3

Prediction search done on NetPhos 2.0 server, which produces neural network predictions for serine, threonine and tyrosine phosphorylation sites in eukaryotic proteins.

420 Sequence

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MSGRRPRTTSFAESCKPVQQPSAFGSMKVS RDKDGSKVTTVVATPGQGPDRPQEVSYTDTKVI GNGSFGVVYQAKLCDSG
LVAIKKVLQDKRFKNRELQIMRKL DHCNIVRLRYFFYS SGEKKDEVY LNLVLDYVPETVYRVARHYSRAKQTL PVIYVKI
YMYQLFRSLAYIHSFGICH RDIKPQNLLLD PDTAVLKL CDFGSAKQLVRGEPNVSYICS RYYRAPELIFGATDY TSSIDV
WSAGCVLAE LLLGQPIFP GDSGVDQLVEI IKVLGTP TREQIREMNP NYTEFKFPQ IKAHPWTKVFRP RTPPEAIALCSRI
LEYTPTARLTPLEACAHSFFDEL RDPNVKLPNGR DTPALFNFTTQELSSNPPLATI LIPPHARIQAAA STPTNATAASDA
NTGDRGQTNNAASASASNST
.....S...S.....S.....S.....SY.....
.....SS.....Y.....Y.....
.....SY.....Y.S.....
.....S.....Y.....
.....S.....S.....
.....S.....

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Phosphorylation sites predicted: Ser: 13 Tyr: 6

DISPHOS (Disorder-Enhanced Phosphorylation Sites Predictor) Results

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MSGRRPRTTSFAESCKPVQQPSAFGSMKVS RDKDGSKVTTVVATPGQGPDRPQEVSYTDTKVI GNGSFGVVYQ
LVAIKKVLQDKRFKNRELQIMRKL DHCNIVRLRYFFYS SGEKKDEVY LNLVLDYVPETVYRVARHYSRAKQTL
YMYQLFRSLAYIHSFGICH RDIKPQNLLLD PDTAVLKL CDFGSAKQLVRGEPNVSYICS RYYRAPELIFGAT
WSAGCVLAE LLLGQPIFP GDSGVDQLVEI IKVLGTP TREQIREMNP NYTEFKFPQ IKAHPWTKVFRP RTPPE
LEYTPTARLTPLEACAHSFFDEL RDPNVKLPNGR DTPALFNFTTQELSSNPPLATI LIPPHARIQAAA STPT
NTGDRGQTNNAASASASNST

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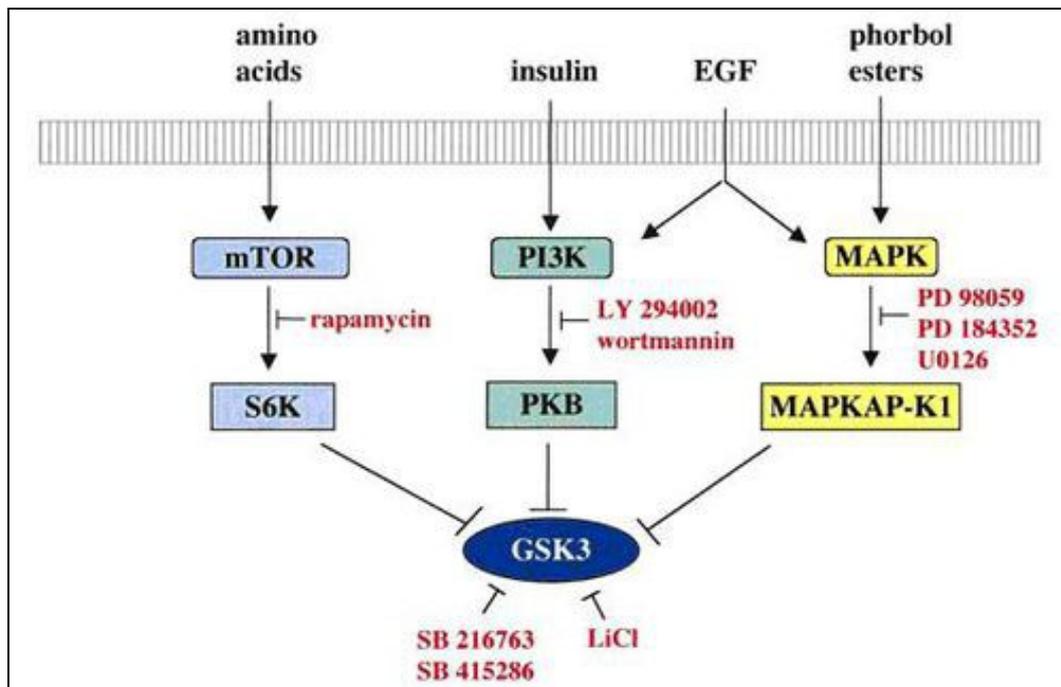
Amino Acid Sequence

GSK3B_HUMAN consists of 420 amino acids sequemnce.

10	20	30	40	50	
MSGRPRTTSE	AESCKPVQQP	SAFGSMKVS	RDKDGSKVTTV	VATPGQGPDR	PQEVSYTD
70	80	90	100	110	1
VIGHGSEFGVV	YQAKLCDSGE	LVAIKKVLQD	KRFKHRELQI	MRKLDHCNIV	RLRYFFYS
130	140	150	160	170	1
EKKDEVYLN	VLDYVPETVY	RVARHYSRAK	QTLPVIIYVKL	YMYQLFRSLA	YIHSFGIC
190	200	210	220	230	2
DIKPQNLLLD	PDTAVLKLCD	FGSAKQLVRG	EPNVSYICSR	YYRAPELIFG	ATDYTSSI
250	260	270	280	290	3
WSAGCVLAEL	LLGQPIFPGD	SGVDQLVEII	KVLGTPTREQ	IREMNPNYTE	FKFPQIKA
310	320	330	340	350	3
WTKVFRPRT	PEAIALCSRL	LEYTPARLT	PLEACAHSEF	DELRDPNVKL	PNGRDTPA
370	380	390	400	410	4
NFTTQELSSN	PPLATILIPP	HARIQAAAST	PTNATAASDA	NTGDRGQTNN	AASASASN

Ways to inhibit GSK3

Possible ways in the art to inhibit GSK3 is illustrated in following figure:



Beta-catenin

Structure

Beta-catenin consists of 781 amino acid residue.



Amino Acid Sequence

1 MATQADLMEL DMAMEPDRKA AVSHWQQQSY LDSGIHSGAT TTAPSLSGKG NPEEDVDTS
 61 QVLYEWEQGF SQSFTQEQA DIDGQYAMTR AQRVRAAMFP ETLDEGMQIP STQFDAAHPT
 121 NVQRLAEP SQ MLKHAVVNL NYQDDAELAT RAIPELTKLL NDEDQVVV NK AAVMVHQLSK
 181 KEASRHAIMR SPQMVSIAVR TMQNTNDVET ARCTAGTLHN LSHHREGLLA IFKSGGIPAL
 241 VKMLGSPVDS VLFYAITTLH NLLHQEGAK MAVRLAGGLQ KMVALLNKTN VKFLAITTDC
 301 LQILAYGNQE SKLILASGG PQALVNIMRT YTYEKLLWTT SRVLKVLSVC SSKNPAIVEA
 361 GGMQALGLHL TDPSQRLVQN CLWTLRNLSD AATKQEGMEG LLGTLVQLLG SDDINVVTCA
 421 AGILSNLTCN NYKNKMMVCQ VGGIEALVRT VLRAGDREDI TEPAICALRH LTSRHQEAEM
 481 AQNAVRLHYG LPVVVKLLHP PSHWPLIKAT VGLIRNLALC PANHAPLREQ GAIPRLVQLL
 541 VRAHQDTQRR TSMGGTQQQF VEGVRMEEIV EGCTGALHIL ARDVHNRIVI RGLNTIPLFV
 601 QLLYSPIENI QRVAAGVLC E LAQDKEAAEA IEAEGATAPL TELLHSRNEG VATYAAAVLF
 661 RMSEDKPDQY KKRLSVELTS SLFRTEPMAW NETADLGLDI GAQGEPLGYR QDDPSYRSFH
 721 SGGYGQDALG MDPMEHEMG GHHPGADYPV DGLPDLGHAQ DLMDGLPPGD SNQLAWFDTD
 781 I

Role of beta catenin

- Stabilized β -catenin can induce new hair follicles and trichofolliculoma-like tumors in skin. [source](#)
- Follicular (hair) and epidermal stem cells are located in the bulge region.
- In the absence of β -catenin, stem cells can differentiate into the epidermal lineage but not into the hair follicular lineage. [source](#)
- In a research, expression of stabilized β -catenin in the epidermis of transgenic mice resulted in hair follicle morphogenesis. [source](#)

