

# 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

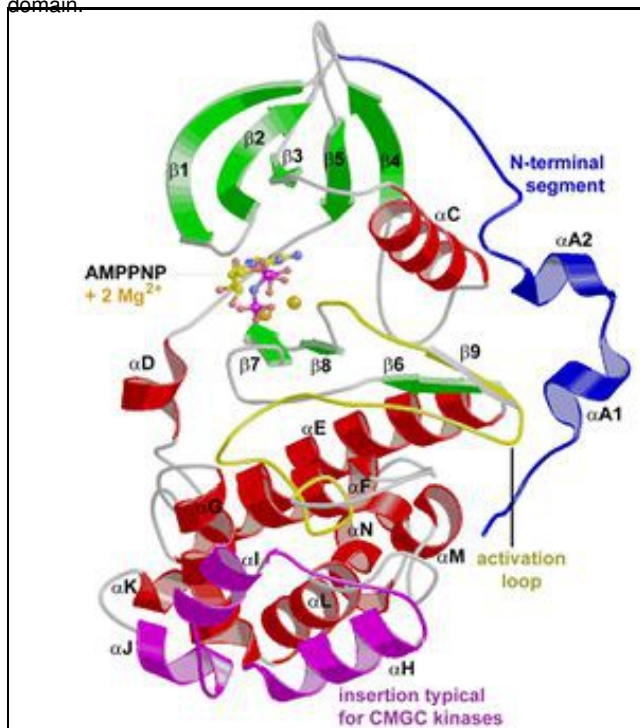
**Gene name :**Name: GSK3A

**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
MSGRPRTTSFAESCKPVQQPSAFGSMKVS RDKDGSKVTTVVATPGQGPDRPQEVSYTDTKVI GNGSFGVVYQAKLCDSGH
LVAIKKVLQDKRFKNRELQIMRKLDHCNIVRLRYFFYS SGEKKDEVY LNLVLDYVPETVYRVARHYSRAKQ TLPVIYVKI
YMYQLFRSLAYIHSFGICH RDIKPQNLLLDPD TAVLKLCDFGSAKQLVRGEPNVSYICS RYYRAPELIFGATDYTSSIDV
WSAGCVLAE LLLGQPIFP GDSGVDQLVEI I KVLGTP TREQIREMNP NYTEFKFPQ IKAHPWTKVFRP RTPPEAIALCSRI
LEYTPTARLT PLEACAH SFFDEL RDPNVKLPNGR DTPALFNFTTQELSSNPPLATI LIPPHARIQAAASTPTNATAASDA
NTGDRGQTNNAASASASNST
.....S...S.....S.....S.....SY.....
.....SS.....Y.....Y.....
.....SY.....Y.S.....
.....S.....Y.....
.....S.....S.....
.....S.....
Phosphorylation sites predicted:                      Ser: 13 Tyr: 6

#### DISPHOS (Disorder-Enhanced Phosphorylation Sites Predictor) Results

MSGRPRTTSFAESCKPVQQPSAFGSMKVS RDKDGSKVTTVVATPGQGPDRPQEVSYTDTKVI GNGSFGVVYQ
LVAIKKVLQDKRFKNRELQIMRKLDHCNIVRLRYFFYS SGEKKDEVY LNLVLDYVPETVYRVARHYSRAKQ T
YMYQLFRSLAYIHSFGICH RDIKPQNLLLDPD TAVLKLCDFGSAKQLVRGEPNVSYICS RYYRAPELIFGAT
WSAGCVLAE LLLGQPIFP GDSGVDQLVEI I KVLGTP TREQIREMNP NYTEFKFPQ IKAHPWTKVFRP RTPPE
LEYTPTARLT PLEACAH SFFDEL RDPNVKLPNGR DTPALFNFTTQELSSNPPLATI LIPPHARIQAAASTPT
NTGDRGQTNNAASASASNST

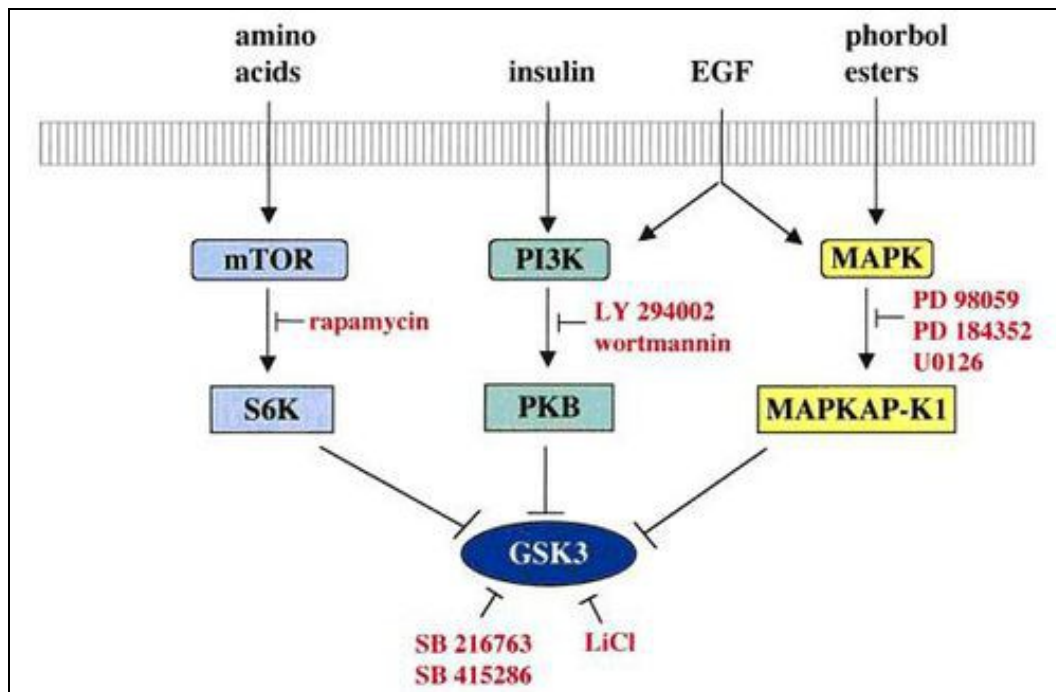
#### Amino Acid Sequence

GSK3B\_HUMAN consists of 420 amino acids sequemnce.

10	20	30	40	50	
MSGRPRTTSF	AESCKPVQQP	SAFGSMKVS	RDKDGSKVTT	VATPGQGPDR	PQEVSYTD
70	80	90	100	110	120
VIGNGSFGVV	YQAKLCDSGE	LVAIKKVLQD	KRFKHRELQI	MRKLDHCNIV	RLRYFFYS
130	140	150	160	170	180
EKKDEVYLN	VLDYVPETVY	RVARHYSRAK	QTLPVIIYVK	YMYQLFRSLA	YIHSFGIC
190	200	210	220	230	240
DIKPQNLLD	PDTAVLKLCD	FGSAKQLVRG	EPNVSYICSR	YYRAPELIFG	ATDYTSSI
250	260	270	280	290	300
WSAGCVLAEL	LLGQPIFPGD	SGVDQLVEII	KVLGTPTREQ	IREMNPNYTE	FKFPQIKA
310	320	330	340	350	360
WTKVFRPRTP	PEAIALCSRL	LEYTPTARLT	PLEACAHSEF	DELRDPNVKL	PNGRDTPA
370	380	390	400	410	420
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.

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- The diagram illustrates the Wnt signaling pathway in two states: resting and activated.
- Resting State (Left):** In the absence of Wnt, a destruction complex composed of Axin, GSK, APC, and  $\beta$ -Cat targets  $\beta$ -Cat for proteolysis. This process is regulated by ATP and ADP. The resulting  $\beta$ -Cat fragments are shown in the cytoplasm, while the nucleus is depicted as a separate compartment.
- Activated State (Right):** Upon Wnt stimulation, the Wnt ligand binds to the receptor complex (FRZ, DSH, G, Axin, APC). This leads to the inhibition of the destruction complex (labeled '1'), allowing  $\beta$ -Cat to accumulate. The accumulated  $\beta$ -Cat then translocates into the nucleus (labeled '2') where it forms a complex with LEF to initiate transcription.