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

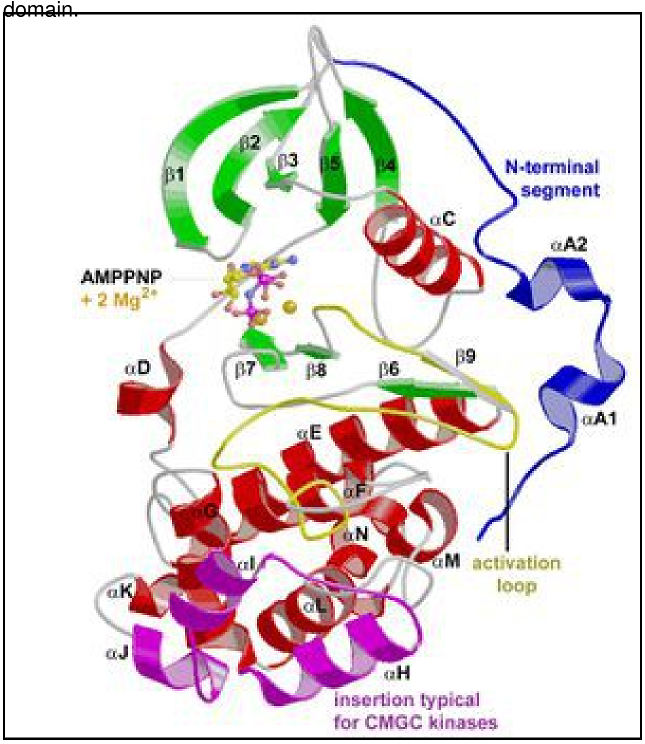
Gene name : Name: GSK3A

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

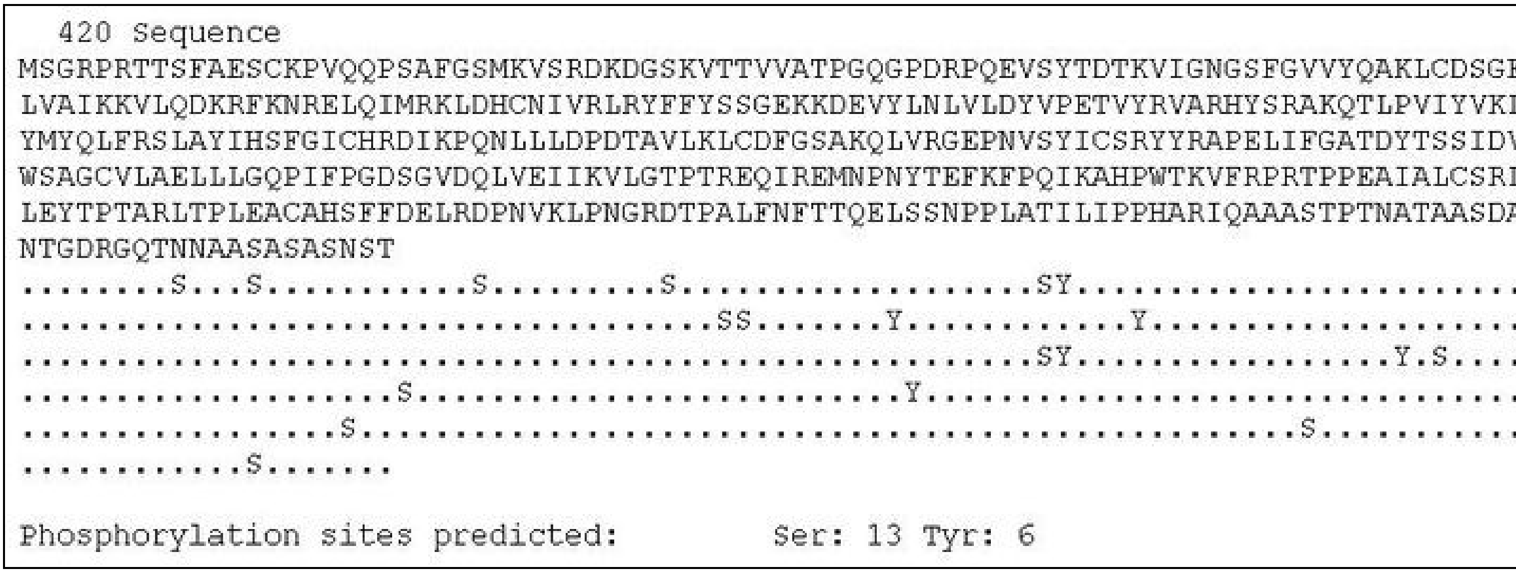
Atomic composition:

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

        - Oxygen O 618
        - Sulfur S 14
    - Formula: $C_{2085}H_{3285}N_{575}O_{618}S_{14}$
    - 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.



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  420 Sequence
MSGRPRTTSFAESCKPVQQPSAFGSMKVSRDKDGSKVTTVVATPGQGPDRPQEVSYTDTKVIGNGSFGVVYQAKLCDSG
LVAIKKVLQDKRFKNRELQIMRKLDHCNIVRLRYFFYSSGEKKDEVYLNLVLDYVPETVYRVARHYSRAKQTLPVIYVK
YMYQLFRSLAYIHSFGICHRDIKPQNLLLDPDTAVLKLCDFGSAKQLVRGEPNVSYICSRYYRAPELIFGATDYTSSID
WSAGCVLAELLLGQPIFPGDSGVDQLVEIIKVLGTPTREQIREMNPNYTEFKFPQIKAHPWTKVFRPRTPPEAIALCSR
LEYTPTARLTPLEACAHSFFDELRDPNVKLPNGRDTPALFNFTTQELSSNPPLATILIPPHARIQAAASTPTNATAASD
NTGDRGQTNNAASASASNST
........S...S...........S.........S...................SY.......................
.....................................SS.......Y............Y...................
......................................................SY.................Y.S...
....................S..........................Y...............................
.................S..................................................S..........
............S.......

Phosphorylation sites predicted:      Ser: 13 Tyr: 6
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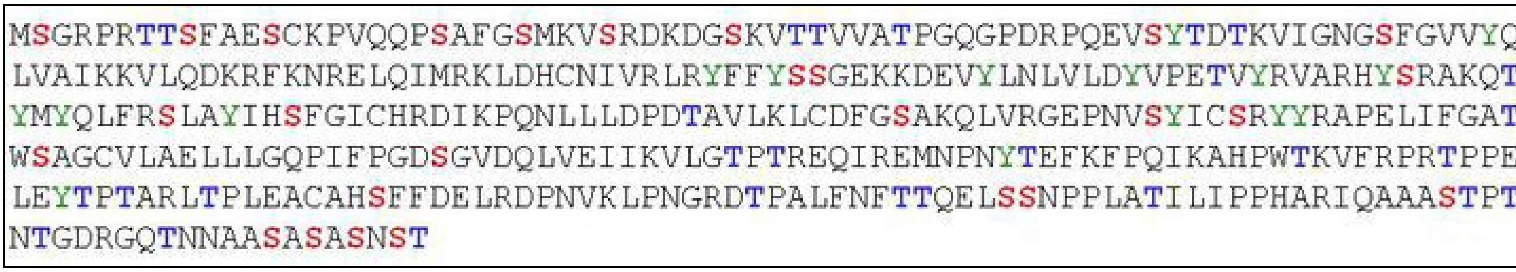
DISPHOS (Disorder-Enhanced Phosphorylation Sites Predictor) Results



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MSGRPRTTSFAESCKPVQQPSAFGSMKVSRDKDGSKVTTVVATPGQGPDRPQEVSYTDTKVIGNGSFGVVY
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YMYQLFRSLAYIHSFGICHRDIKPQNLLLDPDTAVLKLCDFGSAKQLVRGEPNVSYICSRYYRAPELIFGAT
WSAGCVLAELLLGQPIFPGDSGVDQLVEIIKVLGTPTREQIREMNPNYTEFKFPQIKAHPWTKVFRPRTPPE
LEYTPTARLTPLEACAHSFFDELRDPNVKLPNGRDTPALFNFTTQELSSNPPLATILIPPHARIQAAASTPT
NTGDRGQTNNAASASASNST
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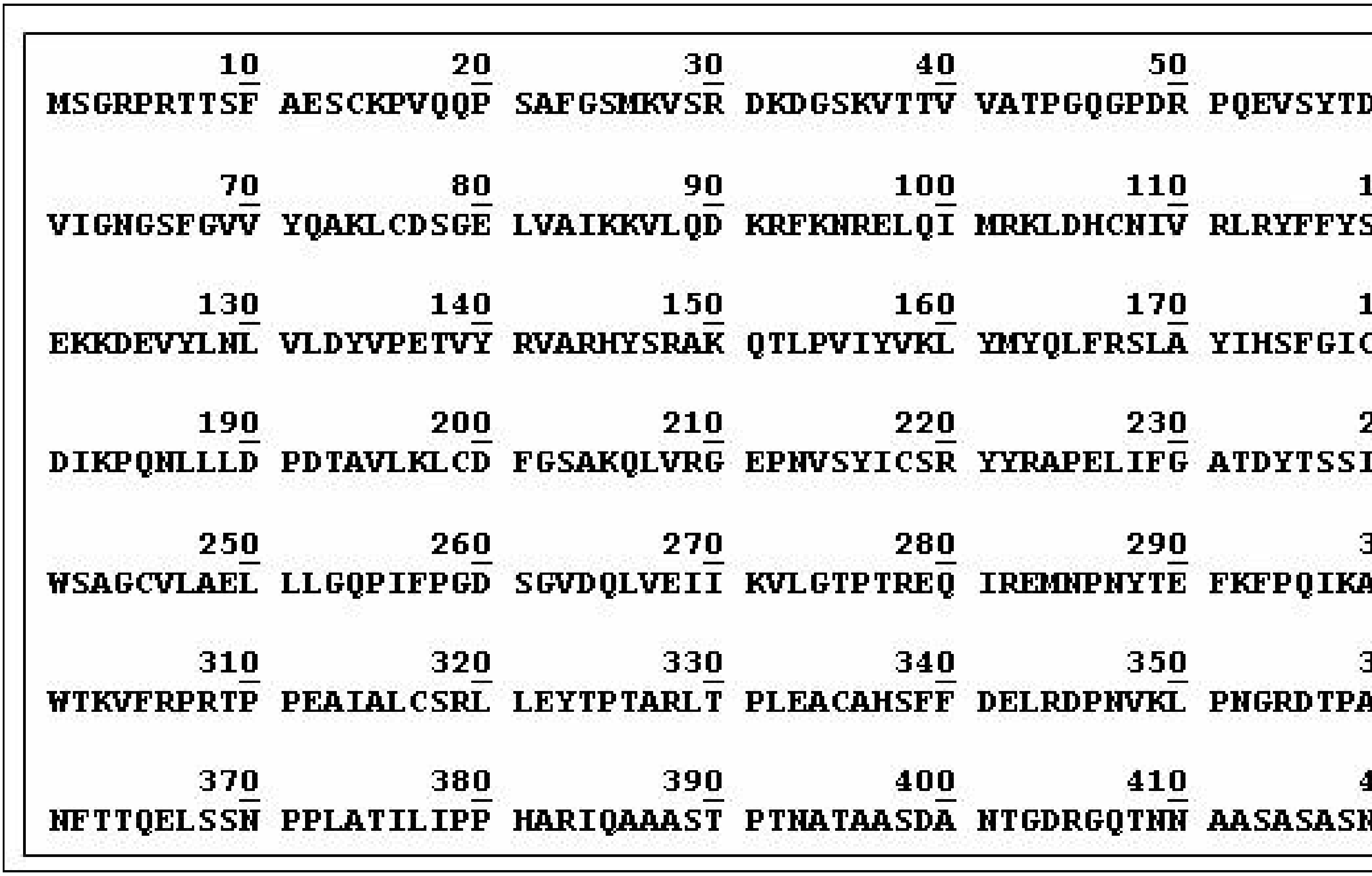
Amino Acid Sequence

GSK3B_HUMAN consists of 420 amino acids sequemnce.



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        10         20         30         40         50
MSGRPRTTSF AESCKPVQQP SAFGSMKVSR DKDGSKVTTV VATPGQGPDR PQEVSYTD

        70         80         90        100        110          1
VIGNGSFGVV YQAKLCDSGE LVAIKKVLQD KRFKNRELQI MRKLDHCNIV RLRYFFYS

       130        140        150        160        170          1
EKKDEVYLNL VLDYVPETVY RVARHYSRAK QTLPVIYVKL 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
WTKVFRPRTP PEAIALCSRL LEYTPTARLT PLEACAHSFF DELRDPNVKL PNGRDTPA

       370        380        390        400        410          4
NFTTQELSSN PPLATILIPP HARIQAAAST PTNATAASDA NTGDRGQTNN AASASASN
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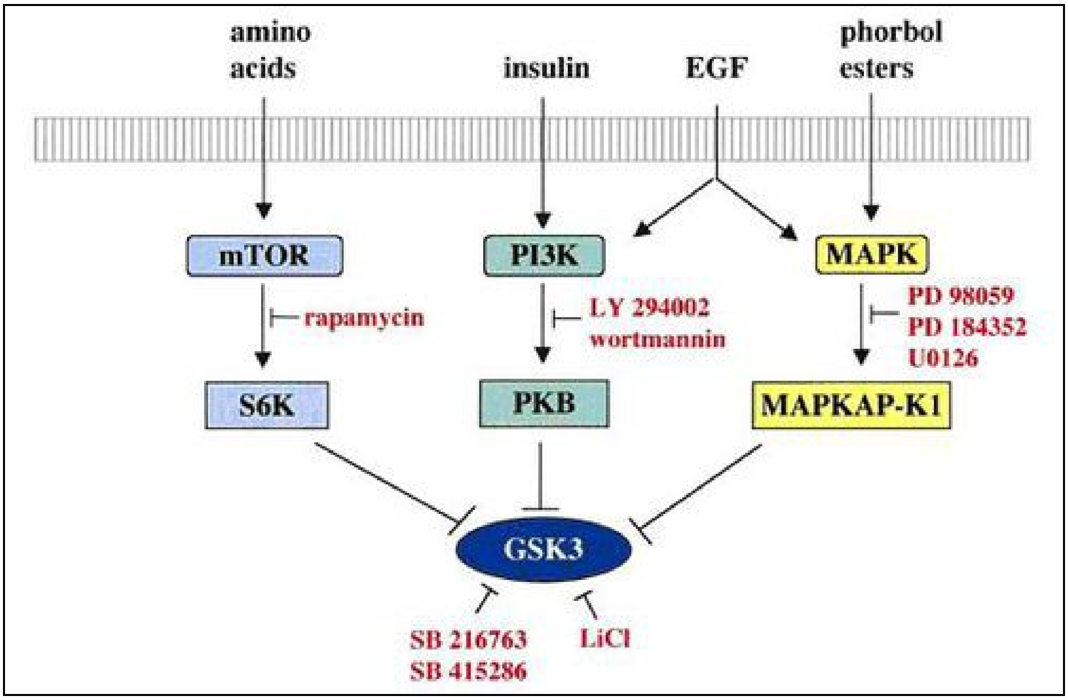
Ways to inhibit GSK3

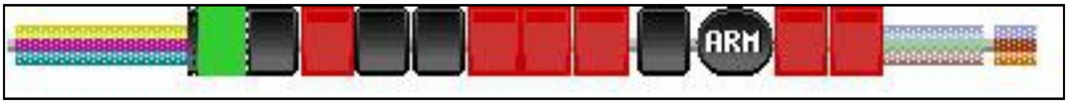
Possible ways in the art to inihibit GSK3 is illustrated in following figure:



Beta-catenin

Structure

Beta-catenin consists of 781 amino acid residue.



Amino Acid Sequence

1 MATQADLMEL DMAMEPDRKA AVSHWQQQSY LDSGIHSGAT TTAPSLSGKG NPEEEDVDTS
61 QVLYEWEQGF SQSFTQEQVA DIDGQYAMTR AQRVRAAMFP ETLDEGMQIP STQFDAAHPT
121 NVQRLAEPSQ MLKHAVVNLI NYQDDAELAT RAIPELTKLL NDEDQVVVNK AAVMVHQLSK
181 KEASRHAIMR SPQMVSAIVR TMQNTNDVET ARCTAGTLHN LSHHREGLLA IFKSGGIPAL
241 VKMLGSPVDS VLFYAITTLH NLLLHQEGAK MAVRLAGGLQ KMVALLNKTN VKFLAITTDC
301 LQILAYGNQE SKLIILASGG PQALVNIMRT YTYEKLLWTT SRVLKVLSVC SSNKPAIVEA
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 QRVAAGVLCE LAQDKEAAEA IEAEGATAPL TELLHSRNEG VATYAAAVLF
661 RMSEDKPQDY KKRLSVELTS SLFRTEPMAW NETADLGLDI GAQGEPLGYR QDDPSYRSFH
721 SGGYGQDALG MDPMMEHEMG GHHPGADYPV DGLPDLGHAQ DLMDGLPPGD SNQLAWFDTD
781 I

Role of beta catenin

- Stabilized ?-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 ?-catenin, stem cells can differentiate into the epidermal lineage but not into the hair follicular lineage. source
- In a research, expression of stabilized ?-catenin in the epidermis of transgenic mice resulted in hair follicle morphogenesis. source