Research Paper Anatomy

In Silico analysis of Noggin gene and its protein structure

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ABSTRACT

Noggin is a glycoprotein predominantly expressed by the dorsal mesoderm during embryogenesis and is secreted as a covalently linked homodimer. Noggin is essential for cartilage morphogenesis and joint formation. The human Noggin gene (NOG; MIM #602991), spanning ~1.9 kb of genomic DNA on chromosome 17q22 (NM_005450.4), comprises a single coding exon, and encodes a 1.9 kb mRNA, which is translated into a 232-amino acid N-glycosylated protein (NP_005441) with a molecular mass of 25.7 kDa (UniProt (NOGG_HUMAN, # Q13253).Bioinformatics tools were used to determine structure modeling and verification of protein by In silicoexperimentation,using Swiss-model software and MEME software for determine structute and conserved motifs identification of protein,for confirmation of protein structure using Z-score and Errat server.

Introduction

The secreted protein Noggin (Noggin1) was first discovered in Xenopus as a neural inducer produced by Spemann's organizer (Smith and Harland, 1992). Noggin1 can bind to members of one of two subgroups of the TGF cytokines, bone morphogenetic proteins (BMPs), thereby preventing BMP binding to type I and type II serine-threonine kinase receptors and inhibiting signalling mediated by Smad1/5/8 (Groppe et al., 2002; Zimmerman et al.,1996). Because of this function, Noggin1 plays a key role in many processes, including induction of neural tissue and skeletal muscles in early embryogenesis (Smith and Harland, 1992), development of cartilage (Brunet et al., 1998), and differentiation of hair follicles (Botchkarev et al., 1999)

Noggin is a glycoprotein predominantly expressed by the dorsal mesoderm during embryogenesis and is secreted as a covalently linked homodimer. Noggin is essential for cartilage morphogenesis and joint formation. It is an inhibitor of bone morphogenic proteins (BMP) signaling which is required for growth and patterning of the neural tube and somite. Defects in Noggin are a cause of symphalangism proximal syndrome (SYM1), of multiplesynostoses syndrome 1 (SYNS1), of the tarsal-carpal coalition syndrome (TCC), of stapes ankylosis with broad thumb and toes, and of brachydactyly type B2 (BDB2).

The human Noggin gene (NOG; MIM #602991), spanning ~1.9 kbof genomic DNA on chromosome 17q22 (NM_005450.4), comprises asingle coding exon, and encodes a 1.9 kb mRNA, which is translatedinto a 232-amino acid N-glycosylated protein (NP_005441) with amolecular mass of 25.7 kDa (UniProt(NOGG_HUMAN, #Q13253). Itcan be further classified by gene Ontology (GO) categories (www.geneontology.org) of biological processes of the BMP signaling path-way, cartilage development,embryonic digitandskeletaljointmorpho-genesis, and various regulatory pathways. Noggin acts as a negative modulator of the Bone morphogenetic protein (Bmp) signaling path-way by sequestering Bmps 2,4,6, and 7 in aninactive complex. It plays a critical role in early embryogenesis by inducing differentiationand development of neural tissue, skeletal muscles, cartilage and hairfollicles[13–15]

and also has a role in the development of the headstructures, including the telencephalon and eyes[16,17]

What is the normal function of the NOG gene?

The NOG gene provides instructions for making a protein called noggin. This protein is involved in the development of many body tissues, including nerve tissue, muscles, and bones. Noggin's role in bone development makes it important for proper joint formation.

Noggin interacts with members of a group of proteins called bone morphogenetic proteins begi(BMPs). These proteins

help control the development of bone and other tissues. In order to n these developmental processes, BMPs attach (bind) to other proteins called receptors, and this binding stimulates specific cellular processes. The noggin protein regulates the activity of certain BMPs by attaching to them and blocking them from binding to the receptor, which leads to a decrease in BMP signaling.

Material and Method

Structural information obtained by protein modeling

SWISS-MODEL, comparative modeling software was executed tobuild protein models from the templates obtained from eithersequence similarity or fold recognition. Swiss model is a fullyautomated server for protein structure homology-modelling. Itis accessible through expasy web server. (Arnold K. et al, 2006),(Kiefer F et al, 2009), (Guex N et al, 2009).Esypred 3D was usedfor modeling of native NOG structure. (Lambert C et al, 2002).Schematic distribution of respective conserved motifs:identified by means of MEME software.theiri.d is appMEME_4.9.11423737161648-474824057.

Discussion&Result

Structure modelling

Protein modelling plays a key role in exploring sequence structure relationships when experimental data are missing. Modelling techniques using evolutionary information, in particular homology/comparative modelling, developed into standardized pipelines over recent years.

In this model Fig-1shows,HumanNogggin protein having Zero or one per sequence, having three motifs, in their structure Minimum motif width 6 and Maximum motif width 50, in this structure model used protein sequence, shortest sequence (residue) and longest sequence residue is 223 and average length (residue) is 223.0 and total length (residue) is 223.

In this model Fig-2 shows, We developed a local model quality estimation method for membrane proteins ('QMEANBrane') by combining statistical potentials trained on membrane protein structures. The increasing number of available experimental membrane protein structures allowed us to train membrane-specific statistical potentials that approach statistical saturation.

In this model Fig-3 shows,The Z-score is -1.46, and the plot informs us that the score for high-resolution X-ray structures on average is around 0. We can see from the plot above, that while the values for C interactions, all-atom interactions and solvation energy are rather close to zero, which also causes our overall score to deviate from the ideal value. We can also get the PDB coordinates of the modeled structure.
In this model Fig-4shows,Comparision with Non-redundant set of PDB structures.

In this model Fig-5 shows, Ramachandran plot statistics for determine protein structure and the position of amino acids (aa), If the % of aa is more than 88 % in allowed region the protein model is good for in silico studies.

In this model Fig-6 shows, ERRAT is a protein structure verification algorithm that is especially well-suited for evaluating the progress of crystallographic model building and refinement. The program works by analyzing the statistics of non-bonded interactions between different atom types.

Ramachandran plot is when on x-axis You put value of phi torsion angle, and on y-axis psi angle is. Both from one residue of protein. By comparing position of your residue on that plot, with a model plot where allowed and favourite areas are marked You can evaluate structure of Your protein.

MEME is a tool for discovering motifs in a group of related nucleotide or peptide sequences.

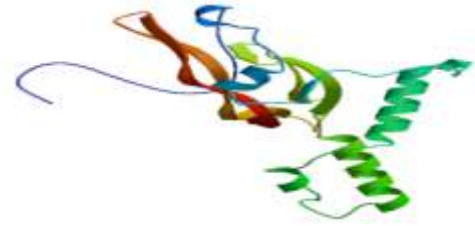

Fig 1 :3 D structure of Noggin protein modeled by SWISS-MODEL

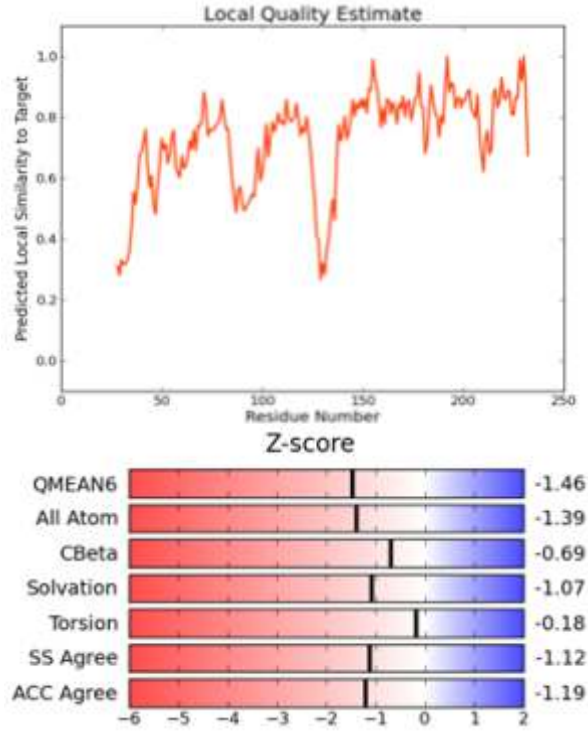

Fig-2and 3 : Predicted similarity showing accuracy

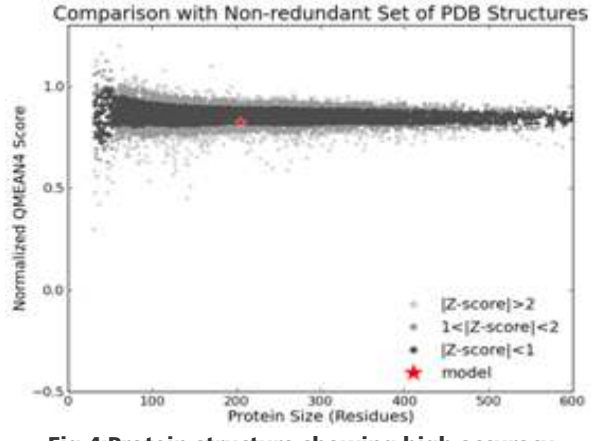

Fig-4:Protein structure showing high accuracy

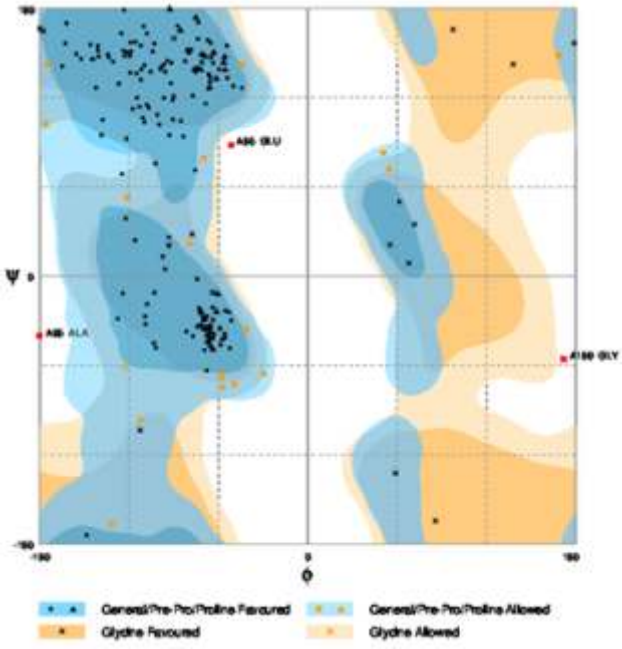

Fig-5Ramachandran Plot

The modeled structure of Noggin was refined using RAMPAGE and Erratserver.The stereo chemical properties based on backbone conformation were evaluated by inspection of Psi/Phi/Chi/Omega angle using Ramachandran plot of PDBSum database using PROCHECK server (MorrisAL. et al,1992).Structure refinement was done using RAMPAGE (LovellSC. et al, 2003).

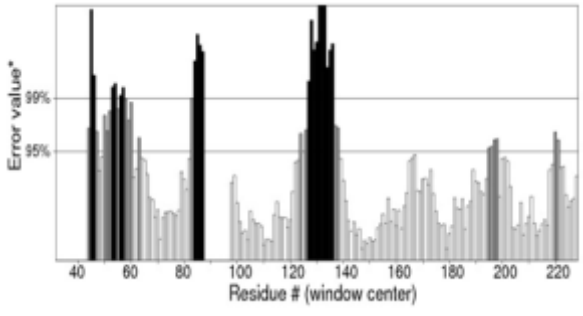

Fig-6.Plot to determine the Error valueshowing negligible error

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