Chapter 32
An Optimized In Silico Neuroinformatics Approach: Positive Regulation via DNA Interaction in Cellular Decisions for Arg to Ala Mutation in SOX11

Arundhati Banerjee
National Institute of Technology, India

Sujay Ray
University of Kalyani, India

ABSTRACT

A computationally optimized molecular analysis into the cell-fate regulations from embryonic development is one of the unexplored zones in human neurogenic field. It is governed by SOX11 (Sex determining regions-Y bOX-11) protein domain's interaction with DNA. In the present study, 3D monomer of the responsible domain of SOX11 was constructed, simulated and analyzed. Residues indulged with DNA interaction were examined. The observed conserved residue, Arg3 and Arg16 in the wild-type SOX11-DNA interaction were mutated with Ala3 and Ala16. Mutated SOX11-HMG protein sequence was re-modeled and optimized. Residue-level alteration on DNA interaction was examined. On mutation, stability of the proteins (on DNA interaction) and protein-DNA complexes were discerned via energy-calculating parameters, solvent-accessibility area, electrostatic surface-potential and conformational switching, with supportive statistical significance. Therefore, this probe provides an outlook to discern SOX11 to interact firmly with DNA via mutations and thereby perform cell-fate determinations more efficiently.

INTRODUCTION

Cell fate determination is an essential investigation in the neurogenic field for humans. The cell fate determination phenomena for the growth of a specific cell (or embryo) into the ultimate cell type (or organism) holds a paramount zone in the cytology and development. *Sox* transcription factor genes are

DOI: 10.4018/978-1-5225-0058-2.ch032

found to play key roles as regulators of cell fate decisions beginning from the embryonic development (Megan & Peter, 2002). They are highly responsible in genomic organization (Megan & Peter, 2002). SOX (Sex determining regions-Y bOX) proteins bind sequence-specifically to the DNA with the aid of a particular domain. This domain allows the participation of the protein as factors for transcription and is well-known as the high-mobility group (HMG) domain (Sarkar & Hochedlinger, 2013). Accumulating evidence documents them to play essentially necessary role in homeostasis and regeneration performance of the tissues in the adults (Bowles, Schepers & Koopman, 2000). Several proteomics related experimental studies involving yeast-two hybrid assays as well as PCR studies have been investigated for the examinations in wet-laboratory works (Bowles, Schepers & Koopman, 2000).

These developmentally essential Sox family regulate several different zones of growth, coordination and maturity, including not only sex determination but also neuronal development. Initially, the switching-over to the migratory state of the cerebellums' epithelial granule cells is carried out by *Sox2* and *Sox3* (Rex et.al., 1998). Thereafter, *Sox11* aids in differentiating these migrated granule cells to their respective granule neurons (Rex et.al., 1998).

The brain with the assistance of the dentate gyrus and the progenitor cells; generates novel neurons, during the entire growth and maturation of mammals (Bowles, Schepers & Koopman, 2000). The extrinsic synapses further firmly control the complicated production of the newly developed functional neurons (Bowles, Schepers & Koopman, 2000). SOX11 is recognized to be notably present in the neurogenic areas of the adult brain as a paramount protein for transcription (Anja, Tobias, Marcela, & Chichung, 2009). The HMG-box transcription factor: SOX11 was studied to maneuver in undifferentiated neural stem cells (Maria, Martin, Michal, Thomas & Jonas, 2006). They further encourage cell cycle exit and commence a neurogenic program (Maria, Martin, Michal, Thomas & Jonas, 2006). Documentation reveals SOX11 to function as transcriptional activator (Maria, Martin, Michal, Thomas & Jonas, 2006). Developmental anomalies are raised when these essential proteins get mutated.

Few previous studies have suggested the fact of the interaction of few of the SOX proteins with DNA (Jauch, Ng, Narasimhan, & Kolatkar, 2012). But so far, there are no such documentations with the performance of the vital regulatory and the molecular mechanisms in the Sox family, with a prior and dominating focus on the neurogenic field for the decisions for the developed cells at every instance. So, for the purpose, the molecular and residue level approach for the cytological fate determination governor; SOX11 HMG domain, its interactions with DNA and mutational alterations was essential to be discerned.

In the present scenario, therefore, the probe focuses to explore the molecular level participation for the involvement of SOX11 protein's HMG domain in the performance for the regulation of cell fate decisions. The computational 3D functional tertiary state of SOX11 HMG domain was prepared by homology modeling after satisfying their varied stereo-chemical properties. This modeled protein was further docked with the known DNA model that was extracted from the documented X-Ray Crystal complex structure of SOX4-HMG domain and DNA complex (Jauch, Ng, Narasimhan, & Kolatkar, 2012). Both the structures were energy optimized and were simulated separately. The study further followed with the formation of the DNA-protein complex through protein-DNA docking techniques. The best complex model was selected via comprehensive studies and the complex structure was also energy optimized. Not only were the interactions between the DNA with the modelled SOX11-HMG domain, but also the binding residues were analysed then-after. The HMG domains from all the SOX proteins were extracted and these multiple sequences of the HMG domains were aligned to observe their conserved residues. Those conserved residues that were also included in the binding regions of