A Protein Moonlighting Based Model to Reveal Transcription Factor Druggability for Prostate Carcinoma

Sagnik Sen

Jadavpur University Faculty of Engineering and Technology

Ashmita Dey

Jadavpur University Faculty of Engineering and Technology

Ujjwal Maulik (✉ ujjwal.maulik@jadavpuruniversity.in)

Jadavpur University Faculty of Engineering and Technology

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Abstract

Background

Prostate cancer is the second leading cause of cancer-related death in men in the United States. Metastasis shows poor survival even though the recovery rate is high. In spite of numerous studies regarding prostate carcinoma, multiple questions are still unanswered. In this regard, gene regulatory network can uncover the mechanisms behind cancer progression, and metastasis. In the regulatory network, among the three prime molecular members, transcription factors and microRNAs are known for their regulatory activity where transcription factor can target both microRNAs and genes. Under a feed forward loop, transcription factors can be a good druggable candidate. However, due to the dynamic nature of transcription factors, designing an appropriate drug becomes challenging.

Result

We have proposed a computational model to study the uncertainty of transcription factors and suggest the appropriate cellular conditions for drug targeting. We have selected feed-forward loops depending on the shared list of the functional annotations among transcription factors, genes, and miRNAs. From the potential feed forward loop cores, six transcription factors were identified as druggable targets, which include AR, CEBPB, CREB1, ETS1, NFKB1, and RELA. The selected transcription factors have been investigated based on the evolutionary co-variance study, post-translation modifications, and disordered region identification. The structural unrest of the selected transcription factors can be observed from outcomes. Comparing the results of the aforementioned analyses, probable binding clefts have also been identified. Transcription factors are known for their Protein Moonlighting properties, which provide unrelated multi-functionalities within the same or different subcellular localizations. Following that, we have identified such functions that are suitable for drug targeting. Finally, we have tried to identify membraneless organelles for providing more specificity to the proposed time and space theory.

Conclusion

The study has provided certain possibilities on TF based therapeutics. The controlled dynamic nature of the TF may have enhanced the chances where TFs can be considered as one of the prime drug targets. The usual presence of TF at nucleus cannot explain its functional multiplicity whereas nucleus speckles can help to explain it. Finally, the combination of membranless phase separation and protein moonlighting has provided possible druggable period within the biological clock.

Full Text

Due to technical limitations, full-text HTML conversion of this manuscript could not be completed. However, the manuscript can be downloaded and accessed as a PDF.

Figures

Figure 1

The circos plot to represent the association of the selected TFs with the shared pathways. Four pathways are found common among the selected molecular regulators including prostate cancer. The color and different size of the ribbon shows the type of relation depending on the p-value of the pathway and its corresponding TFs. The circos plot is used for better visualization of the tabular data. Here, the ribbons are connected between the TFs and their sharing pathway. The extent of the association is represented

Figure 3

A weighted network GDCA and corresponding color modules based on over all residual co-variation from DI score.

Figure 4

The representation of the residues having post transnational modification for each selected TFs.

Figure 5

The overlapped areas obtained from PONDR and IUPred databases. Result from PONDR and IUPred is represented with orange and grey color respectively.

Figure 6

The stability score of the amino acids of six TFs along with their bonds occurred in a particular residue. Torsion, Van der Waals, Chi and Cis-bond are represented with color yellow, green, red and orange respectively.

Figure 7

Top five diseases, based on the p-values, of each TFs are selected to establish the network. Green colour nodes are diseases, connected with all four TFs (red oval nodes). Green colour nodes represent the diseases targeted by five out of six TFs.

Supplementary Files

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