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Research Topic: Investigation of Complex Signaling Processes in p53 Regulatory Pathways using Graph Theory

Abstract

Cancer is a complex disease. Apart from the cancer(s) common in Homo *sapiens* Breast, Cervical and Ovarian cancer are the leading cause of deaths in women's worldwide. Breast cancer being the second most cause of death around the globe, it is followed by ovarian and cervical not only in pathology also mortality rate. The present amount of knowledge given by high-throughput screening in these cancer(s) fills up one face of the coin (i.e. individual study) while the other face (systems view) only has a glimpse. Thus, this gap between the experimental and theoretical analysis gives us the opportunity to rediscover the underlying principles of cellular automata under cancerous condition. Also, to define new avenues of research like self--tolerance, stability, self--organisation and multifractility present.

The present study gives the detailed account of the various important regulators that interacts with p53 directly or indirectly via signalling molecules in complex signal processing under normal or cancerous condition. Some of the work likes Notch--Delta (prominently associated with ovarian cancer) provides the view of control by p53 and Gsk3-β provides the link between two or more cross--talks. These complex cross--talk between these important pathways are reflected both in dynamics of p53 and the network formed at that state (using time series). So, we could able to find 5 distinct dynamical states along with the fractality of the system dynamics. Further, some of the important behaviours of the system can be studied using various time series analysis techniques, such as visibility graph, information theoretical analysis and multifractal analysis. Moreover, we also studied complex networks constructed from the experimentally verified genes, and using well known human databases and related resources. Thus, the study is divided in to two major parts first focuses on the network theoretical approach and second part tries to bring up the behaviour of p53 in approximately real situations. In the following paragraphs we have provided brief accounts of the individual studies and tried to co-relate them, it is as follows.

Key findings

- We constructed complex breast, cervical and ovarian cancer network from experimentally verified genes is found to obey hierarchical scale free features organized by topology of heterogeneous modules coordinated by diverse leading hubs.

- The networks was found to have modular structure are devised by fractal rules with the absence of centrality-lethality rule.
- We devised a method to identify few fundamental key regulators from a large number of leading hubs, which are deeply rooted in the network, serve as backbones of it and key regulators from grassroots level to complete network structure.
- We identified eleven, seven and five fundamental key regulators (FKRs) in breast, cervical and ovarian cancer.
- Out of these FKRs p53 (keeping low profile), AKT1 plays central role in two ways, first it serves as main regulator of ovarian cancer network, and second serves as key cross-talk agent of other fundamental key regulators, but exhibits disassortive property.
- p53-Mdm2-miR-125b regulatory network induced in p53-MDM2 auto-regulatory loop by molecules (miRNAs and nutilin), effect p53 dynamics and drives the system to various dynamical states.
- The stress system prefers to stay in normal dynamical state (in case of miRNA-125b induction), while on the other hand in case of miRNA controlling MTBP the system prefers apoptotic state.
- The presence of switching mechanism at different dynamical states of p53 corresponds to various cellular states.

Implication of the study

We hope this study may highlight the switching mechanism at different dynamical states of p53 corresponds to various cellular states. These studies show that the introduction of stress in the p53 regulatory network allows switching the stabilized p53 state to oscillatory dynamics via DNA damage and further excess stress may lead to apoptosis. This stress system prefers to stay in an active dynamical state which has simple fractal rule subjected to the optimal fluctuations available due to active molecular interaction driven by stress. However, the system still associates a group of few hubs (assortive topology), but not in dependent manner (absence of these hubs do not cause system's breakdown), for better signal processing and system regulation. Then this stress signal is propagated throughout the pathways, and found to inherit all the properties of the propagator pathway to the receiver pathways may be with slight modifications in them. This excellent co-ordination in cross-talk helps the system to save it from one directional apoptosis (once the system falls in this phase, it can never come back to normal situation) by regulating available active molecular interaction. This regulating mechanism could be different depending on the type of stress induced in the system. It may also open up new understanding on perturbation in the network which affect in local stability to global stability in network will give deep insight in how natural networks self-organized subject to the perturbations in the network.