

Comparison of molecular signatures in large-scale protein interaction networks in normal and cancer conditions of brain, cervix, lung, ovary and prostate

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Abstract—Background: Cancer, the disease of intricateness, has remained beyond our complete perception so far. Network systems biology (termed NSB) is one of the most recent approaches to understand the unsolved problems of cancer development. From this perspective, differential protein networks (PINs) have been developed based on the expression and interaction data of brain, cervix, lung, ovary and prostate for normal and cancer conditions. **Methods:** Differential expression database GeneHub-GEPIS and interaction database STRING were applied for primary data retrieval. Cytoscape platform and related plugins named network analyzer; MCODE and ModuLand were used for visualization of complex networks and subsequent analysis. **Results:** Significant differences were observed among different common network parameters between normal and cancer states. Moreover, molecular complex numbers and overlapping modularization found to be varying significantly between normal and cancerous tissues. The number of the ranked molecular complex and the nodes involved in the overlapping modules were meaningfully higher in cancer condition. We identified 79 commonly up-regulated and 6 down-regulated proteins in all five tissues. Number of nodes, edges; multi edge node pair, and average number of neighbor are found with significant fluctuations in case of cervix and ovarian tissues. Cluster analysis showed that the association of Myc and Cdk4 proteins is very close with other proteins within the network. Cervix and ovarian tissue showed higher increment of the molecular complex number and overlapping module network during cancer in comparison to normal state. **Conclusions:** The differential molecular signatures identified from the work can be studied further to understand the cancer signaling process, and potential therapeutic and detection approach.

Key words: Cancer, NSB, GeneHub-GEPIS, Cytoscape, Myc, Cervix, Ovary

INTRODUCTION

Cancer is an abnormal manifestation caused by the process of tumorigenesis due to the mutation in oncogenes and tumor suppressor genes. Mutation produces chromosomal aberration, genomic and proteomic instability and finally, abnormal proliferation and differentiation. Different methods such as clonal genetic

model, epigenetic model and cancer stem cell model tried to uncover the complicatedness of cancer (Shackleton et al., 2009). However, most of these approaches bring little satisfactory results to unfold cancer completely. The stochastic nature of cancer initiation requires the dynamic approach to endue their non-linear function resulting in the alternation at both genomic and proteomic level (Bizzarri and Cucina,

2014). Notably, cancer forms an extreme interactive complexity and progresses due to the association of multiple interactions of numerous constituents of cells and tissues (Sonnenschein et al., 2014). The interconnection gene map uncovered significant interconnectivity between known and candidate cancer gene products, providing unbiased evidence for an expanded functional cancer landscape while demonstrating how high-quality interaction models will help “connect the dots” of the genomic revolution (Rolland et al., 2014). And the tremendous work of Cancer Genome Atlas Research Network (<http://cancergenome.nih.gov/>) opens a new era to develop therapy against cancer by mapping the genetic changes in 20 cancers. An integrative study like NSB could be a better way to understand the intricate pattern of cancer. Comparative analysis of changes in protein-protein interaction (PPI) network's features between normal and cancer condition can be a handy tool to decipher the conversion of a normal cell into a cancer one (Islam et al., 2013). Generally, bimolecular networks divide into modules according to the concentration of the nodes in the network. The modules are the subsets of the network that indicate the connectedness among the nodes within the module through edges. The nodes involved in a module are highly connected with each other (Rives and Galitski, 2003). Importantly, the identification of such modules in a network is essential to understand the structural and functional features of a network (Barabási et al., 2011).

However, pharmaceutical bioinformatics is impending towards *in silico* molecular target analysis and developing computational tools for delineating the concept of modern therapeutics. As a result, cancer-specific PPI network scanning can serve as candidates of drug target for developing novel cancer therapy (Jeon et al., 2014). The objective of our work was to analyze the complex differential PPI networks in normal and cancer condition of brain, cervix, lung, ovary and prostate. Our analysis based on the gene expression and interaction data for the proteins involved in cancer signaling pathways. MCODE was used to find the highly interconnected regions (clusters) of the networks (Stevens et al., 2014). Another method ModuLand was used for identification of the hierarchical layers of overlapping modules and crucial nodes of the networks (Szalay-Beko et al., 2012). Tissue-specific networks analysis methods can be used to predict lineage-specific responses to uneasiness, identify the

changing functional roles of genes expression across tissues and brighten relationships among diseases (Greene et al., 2015). In contrast with tissue-naive networks and cancer, which help to assume that the function of genes across tissues, these maps can answer biological questions that are specific to a single gene in a single tissue.

MATERIALS AND METHODS

Data retrieval

Cancer cell map database PC (<http://www.pathwaycommons.org/pc/home.do>) was used to make a list of protein molecules involved in major cancer signal transduction pathways (Cerami et al., 2010). We considered ten major signal transduction pathways are α -6- β -4-integrin, androgen receptor, kit receptor, Egfr1, Hh, Wnt, Id, Notch, Tgf β R and Tnfa/NF-kB. Expression of different protein molecules in both normal and cancer condition for selected tissues was accumulated by GeneHub-GEPIS (<http://researchpubic.gene.com/Research/genentech/genehub-gepis/index.html>) (Zhang et al., 2007).

Construction and analysis of differential networks

Possible PPIs was studied through STRING (<http://string.embl.de/>) (Mering, 2003). Differential protein expression of selected tissues for normal and cancer state were studied using GeneHub-GEPIS. Java programming language was used to determine the valid interactions by using Textpad 4.42 version. In that case, expressed proteins were assigned value 1 and unexpressed proteins were assigned value 0. Then binary calculation was utilized to determine the valid interactions. Only 1+1=1 represents valid interaction and 1+0=0, 0+1=0, 0+0=0 denotes invalid interactions. In the algorithm, the interaction is stated as yes (1) or no (0). From the biophysics point of view, this is a bold simplification. We understand that this is the common use in this strategy but a comment indicating that reality is more complicated is also necessary. We also performed a weight for the interaction strength which indeed a good option (Data not shown). Cytoscape 2.8.3 version was used to construct the PPI networks for both normal and cancer condition for the tissues. Network analyzer, a plugin of Cytoscape software package was used to analyze the simple network parameters (Shannon, 2003).

Identification of common cluster in PPI networks

The protein expressions were studied to determine whether they are up-regulated or down-regulated during transformation into cancer state from normal one. The proteins that were commonly up-regulated and down-regulated in all studied tissues during cancer condition were identified. Their relevant interactions were identified; while commonly down-regulated proteins were ignored (contributions of only six commonly down-regulated proteins were negligible). We used the computational methods as described by Rahman et al., 2013 (Rahman et al., 2013). In brief, Microsoft Excel 2010 was used to subtract normal condition expression (digital expression unit) value from cancer condition expression of signaling proteins and TextPad 4.42 version was used to code in JAVA programming language to isolate up-regulated proteins from down-regulated one. Interactions within these commonly up-regulated proteins during cancer condition were depicted in networks constructed with Cytoscape 2.8.3 version (Smoot et al., 2010). Using the human PPI network as a backbone, (Srihari and Ragan, 2013) infer two tissue condition-specific PPI networks, one for normal and one for tumor, by incorporating expression and mutation profiles of genes in the two conditions, they systematically tracking of dysregulated modules and identified novel genes in cancer.

Network modularity analysis

Module discovery in biological networks has been extremely powerful for elucidating molecular machinery underlying physiological and disease phenotypes. Numerous approaches have been advanced to mine such networks for identifying biological modules, including methods for clustering interactions and those based on topological features of the network such as degree and betweenness centrality (Mitra et al., 2013).

Briefly, MCODE and ModuLandcytoscape plugins were used to analyze network modularity (Bader and Hogue, 2003; Szalay-Beko et al., 2012). One hand MCODE needed to detect molecular complexes those were the densely connected regions in protein interaction network. On other hand, ModuLand was used to determine the overlapping network modules. Unweighted network option was used with default value 1 to create correlation matrix and module correlation histogram. The graph related parameters were studied by the measure option of ModuLand.

RESULTS AND DISCUSSION

Network analyzer study

Primarily we analyzed the PINs for the brain, cervix, lung, ovary and prostate tissue in both normal and cancer conditions. We observed some fluctuations in the parameters during cancer condition comparison to normal ones. A number of nodes, number of edges, multi-edge node pair, and average number of neighbor are higher in all five tissues in cancer condition. Interestingly, significant fluctuations in different parameter found in case of cervix and ovarian tissues. **Fig. 1 (1a and 1b)** represents the biolayout of protein interaction network for ovary and cervix in normal and cancer condition. These changes indicated the strengthening of modules possibly abetting cancer. All other biolayout of protein interaction networks were shown in **Supplementary file S1 (S1a1, S1a2; S1b1, S1b2; S1c1, S1c2)**. (Srihari and Ragan, 2013) performed a straightforward systematic identification and comparison of modules across pancreatic normal and cancer tissue conditions by integrating PPI and gene-expression data. They found some modules showed differences in gene regulation to prompt pancreatic and breast cancer. However, genomic alterations in lung cancers have not been comprehensively characterized, and no molecularly targeted agents have been specifically developed yet. Notably, the Cancer Genome Atlas Research Network analyzed squamous cell lung cancers and found statistically recurrent mutations in 11 genes, including mutation of TP53. They discovered loss-of-function mutations in the HLA-A class I MHC gene. Additionally TCGA identified significantly altered pathways included NFE2L2, KEAP1, phosphatidylinositol-3-OH kinase, CDKN2A and RB1 (Willett et al., 2013).

From our network analyzer data, it is a clear indication that there may be some candidate proteins which are responsible for the abnormal proliferation in cancer, and are not able to be expressed in normal condition. On the other hand, network density and characteristics path length are always lower in cancer condition for all five tissues. However, it is also revealed that the nodes within the networks are more connected to each other and form clusters in cancer condition. Other network parameters also have shown different degree of fluctuation during cancer condition in comparison to normal state. List of common network parameters for both the normal and cancerous condition showed in **Table 1**.

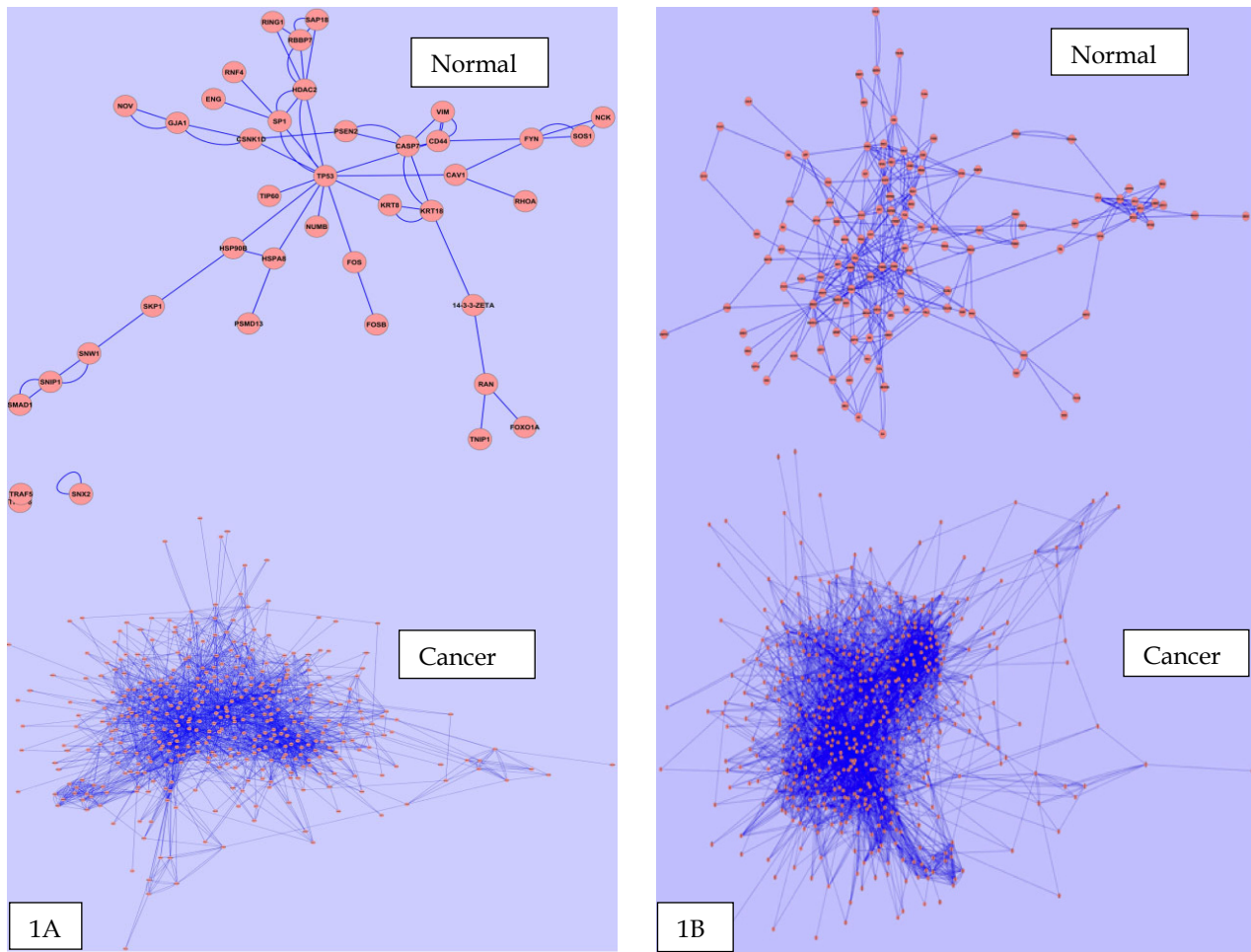


Figure 1. BioLayout of protein interaction network for cervix (1A) and ovary (1B) in normal and cancer condition.

Table 1. Common network parameters for both the normal and cancerous condition

Parameter	Brain		Cervix		Lung		Ovary		Prostate	
	Normal	Cancer	Normal	Cancer	Normal	Cancer	Normal	Cancer	Normal	Cancer
Clustering co-efficient	0.307	0.302	0.150	0.295	0.306	0.306	0.284	0.303	0.289	0.294
Connected component	1	1	3	1	1	1	1	1	1	1
Network diameter	6	6	10	7	6	6	9	7	6	6
Network radius	4	4	1	4	4	4	5	4	4	4
Network centralization	0.152	0.163	0.236	0.176	0.166	0.160	0.185	0.156	0.179	0.171
Shortest path	372710 (100%)	326612 (100%)	1334 (100%)	156420 (100%)	196692 (100%)	259590 (100%)	14762 (100%)	260610 (100%)	154842 (100%)	202950 (100%)
Characteristics path length	2.749	2.766	3.907	2.862	2.800	2.801	3.436	2.804	2.826	2.805
Avg. number of neighbor	17.375	16.203	2.25	11.929	13.766	14.835	5.0	14.849	12.061	13.259
Number of the node	611	572	40	396	444	510	122	511	394	451
Number of the edge	7047	6134	61	3111	4032	5010	389	5098	3107	3937
Network density	0.028	0.028	0.058	0.030	0.031	0.029	0.041	0.029	0.031	0.029
Network heterogeneity	0.898	0.895	0.775	0.873	0.916	0.894	0.850	0.879	0.930	0.900
Isolated nodes	0	0	1	0	0	0	0	0	0	0
Number of the self-loops	1	1	1	1	1	1	1	0	1	1
Multi-edge node pair	1738	1499	15	6.405	975	1226	83	1304	730	946

We analyzed the up-regulated and down-regulated proteins in cancer condition from the expression data (**Supplementary file S2: S2a and S2b**). We found 79 commonly up-regulated and 6 commonly down-regulated proteins in all five tissues (**Fig. 2**). Eng, FHL1, FO5, FOSB, MITF and SAP1B were the commonly down-regulated genes. However, the Cancer Genome Atlas Network characterized somatic alterations in colorectal cancer of 276 specimens. They found silencing of MLH1 and polymerase e (POLE) due to hypermutation, and mutated version of APC, TP53, SMAD4, PIK3CA, KRAS, ARID1A, SOX9 and FAM123B (Network, 2012). TCGA Integrative analyzes suggest new markers for aggressive colorectal carcinoma and an important role for MYC-directed transcriptional activation and repression.

In our studied samples, the commonly down-regulated proteins were very few in number, we ignored them. The network of commonly 79 up-regulated proteins forms a cluster within the network. Cluster analysis showed that the association of MYC and CDK4 proteins is very close with other proteins within the network (**Fig. 3**). The association of c-MYC and CDK4 proteins has actually been well known from in vivo experiment (Lapenna and Giordano, 2009). Moreover, Myc and Cdk4 is also well established therapeutic target in studying different cancers (Choi, 2011), but the different forms of MYC (n- and l-myc) yet to know. It is crucial that MYC plays important role in cancer progression by inactivating the checkpoints protein such as p53. MYC also activates ribosomal and mitochondrial biogenesis, glucose metabolism, glutamine metabolism, lipid synthesis, cell cycle progression which is responsible for cancer cell growth (Miller et al., 2012; Tansey, 2014). Independently p21 can promote oncogenesis by promoting the assembly of complexes of cyclin D with Cdk4 (Abbas and Dutta, 2009). Aberrant expression of the cell cycle associated protein cdk4 in cervical carcinomas (Skomedal et al., 1999). The growth of BG-1 ovarian cancer cells is promoted by via up-regulation of Cdk4 genes (Choi, 2011). MYC and Cdk4 are well-known drug target against cancer (Hermeking, 2003; Lapenna and Giordano, 2009).

Molecular complex detection

Molecular complex detection (MCODE) method has been used to detect possible modules that could be said as molecular complexes. Nevertheless, the rank molecules are in a consecutive order as per their score value where the number of molecular complexes is varied between normal and cancer condition. In all cases, possible molecular complex numbers are higher in cancer condition except the brain. Molecular complex number is significantly increased (at $p\text{-value} \leq 0.05$) between normal and cancer conditions (**Supplementary file S3**). Similar result was also found in previous studies (at $p\text{-value} \leq 0.05$) of Islam et al., 2013 (Islam et al., 2013). The ranked molecular complex numbers of normal and cancer protein interaction networks are 35 and 31 for brain, 6 and 30 for cervix, 24 and 30 for lung, 14 and 33 for ovary and 14 and 25 for prostate, respectively. However, cervix and ovarian cancer showed higher increment of the molecular complex number during cancer in comparison to normal state (**Fig. 4**). All other tissues molecular complex data has been represented in **Supplementary 4 (S4a1, S4a2; S4b1, S4b2; S4c1, S4c2)**. The Cancer Genome Atlas project (TCGA) has analyzed 805 high-grade serous ovarian cancer and found TP53 mutations in nearly all; several genes mutated at lower frequencies including NF1, BRCA1, BRCA2, RB1 and CDK12; and reported NOTCH and FOXM1 signaling are involved in serous ovarian cancer (Network, 2012). Additionally, TCGA network identified 22 genes for which inhibitors already exist were identified in regions of recurrent amplification.

In our MCODE analysis parameters e.g. scores, nodes and edges of the molecular complex networks are also varied between normal and cancer condition for each tissue. It has already been identified that disease genes show higher degree of connectivity in comparison to non-disease genes in the cases of expression and interaction of proteins (Jonsson and Bates, 2006). Moreover, some studies also indicate that in cancer condition the protein shows higher degree of connectivity in comparison to normal state (Sun and Zhao, 2010).

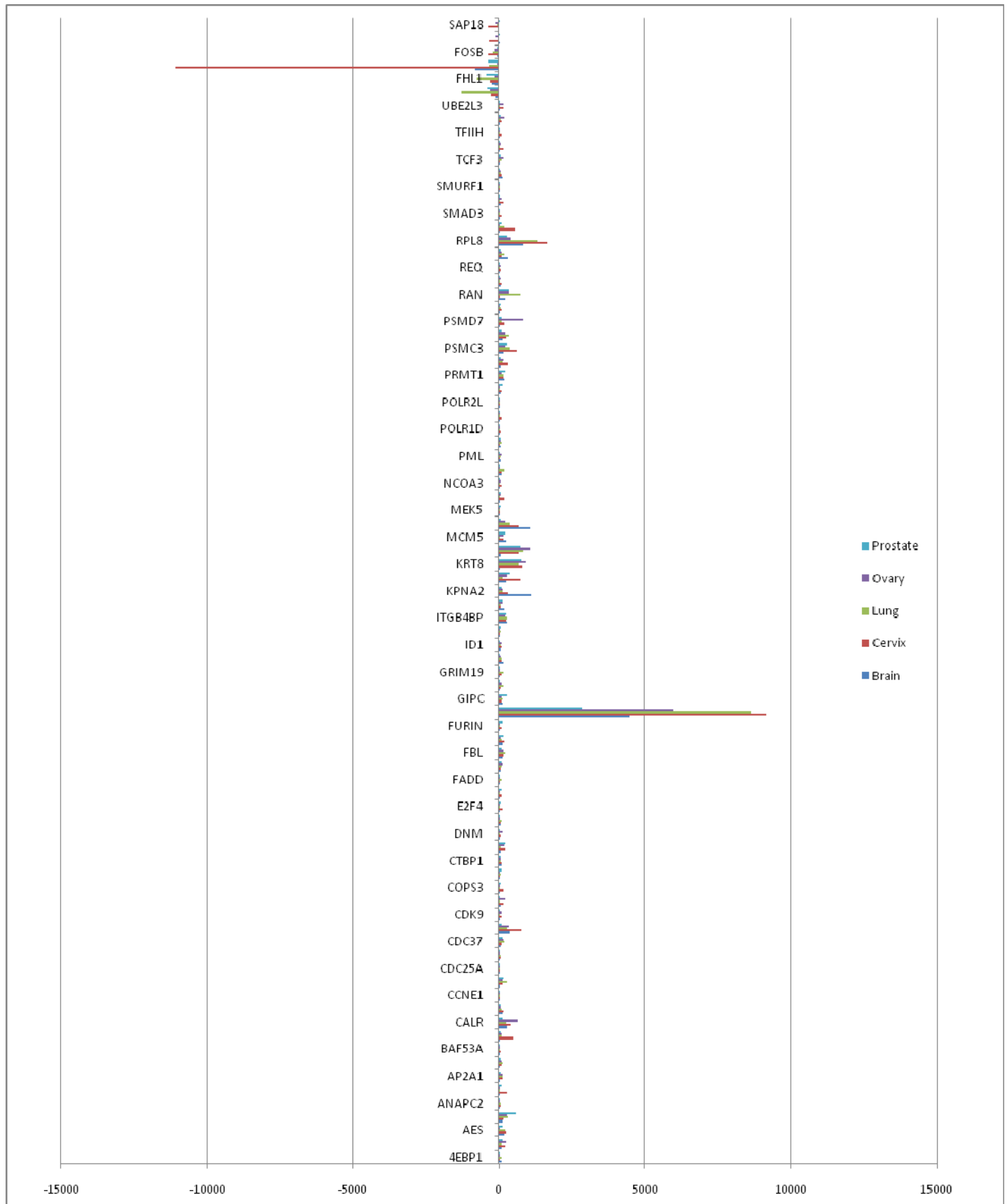


Figure 2. Commonly up-regulated and down-regulated proteins in all five cancerous tissues. Y axis: five tissues digital expression unit (DEU) in cancer condition and X axis: upregulated and downregulated proteins in cancer condition.

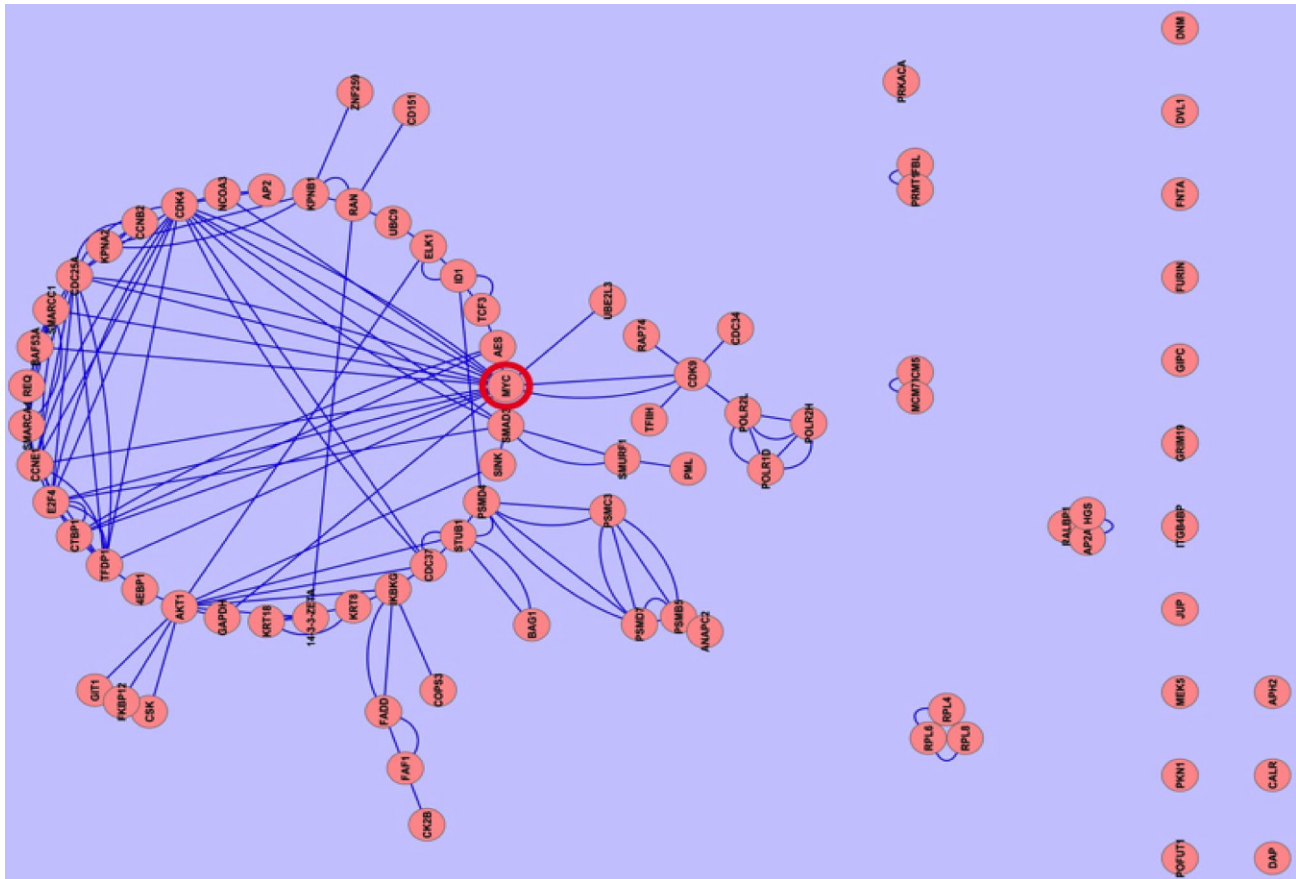


Figure 3. Interaction among commonly up-regulated proteins in all five tissues during cancer condition.

4A: MCODE analysis of protein interaction network in cervix

Network	Details	Network	Details	Network	Details	Network	Details	Network	Details
	Rank: 1 Score: 2 Nodes: 3 Edges: 6		Rank: 1 Score: 8.059 Nodes: 17 Edges: 137		Rank: 7 Score: 2.6 Nodes: 5 Edges: 14		Rank: 13 Score: 1.333 Nodes: 3 Edges: 4		Rank: 19 Score: 1 Nodes: 2 Edges: 2
	Rank: 2 Score: 1.4 Nodes: 5 Edges: 7		Rank: 2 Score: 5.522 Nodes: 23 Edges: 127		Rank: 8 Score: 2.375 Nodes: 14 Edges: 38		Rank: 14 Score: 1.333 Nodes: 3 Edges: 4		Rank: 20 Score: 1 Nodes: 2 Edges: 2
	Rank: 3 Score: 1 Nodes: 2 Edges: 2		Rank: 3 Score: 4 Nodes: 8 Edges: 20		Rank: 9 Score: 1.875 Nodes: 6 Edges: 30		Rank: 16 Score: 1 Nodes: 3 Edges: 2		Rank: 21 Score: 1 Nodes: 2 Edges: 2
	Rank: 4 Score: 1 Nodes: 2 Edges: 2		Rank: 4 Score: 3.8 Nodes: 20 Edges: 76		Rank: 10 Score: 1.824 Nodes: 17 Edges: 31		Rank: 16 Score: 1 Nodes: 2 Edges: 2		Rank: 22 Score: 1 Nodes: 3 Edges: 3
	Rank: 5 Score: 1 Nodes: 2 Edges: 2		Rank: 5 Score: 3.2 Nodes: 5 Edges: 16		Rank: 11 Score: 1.75 Nodes: 4 Edges: 7		Rank: 17 Score: 1 Nodes: 2 Edges: 2		Rank: 23 Score: 1 Nodes: 2 Edges: 2
	Rank: 6 Score: 1 Nodes: 2 Edges: 2		Rank: 6 Score: 3.047 Nodes: 15 Edges: 46		Rank: 12 Score: 1.667 Nodes: 6 Edges: 10		Rank: 18 Score: 1 Nodes: 2 Edges: 2		Rank: 24 Score: 1 Nodes: 2 Edges: 2

Normal state

Cancer state

4B: MCODE analysis of protein interaction network in ovary

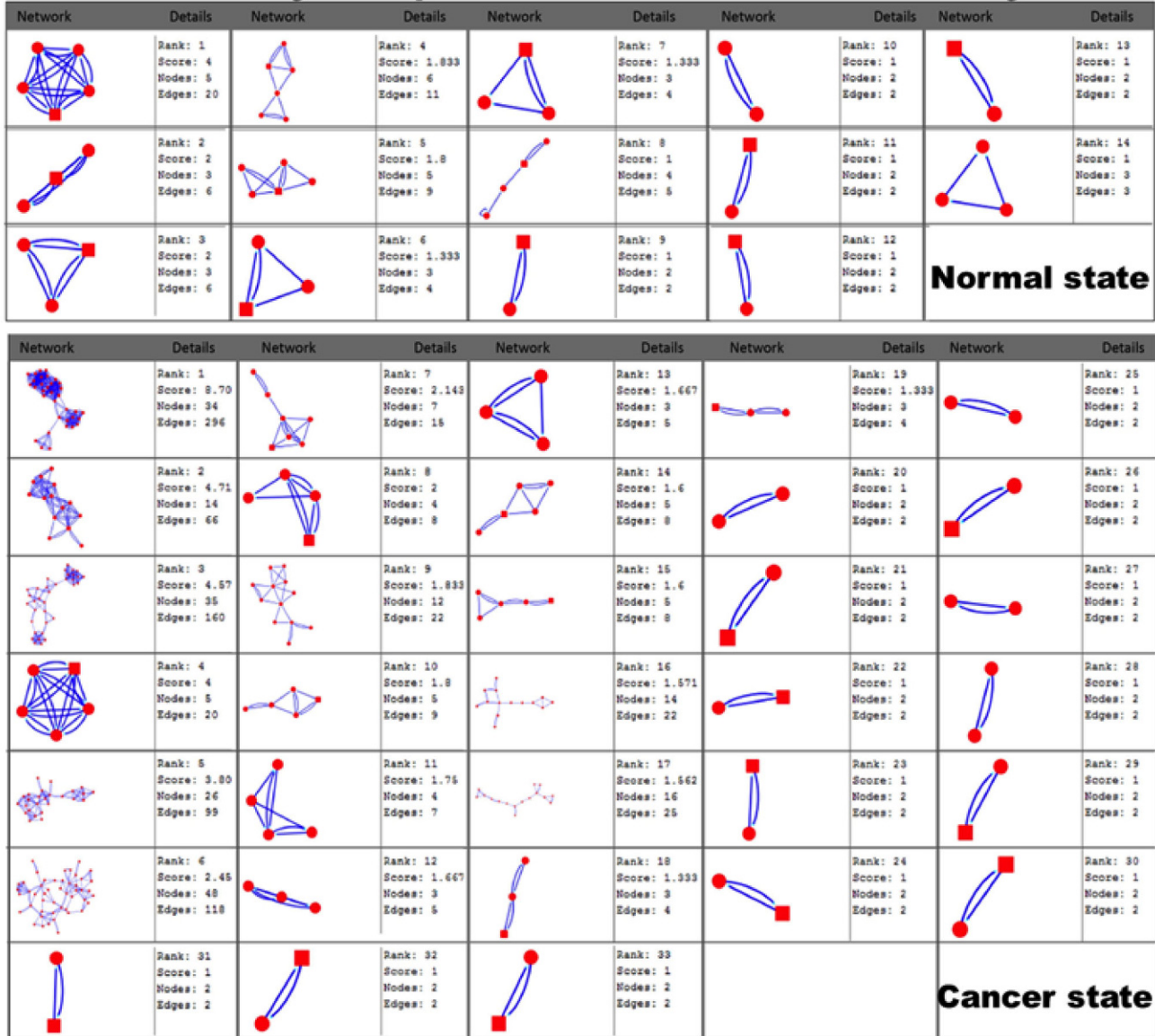


Figure 4. MCODE analysis of protein interaction network in 4A: Cervix and 4B: ovary for normal and cancerous tissue.

ModuLand study

Discovery of active modules has shown the way for diagnostic and therapeutic interventions. For instance, active modules showing the patterns of gene expression correlated with specific disease phenotypes can help to develop valuable biomarkers for disease classification (Mitra et al., 2013). However, our ModuLand study showed that overlapping modules between normal and cancer states were different for all five tissues (Fig. 5). In the brain, numbers of nodes and edge forming the overlapping networks were decreased in cancer condition (Fig. 5A). But, in other cases, the node and the edge number forming the

overlapping network were increased. The highest fluctuation of overlapping module occurs in case of ovary (Fig. 5D). In ovary, the number of nodes forming the overlapping module was 5 in normal tissue and 11 in cancer. The nodes of the overlapping module can be said as the crucial nodes with module centrality of the respective network. The important network properties of the overlapping modules were also shown the different degree of fluctuation, which has been compared (Supplementary file S5: S5a1, S5a2; S5b1, S5b2; S5c1, S5c2; S5d1, S5d2; S5e1, S5e2). Module-based biomarkers achieve greater predictive power and reproducibility over single gene markers, as demonstrated for the classification of several forms of cancers in-

cluding breast cancers (Chuang et al., 2007), ovarian cancer (Bapat et al., 2010) and glioblastomas (Miller et al., 2011). Because active modules can reveal pathway-centric insights reinforced by multiple lines of evidence, they naturally provide mechanistic explana-

tions for complex traits and multi-genic diseases like cancer. Moreover, active modules can assist in the discovery of drug-target pathways and in predicting response to chemotherapy.

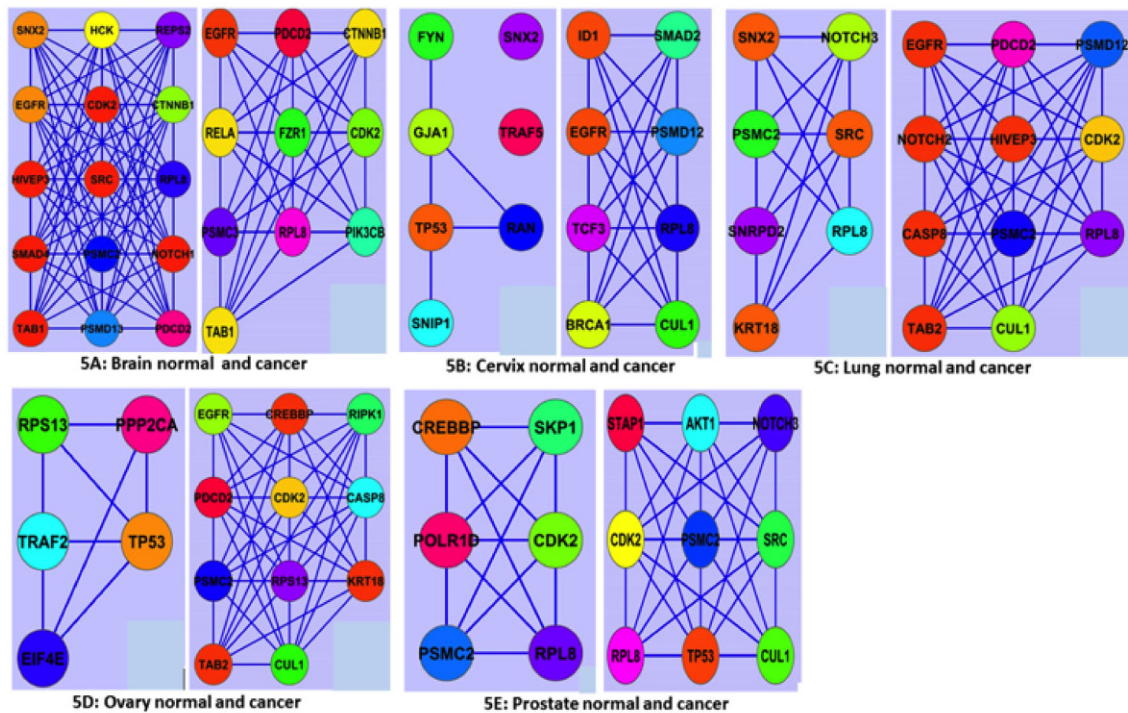


Figure 5. The overlapping modules in normal and cancer condition for Brain (5A), cervix (5B), lung (5C), ovary (5D) and prostate (5E) tissues.

The correlation among the nodes of the overlapping modules was represented by correlation matrix and correlation histogram. Correlation matrix represents possible interactions of the overlapping modules at a certain threshold level (here 1.0). Correlation matrix (Supplementary file S6: S6a1, S6a2; S6b1, S6b2; S6c1, S6c2; S6d1, S6d2; S6e1, S6e2) and histogram indicate that the nodes of overlapping modules show different degree of interaction in normal and cancer condition (Fig. 6). Number of the nodes involved in overlapping modules is significantly increased (at $p\text{-value} \leq 0.01$) between normal and cancer conditions in all five tissues except brain (Supplementary file S7).

This study speculates cancer associated complexes which are real biologically functional units and leads us to stride on the biological reality. However, our comprehensive network modularity analysis can address the molecular signatures which can be the promising candidates of drug target for cancer therapy. The network modularity robustness, on the other hand,

can provide a new paradigm to understand the relationship between cellular networks and cancer de-meanors. In our study, brain shows different results in both detection of molecular complex and detection of overlapping modules.

Unlike other tissues, number of ranked molecular complexes and nodes involved in the overlapping module are lower in cancer condition. Intriguingly, cancers having the protein interaction networks of lower molecular complex with less modular signaling are more curable than others. Here we considered commonly used un-weighted and static network which may lower its reliability to understand the real the dynamic physical nature of living tissues. The further expedition is required for better understanding of the networking level of biological processes of cancer.

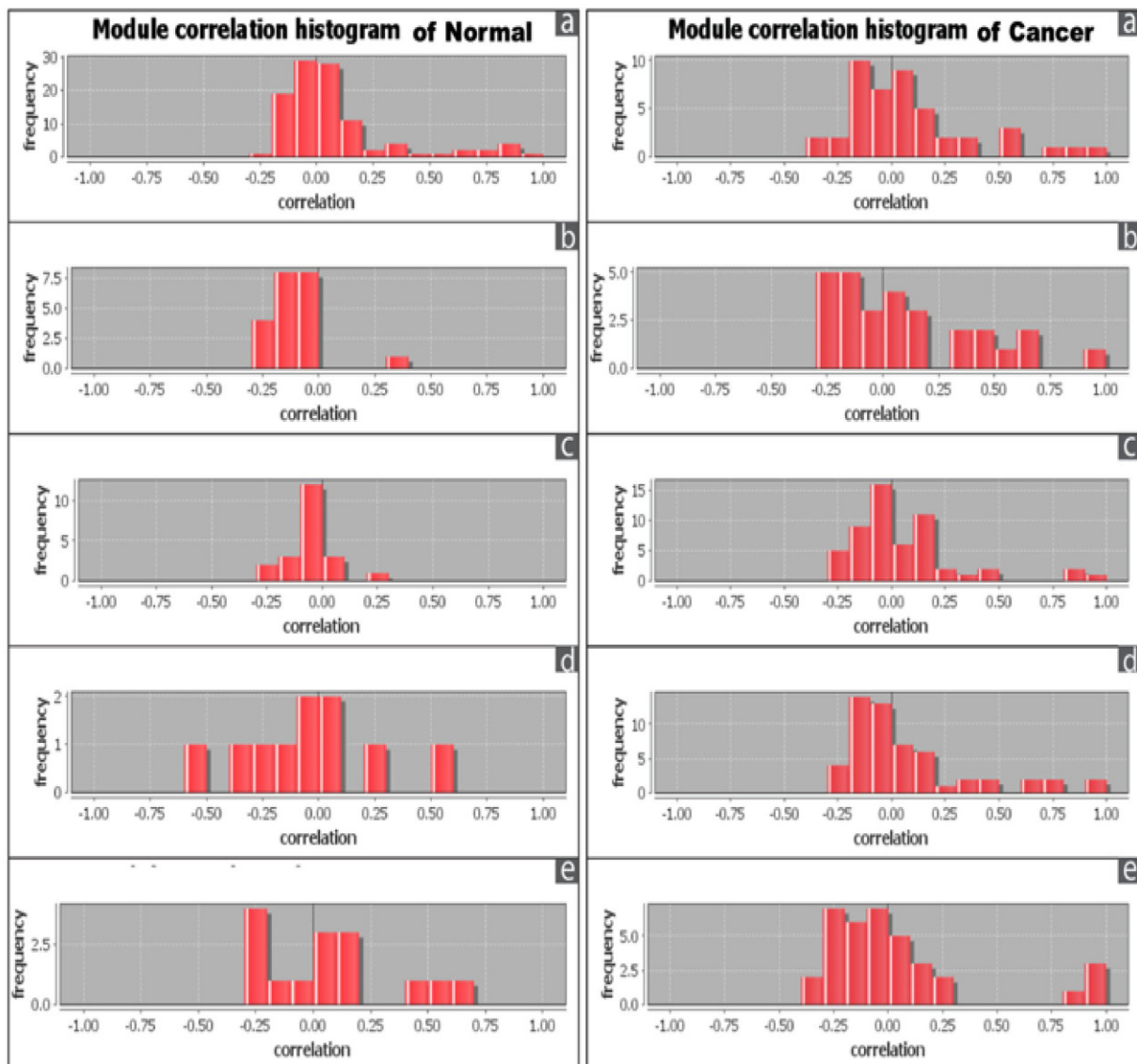


Figure 6. Correlation histogram of normal and cancerous tissues of brain (A), cervix (B), lung (C), ovary (D) and prostate (E).

Author Contributions

RSB, MFI, MSR and KMTR have contributed to idea development, computational analysis and interpretation. RSB, MFI, KMTR and MSR have contributed to data mining, maintenance and processing. All the authors have contributed to the writing of the paper and provide critical feedback on the manuscript and read and approved the final manuscript. This work is supervised by SMEB.

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Competing interests

The authors declare that they have no competing interests.

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References

- Abbas, T., and Dutta, A. (2009). p21 in cancer: intricate networks and multiple activities. *Nature Reviews Cancer* 9, 400-414.
- Bader, G.D., and Hogue, C.W. (2003). An automated method for finding molecular complexes in large protein interaction networks. *BMC bioinformatics* 4, 1.
- Bapat, S.A., Krishnan, A., Ghanate, A.D., Kusumbe, A.P., and Kalra, R.S. (2010). Gene Expression: Protein Interaction Systems Network Modeling Identifies Transformation-Associated Molecules and Pathways in Ovarian Cancer. *Cancer Research* 70, 4809-4819.
- Barabási, A.-L., Gulbahce, N., and Loscalzo, J. (2011). Network medicine: a network-based approach to human disease. *Nat Rev Genet* 12, 56-68.
- Bizzarri, M., and Cucina, A. (2014). Tumor and the Microenvironment: A Chance to Reframe the Paradigm of Carcinogenesis? *BioMed Research International* 2014, 1-9.
- Cerami, E.G., Gross, B.E., Demir, E., Rodchenkov, I., Babur, O., Anwar, N., Schultz, N., Bader, G.D., and Sander, C. (2010). Pathway Commons, a web resource for biological pathway data. *Nucleic Acids Research* 39, D685-D690.
- Choi, K.-C. (2011). Cell growth of BG-1 ovarian cancer cells is promoted by di-n-butyl phthalate and hexabromocyclododecane via upregulation of the cyclin D and cyclin-dependent kinase-4 genes. *Molecular Medicine Reports*.
- Chuang, H.-Y., Lee, E., Liu, Y.-T., Lee, D., and Ideker, T. (2007). Network-based classification of breast cancer metastasis. *Mol Syst Biol* 3.
- Greene, C.S., Krishnan, A., Wong, A.K., Ricciotti, E., Zelaya, R.A., Himmelstein, D.S., Zhang, R., Hartmann, B.M., Zaslavsky, E., Sealfon, S.C., et al. (2015). Understanding multicellular function and disease with human tissue-specific networks. *Nature Genetics* 47, 569-576.
- Hermeking, H. (2003). The MYC Oncogene as a Cancer Drug Target. *Current Cancer Drug Targets* 3, 163-175.
- Islam, M., Hoque, M., Banik, R., Roy, S., Sumi, S., Hassan, F.M., Tomal, M.T., Ullah, A., and Rahman, K.M. (2013). Comparative analysis of differential network modularity in tissue specific normal and cancer protein interaction networks. *J Clin Bioinformatics* 3, 19.
- Jeon, J., Nim, S., Teyra, J., Datti, A., Wrana, J.L., Sidhu, S.S., Moffat, J., and Kim, P.M. (2014). A systematic approach to identify novel cancer drug targets using machine learning, inhibitor design and high-throughput screening. *Genome Medicine* 6, 57.
- Jonsson, P.F., and Bates, P.A. (2006). Global topological features of cancer proteins in the human interactome. *Bioinformatics* 22, 2291-2297.
- Lapenna, S., and Giordano, A. (2009). Cell cycle kinases as therapeutic targets for cancer. *Nature Reviews Drug Discovery* 8, 547-566.
- Mering, C.v. (2003). STRING: a database of predicted functional associations between proteins. *Nucleic Acids Research* 31, 258-261.
- Miller, C.A., Settle, S.H., Sulman, E.P., Aldape, K.D., and Milosavljevic, A. (2011). Discovering functional modules by identifying recurrent and mutually exclusive mutational patterns in tumors. *BMC Med Genomics* 4, 34.
- Miller, D.M., Thomas, S.D., Islam, A., Muench, D., and Sedoris, K. (2012). c-Myc and Cancer Metabolism. *Clinical Cancer Research* 18, 5546-5553.
- Mitra, K., Carvunis, A.-R., Ramesh, S.K., and Ideker, T. (2013). Integrative approaches for finding modular structure in biological networks. *Nat Rev Genet* 14, 719-732.
- Network, T.C.G.A.R. (2012). Erratum: Integrated genomic analyses of ovarian carcinoma. *Nature* 490, 292-292.
- Rahman, K.T., Islam, M.F., Banik, R.S., Honi, U., Diba, F.S., Sumi, S.S., Kabir, S.M.T., and Akhter, M.S. (2013). Changes in protein interaction networks between normal and cancer conditions: Total chaos or ordered disorder? *Network Biology* 3, 15.
- Rives, A.W., and Galitski, T. (2003). Modular organization of cellular networks. *Proceedings of the National Academy of Sciences* 100, 1128-1133.
- Rolland, T., Taşan, M., Charloreaux, B., Pevzner, S.J., Zhong, Q., Sahni, N., Yi, S., Lemmens, I., Fontanillo, C., and Mosca, R. (2014). A proteome-scale map of the human interactome network. *Cell* 159, 1212-1226.
- Shackleton, M., Quintana, E., Fearon, E.R., and Morrison, S.J. (2009). Heterogeneity in Cancer: Cancer Stem Cells versus Clonal Evolution. *Cell* 138, 822-829.
- Shannon, P. (2003). Cytoscape: A Software Environment for Integrated Models of Biomolecular Interaction Networks. *Genome Research* 13, 2498-2504.
- Skomedal, H., Kristensen, G.B., Lie, A.K., and Holm, R. (1999). Aberrant Expression of the Cell Cycle Associated Proteins TP53, MDM2, p21, p27, cdk4, Cyclin D1, RB, and EGFR in Cervical Carcinomas. *Gynecologic Oncology* 73, 223-228.
- Smoot, M.E., Ono, K., Ruscheinski, J., Wang, P.L., and Ideker, T. (2010). Cytoscape 2.8: new features for data integration and network visualization. *Bioinformatics* 27, 431-432.
- Sonnenschein, C., Soto, A.M., Rangarajan, A., and Kulkarni, P. (2014). Competing views on cancer. *J Biosci* 39, 281-302.
- Srihari, S., and Ragan, M.A. (2013). Systematic tracking of dysregulated modules identifies novel genes in cancer. *Bioinformatics* 29, 1553-1561.
- Stevens, A., Meyer, S., Hanson, D., Clayton, P., and Donn, R. (2014). Network analysis identifies protein clusters of functional importance in juvenile idiopathic arthritis. *Arthritis Res Ther* 16, R109.
- Sun, J., and Zhao, Z. (2010). A comparative study of cancer proteins in the human protein-protein interaction network. *BMC Genomics* 11, S5.
- Szalay-Beko, M., Palotai, R., Szappanos, B., Kovacs, I.A., Papp, B., and Csermely, P. (2012). ModuLand plug-in for Cytoscape: determination of hierarchical layers of overlapping network modules and community centrality. *Bioinformatics* 28, 2202-2204.
- Tansey, W.P. (2014). Mammalian MYC Proteins and Cancer. *New Journal of Science* 2014, 1-27.
- Willett, C.G., Chang, D.T., Czito, B.G., Meyer, J., and Wo, J. (2013). Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. *Nature* 2012.(5). *International Journal of Radiation Oncology Biology Physics* 86, 2.
- Zhang, Y., Luoh, S.M., Hon, L.S., Baertsch, R., Wood, W.I., and Zhang, Z. (2007). GeneHub-GEPIs: digital expression profiling for normal and cancer tissues based on an integrated gene database. *Nucleic Acids Research* 35, W152-W158.

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