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Research Article

Altered gene expression pattern due to different tumor percentage affects functions

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Abstract: High-throughput data are produced on a big scale and at several levels in order to comprehend complex diseases including cancer, diabetes, and kidney disorders. A significant obstacle still exists, nonetheless, in extracting useful information from huge datasets for a thorough comprehension of cell phenotypes and disease pathogenesis. Big data is created to address biological concerns as a result of technological advancements, and it is always easy for biologists and computer scientists to collaborate to streamline the massive datasets and extract the information that is relevant and physiologically important. In order to achieve this, we have classified using expression datasets and inferred the corresponding functional annotation using a computational technique. In order to analyze changes in gene expression and functional annotation, we employed a dataset of prostate cancer patients with normal and variable tumor percentages. We have chosen a gene expression omnibus (GEO) dataset that includes human samples with a range of tumor percentages (0--85%). We arranged the samples according to tumor proportion in ascending order and compared them to the control group (samples with no tumor) to look for changes in gene expression and developed functions as the tumor percentage increased. When the tumor percentage is less than 50%, we see some fluctuation in the number of differentially expressed genes (DEGs), but after that, it increases exponentially. In terms of the pathways, there is a lot of variation in the number of enriched pathways, with tumor < 50% not increasing, while several cancer-associated pathways seem to be enriched for nearly all the different tumor percentages. Our analysis leads us to the conclusion that whereas a number of cancer-associated pathways are consistently enriched for all tumor percentages, the number of differentially expressed genes (DEGs) grows as the tumor percentage rises while the enriched pathways do not. Insulin resistance, acute myeloid leukemia, basal TFs, HIF1-a, neurotrophin, base excision repair, ErbB, VEGF, and mTOR signaling pathways are among the top-ranked enriched pathways. RPP30, SRP14, CCNE1, PRKAR1A, ABCF2, PCMT1, TUBA1C, STOML2, PPP2R4, and TPI1 are possible pathway components.

Keywords: Prostate cancer; tumor percentage; gene expression profiling; network analysis; functional impact

1. Introduction

The post-genomics era's development in recent decades has produced enormous amounts of "big data" in the biological sciences, which opens up a wide range of interdisciplinary applications. Large datasets have also made it more difficult to handle, analyze, mine, store, and decipher relevant information. Numerous biological databases contain a variety of dataset kinds. In the biological sciences, databases like TCGA, Oncomine, Nephroseq, and GEO (gene expression omnibus) are commonly utilized. Numerous datasets pertaining to diabetes, cancer, and other biological issues are stored in these databases[1-10].

Prostate cancer is the fifth most prevalent cause of death for men globally and the second most common type of cancer to be diagnosed. Prostate cancer is frequently treated with androgen deprivation therapy, however resistance frequently

reduces the benefits of this treatment for survival. Although immunotherapy has shown enormous promise in the treatment of solid tumors, patients with prostate cancer have not shown clinically significant improvements, underlining unique limitations of this therapeutic method. Therefore, it's critical to investigate new ways to improve prostate cancer immunotherapy's effectiveness in concert.

Beneath the bladder and encircling the urethra lies the male reproductive auxiliary organ known as the prostate gland. Contributing vital secretions to semen, which produce ejaculate and preserve sperm viability, is the primary role of the prostate. Usually in the mid-to-late stage of life, the cells in the prostate gland can develop into tumors. The mature human prostate has fibromuscular and periurethral areas in addition to central, transitional, and peripheral zones. The peripheral zone contributes most to normal prostate function in young adult men and comprises more than 70% of the prostate glandular tissue. Nearly 80% of prostate tumors originate in this region, making it the most frequent site of origin for neoplasms in the aging prostate. The typical gland is made up of stroma-embedded ducts and acini. The basement membrane is created by a layer of basal epithelium around a single layer of simple, columnar epithelium seen in the ducts and acini. The stromal cells that support spontaneous contractility and avoid fluid stagnation are mostly smooth muscle myocytes, to which this layer of extracellular matrix is attached. Fibroblasts are also found in the stroma, and they primarily support the ducts in the adult prostate. However, it is thought that fibroblast paracrine signaling plays a crucial role in the patterning of the duct during prostate development. According to laboratory data, these stromal fibroblasts have the ability to proliferate in the tumor microenvironment, also known as the tumor stroma, by triggering survival signaling and causing epithelial transformation. They are also thought to play a role in the long-term growth of cancer cells after treatment. Importantly, the androgen receptor (AR), which is thought to be the cause of hormone reliance in prostate cancer, is encoded by AR, which is highly expressed by these epithelial cells in both healthy and malignant organs. Furthermore, these cells release a serine protease called prostate-specific antigen (PSA), which is used to identify and diagnose prostate cancer. PSA is transcriptionally activated by the AR and is often higher in individuals with prostate cancer.

Prostate cancer affects millions of men annually. The disease is one of the most prevalent solid cancers in high-income areas, and the prognosis varies greatly depending on age, ethnicity, genetic background, and stage of progression. Based on the patient's health status and the tumor's histological, anatomical, and molecular characteristics, one can predict the course of a particular person's illness. Living with prostate cancer for many men entails following a customized treatment plan for a slow-growing, frequently indolent tumor; however, for many others, relapse is anticipated after a definitive treatment, which may be swift, forceful, and, in rare instances, insensitive to standard care. As of right now, there is no foolproof way to tell aggressive tumors from indolent ones. But over the past century, significant advancements have changed the prognosis for patients with prostate cancer. These include the groundbreaking finding that the disease is hormone-dependent and the high therapeutic efficacy of using selective inhibitors to target this crucial characteristic, which is now known to be the high expression and frequent genetic amplification of AR. Specifically, the last ten years have witnessed unheard-of breakthroughs in proteome profiling, mRNA sequencing, and whole-genome DNA sequencing, which have offered unique insights into the genetic underpinnings thought to underlie various prostate cancer subtypes and subpathologies. Furthermore, significant advancements in PSA screening protocols and imaging modalities have resulted in their growing usage in the diagnosis of prostate cancer.

The identification of pathogenetically unique tumor types is the primary source of target-specificity in the treatment of complicated diseases, particularly cancer. Enhancements in tumor classification are usually beneficial to therapeutic methods. Target-specific therapy can increase efficacy and limit harm by employing improved classification. Numerous methods and technologies have been used in the past to retrieve biological datasets from these databases. For cancer molecular classification Cancer classification has been split into two difficulties by Golub TR et al.[11]: class prediction and class discovery. In this study, we have chosen a prostate cancer dataset that includes samples with different tumor percentages in order to comprehend how the pattern of gene expression and subsequent functions change as the tumor percentage rises[2, 5, 12-20].

Here, we have chosen a gene expression omnibus (GEO) dataset that contains human samples with a range of tumor percentages (0--85%). We arranged the samples according to tumor proportion in ascending order and compared them to the control group (samples with no tumor) to look for changes in gene expression and developed functions as the tumor percentage increased. Our findings suggest that whereas a number of cancer-associated pathways are consistently enriched for all tumor percentages, the number of differentially expressed genes (DEGs) grows as the tumor percentage rises but the enriched pathways do not. Insulin resistance, acute myeloid leukemia, basal TFs, HIF1-a, neurotrophin, base excision repair, ErbB, VEGF, and mTOR signaling pathways are among the top-ranked enriched pathways. RPP30, SRP14, CCNE1, PRKAR1A, ABCF2, PCMT1, TUBA1C, STOML2, PPP2R4, and TPI1 are possible pathway components.

2. Methods

We have utilized the GEO gene expression profiling array dataset (GSE17951[11]) for prostate cancer. We have included both normal (69) and tumor (68) samples from this expression dataset in our study. Tumor samples range in tumor percentage from 0.5 to 85%. Affymetrix Human Genome U133 Plus 2.0 Array results were used to create these gene expression profiling datasets. There are 154 samples in this dataset (69 normal or tumor-free, 68 with a tumor percentage of up to 85%, and 17 nearby stroma samples); the latter 17 samples have been removed from the analysis. We have analyzed the tumor and normal samples for differential gene expression analysis such that we have 32 DEG lists for 68 samples (tumor % > 0.0). In summary, raw fille processing, intensity computation, and normalization are the fundamental processes that are engaged in the entire investigation. The most popular methods for normalization are EB, RMA, and GCRMA. Here, we have normalized raw intensity using EB[21-27]. Following normalization, we go on to our objective, which is to comprehend the patterns of gene expression and the functions that may be deduced from them[28-43].

MATLAB functions, such as mattest, have been utilized for statistical analysis and the prediction of differential gene expression. We used the KEGG database for pathway analysis and wrote our own tool for network and pathway analysis (Figure 1a). Throughout the project, FunCoup2.0 was utilized to generate the DEGs networks, and Cytoscape[44] was utilized to visualize the networks. We have used MATLAB for the majority of our coding and computations. Four sorts of functional couplings or linkages, including protein complexes, physical interactions between proteins, metabolic processes, and signaling pathways, are predicted by FunCoup[45].

3. Results

3.1. Gene expression profiling and the associated functions for varying tumor percentages: As indicated in the workflow Figure 1a, we have first chosen the data of interest (raw expression dataset) GSE1795 and processed it till normalization and log2 values of all the mapped genes are obtained. There are 154 samples in this dataset (69 normal or tumor-free, 68 with a tumor percentage of up to 85%, and 17 nearby stroma samples); the latter 17 samples have been removed from the analysis. We have analyzed the tumor and normal samples for differential gene expression analysis such that we have 32 DEG lists for 68 samples (tumor % > 0.0).

In this study, we examined the DEGs (Figures 1b and c) at varying tumor percentages and found that many genes are frequently altered regardless of tumor percentage, and that the number of DEGs rises as tumor percent rises (Figure 1c), but the number of pathways does not follow the same pattern (Figured 1). The number of enriched pathways varies significantly at lower tumor percentages, but it roughly stabilizes in samples with tumor percentages greater than 50%.

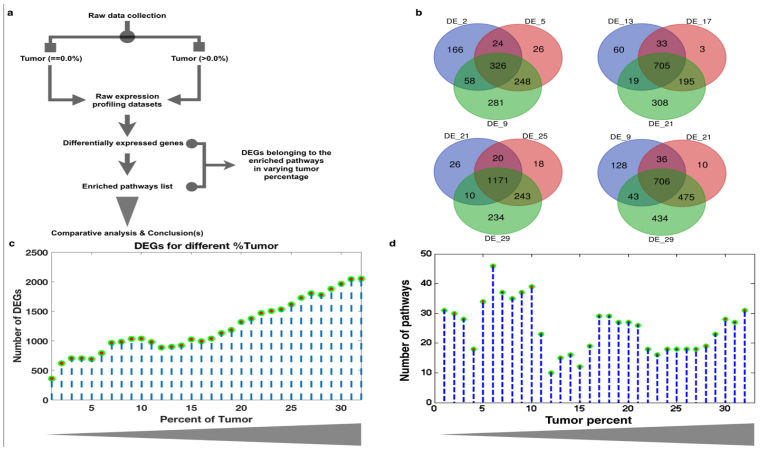

Figure 1. Evolution of DEGs with the increase in tumor percentage. (a) Workflow. (b) Venn diagram to display the DEGs. (c) Evolution of DEGs with the increase in Tumor percentage: To analyze the DEGs for different percent of tumor in the biopsy samples, we have arranged the tumor samples based in increase order. In each step we add next two samples with higher tumor percent and have calculated DEGs. We observe that with the increase in tumor percentage number of DEGs are increased which means that the samples with higher tumor percent have higher level of gene expression aberrations. (d) Evolved enriched pathways with the increase in tumor percentage.

3.2. Top ranked enriched pathways and DEGs: Following the prediction of DEGs and enriched pathways, we examined enriched pathways and genes that were nearly changed in every tumor sample. The top ranked pathways that are commonly changed are insulin resistance, AML, basal TFs, HIF-1, neurotrophin, base excision repair, and ErbB signaling (Figure 2a). The top ranked genes are RPP30, SRP14, CCNE1, PRKAR1A, ABCF2, PCMT1, TUBA1C, STOML2, PPP2R4, TPI1, TUBB2B, and so on (Figure 2b). It is known that the identified genes and pathways contribute to cancer either directly or indirectly. The bulk of the top-ranked pathways (Figure 2a) belong to overall enriched pathways (between normal and

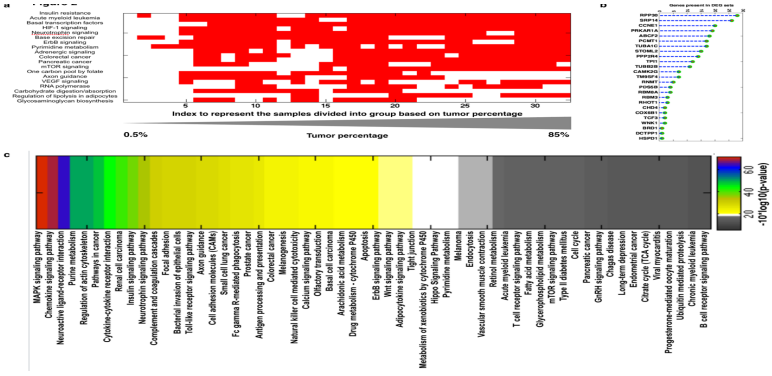

Figure 2. Major pathways and and their potential components. (a) Top ranked enriched pathways for different tumor percentage, (b) top ranked genes, and (c) Enriched pathways (between normal and tumor) analyzed for prostate cancer without classifying tumor percentage (GSE17951).

tumor samples) (Figure 2c), as we have incorporated additional data (GSE17951) to portray the enriched pathways for greater clarity.

3.3. Network-level understanding of the DEGs: We have created the network of DEGs at extremely low tumor percentages (0.0%) and up to the maximum (85%) following the analysis of the DEGs and the enriched pathways. The DEGs at five distinct tumor percentages are covered by the first through the fifth of these five networks (Figure 3). Nearly every gene that is frequently differentially expressed is covered by the DEGs list that we have created for the network. Even in the network, we find that the majority of the genes are frequently involved. These genes are known to have very high connectivities, and the node degree distribution is power law distributed (Figure 3). It is also known that these genes may or may not be involved in cancer. Genes that are overexpressed at the start when the tumor percentage is less than six and have stronger connection throughout, regardless of tumor %, are shown by the nodes with red color boundaries (Figure 3). This leads us to believe that these genes may be responsible for the development of prostate cancer in humans. A list of genes that are overexpressed across the tumor proportion is displayed in Figure 4 and for which we have examined the clinical importance. There are some genes that are overexpressed in over 5% of patients; to address this, we have the TCGA database through cBioPortal.

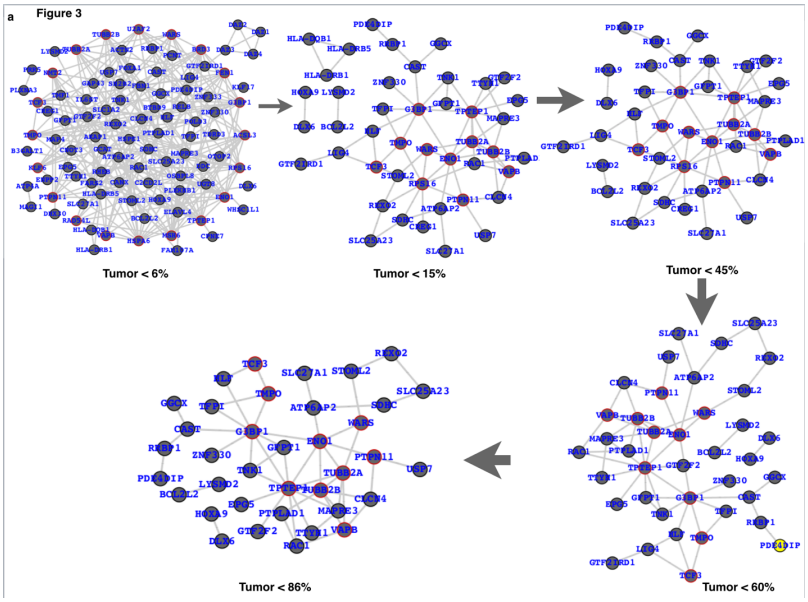

Figure 3. Networks of DEGs. Here, the arrow thickness between the networks refer that the next network is for the DEGs at higher tumor percentage. The nodes with red color boundary are those genes which are overexpressed in the beginning when tumor percentage is less than 6 and have higher connectivity throughout irrespective of tumor percentage.

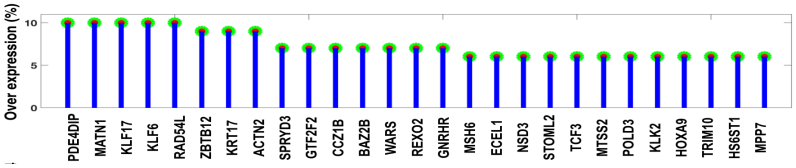

Figure 4. Clinical significance of some of the DEGs which display higher connectivities. These genes are overexpressed in prostate cancer sample (TCGA database). The percentage represents the number of patients with the respective genes overexpression.

4. Dicussion: The development of the post-genomics period in recent decades has produced a large amount of "big data" in the biological sciences, which opens up a wide range of interdisciplinary applications. The enormous volume of datasets has also made it more difficult to handle, process, mine, store, and extract useful information. Numerous studies on various forms of cancer have been conducted, and the raw data from these studies are openly accessible. Numerous research at various levels have been conducted. We have chosen a dataset from the early work that includes both normal samples and patients with varying tumor percentages. In order to comprehend how the gene expression pattern and resulting functions change as the tumor proportion rises, we have chosen this prostate cancer dataset with different tumor percentages[17, 23, 46-60].

The gene expression omnibus (GEO) GSE17951 dataset includes human subjects with a range of tumor percentages (0--85%). We arranged the samples according to tumor proportion in ascending order and compared them to the control group (samples with no tumor) to look for changes in gene expression and developed functions as the tumor percentage increased. Our research leads us to the conclusion that whereas a number of cancer-associated pathways are consistently enriched for all tumor percentages, the number of differentially expressed genes (DEGs) grows as the tumor percentage rises while the enriched pathways do not. To display the enriched pathways, we have also included extra data. As we can see in Figure 2c, the bulk of the top-ranked pathways (Figure 2a) are part of the overall enriched pathways (between normal and tumor samples).

In contrast, we concentrated on the dataset and primarily identified those genes and pathways that continuously remain altered regardless of the tumor percentage. Previous research, even in similar types of cancer, has revealed intriguing genes and pathways associated with the specific type of cancer. Remarkably, the most commonly altered pathways are insulin resistance, AML, basal TFs, HIF-1, neurotrophin, base excision repair, and ErbB signaling (Figure 2a). The most frequently altered genes are RPP30, SRP14, CCNE1, PRKAR1A, ABCF2, PCMT1, TUBA1C, STOML2, PPP2R4, TPI1, TUBB2B, and so on (Figure 2b). It provides accurate information about the genes and pathways that may show promise in the selective targeting of prostate cancer and aids in its comprehension and use for diagnostic purposes.

Multidisciplinary research on prostate cancer is quite busy and currently includes computational biology in addition to laboratory and clinical science. Among these studies are the exploration of novel preclinical hypotheses, the

experimental confirmation of scientific discoveries, and the application of these discoveries in clinical settings. Before conducting clinical studies to try to enhance disease management, several steps are crucial. The design and specificity of new medicines and treatment plans, such as those that more effectively target important aspects of AR biochemistry, have also improved as a result of a greater understanding of the disease's molecular underpinnings. From improved biological knowledge of each disease stage that influences clinical care to early illness identification and therapy, progress is ongoing in a number of domains[61-68].

Millions of men throughout the world suffer from prostate cancer. The illness makes up 7% of newly diagnosed male cancers worldwide (15% in industrialized nations), making it the second most frequent cancer in males after lung cancer. Prostate cancer is also one of the top causes of cancer-associated death in males, with over 1.2 million new cases diagnosed and over 350,000 deaths worldwide each year. The risk of prostate cancer rises significantly with age, and more than 85% of newly diagnosed cases occur in people over 60. Therefore, areas with high life expectancy, like the USA and the UK, have a notably high prevalence of prostate cancer. Globally, the incidence of prostate cancer is positively correlated with both GDP and the human development index (HDI), meaning that developed countries typically have greater incidences than undeveloped countries. It's interesting to note that, although the incidence is rising in these regions, certain Asian nations with high HDIs, including South Korea and Japan, have relatively lower incidences than Western nations with comparable high HDIs[69-90].

Since greater screening frequency is linked to increased incidence through overdiagnosis, the rise in incidence may be the result of increased awareness of prostate cancer brought about by access to diagnostic screening in many of these regions. Furthermore, these areas have the highest age-standardized mortality rates from prostate cancer, while early detection access is anticipated to lower these rates. Repeated screening lowers the mortality rate from prostate cancer and boosts the diagnosis of all prostate tumors, including indolent ones, according to European studies using long-term follow-up data. The causes of the increasing age-adjusted mortality in emerging countries may also be related to the fact that economic development is linked to a rise in prostate cancer risk factors that surpasses the advantages of advancements in public health and treatment. Although there is insufficient evidence to support an impact on disease incidence, non-heritable variables such as obesity, cigarette smoke exposure, and a primarily Western diet are generally believed to increase prostate cancer-related mortality.

5. Conclusions: Our research leads us to the conclusion that whereas a number of cancer-associated pathways are consistently enriched for all tumor percentages, the number of differentially expressed genes (DEGs) grows as the tumor percentage rises while the enriched pathways do not. This indicates that, regardless of the tumor percentage, only specific pathways may be changed in cases of prostate cancer.

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Data Availability Statement: All the related data are supplied in this work or have been referenced properly.

References

1. Mobashir, M., et al., *An Approach for Systems-Level Understanding of Prostate Cancer from High-Throughput Data Integration to Pathway Modeling and Simulation.* Cells, 2022. **11**(24). https://doi.org/10.3390/cells11244121

2. Bailey, M.H., et al., *Comprehensive Characterization of Cancer Driver Genes and Mutations.* Cell, 2018. **173**(2): p. 371-385.e18. https://doi.org/10.1016/j.cell.2018.02.060
3. Chen, B.-S. and C.-W. Li, *Constructing an integrated genetic and epigenetic cellular network for whole cellular mechanism using high-throughput next-generation sequencing data.* BMC Systems Biology, 2016. **10**(1): p. 18. https://doi.org/10.1186/s12918-016-0256-5
4. Consortium, I.C.G., et al., *International network of cancer genome projects.* Nature, 2010. **464**(7291): p. 993-998. https://doi.org/10.1038/nature08987
5. Derry, J.M., et al., *Developing predictive molecular maps of human disease through community-based modeling.* Nat Genet, 2012. **44**(2): p. 127-30. https://doi.org/10.1038/ng.1089
6. Hanahan, D., *Hallmarks of Cancer: New Dimensions.* Cancer Discov, 2022. **12**(1): p. 31-46. https://doi.org/10.1158/2159-8290.CD-21-1059
7. Hoadley, K.A., et al., *Multiplatform Analysis of 12 Cancer Types Reveals Molecular Classification within and across Tissues of Origin.* Cell, 2014. **158**(4): p. 929-944. https://doi.org/10.1016/j.cell.2014.06.049
8. Jiang, P., et al., *Big data in basic and translational cancer research.* Nat Rev Cancer, 2022. **22**(11): p. 625-639. https://doi.org/10.1038/s41568-022-00502-0
9. Leiserson, M.D.M., et al., *Pan-cancer network analysis identifies combinations of rare somatic mutations across pathways and protein complexes.* Nature Genetics, 2015. **47**(2): p. 106-114. https://doi.org/10.1038/ng.3168
10. Martínez-Jiménez, F., et al., *A compendium of mutational cancer driver genes.* Nature Reviews Cancer, 2020. **20**(10): p. 555-572. https://doi.org/10.1038/s41568-020-0290-x
11. Golub, T.R., et al., *Molecular classification of cancer: class discovery and class prediction by gene expression monitoring.* Science, 1999. **286**(5439): p. 531-7. https://doi.org/10.1126/science.286.5439.531
12. Albiges, L., et al., *First-line Nivolumab plus Ipilimumab Versus Sunitinib in Patients Without Nephrectomy and With an Evaluable Primary Renal Tumor in the CheckMate 214 Trial.* Eur Urol, 2022. **81**(3): p. 266-271. https://doi.org/10.1016/j.eururo.2021.10.001
13. Albiges, L., et al., *Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial.* ESMO Open, 2020. **5**(6): p. e001079. https://doi.org/10.1136/esmoopen-2020-001079
14. Choueiri, T.K., et al., *Cabozantinib plus Nivolumab and Ipilimumab in Renal-Cell Carcinoma.* N Engl J Med, 2023. **388**(19): p. 1767-1778. https://doi.org/10.1056/NEJMoa2212851
15. Coley, H.M., *Overcoming multidrug resistance in cancer: clinical studies of p-glycoprotein inhibitors.* Methods Mol Biol, 2010. **596**: p. 341-58. https://doi.org/10.1007/978-1-60761-416-6_15
16. Ling, S., et al., *Extremely high genetic diversity in a single tumor points to prevalence of non-Darwinian cell evolution.* Proc Natl Acad Sci U S A, 2015. **112**(47): p. E6496-505. https://doi.org/10.1073/pnas.1519556112
17. McLendon, R., et al., *Comprehensive genomic characterization defines human glioblastoma genes and core pathways.* Nature, 2008. **455**(7216): p. 1061-1068. https://doi.org/10.1038/nature07385
18. Petrov, I. and A. Alexeyenko, *EviCor: Interactive Web Platform for Exploration of Molecular Features and Response to Anti-cancer Drugs.* J Mol Biol, 2022. **434**(11): p. 167528. https://doi.org/10.1016/j.jmb.2022.167528
19. Thorsson, V., et al., *The Immune Landscape of Cancer.* Immunity, 2018. **48**(4): p. 812-830.e14. https://doi.org/10.1016/j.immuni.2018.03.023
20. Usset, J., et al., *Five latent factors underlie response to immunotherapy.* Nat Genet, 2024. https://doi.org/10.1038/s41588-024-01899-0
21. Agell, L., et al., *A 12-Gene Expression Signature Is Associated with Aggressive Histological in Prostate Cancer SEC14L1 and TCEB1 Genes Are Potential Markers of Progression.* The American Journal of Pathology, 2012. **181**(5): p. 1585-1594. https://doi.org/10.1016/j.ajpath.2012.08.005
22. Barrett, T., et al., *NCBI GEO: archive for functional genomics data sets--update.* Nucleic Acids Res, 2013. **41**(Database issue): p. D991-5. https://doi.org/10.1093/nar/gks1193
23. Cordero, F., M. Botta, and R.A. Calogero, *Microarray data analysis and mining approaches.* Briefings in Functional Genomics, 2007. **6**(4): p. 265-281. https://doi.org/10.1093/bfgp/elm034
24. Eisen, M.B., et al., *Cluster analysis and display of genome-wide expression patterns.* Proc Natl Acad Sci U S A, 1998. **95**(25): p. 14863-8. https://doi.org/10.1073/pnas.95.25.14863
25. Friedman, N., et al., *Using Bayesian Networks to Analyze Expression Data.* Journal of Computational Biology, 2000. **7**(3-4): p. 601-620. https://doi.org/10.1089/106652700750050961
26. Geyer, F.C. and J.S. Reis-Filho, *Microarray-based Gene Expression Profiling as a Clinical Tool for Breast Cancer Management: Are We There Yet?* International Journal of Surgical Pathology, 2009. **17**(4): p. 285-302. https://doi.org/10.1177/1066896908328577
27. Hughes, T.R. and D.D. Shoemaker, *DNA microarrays for expression profiling.* Current Opinion in Chemical Biology, 2001. **5**(1): p. 21-25. https://doi.org/10.1016/s1367-5931(00)00163-0

28. Alammari, D. and N. Helmi, *An integrated approach for herbal drugs to target GSK3B and its linkage with melanoma and type-2 diabetes.* Global Journal of Basic Science, 2024. **1**(2): p. 1-13. https://doi.org/10.63454/jbs20000014
29. Almowallad, S., R. Jeet, and M. Mobashir, *A systems pharmacology approach for targeted study of potential inflammatory pathways and their genes in atherosclerosis.* Global Journal of Basic Science, 2024. **6**(1): p. 1-12. https://doi.org/10.63454/jbs20000006
30. Bajrai, L., et al., *A computational approach reveals the critical role of PARK2 gene and the potential infectious pathways and HPV infection in colorectal cancer.* Global Journal of Basic Science, 2025. **1**(4): p. 1-11. https://doi.org/10.63454/jbs20000013
31. Choudhry, H., et al., *Study of APOBEC3B focused breast cancer pathways and the clinical relevance.* Global Journal of Basic Science, 2024. **2**(1): p. 1-12. https://doi.org/10.63454/jbs20000002
32. Helmi, N. and D. Alammari, *An integrated approach for the study of APOBEC3B associated genes and its impact on hypoxic and immune signaling pathways in ovarian cancer.* Global Journal of Basic Science, 2024. **1**(2): p. 1-8. https://doi.org/10.63454/jbs20000012
33. Islam, S. and M. Tarek, *Impact of measles virus infection on immune signaling pathways in human lung cancer cell lines.* Global Journal of Basic Science, 2025. **1**(5): p. 1-13. https://doi.org/10.63454/jbs20000011
34. Qahwaji, R., et al., *A network-guided approach for unraveling potential phar-ma-cological role of JAK2 and analysis of the frequency the mutations in myeloproliferative neoplasm Saudi Patients.* Global Journal of Basic Science, 2025. **1**(5): p. 1-17. https://doi.org/10.63454/jbs20000024
35. Ahmed, S., et al., *A Network-Guided Approach to Discover Phytochemical-Based Anticancer Therapy: Targeting MARK4 for Hepatocellular Carcinoma.* Front Oncol, 2022. **12**: p. 914032. https://doi.org/10.3389/fonc.2022.914032
36. Anwer, S.T., et al., *Synthesis of Silver Nano Particles Using Myricetin and the In-Vitro Assessment of Anti-Colorectal Cancer Activity: In-Silico Integration.* Int J Mol Sci, 2022. **23**(19). https://doi.org/10.3390/ijms231911024
37. Bajrai, L.H., et al., *Gene Expression Profiling of Early Acute Febrile Stage of Dengue Infection and Its Comparative Analysis With Streptococcus pneumoniae Infection.* Front Cell Infect Microbiol, 2021. **11**: p. 707905. https://doi.org/10.3389/fcimb.2021.707905
38. Bajrai, L.H., et al., *Understanding the role of potential pathways and its components including hypoxia and immune system in case of oral cancer.* Sci Rep, 2021. **11**(1): p. 19576. https://doi.org/10.1038/s41598-021-98031-7
39. El-Kafrawy, S.A., et al., *Genomic profiling and network-level understanding uncover the potential genes and the pathways in hepatocellular carcinoma.* Front Genet, 2022. **13**: p. 880440. https://doi.org/10.3389/fgene.2022.880440
40. Eldakhakhny, B.M., et al., *In-Silico Study of Immune System Associated Genes in Case of Type-2 Diabetes With Insulin Action and Resistance, and/or Obesity.* Front Endocrinol (Lausanne), 2021. **12**: p. 641888. https://doi.org/10.3389/fendo.2021.641888
41. Helmi, N., D. Alammari, and M. Mobashir, *Role of Potential COVID-19 Immune System Associated Genes and the Potential Pathways Linkage with Type-2 Diabetes.* Comb Chem High Throughput Screen, 2022. **25**(14): p. 2452-2462. https://doi.org/10.2174/1386207324666210804124416
42. Khouja, H.I., et al., *Multi-staged gene expression profiling reveals potential genes and the critical pathways in kidney cancer.* Sci Rep, 2022. **12**(1): p. 7240. https://doi.org/10.1038/s41598-022-11143-6
43. Krishnamoorthy, P.K.P., et al., *In-silico study reveals immunological signaling pathways, their genes, and potential herbal drug targets in ovarian cancer.* Informatics in Medicine Unlocked, 2020. **20**: p. 100422. https://doi.org/10.1016/j.imu.2020.100422
44. Shannon, P., et al., *Cytoscape: a software environment for integrated models of biomolecular interaction networks.* Genome Res, 2003. **13**(11): p. 2498-504. https://doi.org/10.1101/gr.1239303
45. Alexeyenko, A., et al., *Comparative interactomics with Funcoup 2.0.* Nucleic Acids Research, 2012. **40**(D1): p. D821-D828. https://doi.org/10.1093/nar/gkr1062
46. Qahwaji, R., et al., *Pharmacogenomics: A Genetic Approach to Drug Development and Therapy.* Pharmaceuticals, 2024. **17**(7). https://doi.org/10.3390/ph17070940
47. Jones, P.A. and S.B. Baylin, *The Epigenomics of Cancer.* Cell, 2007. **128**(4): p. 683-692. https://doi.org/10.1016/j.cell.2007.01.029
48. Stricker, S.H., A. Köferle, and S. Beck, *From profiles to function in epigenomics.* Nature Reviews Genetics, 2017. **18**(1): p. 51-66. https://doi.org/10.1038/nrg.2016.138
49. Bader, G.D., et al., *Functional genomics and proteomics: charting a multidimensional map of the yeast cell.* Trends in Cell Biology, 2003. **13**(7): p. 344-356. https://doi.org/10.1016/s0962-8924(03)00127-2
50. Berger, B., J. Peng, and M. Singh, *Computational solutions for omics data.* Nature Reviews Genetics, 2013. **14**(5): p. 333-346. https://doi.org/10.1038/nrg3433
51. Castro-Giner, F., P. Ratcliffe, and I. Tomlinson, *The mini-driver model of polygenic cancer evolution.* Nature Reviews Cancer, 2015. **15**(11): p. 680-685. https://doi.org/10.1038/nrc3999
52. Friedman, A.A., et al., *Precision medicine for cancer with next-generation functional diagnostics.* Nat Rev Cancer, 2015. **15**(12): p. 747-56. https://doi.org/10.1038/nrc4015

53. Frings, O., et al., *Network Analysis of Functional Genomics Data: Application to Avian Sex-Biased Gene Expression.* The Scientific World Journal, 2012. **2012**: p. 130491. https://doi.org/10.1100/2012/130491
54. Garg, R. and M. Jain, *Legume Genomics, Methods and Protocols.* Methods in Molecular Biology, 2013. **1069**: p. 43-58. https://doi.org/10.1007/978-1-62703-613-9_4
55. Gerlinger, M., et al., *Intratumor heterogeneity and branched evolution revealed by multiregion sequencing.* N Engl J Med, 2012. **366**(10): p. 883-892. https://doi.org/10.1056/NEJMoa1113205
56. Hawkins, R.D., G.C. Hon, and B. Ren, *Next-generation genomics: an integrative approach.* Nature Reviews Genetics, 2010. **11**(7): p. 476-486. https://doi.org/10.1038/nrg2795
57. Hayes, D.N. and W.Y. Kim, *The next steps in next-gen sequencing of cancer genomes.* Journal of Clinical Investigation, 2015. **125**(2): p. 462-468. https://doi.org/10.1172/jci68339
58. Pagel, P., et al., *Comparative Genomics.* Methods in Molecular Biology, 2007. **396**: p. 3-15. https://doi.org/10.1007/978-1-59745-515-2_1
59. Vuong, H., et al., *Functional consequences of somatic mutations in cancer using protein pocket-based prioritization approach.* Genome Medicine, 2014. **6**(10): p. 81. https://doi.org/10.1186/s13073-014-0081-7
60. Zhang, K. and H. Wang, *Cancer Genome Atlas Pan-cancer Analysis Project.* Chinese Journal of Lung Cancer, 2015. **18**(4): p. 219-223. https://doi.org/10.3779/j.issn.1009-3419.2015.04.02
61. Ahmed, H.U., *The Index Lesion and the Origin of Prostate Cancer.* The New England Journal of Medicine, 2009. **361**(17): p. 1704-1706. https://doi.org/10.1056/nejmcibr0905562
62. Alers, J.C., et al., *Identification of Genetic Markers for Prostatic Cancer Progression.* Laboratory Investigation, 2000. **80**(6): p. 931-942. https://doi.org/10.1038/labinvest.3780096
63. Andriole, G.L. and W.J. Catalona, *Prostate carcinoma.* Annu Rev Med, 1994. **45**: p. 351-9. https://doi.org/10.1146/annurev.med.45.1.351
64. Andriole, G.L. and W.J. Catalona, *The Diagnosis and Treatment of Prostate Cancer.* Annual Review of Medicine, 1991. **42**(1): p. 9-15. https://doi.org/10.1146/annurev.me.42.020191.000301
65. Baca, Sylvan C., et al., *Punctuated Evolution of Prostate Cancer Genomes.* Cell, 2013. **153**(3): p. 666-677. https://doi.org/10.1016/j.cell.2013.03.021
66. Berger, M.F., et al., *The genomic complexity of primary human prostate cancer.* Nature, 2011. **470**(7333): p. 214-220. https://doi.org/10.1038/nature09744
67. Best, C.J.M., et al., *Molecular Alterations in Primary Prostate Cancer after Androgen Ablation Therapy.* Clinical Cancer Research, 2005. **11**(19): p. 6823-6834. https://doi.org/10.1038/nature09744
68. Bibikova, M., et al., *Expression signatures that correlated with Gleason score and relapse in prostate cancer.* Genomics, 2007. **89**(6): p. 666-672. https://doi.org/10.1016/j.ygeno.2007.02.005
69. Bismar, T.A., et al., *Defining Aggressive Prostate Cancer Using a 12-Gene Model.* Neoplasia, 2006. **8**(1): p. 59-68. https://doi.org/10.1593/neo.05664
70. Bolla, M., et al., *Duration of Androgen Suppression in the Treatment of Prostate Cancer.* New England Journal of Medicine, 2009. **360**(24): p. 2516-2527. https://doi.org/10.1056/nejmoa0810095
71. Boutros, P.C., et al., *Spatial genomic heterogeneity within localized, multifocal prostate cancer.* Nature Genetics, 2015. **47**(7): p. 736-745. https://doi.org/10.1038/ng.3315
72. Bray, F., et al., *Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.* CA Cancer J Clin, 2024. **74**(3): p. 229-263. https://doi.org/10.3322/caac.21834
73. Canby-Hagino, E.D. and I.M. Thompson, *Mechanisms of Disease: prostate cancer—a model for cancer chemoprevention in clinical practice.* Nature Clinical Practice Oncology, 2005. **2**(5): p. 255-261. https://doi.org/10.1038/ncponc0172
74. Carreira, S., et al., *Tumor clone dynamics in lethal prostate cancer.* Science Translational Medicine, 2014. **6**(254): p. 254ra125. https://doi.org/10.1126/scitranslmed.3009448
75. Cerchiari, A.E., et al., *A strategy for tissue self-organization that is robust to cellular heterogeneity and plasticity.* Proceedings of the National Academy of Sciences, 2015. **112**(7): p. 2287-2292. https://doi.org/10.1073/pnas.1410776112
76. Chan, N., M. Milosevic, and R.G. Bristow, *Tumor hypoxia, DNA repair and prostate cancer progression: new targets and new therapies.* Future Oncology, 2007. **3**(3): p. 329-341. https://doi.org/10.2217/14796694.3.3.329
77. Choudhury, A.D., et al., *The Role of Genetic Markers in the Management of Prostate Cancer.* European Urology, 2012. **62**(4): p. 577-587. https://doi.org/10.1016/j.eururo.2012.05.054
78. Culig, Z., *Genetic Markers in Prostate Cancer: Progress and Limitations.* European Urology, 2012. **62**(4): p. 588-589. https://doi.org/10.1016/j.eururo.2012.06.040
79. Culig, Z. and F.R. Santer, *Androgen receptor signaling in prostate cancer.* Cancer and Metastasis Reviews, 2014. **33**(2-3): p. 413-427. https://doi.org/10.1007/s10555-013-9474-0
80. Debes, J.D. and D.J. Tindall, *The role of androgens and the androgen receptor in prostate cancer.* Cancer Letters, 2002. **187**(1-2): p. 1-7. https://doi.org/10.1016/s0304-3835(02)00413-5
81. Dhanasekaran, S.M., et al., *Delineation of prognostic biomarkers in prostate cancer.* Nature, 2001. **412**(6849): p. 822-826. https://doi.org/10.1038/35090585

82. Dong, J.-T., et al., *KAI1, a Metastasis Suppressor Gene for Prostate Cancer on Human Chromosome 11p11.2.* Science, 1995. **268**(5212): p. 884-886. https://doi.org/10.1126/science.7754374
83. Glinsky, G.V., et al., *Gene expression profiling predicts clinical outcome of prostate cancer.* Journal of Clinical Investigation, 2004. **113**(6): p. 913-923. https://doi.org/10.1172/jci20032
84. Goldstein, A.S., et al., *Identification of a Cell of Origin for Human Prostate Cancer.* Science, 2010. **329**(5991): p. 568-571. https://doi.org/10.1126/science.1189992
85. Goldstein, A.S., Y. Zong, and O.N. Witte, *A Two-Step Toward Personalized Therapies for Prostate Cancer.* Science Translational Medicine, 2011. **3**(72): p. 72ps7. https://doi.org/10.1126/scitranslmed.3002169
86. Grossmann, M.E., H. Huang, and D.J. Tindall, *Androgen Receptor Signaling in Androgen-Refractory Prostate Cancer.* JNCI: Journal of the National Cancer Institute, 2001. **93**(22): p. 1687-1697. https://doi.org/10.1093/jnci/93.22.1687
87. Haffner, M.C., et al., *Tracking the clonal origin of lethal prostate cancer.* Journal of Clinical Investigation, 2013. **123**(11): p. 4918-4922. https://doi.org/10.1172/jci70354
88. Henshall, S.M., et al., *Survival analysis of genome-wide gene expression profiles of prostate cancers identifies new prognostic targets of disease relapse.* Cancer research, 2003. **63**(14): p. 4196-203. https://app.readcube.com/library/13da053b-6958-47c0-9554-e2a5ffb811c6/item/7a719c22-2ef3-4830-b0b4-da8f4f27594d
89. Hieronymus, H., et al., *Copy number alteration burden predicts prostate cancer relapse.* Proceedings of the National Academy of Sciences, 2014. **111**(30): p. 11139-11144. https://doi.org/10.1073/pnas.1411446111
90. Irshad, S., et al., *A Molecular Signature Predictive of Indolent Prostate Cancer.* Science Translational Medicine, 2013. **5**(202): p. 202ra122. https://doi.org/10.1126/scitranslmed.3006408