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Review

Advances in Research on Immune Mechanism of Prostate Cancer Based on Bioinformatics

Xiao-Wu Pi, Ying Xiong✉

Department of Urology, School of Medicine, The First Clinical Medical College, Yangtze University, Jingzhou, Hubei 434023, China

✉ **Correspondence**
Ying Xiong, Department of Urology, The First Affiliated Hospital of Yangtze University, Jingzhou, Hubei 434000, China. Email: 31350266@qq.com. Telephone number: 86-18163138805.
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Abstract

The incidence of prostate cancer, one of the most common cancers in the male urogenital system, is increasing year by year. At present, the research on the immune mechanism of prostate cancer is not well discerned. In recent years, the application of bioinformatics in the study of the immune mechanism of prostate cancer has been rapidly developed, which has not only brought new modes for the research on the prostate cancer development and immune mechanisms, but also has been recognized as the current hot spot in tumor research. This paper reviews the related applications of bioinformatics in the study of the immune mechanism of prostate cancer and summarizes the development trend.

Keywords: Bioinformatics; Immunotherapy; Programmed Death Protein 1 (PD-1); Prostate Cancer (PCa); Castration-Resistant Prostate Cancer (CRPC); miRNA; Tumor Markers.

Introduction

Prostate cancer (PCa) is one of the most common cancers in the male urinary system. Patients with early-stage localized prostate cancer are generally treated with radical surgery or radiation therapy. However, both options used for patients were accompanied with a 20% to 50% chance of tumor recurrence (1). Metastatic prostate cancer usually received androgen deprivation therapy, including bilateral orchiectomy or chemical castration (2). Although androgen deprivation therapy has a significant short-term effect, the subsequent side effect was also obvious, and patients would eventually progress to castration-resistant prostate cancer

(CRPC) (3). What's more, there is no radical treatment plan for CRPC, while the prognosis is poor. Recently, it has been found that androgen deprivation in prostate cancer patients has a potential effect on the immune system, which has triggered the enthusiasm of scholars to study the immune mechanism of prostate cancer. The rapid development of the research on tumor immune mechanism made bioinformatics well known as it was widely applied in tumor analysis and tumor microenvironment and system immune identification (4).

Bioinformatics is a discipline that integrates computer information technology, biology and statistics and is used for collection and analysis. It mainly studies the structural information and functional omics of genomes, proteins and biological macromolecules (5). With the accumulation of a large amount of biomedical data of oncology, bioinformatics can be used to analyze various types of molecules of different systems from holistic level to systematic level, thereby revealing their mutual functional connections (6). At present, research on tumor immune evaluation is conducted based on bioinformatics, including T cell receptor sequencing, immune microenvironment deconvolution, predicted neoantigen, human leukocyte antigen (HLA) status description, etc., making rapid development in the study of tumor immune mechanism (4).

1. Application of bioinformatics in tumor research

1.1 Construction of tumor and immunity-related bioinformatics databases

The establishment of the database is the key to the reserve of tumor and immune information, but also is the core stone of research. Through the analysis of many tumor samples, it is possible to obtain regular conclusions that are difficult to obtain in a single experiment, and concurrently provide researchers with convenient data analysis services and data sharing platform (6). For now the main databases include The Cancer Genome Atlas (TCGA) database, a platform for researchers to download and assess free public datasets from the National Cancer Institute (NCI) and National Human Genome Research Institute (NHGRI) (https://cancergenome.nih.gov/) (7), CGHub database (https://cghub.ucsc.edu), ICGC database (https://icgc.org) and other comprehensive tumor databases. The main databases related to immunity are as follows: a. Cytokines: Cytokine Family cDNA Database (dbCFC); b. Immune cells: Proteome Database of Human T helper Cells; c. Tumor immunity: Proteome Database of Human T helper Cells; d. Antigen epitope analysis: epipredict, NetMHC 2.1 Server; e. Comprehensive database: The Immunology Database and Analysis Portal (Immport). Drug and tumor databases include canSAR database (8), CMap database (9), and DrugBank database (10).

1.2 Exploration of tumor biospecific molecules

The data of a certain type of tumor needed to be studied in the database were collected and statistically analyzed. Go analysis and KEGG pathway analysis were carried out by R language and other tools. They provide clinical information

from large samples through TCGA and geo databases and use bioinformatics platform tools, such as string database (https://string-db.org), Cytoscape (https://cytoscape.org), CIBERSORTESTIMA, Te and GSEA (http://software.broadinstitute.org/gsea/msigdb/index.jsp). Methods are to evaluate the abundance and distribution of immune cell members in prostate cancer expression matrix in mixed cell population (11). They used GSEA to study the biological function of target genes in prostate cancer. Finally, the key signal molecules were found.

1.3 Research and development of tumor drugs

The drug bioinformatics databases (such as canSAR database, CMap database and DrugBank database) are applied to the specific genes or protein molecules that have been analyzed to screen out the potential drugs for the specific protein molecules or transduction pathways (12). The research and development trend of tumor immunotherapy drugs is explored by the Cortellis database from the perspectives of research and development status, indications, and effect targets (13).

1.4 Algorithms of tumor bioinformatics

CIBERSORT (14) (http://cibersort.stanford.edu is a deconvolution/) algorithm was developed by Bindea G. It can estimate the cell composition of complex tissues based on standardized gene expression data. This method can quantify the abundance of specific cell types.

TMB (15) is the total number of mutations per megabase in tumor tissue. To a certain extent, it can be understood that the larger the total number of changed codes in a unit region, the higher the tumor mutation load (TMB), the more oncogenic mutations may be associated with the corresponding tumor, and the more prominent the personality of each tumor is, and the more different it is from normal cells.

ESTIMATE (16) (Estimation of STromal and Immune cells in MAlignant Tumor tissues using Expression data) is a tool for predicting tumor purity, and the presence of infiltrating stromal/immune cells in tumor tissues using gene expression data. ESTIMATE algorithm is based on single sample Gene Set Enrichment Analysis and generates three scores: stromal score (that captures the presence of stroma in tumor tissue), immune score (that represents the infiltration of immune cells in tumor tissue) and estimate score (that infers tumor purity).

2. Application of bioinformatics in the study of PCa immune mechanism

The latest drugs targeting the immune system showed positive results in various types of tumors (17), which promoted the enthusiasm of researchers on the study of immunotherapy for prostate cancer. Nevertheless, the verification experiments of a variety of immune preparations or vaccines that were currently under way or had ended manifested that the clinical effect of immunotherapy for prostate cancer was not satisfied (18). So far, various immune experiments had seen mixed results (19). Therefore, the research on PCa immunity is still a

current hot topic. As a new research approach, the study on PCa immune mechanism based on bioinformatics had been widely adopted to provide clues for the early diagnosis, treatment and prognosis of androgen-insensitive prostate cancer (AIPC) (20).

2.1 Application of Bioinformatics in exploring AIPC immune mechanism at the level of gene expression

In recent years, a new type of gene regulatory factors (e.g. microRNA or miRNA) had been identified to participate in cell differentiation, proliferation, and apoptosis (21), as well as regulate multiple immune regulation processes (22). Gopalakrishnan, V. (23) *et al.* showed evidence that miRNAs played a key role in the PCa immune microenvironment. Effective immune regulation could correct the natural immune inhibition and escape from microenvironment existing in tumors and could direct immune responses against cancer cells (24). It was reported that miRNAs mainly regulated the immune process in four ways: a. by stimulating antigen-specific T cells to form a cancer vaccine; b. by modulating cytokines to stimulate adaptive or innate immune cells; c. by adoptive cell therapy; d. by blocking immune checkpoint molecules, as shown in Figure 1.

As an example, Feng et al. (25) retrieved PCa-related regulatory miRNAs using gene chip data based on bioinformatics and revealed that miR-148 and miR-152 had low expression in PCa. They verified that the miR-148/152 family gave a play to inhibiting PCa through an in vitro xenotransplantation tumor model. Liu et al. (26). Further explored that in the tumor immune regulation process, miR-148/152 inhibited the production of cytokines including Interleukin 12 （IL-12）, IL-6, tumor necrosis factor-a（TNF-a） and interferon（IFN-b） by targeting CaMKIIa, upregulated the expression of major histocompatibility complex class（MHC-II,） and inhibited the proliferation of specific T cells that were initiated by DCs (dendritic cells). As a result, miRNA-148/152 can be used as a regulator to regulate the innate response of DCs, which may contribute to PCa immune homeostasis and immune regulation.

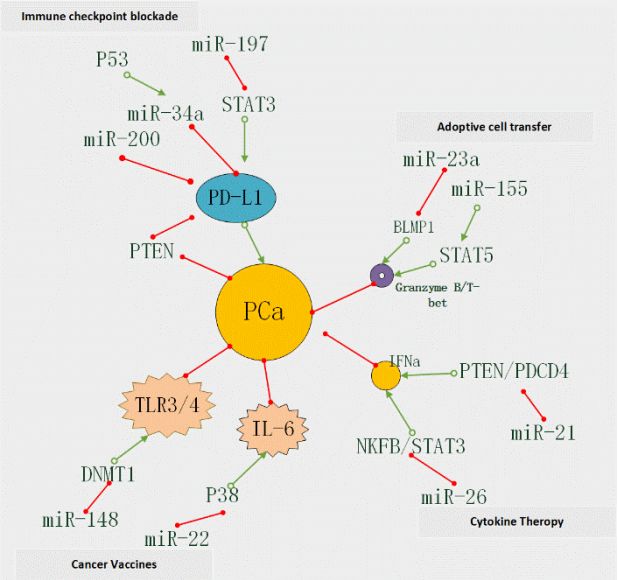

Figure 1. Potential diagnostic and therapeutic applications of miRNAs in immunotherapy. Molecular mechanisms of related miRNAs and their main targets in participating in and regulating four aspects of immunotherapies. The red double-dotted line indicated inhibition; the green arrow indicated up-regulation.

Ye et al. retrieved the GSE64318 and GSE46602 datasets from Gene Expression Omnibu（ Gene Expression Omnibusin(GEO)

datasets in National Center of Biotechnology Information(NCBI) , https://www.ncbi.nlm.nih.gov/geo/ ） to obtain differentially expressed miRNA, messenger RNA （mRNA）and long non-coding RNA（lncRNA）. Through SRTING co-expression analysis, the mRNA-miRNA-lncRNA interaction network was constructed to identify that miR-23 was the key regulator, which played an important role in PCa regulation (27). Another study provided an empirical articulation to show that miR-23~27~24 clusters could perform multi-facet biological regulations of T cells. Among them, miR-23 could regulate T cells to synergistically limit Th2 immune response by directly and indirectly targeting IL-4/13. Under external stimulation, T cells differentiated into effector Th cells to produce a protective immune response. The high expression of miR-23 would inhibit this regulation and change the PCa microenvironment, thereby leading to the immune escape (28).

2.2 Application of bioinformatics in exploring PCa immunity-related markers at the level of protein molecular

As the ideal biological molecules for predicting clinical prognosis, biomarkers are mainly used for disease screening, characterization and detection (29). PSA, the most important biomarker for prostate cancer at the present time, had been widely applied in clinic, but its specificity was low, and it was apt to present false positives (30). It was an active research area to find immune biomarkers in PCa, where most studies had focused on identifying immune activation as a clinical benefit, such as certain genomic changes of the expression of HLA-DRB1*11 or HLA-A*24 alleles (31). No biomarkers that clearly reflect the immune response of PCa have been found so far.

Zhou et al. (32) used the data from TumorImmune Estimation Resource (TIMER) to analyze the expression of collagen triple helix repeat containing 1 (CTHRC1), programmed cell death protein-1 (PD-1) and programmed cell death ligand-1 (PD-L1). They found that the expression of CTHRC1 was positively correlated with the expression of PD-1 and PD-L1 in the TCGA cohort, and the expression of PD-1/PD-L1 in patients with PRAD recurrence was significantly higher than that in patients without recurrence. GO/KEGG enrichment analysis of CTHRC1 further showed that the expression of CTHRC1 was related to the expression of PCa's matrix metalloproteinase-9, mucin 1 and solute carrier organic anion transporter family member 2B1 genes, and the changes in these expressions may be related to the regulation of the tumor microenvironment.

Wang et al. identified key genes related to CRPC immunity and defined effective biomarkers. They retrieved multiple mRNA microarray data in the GEO database based on bioinformatics to analyze the genetic differences between CRPC and immunity-related prostate cancer. The differential genes were subjected to functional enrichment analysis and protein-protein interaction analysis to screen out a key gene Jagged-1 (JAG1) with important functions. Finally, the TCGA database was used

for verification and survival analysis, which further proved the importance of JAG1 (33). JAG1 can reduce T regulatory cells and improve anti-tumor immune response by reducing the expression of PD-1 in CD8+Tem cells. Accordingly, the low expression of JAG1 of prostate cancer led the PD-1 expression in CD8+Tem cells to be down-regulated to inhibit the anti-tumor immune response (34).

2.3 Application of bioinformatics in screening PCa immunity-related drugs

Research on potential immunity-related drugs based on bioinformatics is a current hot spot. A deluge of data is generated during the drug development process, and these data are exactly utilized to establish large databases to analyze and identify new drug targets (35). For example, the CMap database, DrugBank database and canSAR database are the drug-related databases that we often use. The genes we need to analyze are screened through the Immport database and then matched with the CMap database for expression profile. The most consistent drug-disease-genome is mined by statistical analysis, and combined with the DrugBank database for drug mining, a high priority drug list is returned. Li et al. (36) combined the key genes of AIPC with the CMap database to analyze and revealed that the drug target genes were significantly cross-enriched with the key genes of AIPC and had a clear correlation with the inhibition of the expression of AIPC related genes, indicating the high reliability of the drug target genes. In the meantime, related drugs, methiodazine and novobiocin, were enriched, which were verified to have a certain inhibitory effects on prostate cancer cells by experimental methods such as the MTT method. The canSAR database is also currently widely used in drug research and development. It combines pharmacology, drug and chemical data, structural biology, protein networks, and comprehensive “drug possibility” assessments to provide clues for researchers in cancer and drug research and development. Wedge et al. (37) excavated the target gene according to the AIPC mutation gene profile and enriched the target protein through the PPI interaction network. Matched with the canSAR database, a total of 11 approved therapeutic targets 7 investigational drug targets were obtained, including BRAF, HDAC3, etc. These proteins were used as drug targets in clinical trials. On the other hand, it was found in some studies that BRAF and HDAC3 protein molecules can be used as tumor inhibitors. As an example, Kuske et al. (38), underpinned by the PubMed database, comprehensively retrieved and analyzed the pre-clinical and clinical studies on the combination of BRAFi/MEKi and immune checkpoint inhibitors. They observed that BRAF inhibitors (BRAFi) produced an immunity-stimulation tumor microenvironment, increased the infiltration of immune cells into the tumor, and did not have negative effects on immune cells in the body. The existing data implies that BRAFi has a favorable effect on the overall anti-tumor immunity and tumor microenvironment. As PD-L1 is expressed on the surface of tumor cells, its expression level is the main factor reflecting the effect of checkpoint

immunotherapy. Hu et al. (39) carried out an experiment to explore the correlation between the expressions of Histone deacetylase 3 (HDAC3) and PD-L1 in PCa and concluded that the specific inhibitor of HDAC3 could reduce the expression level of PD-L1 in tumor cells, and finally verified that HDAC3 regulated the expression of PD-L1 at the transcription level through the STAT3 pathway. Thus, HDAC3 inhibitors may be used to improve immunotherapy for prostate cancer.

3. Latest direction of bioinformatics in the research of PCa immune mechanism

Evidence shows that the characteristics of tumor infiltrating immune cells (TIICs) are closely related to the occurrence and development of tumors, and the types and expression levels of TIICs have certain predictive value for the survival of patients. As specific drugs targeting TIICs can significantly improve clinical efficacy, TIICs have become a research hotspot for immune checkpoint therapy (40). Therefore, a comprehensive analysis of the immune components in the process of tumorigenesis is beneficial to making more accurate diagnostic evaluation or prognostic evaluation of cancer patients (41). CiberSort, a new algorithm developed based on bioinformatics, evaluated the abundance of cell members in a mixed cell population through a gene expression matrix. The method could better investigate the diversity and regionality of TIICs in different tumor tissues (42). Many studies have used CiberSort to identify the immune cell composition of various cancers due to its better performance than other traditional methods (41).

Additionally, the proliferation and survival of tumor cells are greatly affected by the PCa tumor microenvironment, which is a dynamic environment composed of stromal cells, immune cells, endothelial progenitor cells (EPC), extracellular matrix (ECM), growth factors, and cytokines. Each cell component in the microenvironment plays a crucial role in the immune regulation of PCa. As a result, Estimate—the newly developed algorithm for evaluating the tumor microenvironment is based on single-sample gene set to enrich and analyze and generates stromal and immune score to predict the infiltration of tumor stromal cells and immune cells (43). The accuracy of the algorithm was verified in various tumor studies, such as glioblastoma (44), colon cancer (45).

The tumor mutation burden (TMB), which is also related to tumor immunity, is defined as the number of somatic mutations of the genomic sequence being queried per megabase. TMB is optimally calculated by the whole exome sequencing (WES) (46), which can be utilized to identify cancer patients who are most likely to respond to immune checkpoint inhibitors. It has been recently used as a biomarker responding to immune checkpoint inhibitors of various cancer types. In relevant studies, it was found that PD-1/PD-L1 block treatment was used for several tumors including melanocarcinoma, non-small cell lung cancer, etc., and high TMB was positively correlated with therapeutic effect improvement. Also, cancer population such as bladder cancer and microsatellite instability with high TMB was positively correlated with

improved prognosis (47-50).

Ye et al. (51) extracted gene set data from TCGA and GEO databases based on bioinformatics and evaluated the proportion of TIIC infiltration in colon cancer using ssGSEA and CIBERSORT tools. They revealed that some TIICs can be used for prognosis evaluation. Through immunohistochemistry (IHC) verification analysis, both results indicated that TAN, Treg and TAM were significantly related to the prognosis of CRC patients and were independent prognostic factors. Yan *et al.* (52) retrieved the expression profile data of acute myeloid leukemia in the TCGA database based on bioinformatics and adopted the ESTIMATE algorithm to calculate the immune score and stromal score. Then, according to the score groups, the differentially expressed genes (DEG) were determined, and key genes were further identified by the survival analysis of DEGs. Finally, the GO/KEGG analysis of key genes implied that these genes were mainly associated with immune/inflammatory response.

With the development of "omics" mechanism, the microenvironment of PCa reveals more deeply the heterogeneity of single cell in microenvironment (53), that is, single cell has great differences in different phenotypes or unique transcriptome, which leads to the heterogeneous cell population may affect the function, characteristics and expression of the whole cell population.

The application of single cell sequencing in bioinformatics. In 2018, Henry et al. Performed single cell RNA sequencing (scRNA-seq) on about 98,000 PCa cells from five young adults(54). Because of the heterogeneity of cell population, in the identification of benign and malignant cell populations, single cell sequencing can identify the cell sources of benign prostatic hyperplasia (PH) and PCa and can identify the heterogeneity of cells in the CRPC microenvironment, which can provide a great basis for patients to provide cell targeted drug therapy in clinic (55).

Through the brief description of the above-mentioned tumor immune infiltration, tumor microenvironment and tumor mutation burden, as well as its application in colon cancer and acute myeloid leukemia, the author opines that PCa can provide a variety of antigen targets for cancer immunotherapy as prostate gland is a highly differentiated and gender-specific organ. Secondly, the slow growth of PCa in the early stage can leave time for the formation of immune responses (56), so the potential immunotherapy targets of PCa are able to be explored based on the above bioinformatics methods. However, no similar papers are retrieved in PubMed database. Finally, the author summarizes the research of other tumors based on bioinformatics to construct a new technical route of PCa immune mechanism.

However, bioinformatics also has its shortcomings. Gene expression profile data comes from gene chip experiments containing data packet experiments, chip design methods, etc., and the resulting data errors and noise signals are very common, which requires experimenters to use a chip database that conforms to the MIAME principle when selecting

chips (57), and repeatedly extract chip data to reduce random errors. In addition, the alternative of differential genes will also give rise to certain deviations due to personal subjective factors. Moreover, even though new bioinformatics methods and a large amount of accumulated data were adopted, it is undeniable that as of now, checkpoint inhibitors have not been effective in CRPC, and the tumor microenvironment of immune inhibition, low mutation burden and low expression of PD-L1 commonly seen in PCa tumors have led to unsatisfactory results in relevant studies. It is currently being evaluated to improve PCa treatment status by combining multiple immunotherapies or combing immunotherapy with chemotherapy/radiotherapy based on bioinformatics. The SiPuleucel-T has also been seen to be successfully applied to PCa, and with the development of technology, the benefits of bioinformatics are becoming obvious, so the hope of PCa immunotherapy is approaching.

Declarations

1) ***Consent to publication***

We declare that all authors agreed to publish the manuscript at this journal based on the signed Copyright Transfer Agreement and followed publication ethics.

2) ***Ethical approval and consent to participants***

Not applicable.

3) ***Disclosure of conflict of interests***

We declare that no conflict of interest exists.

4) ***Funding***

None

5) ***Availability of data and material***

We declare that the data supporting the results reported in the article are available in the published article.

6) ***Authors' Contributions***

Authors contributed to this paper with the design (XWP and YX), literature search (XWP), drafting (XWP), revision (XWP and YX), editing (XWP and YX) and final approval (XWP and YX).

7) ***Acknowledgement***

None

8) ***Authors' biography***

None

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