Cancer Bioinformatics in Cancer Therapy

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Abstract

Last three decades, this world witnesses a rapid progress of biomarkers and bioinformatics in a lot of biomedical study. Cancer bioinformatics is one of such important omics areas. Same as other biological techniques, bioinformatics are presently not Omni-potent. Despite technical advances, cancer bioinformatics has its own limitations at this stage. This article will overview bioinformatics in cancer study and clinical applications—advantages and limitations associated with cancer therapeutics and drug developments. Finally, creative ideas and future perspectives are highlighted.

Keywords: Cancer Bioinformatics; Cancer Stem Cells; Cancer Therapy; Drug Developments; Neoplasm Metastasis; Personalized Cancer Therapy

Introduction

Background

Cancer remains to be a serious human health problem that claims life about 7-10 million people annually in the world. During last 30 years, this world witnesses a rapid progress of bioinformatics study and wide-range of clinical applications worldwide. Since cancer bioinformatics diagnostic systems have advantages and shortcomings, their popularity in cancer practices need to promote worldwide. Many obstacles need to be overcome. The object of this study is to promote cancer bioinformatics diagnostic strategy in clinical cancer trials. This article not only offers a panorama of bioinformatics in cancer researches and wide-range of clinical applications, but also highlights possible improvements in the future.

A Role in Cancer Diagnosis and Drug Response Predictions

Cancer is a progressive disease and genetic and molecular abnormalities are growing in an enlarged tumor tissues [1,2]. The best therapeutics in the clinic should be designed according to this changeable state. Nonetheless, different types of cancer genesis are caused by different genetic alterations, such as mutation, translocation, deletion, replication and metabolisms [3,4]. Bioinformatics diagnosis is useful for therapeutic prediction by revealing this ever-change cancer malignant state. Certainly, many categories of personalized cancer therapies are widely utilized globally [5-9]. In this article, the scenarios of cancer bioinformatics studies and clinical applications are introduced.

Technical Analysis

Oncologic Identification (Bioinformatics Hallmarks) In Different Cancer Categories

Cancer is a different disease with an identical pathological property of unlimited growth, invasion and metastasis in distant tissues. Overall, it is classified unto six hallmarks-(Table 1) [4]. Different cancer hallmarks can be observed by different bioinformatics and predicted to different anticancer drug responses and choices.

<table>
<thead>
<tr>
<th>Hallmarks of cancer</th>
<th>Possible molecular or pathological mechanisms</th>
</tr>
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<tbody>
<tr>
<td>Sustaining proliferative signaling</td>
<td>Somatic mutation, unlimited proliferative, signal overridden, environmental stress</td>
</tr>
<tr>
<td>Resisting cell death</td>
<td>Apoptosis (caspases, Bcl-2, Bax etc) and autophagy</td>
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<tr>
<td>Inducing angiogenesis</td>
<td>Vascular, inflammatory factors (VEGF, TNF) and so on</td>
</tr>
<tr>
<td>Evading growth suppressors</td>
<td>Tumor growth suppressors (RB, TP53) etc</td>
</tr>
</tbody>
</table>
Enabling replicative immortality | Telomerase
---|---
Invasion and metastasis | Different pathologic stages and molecular changes

Table 1: Biology and pathology mechanisms of cancer.

**From Biomarkers to Bioinformatics**

Cancer biomarker detections are pioneered with several tumor pathogenic molecules (commonly protein or glycol-protein, such as α-feto proteins or CEA). Hospitals diagnose these molecules (biomarkers) one by one. Targeted monoclonal antibodies or other targeted anticancer drugs are proposed to exhibit higher therapeutic efficacies against escalated cancer biomarkers and tumor growth in patients.

Cancer bioinformatics methods are relatively high throughput (generally > 10 biomolecules by modern chromatography; >5000 genetic allele polymorphisms by micro-arrays including tumorigenic initiators, promoters, somatic mutations, transcriptions by reversed-RNA sequencing with PCR-related techniques and so on [10-18].

Since tumors are progressive and chronic diseases with more than a hundred genetic changes of a single cell in advanced cancer patients [6], high-throughput methodology is needed to identify ever-changing underlying cancer abnormalities in cells (plasticity) [19-21]. The multidisciplinary nature of bioinformatics makes them relatively easier for pathological grading and therapeutic response prediction. Thanks to the fast-pace of bioinformatics technical evolutions and the assistance of mathematical or computational network [9-18], cancer bioinformatics determinations and analyses need lower and lower running-costs [22-24]. Individualized treatment based on detecting genetic or molecular variations by different modern strategies is growing popularity. High throughput bioinformatics detecting may help to transform clinical diagnosis from several molecules into several hundred molecule-based strategies in the future. It relies on balance between clinical benefits and economic considerations (hospital conditions) if possible [23,24].

Since the heterogeneity of cancer origin and genesis factors is increased with disease progresses and cancer metastasis, it suggests that some hidden rules behind scenes are not established (Figure 1). Currently, we are too naïve to believe that tumor bioinformatics can be understood all tumor biological information by detecting only one tumor biopsy or surgery samples. How to optimize diagnostic or drug predictive strategies is still a mystery. Thence, the hidden rule discoveries by bioinformatics translation into therapeutic paradigms are inevitable future studies and trends.

![Figure 1: A picture of cancer genetic/molecular progressions in each solid tumor advancement.](image)

**Cancer Genomes**

Cancers commonly originate through a variety of genetic dysfunction unto molecular malformation. Knowing the cancer genome can help us to understand the origin and advancements of cancers cells and/or variable response of pharmacotherapy [5-9, 25]. Yet, this medical cliché needs to be customized in the clinic. Approximately more than one thousand types of genetic abnormality can be found in advancing tumors within human bodies. To judge with this great change of cancer genome and more than 100 anticancer drugs worldwide, understanding patho-therapeutic relationships before formal cancer medications in the clinic is required. Even with a certain amount of tumor type, such as lung cancer, ovarian or mammary cancer, the responses to the same anticancer drugs may vary from patient to patient.

Bioinformatics, a genomics-supportive approach that provide a variety of technical capabilities can analyze DNA, RNA, proteins, glycoligands and metabolisms for single level or as a whole in cancer patients.

In the earliest era, biomarkers or bioinformatics evaluation was to meet the requirement of patients' prognoses [10] or classify tumor origins [11] in the clinic. More recently, the advancing utility of cancer biomarkers or bioinformatics in predicting anticancer drug responses is validated.

**Getting Popularity in The Clinic**

Finding the bioinformatics changes in cancer tissues is only the first step in clinical cancer trials; the choice of effective targeted
anticancer drugs for individual cancer patients is the new challenge in the clinical trials [5-9]. The detection of cancer bioinformatics without therapeutic response prediction is meaningless and waste of time and money. Thence, bioinformatics-therapeutic relation must be built. Validity of the cancer biomarkers or bioinformatics that drug response is general topic for bioinformatics applications. To achieve this goal, effectively targeted anticancer drugs are needed [26-29]. If we do not equip with useful drugs, we cannot properly control cancer growths and metastasis no matter how crystal clear we know oncologic features by cancer bioinformatics. Development and approval of more effective targeted anticancer drugs are indispensable for personalized cancer medicine [26-29].

**Mathematical Modality and Computational Network**

**Reduce the Complexity of Biological Study**

The complex interaction and interplay between molecular-to-molecular and tumor-normal cells can be fully discovered by biomedical techniques alone. Increasing complexity of genes and molecules can be gradually monitored or analyzed by mathematic or computational network. (Figure 1) shows that great number of mutant genes or molecules is increased along with tumor progresses and neoplasm metastasis. The mathematical treatments of cancer bioinformatics data can help some cancer therapists who have little knowledge of cutting-edge biomedical technology to perform cancer therapeutic efficacy predictions in the clinic.

**Advantage of Mathematical Work**

Advantage of mathematics in bioinformatics data analysis is obvious and straightforward-pervasive in various fields of biology and medicine [38-42]. Without high-quality mathematics or computational network, doctors will be overwhelmed by wealth of bioinformatics data and do nothing for therapeutic prediction. Mathematical modeling and computational networks are powerful tools for identification of mutated genetic alleles and therapeutic decision-making. These tools help us to identify crucial drug targets, weigh and balance each variable among overall genetic/molecular background in tumor tissues and finally coordinate matched drugs to inhibit or kill tumor cells. In general, since mathematical treatment is an effective means for integrating and coordinating multi-variant data between diagnosis/therapies. This is why mathematical approaches and computational network become growing importance in the fields of ICT in the clinic.

**Biological Rule and Mathematical Participation**

Mathematics data analysis in the field of bioinformatics-based cancer personalized therapies is more than an issue of algebra, exponential or iterative. Understanding of the interplay between diverse cancer genes and pathologic bio-molecules is indispensable. Undiscovered biological rules might also participate. These interplays are not mathematics only, but biological as well. For example, cross-talks between different cell signals are rationale approaches are not easily calculated by regular mathematical systems and network. Furthermore, tumor environmental matrix, metastatic-mediated pathways and cancer stem change also decide tumor progresses and malignancy. Future mathematical capability ought to be more sophisticated than ever before. Moreover, tumor promoters and suppressors are opposite factors for tumor progresses and metastasis. They are sometimes algebra, sometimes exponential and sometimes biology. It depends on the characteristics of different clinical condition. Currently, biological information treatment via mathematical models is often outside our reaches (general oncologists and clinicians). This kind of golden rush is waiting our great explorations. Working together among mathematicians, biologists and therapists is a future topic of cancer genetic or bioinformatics studies-including many types
of systems biology or medicines by teamwork.

**Association Between Oncology and Pharmacology System**

**Overview**

Association and difference between oncologic data (tomography, metastatic stage, genomics and bioinformatics) and pharmacology (drug activity and sensitivity, drug combination choice) for therapeutic prediction in individual cancer patients is obvious. (Figure 2) Looking at different categories of cancer therapeutic strategies are supported by different technologies. Due to the limitation of patho-therapeutic relation knowledge, one strategy of ICT cannot meet all requirements of maximum therapeutic match. It is quite interesting if one technology can provide detail information of both biomedical disciplines (oncology as well as pharmacology) [44-45].

**Oncology (gene/molecular) Pharmacology (drug sensitivity)**

Enter Link To Image

Integration

Mathematical treatment

Optimization of therapeutic regime

Therapeutic benefit gain

Figure 2: Outlook of modern personalized medicine.

**Cancer Pathology and Bioinformatics**

It is recently known that approximately 30,000 genes consist in normal and cancer human cells. Each cancer cell has distinctive and unique set of genetic makeup (up- or down-regulated in a tumor masses than normal cells from these ~30,000 genes) [32]. Only one or two genes are likely to be the original genetic abnormalities for cancer patients. When the genetic status of a tumor is assessed, only an average or overall picture of gene expression is observed. Bioinformatics (genomics, proteomics and metabolomics in cancer cells) reveals larger biological information in individual cancer patients.

Usually, only a few cancer biomarkers are detected in routine diagnostic procedures in general hospitals. The origin of a tumor is unlikely to be fully identified by this hospital routine and drug predictions. More comprehensive approaches for mapping the genetic polymorphisms, biochemical analysis and cytological levels of cancer-associated biomarkers versus increasingly sophisticated mathematical means will meet the requirements of real culprit catch-up. More computer software that supports automatic prediction of drug responses and toxicities (like artificial intelligence AI system) might be developed and especially recommended to future hospitals.

**Emerging Topics for Cancer Bioinformatics**

**Therapies Against Neoplasm Metastasis and Cancer Stem Cells**

Cancer metastasis is the key factor for cancer patients’ deaths (>90 cancer mortality in the clinic) [46-52]. Currently, cancer pharmacotherapy mainly focuses on primary tumors rather than neoplasm metastasis and antimetastatic drugs are not widely developed [46-54]. Moreover, many ICT methods, such as Drug Sensitivity Tests (DST) [55-57] or Pharmacogenomics (PG) [58] are also designed to primary tumors in the clinic. So cancer patients’ survival has been improved in a small extent. Antimetastatic drug developments and studies are not fruitful owing to above-mentioned reasons. Developments of more effective antimetastatic drugs, especially against formed metastatic foci, neoplasm metastasis treatments according to clinical circumstance of patients must be emphasized [50,52]. Some possibilities of assistant therapies by developing more effective, low toxicity supporting drugs and clinical optimizing therapeutic regimes can lead to breakthrough and next-generations of cancer therapies. The state-at-the art systems of cancer bioinformatics studies

Cancer stem cells in tumor tissues commonly decide therapeutic outcomes in the clinic. The cancer stem cells often renew themselves in cancer tissues that processes are hardly manageable by present treatment conventions (drugs and others) [59-62]. These self-renewals of cancer cells increase tumor malignancy in many pathogenesis aspects (dedifferentiation, dormancy, invasion, metastasis, relapse, chemotherapy-refractory, immune-escape and stimulating angiogenesis of tumors) [59-63]. Thus cancer bioinformatics are suitable for revealing ratio and biology of cancer stem cells in the future. Yet, cancer stem cells are less than 10 % in primary or formed metastatic tissues [64], it is still difficult to observe status of cancer stem cells in tumor tissues by present bioinformatics techniques and procedures. Future creative ideas and techniques are desperately needed.

**Drug Combinations and Cancer Bioinformatics**

Since most cancers have diverse genetic alterations and molecular abnormalities, cancer therapeutics is seldom very useful by only one anticancer drug. It has been widely accepted that anticancer drug cocktail instead single drugs might promote the control of cancer progresses and metastasis in clinical trials [65-68]. Similarly, are other chronic diseases, such as HIV/AIDS [69] and type 2 diabetes [70-71]. Most importantly, anticancer drug cocktails need to transform from empirical to science-guided enterprises [67-68]. Cancer bioinformatics is one of such avenue for identifying and choice of anticancer drug combination. Only through this strategy, cancer therapy can make a difference.
Future Perspective

Technical Innovation and Selections

Currently, bioinformatics is diverse in standard techniques and need to be uniformed by manufacturers [6]. In order to safeguard the quality and cost of hospital routines, standard guidelines must be issued internationally every 4-5 years.

Validity of cancer biomarkers or bioinformatics from tumor samples and prediction of anticancer drugs or biotherapies are general schemes for cancer bioinformatics applications. To achieve this goal, effectively drug choices (pharmacology) and clinical genetic/molecular predictions (oncology) must be integrated in the clinic [72-76]. Building central dogma for cancer bioinformatics analysis and drug response predictions is an unavoidable pathway in clinical rationales in the future [77-78].

Four categories of clinical investigations might be useful for cancer biomarker/bioinformatics-based cancer therapies:

- Improve the capacity of identification and validity for system updating of cancer biomarkers or bioinformatics for therapeutic purposes;
- Technical updating for economic considerations-put into large-scale production;
- Balancing between drug responses and toxicities from varying genetic abnormalities; and finally;
- Modern diagnostic systems in the real-time and non-invasive situations in cancer patients [2].

Cost-Reduction and Clinical Optimizing

Personalized cancer therapy (PCT) from detecting cancer biomarkers or bioinformatics is a modern strategy and has a great therapeutic potential in the clinic. However, the cost of cancer biomarker detection (generally $100-5000) is relatively low and cost-effective than other items of cancer treatments. It is especially cost-effective for early stages or young cancer patients owing to high rates of therapeutic survival benefits [15,43].

With the advancement of bioinformatics techniques, ICT with cancer biomarkers/bioinformatics detection will have a great impact in the future [77,78]. It is one of the fastest growing fields of PCT in future. But many important issues for cancer bioinformatics applications are unresolved. Economic consideration and cost-reduction for bioinformatics diagnostics can provide good service for more cancer patients and technical providers. Any unilateral economic benefits will not a healthy one. Finding leverage of these medical services is the key.

Advancing Knowledge

Earliest phase of cancer bioinformatics-based hypothesis and therapeutic studies are come from intuitions. Up to now, there is no good relationship (linear or multi-level) between abnormal cancer biomarker ranges and therapeutic outcomes (especially survival benefits) in clinical trials. Past medical evidence showed that no solid relationship between drug responses and scale or levels of most tumorigenic escalation can be based. To this obvious drawback, advancing knowledge of neoplasm/metastasis/mechanisms of action of anticancer drugs must be investigated in a large-scale. Why and how these clinical manifestations become a reality have yet to be defined. The elevated cancer biomarkers or bioinformatics characters are only parts of molecular basis in tumor growth and metastasis. Thus, breakthroughs within or beyond the bioinformatics techniques may all helpful for the promotion of clinical cancer trials.

Conclusion

Currently, less than 10% of patients use cancer-bioinformatics-based PCT-far behind PG and DST. The techniques and supporting systems in cancer bioinformatics are however developing rapidly-including new idea generations and novel models/drug developments. Cancer bioinformatics is still in its infancy. No decisive role has been played in clinical cancer treatments via this spectrum of techniques. Next generation of PCT strategies (integration of oncology and pharmacology) will play leading role in the future [77-78].

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Competing Interests

Authors have declared that no competing interests exist

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