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EC PHARMACOLOGY AND TOXICOLOGY
Editorial

Whole-Genome Analysis and PPI Networks for Personalized Anticancer Therapy

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Received: March 30, 2021; **Published:** May 27, 2021

Keywords: *Genomic Profiling; Systems Biology; Cancer Treatment; Protein-Protein Interaction; Personalized Medicine*

Current medicine requires precise information on a disease stage, risk factors, and personalized patient's responsiveness to a given intervention or a drug. Personalized medicine is an emerging field, which provides novel approaches to disease's early diagnosis, prevention, and treatment based on individual variability in gene expression profile, environmental factors, and lifestyle. If a disease such as cancer is characterized by a high degree of heterogeneity and has complex pathogenesis, it can display various genomic, epigenomic, and transcriptomic patterns and different sensitivity to treatment options [1,2].

Cancer is a multifactorial, heterogeneous, and complex disorder and a process with non-linear dynamics [3]. To understand cancer complexity various integrative multi-omics (genomics, epigenomics, proteomics, transcriptomics, and metabolomics) technologies along with systems biology and bioinformatics/computational biology approaches are currently being exploited. Furthermore, the integration of whole-genome analysis and gene expression profiling with protein- protein interaction (PPI) network and functional gene enrichment analyses represent an effective strategy [4]. Exploring cancer genomic landscape enables identification of differentially expressed genes (DEGs), somatic mutations, copy number variations (CNVs), gene amplification, DNA methylation/histone modification signatures along with circulating non-coding RNAs (ncRNAs) such as microRNA (miRNA) and long non-coding RNA (lncRNA) patterns specific for a definite cancer type [5]. This provides comprehensive knowledge for understanding tumor heterogeneity, molecular characterization, and classification, elucidating genetic-phenotypic relationships and correct staging of cancer as well as the assessment of cancer risk factors and individual variability in anti-cancer treatment and prevention.

Data obtained by whole-genome sequencing are collected in the integrated online resources and repositories. The most prominent resource is The Cancer Genome Atlas (TCGA) (https://www.genome.gov/) of the National Cancer Institute (NCI) and the National Human Genome Research Institute [6]. Another resource is Catalogue of Somatic Mutations in Cancer (COSMIC) at Sanger Institute, UK, (https://cancer.sanger.ac.uk/) curable to manage cancer somatic mutations data including coding and non-coding mutations, gene fusions, CNVs, and drug-resistance mutations underlying cancer promotion [7]. TCGA project is integrated with Cancer Genomics Hub (CGHub), the online repository of sequencing programs including the Cancer Cell Line Encyclopedia (CCLE) and the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) projects (https://cghub.ucsc.edu) [8]. More recently, the Pan- Cancer Analysis of Whole Genomes (PCAWG) Consortium (http://docs.icgc.org/pcawg) of the International Cancer Genome Consortium (ISGC) and TCGA was established [9]. TCGA and Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/) analysis in combination with

RNA sequencing data, Gene Ontology (GO) (http://geneontology.org/) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway (https://www.genome.jp/kegg/) are used for functional enrichment analysis [10-12]. Such an approach enables the identification of genes associated with cancer cell proliferation, invasion and migration, epithelial-to-mesenchymal transition, immune surveillance, and metabolic reprogramming underlying cancer initiation, progression, and metastasis. Additionally, they contribute to the identification of dysregulated cell signaling pathways and effective strategies in personalized cancer treatment. For example, Zhu and co-workers used TCGA, GO, and KEGG analysis to identify a total of 610 DEGs including 444 upregulated and 166 downregulated genes associated with hepatocellular carcinoma (HCC) [13]. Chen and co-workers used TCGA and GEO analysis to identify 594 DEGs associated with energy metabolism and divided HCC patients into three molecular subtypes with different prognoses [14].

PPI network analysis allows finding hub genes involved in various processes relevant to cancer growth and having the potential to be targeted for anti-cancer therapy. The construction and analysis of networks at different temporal and spatial levels including organism-specific or tissue- specific genomes, proteomes, and metabolomes or at the level of a network sub-circuits is a goal of systems biology [15,16]. Cancer systems biology has arisen as a logical extension and application of systems biology to the field of medical sciences and a reflection of cancer complexity. The complexity of a biological system arises from numerous non-linear interactions between its components [17,18]. Complex systems possess so named emergent properties and functions, which indicate that a system of two components has properties that each individual component does not possess. Further, a system of ten components has properties and functions that a two-component system does not have. This indicates that the behavior of a system is a result of the integration of its properties rather than their summation [19].

Evaluability of PPI network analysis in cancer research can be demonstrated by the following example. Current usage of multi-kinase inhibitors (MKI) such as sorafenib, lenvatinib and regorafenib for cancer treatment is based on the strategy to target a gene or several genes and to affect the entire pathway. However, this approach can fail to be efficient because the receptor tyrosine kinase (RTK)-mediated signaling belongs to redundant pathways, i.e. it has cross-talks that involve other pathways. Redundancy is the ability of two or more elements of a system to perform the same function so that the inactivation of one of them could have no effect on dynamic processes described by the entire network. Redundancy has been shown to be one of the mechanisms underlying anticancer drug resistance [20,21]. The computational framework developed to analyze gene expression data from cancer subsets with different drug responsiveness showed that network connectivity may be dramatically changed by a drug. Thus, describing network structure and features such as redundancy may be used as a basis for the development of a new strategy in personalized anti-cancer therapy.

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Volume 9 Issue 6 June 2021