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SYSTEMS-LEVEL CHARACTERIZATION OF METABOLIC REWIRING IN CANCER PROGRESSION

Dr. Shanmuga Priya M[1], Dr. Soundarya Kasi[2], Dr. Sumathi K[3]

[1]Professor, Pathology, Meenakshi Medical College Hospital & Research Institute, Meenakshi Academy of Higher Education and Research, Enathur, Kanchipuram, Tamil Nadu – 631552, India, Email: spriyapatho@maher.ac.in
[2]Lecturer, Pharmacognosy, Meenakshi College of Pharmacy, Meenakshi Academy of Higher Education and Research, Email: soundaryak@maher.ac.in
[3]Professor, Biochemistry, ORCID: https://orcid.org/0000-0002-0076-7776

ABSTRACT

This paper will explore the systems-level changes of metabolism that contribute to cancer progression with a combined transcriptomic and genomic characterization. The metabolic rewiring of cancer cells is far-reaching and is required to support unregulated proliferation, survival in harsh environments, and invasion. Nevertheless, the complicated interplay of the dysregulation of gene expression, the genomic instability and the changes in metabolic pathways has not been properly comprehended. In this paper, publicly available data sets were used in The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) to conduct an extensive multi-omics analysis on tumor and normal tissue samples. These studies employed RNA-seq to study differentially expressed genes and to characterize the genome through mutation profiling, single nucleotide polymorphism (SNP) analysis and copy number variation (CNV) analysis. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases were used to conduct the functional enrichment analysis to determine important changes in metabolic and signaling pathways. Moreover, a network analysis was also used to identify central hub genes that regulate metabolism during tumor progression using protein-protein interaction (PPI). The results showed a large-scale dysregulation of metabolic pathways related to glycolysis, oxidative phosphorylation, glutamine metabolism, lipid biosynthesis, PI3K-AKT, mTOR signaling, and hypoxia-related pathways. Oncogenic metabolic regulators (MYC, AKT1, HIF1A, KRAS, and mTOR) and tumor suppressor genes (TP53 and PTEN) had considerable transcriptional and genomic changes. Network analysis also established hub genes that are highly connected and coordinate proliferation, survival signaling, and metabolic adaptation in cancer cells. The systems-level framework offers more information about the molecular processes that underly cancer metabolic reprogramming and could be used to identify new biomarkers and therapeutic targets that can be used in precision oncology.

KEYWORDS: Metabolic rewiring; Cancer progression; Multi-omics integration; Transcriptomic profiling; Genomic characterization; KEGG pathway analysis; Proteinprotein interaction network; Cancer metabolism; Precision oncology; Systems biology.

1. INTRODUCTION

One of the major causes of morbidity and mortality in the world is cancer, which is marked with intricate genetic, epigenetic, transcriptomic, and metabolic changes that promote unregulated cell growth, survival, invasion and metastasis [2], [9]. Metabolic rewiring is one of the key characteristics of the cancer that allows the tumor cells to adjust to the high-energy requirements and to survive in the adverse tumor microenvironment [2]. Cancer cells show augmented glycolysis, disturbed lipid metabolism, reliance on glutamine, mitochondrial adjustments and oxidative stress management to maintain quick growth and endurance [3], [10]. The Warburg effect of tumor cells being preferentially aerobic even when oxygen is available is one of the most important metabolic traits of cancer [2]. This modified metabolic pattern assists in quick ATP generation and biosynthetic process needed to develop tumors. Moreover, there are anomalies in lipid biosynthesis, amino acid metabolism, and mitochondrial energy regulation that play a significant role in metabolic adaptations and therapeutic resistance in cancer cells.

Most recent developments in high-throughput sequencing technologies and computational biology have made possible characterization of large-scale cancer-related changes at the molecular scale. RNA-seq offers a method to conduct transcriptomic profiling, which can be useful in the identification of differentially expressed genes in metabolic regulation, and tumor progression [4], whereas genomic profiling is an effective tool that can identify mutations, single nucleotide polymorphisms (SNPs), and copy number variations (CNVs) that define oncogenesis and the occurrence of metabolic dysregulation [9 MYC, KRAS, EGFR, AKT1, PTEN and TP53 are important oncogenes and tumor suppressor genes that play significant roles in the regulation of tumor metabolism and signaling [3], [6].

The multi-omics integration methodologies and systems biology have further advanced the knowledge of cancer metabolism by incorporating both transcriptomic, genomic and signaling pathway data [1], [8]. A number of signaling pathways such as PI3K-AKT, mTOR, and HIF-1 are closely linked to glucose metabolism, cell survival, proliferation, and adaptation to hypoxia in the cancer cells [5], [6], [10]. Past reports have depicted that joint computational methods may locate molecular biomarkers, regulatory networks, and therapeutic targets that are related to tumor advancement [1], [11]. Although great advances have been achieved, most of the available studies concentrate primarily on single-omics analysis, which makes it difficult to understand the intricate relationship between genomic instability and metabolic dysregulation [1], [8]. Moreover, the heterogeneity of tumors and metabolic plasticity predisposes it to be hard to find stable biomarkers and therapeutic targets. As such, a systems level approach is required to have a stronger insight into metabolic rewiring during cancer evolution.This paper presents a combined transcriptomic and genomic framework that defines metabolic rewiring of cancer progression based on freely available TCGA and GEO data. The analysis of the differential gene expression, genomic, pathway enrichment and protein-protein interaction (PPI) network is conducted to determine the main metabolic pathways and regulatory hub genes playing a role in tumor development. The results can be used to identify new biomarkers and therapeutic targets to cause precision oncology.

2. RELATED WORK

A close connection between cancer progression and metabolic reprogramming is that the latter allows tumor cells to survive higher energy requirements, accelerated growth, and unfavorable microenvironment. Faubert et al. [2] emphasized the role of metabolic rewiring in tumor growth and described how changes in glycolysis, mitochondrial metabolism, and nutrient use play part in cancer progression. They have shown in their research that cancer metabolism facilitates the generation of energy, but also processes such as biosynthesis, redox homeostasis, and cellular signaling pathways. Genomic studies of cancer in large scale have enhanced insights into molecular heterogeneity and oncogenic signaling pathway in tumor development. Hoadley et al. [4] conducted molecular classification on over 10,000 tumors and found out that patterns of cell-of-origin greatly determine cancer subtypes and biological behavior.

Oncogenic signaling pathways were also studied by Sanchez-Vega et al. [9] on the basis of TCGA datasets and the authors found significant changes in such pathways as PI3K-AKT, mTOR, and TP53 which are highly correlated with tumor metabolism and survival. In recent years, there has been growing interest in systems-level and multi-omics strategies to cancer biology. Cao et al. [1] suggested the use of a multi-omics integration platform as a means to better subtype cancer and molecular characterize it. Md Rasadul et al. [8] have shown that transcriptomic integration has the potential to determine core metaflammatory regulatory networks that are linked to disease progression. Moreover, Wu et al. [11] applied integrated spatial omics analysis to examine the interaction of metabolic reprogramming and tumor microenvironment in pancreatic cancer.

A number of scientists have studied the molecular processes controlling the metabolic changes in cancer cells. MCL1 was shown by Gui et al. [3] to tune mTORC1 signalling to support tumor bioenergetics and tumorigenesis. The significant roles of mTORC1 and mTORC2 complexes in cancer metabolism, growth, and adaptation to various microenvironmental conditions were discussed by Kim et al. [6].

Previous background research by Kim et al. [5], and Yang et al. [12] had defined key elements of mTOR signaling molecules that partake in nutrient sensing and the activation of kinases. Cross-linkage between oncogenic behavior and metabolic homeostasis is another area of study that has been significantly explored. Tu et al. [10] have shown that USP29 orchestrates the stabilization of MYC and HIF1a, thus facilitating hypoxic tumor metabolism and progression. Koohi and Mehrmohamadi [7] mathematically modeled the association of metabolism and histone methylation of cancer cells, and found epigenetic regulation to be a contributing factor to metabolic adaptation.

Despite the fact that the previous research greatly advanced the knowledge of cancer metabolism, numerous studies were mainly dedicated to either single-omics datasets or one pathway. There is limited comprehensive systems-level integration of transcriptomic, genomic, metabolic, signaling changes. Thus, the current study will be an integrated systems-level characterization of the metabolic rewiring in cancer progression to integrate the transcriptomic with the genomic profiling, the use of pathway enrichment, and network-based methods to identify important drivers of metabolic changes, as well as therapeutic targets.

4. MATERIALS AND METHODS

The general approach that was used to carry out this study in the systems-level characterization of metabolic rewiring during cancer progression is shown in Fig. 1. Dataset collection, transcriptomic analysis, and genomic profiling, as well as the analysis of the differential gene expression, pathway enrichment analysis and the analysis of protein-protein interactions network are the workflow steps involved in the identification of key metabolic regulators and signaling pathways involved in cancer progression.

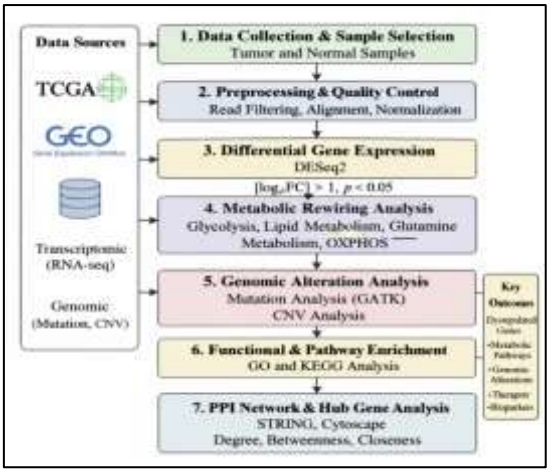

Fig. 1 : Overall Workflow

4.1 Dataset Collection and Sample Selection

The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) databases provided publicly available transcriptomic and genomic information about cancer progression. The selection of tumor and normal tissue samples was based on the access to RNA-seq expression profiles, mutation data, and clinical usefulness. The study did not include samples whose molecular information was incomplete or of low-quality sequencing. The datasets chosen presented detailed molecular data needed to perform an integrated systems-level analysis of metabolic rewiring during cancer progression.

Table 1: Dataset Information

Dataset Source	Cancer Type	Tumor Samples	Normal Samples	Data Type
TCGA	Breast Cancer	320	80	RNA-seq, Mutation
GEO	Lung Cancer	200	40	Transcriptomic
TCGA	Colon Cancer	150	30	Genomic

4.2 Transcriptomic Analysis

Raw RNA-seq data of TCGA and GEO were subjected to quality control and preprocessing in order to delete low-quality reads and sequencing artifacts. The alignment of high-quality reads with human reference genome was done with HISAT2/STAR alignment tools. This was then followed by a quantification of gene expression to gain normalized expression amounts of all genes between tumor and normal samples.

The DESeq2 package was used to perform a differential analysis of gene expression to determine significantly dysregulated genes linked to cancer metabolism and progression. Genes that passed the following thresholds were deemed to be significant:

$|\log_2 FC| > 1$ and $p < 0.05$

The further analysis of both upregulated and downregulated genes was identified related to glycolysis, lipid metabolism, glutamine metabolism, oxidative phosphorylation and cell-cycle regulation.

4.3 Genomic Profiling and Mutation Analysis

Genomic profiling was done to determine the molecular changes that lead to the development of metabolic dysregulation in cancer. Pipelines based on Genome Analysis toolkit (GATK)-based pipelines were used to perform somatic mutation analysis and single nucleotide polymorphism (SNP) identification. Oncogenes and tumor suppressor genes including TP53, KRAS,MYC, AKT1, EGFR, and PTEN, were frequently modified to establish their role in cancer progression. The copy number variation (CNV) analysis was also conducted to determine the genomic amplifications and deletions, which are related to tumor metabolism. The study of gene amplifications associated with proliferative signaling and deletions of regulatory checkpoint genes were looked into to gain insight into their contribution to metabolic changes and tumor survival.

4.4 Metabolic Pathway and Functional Enrichment Analysis

To examine the biological meaning of the dysregulated genes, functional enrichment analysis was conducted with the help of Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases. The

enrichment analysis revealed that biological processes, molecular functions, and metabolic pathways that have been found to be significantly altered are linked with cancer progression. Particular attention was paid to metabolic and signaling pathways that are related to cancer progression and metabolic resettlement. Major analysis has been based on glycolysis and glucose metabolism which has been extensively activated in tumor cells to aid in fast generation of energy and cell growth. The tricarboxylic acid (TCA) cycle and oxidative phosphorylation were also examined in order to assess the mitochondrial metabolic changes and the control of energy within the cancer cells. Moreover, lipid biosynthesis and glutamine metabolism pathways were studied due to their fundamental roles in membrane construction, biosynthetic activity, and nutrient adaptation in tumor growth. The most important oncogenic signaling pathways such as PI3K-AKT and mTOR signaling were also analyzed because they take part in the regulation of cell survival, proliferation, metabolism, and protein synthesis. The Hypoxia-related pathways were also examined to know the adaptation of the cancer cells to the low-oxygen tumor microenvironment. Together these studies assisted in revealing key metabolic pathways and cellular processes leading to tumor growth, survival, and metabolic reprogramming as cancer progresses.

4.6 Protein–Protein Interaction (PPI) Network Analysis

The interaction between proteins (PPI) network analysis was conducted with the help of the STRING database to assess the interactions between dysregulated metabolic and cancer-related genes. The networks of interactions generated were analyzed and visualised using Cytoscape software. Topological parameters like degree centrality, betweenness centrality, and closeness centrality were used to identify hub genes in the protein-protein interaction (PPI) network. Degree centrality is a measure of the number of direct interactions between genes, betweenness centrality is a measure of the position of a gene in terms of linking other parts of the network and finally closeness centrality is a measure of how effectively a gene interacts with the rest of the network. The highly central genes such as MYC, AKT1, TP53, KRAS, HIF1A, and mTOR were found to be key regulators of cancer progression and rewiring of metabolism.

5. RESULTS AND DISCUSSION

5.1 Dataset Overview

TCGA and GEO databases provided integrated transcriptomic and genomic datasets to analyse at the system level how metabolic rewiring in cancer progression occurs. The preprocessing and quality control of the samples resulted in the retaining of 520 tumor samples and 120 normal tissues that were to be further analyzed. Poor quality reads and incompleteness in molecular profiles were discarded in a bid to maintain reliability of the data. RNA-seq expression data were normalized to reduce technical variability among samples, and to provide valid comparison of tumor and normal tissues. The processed datasets had uniform distributions of expression with a minimal batch effect that they are appropriate in subsequent transcriptomic and genomic analysis.

5.2 Differential Expression Results

Analysis of differential gene expression showed significant dysregulation of 2,416 genes, 1,324 were up-regulated, and 1,092 were down-regulated in tumor tissue as compared to normal tissues. Volcano plot analysis was used to indicate how genes were distributed according to statistical significance and expression level, heatmap visualization was used to show that there is a clear clustering of tumor and normal tissue samples.

The expression level of a number of glycolytic and proliferation-related genes such as MYC, AKT1, HK2 and LDHA was significantly higher in cancer cells, which is a sign of increased metabolic activity and rapid cell growth. Conversely, tumor suppressor genes including TP53 and PTEN were reduced, as indicative of a lack of control over apoptotic cellular mechanisms and a loss of genomic stability. These results suggest that cancer pathogenesis is correlated with widespread transcriptional dysregulation and metabolic adaptation and oncogenic signaling pathways.

Table 2 : Differentially Expressed Genes

Gene Symbol	$\log_2 FC$	p-value	Regulation	Biological Role
MYC	3.21	0.0004	Upregulated	Cell proliferation
AKT1	2.87	0.0012	Upregulated	Survival signaling
HK2	2.65	0.0021	Upregulated	Glycolysis
TP53	-2.14	0.0008	Downregulated	Tumor suppression
PTEN	-1.95	0.0017	Downregulated	Cell-cycle regulation

5.3 Metabolic Rewiring Findings

Analysis of metabolic rewiring showed that there were significant changes in several energy metabolism pathways related to tumor progression. Genes related with glycolysis showed a difference of about 2.8 fold in increased expression in tumor tissues than normal tissues and this indicates increased aerobic glycolysis which is as per the Warburg effect. They found a higher rate of uptake of glucose and glycolysis to aid high rates of ATP production and biosynthetic needs in growing cancer cells.

Lipid metabolism pathways, such as fatty acid biosynthesis and cholesterol metabolism, were also found to be significantly dysregulated, and this suggests higher membrane production along with metabolic acclimatization to tumor growth. The metabolic pathways of glutamine showed high expression of the glutaminase-related genes, indicating glutamine addicting as an alternative energy and biosynthetic source of cancer cells.

Mitochondrial metabolism analysis also indicated the development of abnormalities in oxidative phosphorylation and tricarboxylic acid (TCA) cycles regulation. Various oncogenic signaling pathways, such as PI3K-AKT, mTOR, HIF-1, and AMPK were massively enriched and tightly linked to the metabolic adaptation process, hypoxia response, and survival mechanisms in cells. All these observations illustrate that the advanced development of cancer is accompanied by the coordinated metabolic reprogramming to support tumor growth and adaptation to the environment.

5.4 Genomic Alteration Findings

The genomic profiling revealed a number of common mutations and structural genomic changes that caused cancer development and metabolic impairment. The frequency of mutation of TP53 was found to be about 48% in tumor samples, KRAS (32%), EGFR (24%) and Myc alterations were found (18%). The genes play a critical role in proliferation signaling, genomic stability as well as metabolic regulation. The copy number variation (CNV) was conducted that revealed multiple deletions and amplifications of genes related to the development of tumors. MYC and EGFR gene amplifications were significantly linked with elevated proliferative signaling and increased metabolic activity but deletions of TP53 and PTEN were linked with the inability to maintain cell-cycle control and dysfunctional apoptosis. These changes in the genome were all involved in transcriptional dysregulation and metabolic pathway activation of cancer cells.

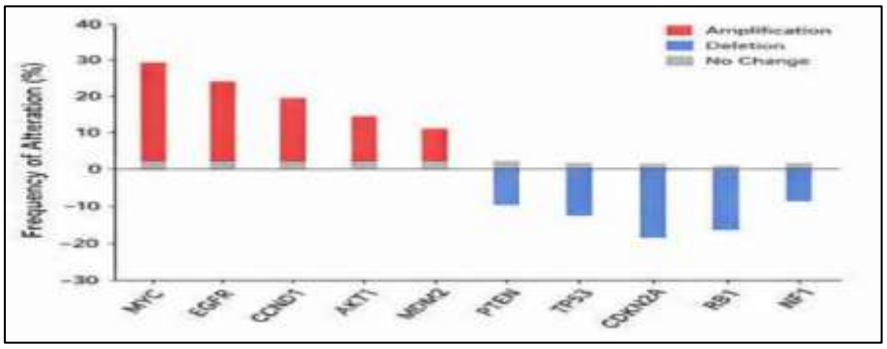

Fig 2: Copy Number Variation (CNV) Overview

TABLE 3 : Significantly Enriched KEGG

Pathway	Gene Count	Enrichment Score	**p-value**
Glycolysis	28	5.61	0.0003
PI3K-AKT Signaling	34	4.92	0.0007
mTOR Signaling	19	4.11	0.0012
Oxidative Phosphorylation	22	3.88	0.0021
HIF-1 Signaling	17	3.45	0.0034

5.6 Integrated Network Interpretatio

The protein-protein interaction (PPI) network analysis has revealed that there are a number of highly connected hub genes that control cancer metabolism and progression. The connected regulatory (Fig. 6) network showed high interaction between MYC, AKT1, HIF1A, mTOR, TP53, and KRAS reflecting their key position in metabolic adjustment and oncogenic signaling.

Topological analysis showed that MYC and AKT1 had the largest degree centrality values indicating that they had strong control over glycolytic and proliferation pathways. HIF1A and mTOR were mainly related to the process of hypoxic adjustment and metabolic control, and TP53 was a key regulator of controls in the form of a critical checkpoint involving genomic stability and metabolic regulation. The systems network analysis showed that cancer changes are a result of the intricate interplay between genomic changes, transcriptional dysregulation, and metabolic pathway activation, and the significance of systems-based analysis in the study of tumor biology.

6. CONCLUSION

This paper provided an integrated transcriptomic and genomic characterization of metabolic rewiring in cancer progression at a systems-level. The results showed that metabolic reprogramming is essential in tumor growth, survival, and adaptation due to the dysregulation of glycolysis, lipid metabolism, glutamine metabolism, and mitochondrial pathways. There are considerable changes in key signaling pathways such as PI3K-AKT, mTOR, HIF-1, and AMPK that also underscored the molecular complexity of cancer metabolism. The combined multi-omics approach was able to pinpoint the essential metabolic drivers, genomic changes, enriched biological pathways, and central regulation hub genes related to tumor progression. Major regulators of metabolic adaptation and oncogenic signaling were identified as important genes like MYC, AKT1, HIF1A, mTOR, and TP53. These results further illuminate the molecular pathways of cancer metabolic rewiring and can be used to realize new biomarkers, therapeutic targets and precision oncology interventions to better diagnose and treat cancer.

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