MicroRNA Gene Regulatory Network Biomarker Analysis in Prostate Cancer

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Abstract

Cancer is one of the cardinal causes of mortality in humans. The mutation is the one who is responsible for the change of gene function and activity that cause disease like cancer. Comprehension on gene regulatory network is a feasible approach to understand the complexity of biology and unrevealing the reconnection between genes and what it is responsible for. This paper discusses prostate cancer analysis using the microRNA gene regulatory network to understand the interaction and function of the gene responsible. MicroRNA are extensively regulated gene expression with the strong inclination as biomarkers for cancer diagnosis, prognosis, and therapy. Some possible candidates for microRNA prostate cancer biomarker are miR-145-5p, miR-204-5p, and miR-648. However further analysis and technologies is needed to reduce the conflict between each data.

Keywords: *prostate cancer, microRNA, gene regulatory network, biomarker, bioinformatics*.

Introduction

The main problem in molecular biology is to comprehend the gene regulatory network. Gene regulatory network orchestrates a critical role in understanding biology in determining the complex phenotype of a cell and understanding cell physiology, including cell differentiation, metabolism, cell cycle, signal transduction. Many biological processes depend on gene regulatory networks to enable vivid insight to understand to cellular process in a living thing, and it can act as a blueprint to observe the relationship among genes. The way to unrevealing the principle relies on the mathematical and computational models. Previously, gene regulatory networks was generated using a clustering approach. However, this approach succumbed to recognize significantly transcriptional network interaction (Chai *et al.*, 2014). So, many computational methods have been devised to construct more robust gene regulatory networks. Mathematical and computational models are the core element in

studying the regulatory network due to two reasons. First, they propose an adequate theoretical framework to investigate dynamic behavior under multiple constraints, and second, they generate an experimentally testable prediction, which can lead to more in-depth insight into the function of gene regulatory network (Sanchez-Osorio *et al.*, 2014).

Cancer is a complex disease, one of them is prostate cancer that has been the second leading in cancer death after lung cancer. Prostate cancer has strong heterogeneity as an outcome of genetic variation. There are many numbers of gene involve is prostate cancer that plays the role of a signaling pathway that makes the finding of the genetic cause of this disease is severe. This study used a system biology approach to predict prostate cancer biomarkers to understand the role of the gene that play roles in the disease.

MicroRNA are small non-coding RNAs of around 20 base pairs with the strong potential as biomarkers (Lin, *et al.,* 2018) and extensively regulate gene expression (Afshar, Xu, & Goutsias, 2014) for disease prediction. In mammals, microRNAs regulate the activity of almost 70% of all protein-coding genes and extensively participate in the regulation of many cellular functions (Afshar, Xu, & Goutsias, 2014). Growing evidence indicates that microRNAs can serve as ideal biomarkers for cancer diagnosis, prognosis, and therapy (Wen, Deng, & Wang, 2014). This gene plays a crucial role in tumorigenesis, and understanding the gene and its interaction help in founding effective treatment.

Objective

Understand and summarize the role of microRNA gene regulatory network as a biomarker in prostate cancer and the pathway in regulation of the phenotype.

Materials and Methods

Search for the research article were found by various resources including PubMed and Google Scholar. The keyword used were “microRNA gene regulatory network”, “prostate cancer”, and “biomarkers”. Five of the research articles published in the time interval 2013 – 2018 were selected as the main reference.

Results

Different kinds of research paper from 2013 until 2018 are identified, and five research papers are selected as bellow at the Table 1:

Table 1. Review Summary

Reference	**Datasets**	**microRNA results**
Zhang *et al.,* 2014	GSE34933 from NCBI Gene Expression Omnibus (GEO)	39 microRNA
Lin *et al.,* 2018	GSE21036 and GSE3325 from NCBI Gene Expression Omnibus (GEO)	618 microRNA
Huang *et al.,* 2014	search in Med-line database with the key words "sepsis or severe sepsis or septic shock," "miRNA or microRNA," and "biomarker or marker or indicator."	10 microRNA
Wen, Deng, & Wang, 2014	Review of a research paper	17 microRNA
Sita-Lumsden *et al.,* 2013	Review of a research paper	85 microRNA

Discussion

Methodology and Challenge

The methodology to develop microRNA diagnostics is the capability to count microRNA titers from plasma and serum. This method requires high precision and has a high risk of contamination, causing variation and insufficient consistency in existing microRNA annotations. Another challenge is specimen collection, RNA extraction, technical issues like qRT-PCR, and data analysis and normalization (Sita-Lumsden *et al.,* 2013). Problems that remain unsolved are normalisation, amplification, and contamination. Normalizing control uses similar input volumes and validated for technical variability because it is not possible to know the total amount of microRNA in body fluid due to extremely low concentration. This approach is undependable because of biological variety. Another area is some studies used pre-amplification reagents to increase the sensitivity of the qRT-PCR, and some are not. That methods requires standardisation to get the same output. The last issue is contaminations, valid microRNA in the serum can be contaminated from cellular blood components. Although some issues make microRNA analysis are not yet to be implemented in the clinic, up to now, studies show that microRNAs have the strong potential to be a biomarker for prostate cancer.

Validation of identified microRNA biomarkers

The validation prosses are using many methods. Some microRNAs are selected for in-vitro validation to detect a difference in their expression by q-PCR technology, and some of them are used for comparison with PubMed literature reports. They are tabulated in the Table 2:

Table 2. MicroRNA Function

Name of microRNA	**Role/Function**
miR-145	Cell invasion and migration in prostate cancer progression.
miR-204-5p	Tumor suppressor, prostate cancer progression and metastasis.
miR-152	Prostate cancer progression and metastasis
miR-101	Activation of known oncogenes driving prostate cancer metastasis
miR-198	Recognise the aggressive behaviour of prostate cancer
miR-200 family	Tumor suppression
miR-21	Onco-miRNA
miR-100	Tumor supression
miR-221/222	Onco-miRNA
miR-143	Tumor suppression
miR-133b	Tumor suppression
miR-205	Tumor suppression
miR-663	Onco-miRNA
miR-221	Onco-miRNA
miR-203	Tumor suppression
miR-34-a	Tumor suppression
miR-101	Tumor suppression
miR-146a	Tumor suppression
miR-375	Tumor suppression
miR-141	Repress the epithelial to mesenchymal transition

Based on the result, many microRNAs were validated as tumor suppressor microRNA based on inferential statistics evidence from a combination of network sub-structural and function analysis. This makes microRNA as a potential biomarker for prostate cancer that can be used for diagnostic, prognostic, and therapy. And miR-648 was elicited as a novel candidate prostate cancer microRNA biomarker using the in-vitro q-PCR experiments and functional analysis enrichment.

Micro RNA as Diagnosis, Prognosis, and Therapy for Prostate Cancer

The study found that some microRNAs are found to be upregulated in cancer patients compared to the normal ones; this associates the role of microRNA in diagnosing patients with prostate cancer. Moltzahn *et al.,* 2011 found that miR-93, miR106a, and miR-24 show inherently low levels in healthy individuals than in cancer patients. Chen *et al.,* 2012 could

differentiate between 80 patients with prostate cancer and 44 patients with benign prostatic hyperplasia using five miRNA panel. Selth *et al.,* 2012 showed that miR-141, miR-298, miR-346, and miR-375 are consistently higher in patients with prostate cancer than a healthy individual.

Some microRNAs have already been implicated in various disease such as miR-451 has been implicated as casual in colorectal cancer, breast cancer, gastric cancer. There are also microRNAs that have not been previously reported to be involved in any disease. MicroRNA that involves in progression of prostate cancer could assist to identify targets for the upcoming therapies. Many of the microRNAs are feature in the tumor suppressor like the miR-375 and miR-101 that can be used for cancer therapy. However, there is a possibility that each microRNA targets other different microRNA and can alter the protein product in several signal transduction pathways resulting in potential off-target effects (Sita-Lumsden *et al.,* 2013). This can be used as an advantage like for instance, miR-27a targets several tumor suppressor genes and inhibit this miR could inhibit tumor growth via several pathways (Sita-Lumsden *et al.,* 2013). Discovering the interaction and connection between each microRNA could reveal an effective therapeutic strategy for cancer treatment and even prevent it.

Although scientist already differentiates many microRNA and their functions, it takes a lot more than that to discover the gene regulatory network for prostate cancer only. The prostate cancer genome is different within each individual, and there is always some mutation that could happen, not to mention all the obstacles like methodology or reference gene error. That will become a challenge to improve the method, technique, technology, analysis, and many more to discover and thoroughly understand the connection between each gene responsible for cancer in our body. This challenge will become possible if we put out best, never give up, and never satisfied with the result to get a more perfect outcome.

Conclusion

Prostate cancer is very complex and MicroRNA has many roles is expressing the phenotype in the prostate cancer such as macromolecule metabolic process, nuclear mRNA splicing, immune response, cell proliferation, mitosis, cell cycle, and many more. To completely understand the regulatory network in prostate cancer, all the gene function and interaction must be fully identified first. This paper summarize biomarker for prostate cancer that useful for effective treatment and the microRNA function in prostate cancer and microRNA candidate that could be linked to prostate cancer. However future analysis needed because of conflicting data and lack of standardization in methodology and lack of suitable reference genes for normalization.

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