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Statistical Modeling of MicroRNA Expression with Human Cancers

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Abstract

MicroRNAs (miRNAs) are small non-coding RNAs (containing about 22 nucleotides) that regulate gene expression. MiRNAs are involved in many different biological processes such as cell proliferation, differentiation, apoptosis, fat metabolism, and human cancer genes; while miRNAs may function as candidates for diagnostic and prognostic biomarkers and predictors of drug response. This paper emphasizes the statistical methods in the analysis of the associations of miRNA gene expression with human cancers and related clinical phenotypes: 1) simple statistical methods include chi-square test, correlation analysis, t-test and one-way ANOVA; 2) regression models include linear and logistic regression; 3) survival analysis approaches such as non-parametric Kaplan-Meier method and log-rank test as well as semi-parametric Cox proportional hazards models have been used for time to event data; 4) multivariate method such as cluster analysis has been used for clustering samples and principal component analysis (PCA) has been used for data mining; 5) Bayesian statistical methods have recently made great inroads into many areas of science, including the assessment of association between miRNA expression and human cancers; and 6) multiple testing.

Keywords: Cancer; MicroRNA; MiRNA; Biomarker; Diagnosis; Regression Models; Non-parametric Methods; Survival Analysis; Multivariate Statistics; Bayesian Methods; Multiple Testing

Background

A microRNA (miRNA) is a small non-coding RNA molecule (containing about 22 nucleotides), which functions in RNA silencing and post-transcriptional regulation of gene expression [1-3]. MiRNAs are involved in many different biological processes such as cell proliferation, differentiation, apoptosis, fat metabolism, and human cancer genes [4-8]. Previous studies suggest that miRNAs expression profiles are correlated with disease pathogenesis and prognosis, and may ultimately be useful in the management of human cancer; while miRNAs may function as candidates for diagnostic and prognostic biomarkers and predictors of drug response. For example, miRNAs can act either as oncogenes or tumor suppressors contributing to initiation and progression of cancer [3,6,9-12]. MiRNA expression can be detected by a two-step polymerase chain reaction process of RT-PCR followed by quantitative PCR [13], microarray [14], and miRNA sequencing [15]. The raw counts of miRNA expression are usually skewed and not meet the assumptions of parametric statistical tests, therefore a log2 transformation is applied [16,17], for example by a weighted trimmed mean of the log expression ratios using the R/Bioconductor package [18,19].

Simple Statistical Methods

Some studies examined the miRNA expression level as a categorical variable, which was dichotomized as low and high level expression based on the median [20-22]. The chi-square test has been used to determine the associations of expression of miRNA-21 with patients' clinical parameters such as lymph node metastasis, clinical stage and poor prognosis in non-small cell lung cancer (NSCLC) as categorical variables [22]. This approach was also used to test the relationship between miRNA-221 expression and binary clinicopathologic features such as histology, p-TNM stage and history of smoking [23]; and the correlation between miRNA-124 down-regulates SOX8 expression and binary clinicopathologic factors such as tumor size, lymph node metastasis, differentiation classification and clinical stage [24].

However, most other studies treated the miRNA expression as a continuous variable. For example, the t-test for two-independent samples has been used to compare the expression values of miRNAs between the control and lung cancer groups [17,25], the expression of miRNA-146 in NSCLC cancer tissue (43 individuals) and normal tissue (32 individuals) [26]. Furthermore, the t-test for paired samples was performed to identify if miRNA-31 is differentially expressed between lung adenocarcinoma and matched normal adjacent tissues using the Cancer Genome Atlas (TCGA) dataset [27]. Moreover, one-way ANOVA was utilized to examine the association between E2F miRNA expression and degree of tumor cell invasion in gastric cancer [28]. Additionally, non-parametric methods such as Wilcoxon sign-rank test for paired samples analysis was used to compare expression of miRNAs across the seven tumor samples in breast cancer [29] and Kruskal-Wallis test was used to determine the significance of miRNAs among the biochemical failure categories [30].

The simple correlation analysis has been used to describe the relationship of miRNA expression with cancer clinical phenotypes. For example, the correlation between miRNA-148a expression and the methylation level of the DNA region encoding miRNA-148a in tissues was evaluated by Pearson's correlation [31]. Other studies used the Spearman's rank correlation analysis to correlate miRNAs with mRNA in the breast cancer samples [32], the alterations of methylation with expression level of miRNA-9-1 gene in the lung tumors [33], and the pairwise miRNA expression in seven types of cancer using the TCGA data [34].

Linear and Logistic Regression Models

The linear and logistic regression models have been used to

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examine the associations of miRNA expression with cancer and clinical phenotypes. For example, linear regression analysis was used to identify the association of 335 miRNAs with recurrent ovarian cancer cell lines [35] and to examine the association between cigarettes per day in lung cancer patients and miRNA expression [36]. Recently, a multiple linear regression analysis was used to investigate the associations of each mRNA transcript with the corresponding miRNAs in colorectal cancer [37].

The binary logistic regression analysis was utilized to select the top 25 miRNA genes with prognostic relevance in neuroblastoma, that is, the miRNAs with the lowest P-value in a model testing miRNA expression levels (below or above the median expression) versus overall survival [38], evaluate the ability of chosen miRNAs to distinguish between breast cancer cases and controls [39], and differentially expressed genes that are regulated by the mRNAs expression between gastric cancer and paired adjacent normal tissues [28]. Multiple logistic regression analyses have been performed to investigate the role of miRNA signature on binary outcomes in neuroblastoma such as cases defined as relapse, progression, or death from disease (progression-free survival), and death (overall survival) comparing with controls defined as nonfailure in the first 3 years of follow-up, adjusted for age at diagnosis, stage and other phenotypes [38]. Another study used a multiple logistic model of specific miRNA biomarkers to predict the presence of menstrual blood [40]. Recently, Zhang et al. [41] evaluated the associations of both human papillomavirus-HPV16 status and IL-1α rs3783553 polymorphism at the miRNA-122 binding site, individually and in combination, with the risk of oral squamous cell carcinoma (OSCC) using both univariate and multivariable logistic regression analyses.

Survival Analysis

The non-parametric Kaplan-Meier method has been used to estimate the survival distributions for expression of miRNA-21 [42], miRNA-148a [31], miRNA-31 [27], miRNA-221 [23], and miRNA-124 in NSCLC [24]; while the log-rank test has been used to analyze the survival differences according to expression between different subgroups [23,24,27,31,42]. Recently, the Kaplan-Meier method was used to estimate the overall survival curves for four miRNAs (miRNA-21, 22, 155 and 210) in the TCGA glioblastoma multiforme dataset using the BRB-Array Tools - R/BioConductor [16]. Another recent study used the Kaplan-Meier survival analysis to estimate the survival distributions for patients in each of 5 subtypes of glioblastoma multiforme based on significant miRNAs and applied the log-rank test to assess the statistical significance between the stratified high- and low-risk survival groups in primary glioblastoma in the TCGA dataset using GraphPad Prism 6.0 statistical software [43].

The semi-parametric Cox proportional hazards model has been widely used to construct respective prognostic miRNA signatures of cancers [21,22,27,42,43]. For example, multivariable Cox proportional hazards model was used to identify the significant influence of miRNA-148a expression on survival, adjusted for gender, age, histologic grade, T stage and smoking status [31]. Another study used the univariable Cox regression analysis to examine the association between 9 continuous miRNA expression and overall survival rate of Glioblastoma Multiforme (GBM) using the TCGA dataset; while multivariable Cox regression analysis was performed by stratifying patients according to age and using MGMT methylation status, IDH1 mutations, pre-treatment, recurrence, and TCGA prognostic classification as covariates [16]. Especially, Mankoo et al. [44] implemented a multivariate Cox Lasso model and median time-to-event prediction algorithm and applied it to two datasets integrated from the four genomic data types (mRNA, DNA methylation, DNA copy-number alteration and miRNA) in the TCGA data.

Multivariate Methods

Multivariate analysis methods such as cluster analysis has been used for clustering samples, and principal component analysis (PCA) has been used for data mining. For example, to identify miRNA expression patterns in breast cancer, one study performed an unsupervised hierarchical complete linkage cluster analysis using Euclidean distance as dissimilarity metric; meanwhile a Pearson χ^2 test and a Goeman global test were used to investigate the association of the sample clustering result with clinicopathological variables [32,45]. Keller et al. [25] analyzed the abundance of 904 miRNAs in serum from eight cancer patients at three time points and from six healthy control individuals and identified clusters based on the identified miRNA signatures, hierarchical clustering and a self-organizing map; while Oberg et al. [46] used PCA and hierarchical cluster analyses to visualize miRNA expression patterns present at a global level in colon cancer. Another study applied a complete linkage hierarchical clustering using the Euclidian distance to compute the dissimilarity of miRNA and samples independently of each other using the normalized data [17]. In addition, Li et al. [21] identified an eight-miRNA (miR-31, miR-196b, miR-766, miR-519a-1, miR-375, miR-187, miR-331 and miR-101-1) signature for the prediction of overall survival of patients with lung adenocarcinoma (LUAD) using supervised principal components method in the TCGA-derived LUAD cohort.

Bayesian Statistics

Bayesian statistical methods have recently made great inroads into many areas of science [47], including the assessment of association between miRNA expression and human cancers. One of the main challenges in modeling the statistical dependence between high-throughput studies is that a large number of measurements (usually in thousands) is available for a relatively small number (usually in tens or hundreds) of patient samples; therefore, classical statistical approaches based on linear models and hierarchical clustering are prone to over-fitting [48,49]. In these situations, Efron [48] recommended accounting for high-dimensionality by using approaches that borrow information across covariates to compensate for the limited information available across samples, which leads to better and more reliable inference.

Several approaches have been developed to address these challenges in various contexts, for example hierarchical Bayesian modeling approaches based on linear shrinkage estimators [50]. For predicting relevant clinical outcomes, Srivastava et al. [51] proposed a flexible statistical machine learning approach that acknowledges and models the interaction between platform-specific measurements through nonlinear kernel machines and borrows information within and between platforms through a hierarchical Bayesian framework. The methods of integrating gene/mRNA expression and miRNA profiles for predicting patient survival times were applied to the TCGA based glioblastoma multiforme (GBM) dataset [51]. Recently, Chekouo et al. [52] proposed a novel Bayesian model to identify miRNAs and their target genes that were associated with survival time by incorporating the miRNA regulatory network through prior distributions.

Multiple Testing

The number of miRNA in human genome is abundant and multiple

outcomes have been measured in many miRNA expression studies. Therefore, the multiple testing issue is a big statistical challenge. The conservative Bonferroni correction (0.05/n, n is the number of tested miRNA) has been used for dealing with multiple testing [53]. Furthermore, the false discovery rate (FDR) based on the Benjamini and Hochberg method [54] was used to correct multiple testing in comparison of miRNA expression levels across different groups [55-57]. Additionally, some studies have used permutation tests to account for multiple testing in comparison of miRNA expression profile, for example, by using 1,000 or 10,000 permutations [36,43,53].

Discussion and Future Direction

The t-test and one-way ANOVA require the assumption of normality of the data; however, such assumption is often violated in practice. Therefore, generalized linear models (GLMs) and generalized linear mixed models (GLMMs) can relax the assumption and deal with binary and counts data. For example, GLMMs can be used to compare the miRNA measures before/after or with/without treatment. Furthermore, non-parametric statistical methods may be alternatives in some specific situations to describe the miRNA data with cancer.

In survival analysis, many studies have focused on non-parametric methods such as Kaplan-Meier method and log-rank test and semi-parametric Cox proportional hazards models. Non-parametric methods have the advantages of no assumptions for the underlying survival distributions; while Cox model made certain assumptions about the nature of hazard function for proportional hazards regression method. In practice, it can be assumed that the survival function is of a certain form such as exponential, Weibull, and so on, with one or more parameters whose values are unknown, to be estimated from real data [58]. Furthermore, if the shape of the survival distribution is known, parametric regression models may produce more efficient estimates than Cox model [59].

Till now, the sample sizes used in miRNA expression studies are relatively small, therefore, Bayesian methods may have some advantages in flexibility and for incorporating information from previous studies. Future studies with large sample sizes will be required to increase the power in detection of the significance and also for adjusting for multiple covariates in regression models. In addition, due to the complex correlation structure between multiple tests, adjusting for multiple testing is a big statistical challenge but is essential in analysis of miRNA expression with human cancers.

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