Modeling of Extracellular Matrix Degradation Processes in Cancer Metastasis Using Covariance Structure Analysis

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1 Introduction

Cancer metastasis is comprised of subsequent processes such as release of cancer cells from a primary focus, their invasion into blood vessels and adhesion to target tissues. Various molecules are involved in each process including overexpression of extracellular matrix (ECM) degrading proteases and abnormality of cell adhesion molecules. Matrix metalloproteinases (MMPs) are ECM degrading enzymes, and excessive degradation of ECM by losing balance between its expression and inhibition is one of critical causes for cancer metastasis. Cancer cells obtain metastatic ability through consecutive transformations, but it is difficult to observe temporal processes of such transformation events. In addition, interaction between pathways are important in cancer progression. In this research, we analyzed a microarray dataset with covariance structure analysis (CSA), which is a sophisticated method to estimate unobservable phenomena. CSA inherits properties of traditional multivariate analysis such as causal analysis, regression analysis and path analysis.

2 Method and Results

Data Set and Preprocess

We used oral cancer microarray dataset [2] measured by Affymetrix HG-U133A (22283 probes), downloaded from NCBI Gene Expression Omnibus (GDS 10623). Total 22 samples (14 samples with lymph node metastasis and eight samples without any metastases) were included in the dataset. Raw CEL files were normalized by robust multichip average (RMA) method using R statistical software (version 2.2.1) and BioConductor 1.6, and exemplar probes were chosen for further analysis.

Analysis 1

We hypothesized six CSA models for MMPs and cancer metastasis. The comprehensive evaluation by $\chi^2$ test, goodness of fit index (GFI), adjusted goodness of fit index (AGFI) and Akaike information criteria (AIC) indicated the model containing type IV collagen degradation was the best model to describe cancer metastasis (Fig. 1).

Analysis 2

We chose five pathways (VEGF, Wnt, cell cycle, TGF-β, apoptosis) from KEGG PATHWAY Database [3] and calculated the first principal components of each pathway by applying principal component analysis (PCA) to the gene expression data. We assumed that each pathway activity was summarized in the first principal component. CSA was utilized to choose appropriate models based on the pathway activity, using the same evaluation methods as Analysis 1. The best model which explained cancer metastasis contained VEGF, Wnt, and TGF-β pathways (Fig. 2).
3 Discussion

Analysis 1
Our result is consistent with previous report that type IV collagen is a main component of basement membrane and its degradation is essential for lymph node metastasis. [1]

Analysis 2
Suppression of TGF-β pathway can cause activation of cell proliferation and tumorigenesis. Because Wnt and VEGF pathways are located in the upstream of cell cycle, upregulation of these pathways may also promote tumor growth.

References

