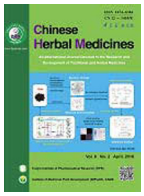

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Review

Application of Connectivity Map Database to Research on Chinese Materia Medica

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ABSTRACT

The connectivity map (CMAP) database is established initially to connect biology, chemistry, and clinical conditions, which helps to discover the connection of disease-gene-drug. The CMAP approach has been applied in the field of drug discovery and development, which is widely recognized. In recently years, CMAP analysis has been applied in the research on Chinese materia medica (CMM). The study of CMM is facing a wide range of challenges, such as complicated ingredients, multiple targets, multiple pathways of action and complex functioning mechanism. The idea of employing CMAP in the CMM research has brought a new perspective for researchers and provides a systematic method for elucidating the mechanism of CMM.

Key words

Chinese materia medica; Chinese materia medica formula; connectivity map; establishing connectivity map database

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1. Introduction

Since the first piece of DNA chip was made by Stanford University (Schena et al, 1995), the development of such technology and the concept of fast and comprehensive characterizing DNA on a chip have been broadly extended. In biological chips, the DNA chip was one of the earliest and most widely used, which could detect the change in the whole genome of drug-treated cells and tissues (Zhang et al, 2008). A study employing chip technology, conducted by Hughes et al (2000), was used to establish gene expression profiles database from 300 different yeast mutants in response of small molecules, and to predict the function of the small molecule by the phenotypical change of yeast transcriptomes.

Based on previous studies, a novel analysis database employing gene expression profiles was developed by Lamb et al (2006), which resulted in the establishment of the connectivity map (CMAP) database. Researchers used small molecule compounds to treat human cell lines, obtaining gene expression profiles data, which was then included in CMAP database. By exploiting gene expression profiling as a common "language" to associate biology, chemistry, and clinical conditions, CMAP database connected disease-gene-drug network regardless of the microarray platforms used (Justin, 2007; Qu and Rajpal, 2012). The remarkable work has brought convenience to scientific researchers by helping them to find the biology significance from CMAP database. In the analysis, researchers could find out the potential correlation of compounds and their inferred mechanism, which provided a new and reliable way for drug development.

Chinese materia medica (CMM) has been used in China for a long history and has good efficacy in prevention and treatment of a variety of diseases. With the CMM receiving more and more attention, the method of CMM research also

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appeared in diversification. Due to the complex mechanism of CMM caused by multiple components and multiple targets, previous methods offered the limited capacity to acquire the comprehensive knowledge for incorporating clinical level to cell level, and even molecular level (Sun and Shu, 2002). However, the CMAP approach, by analyzing of the gene expression profiles of small molecules and CMM, could discover the new function of components of CMM and elucidate the mechanism of CMM. Therefore, such effective research approach of CMAP applied in the field of CMM brought a new perspective for researchers and provided a systematic method for study on the mechanism of CMM.

2. Establishing CMAP database

Lamb et al (2006) established the CMAP database, and the result was published in *Science*. In the early stage of establishing CMAP database, researchers selected 164 distinct small molecule compounds, which represented different biological activities and had been approved by FDA. The selection of cell lines was limited by the experimental requirements, such as whether they could be stably grown over long periods of time, whether they were able to culture in micro plates and whether they were used as reference cells lines in laboratories across the world. In compliance with such requirements, researchers chose four cell lines, breast cancer epithelial cells (MCF7), prostate cancer cells (PC3), leukemia cells (HL60), and melanoma cells (SKMEL5). The concentration and treatment time of the small molecule compounds were also the important factors of the experiment. A relatively high concentration of 10 μmol/L, which was commonly used in high throughput screening based cell assays, was selected as initial treatment concentration. On top of that, researchers also conducted an extra experiment using a subset of compounds across a range of concentration to explore the sensitivity of results to dose. The selection of the time of small molecule compounds treating cells was proved to have an effect on the gene expression profiles. Therefore, 6 and 12 h treatment time were selected as the two time points for small molecule compounds treating cells in the experiment. In the latter part of the work, researchers aimed at improving the CMAP database. The initial profiles of 164 drugs expanded to 1309 FDA-approved small molecules and the cell lines increased to five human cell lines (adding ssMCF7 cell line), generating over 7000 expression profiles in the CMAP database (Qu and Rajpal, 2012). All data were included in the site (http://www.broadinstitute.org/cmap), which could be queried and downloaded for free.

The analytic method of CMAP adopts a nonparametric, rank-based pattern-matching strategy akin to the well-known approach of Gene Set Enrichment Analysis (Subramanian et al, 2005). In the query process, the gene expression profiles data are divided into lists of up-regulated genes and down-regulated genes for the input to CMAP database. The analysis results are presented with a connectivity score ranging from +1 to −1. A positive connectivity score indicates the degree of similarity and a negative score indicates an inverted similarity (Figure 1).

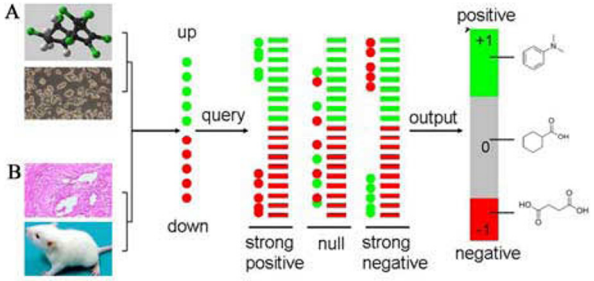

Figure 1 Schematic view of CMAP analysis

Two gene expression data were obtained: (A) gene expression data of compounds treating cells; (B) gene expression data of disease and disease model. After scoring using a pattern-matching algorithm, compounds were ranked by "connectivity score"

3. Application in CMM

Since the establishment of CMAP database, it has been widely used in the field of drug discovery and development. So far, numerous achievements were obtained in many research areas, such as drug repurposing (Zhang et al, 2015; Chang et al, 2010; 2015; Marina et al, 2011; Chiena et al, 2015), lead discovery (Liu et al, 2015; Kumar et al, 2011; Wang et al, 2011; Boyle et al, 2010; Babcock et al, 2013), and elucidating mode of action (Seung et al, 2011; Gheeyaa et al, 2010; Zhang et al, 2012; Hieronymus et al, 2006; D'Arcy et al, 2011). In recent years, CMAP database has been increasingly used in the field of CMM and achieved remarkable outcomes.

3.1 Application to components of CMM

CMM contains diverse ingredients, which address large part of the current CMM research. Recently, a research by Ozcan et al (2015) finds that celastrol isolated from *Tripterygium wilfordii* has significant efficacy against obesity using CMAP database. Researchers obtained the corresponding differentially expressed genes from cells of liver and hypothalamus in mice and analyzed them in CMAP. The resulting scores were converted to absolute enrichment scores for the next analysis. Finally, researchers used all absolute enrichment scores to discover the small molecule celastrol with the highest score to all the other molecules in the CMAP database. Furthermore, the experiment confirmed that celastrol increased leptin sensitivity to suppress food intake and dramatically reduced body weight of obese mice *in vivo*. This work finds candidate drug celastrol for the treatment of obesity, and provides a new method for the discovery of new drugs in CMM.

A recent study conducted by Lee et al (2014) mined the CMAP database to explore the molecular mechanisms of berberine. Berberine, a component of traditional Chinese herbal medicine, is isolated from various medicinal herbs such as *Coptis chinensis* and has a wide range of pharmacological actions including anticancer, antimicrobial, anti-inflammatory, and antidiabetic effects (Tillhon et al, 2012). In this study, researchers obtained berberine-induced differentially expressed genes from the Gene Expression Omnibus (GEO) at

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