Chapter 28
Drug Optimization for Cystic Fibrosis Patients Based on Disease Pathways Crosstalk

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ABSTRACT

Cystic fibrosis (CF) is a common autosomal recessive disease characterized by pancreatic insufficiency and progressive deterioration of lung function. It has been shown that CF is caused by the presence of mutations in both alleles at the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The severity of CF disease reflects the change of molecular mechanism, including DNA mutations on CFTR gene and polymorphic variations in disease modifier genes. Better understanding the differences among different CF severity group is helpful for improving therapeutic plans for patients. In this paper, the authors present a computational network biology approach to screen precision drugs for CF patients, which is based on the intensity of drugs impact on the pathway crosstalk mediated by differential methylation genes. The results indicate that ivacaftor, tezacaftor, and lumacaftor are applicable to all severity cohorts, gefitinib, sorafenib, sunitinib, and imatinib mesylate have the potential to treat intermediary CF patients, and tamoxifen may be useful to mild and sever CF patients.

1. INTRODUCTION

Cystic fibrosis (CF) is attributed to mutations in a single gene leading to dysfunction of the encoded protein, the cystic fibrosis transmembrane conductance regulator (CFTR)(Rafeeq & Murad, 2017). Mutations in the cystic fibrosis transmembrane conductance regulator protein promote dehydration of the airway surface liquid of the lung epithelium, which leads to increased bacterial colonization of CF

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patient lungs(Lyczak, Cannon, & Pier, 2002). Patients with CF suffer from recurrent pulmonary infections, permanent inflammation, pancreatic insufficiency and male infertility(Zhao et al., 2019). Progressive decline in lung function is the primary cause of morbidity and mortality in CF(Breuer, Caudri, Stick, & Turkovic, 2018). It has been extensively investigated that CFTR sequence variants and modifier genes could affect the survival prognosis and clinical treatment outcome of CF patients, which is critical for the improvement of the patient's condition. Also, the severity of CF corresponds to the changes of inner molecular mechanism of it. Thus, it is important to explore the differences among CF patients with different severity to improve therapeutic efficacy.

Crosstalk is generally described in biochemistry and molecular biology as unwanted communication between signaling pathways or signaling molecules. The oncogenesis and progression of CF are linked to essential biological pathways(H. Li, Salomon, Sheppard, Mall, & Galietta, 2017). Some studies have revealed that the crosstalk of pathways could conduct extensively to developmental programs and cell fate(Brechbiel, Miller-Moslin, & Adjei, 2014; Restelli et al., 2016; Xu et al., 2019). Disease-related cells have been found to be able to establish alternative signaling pathways through crosstalk to adapt to drug treatment, resulting in poor clinical outcomes for patients. In addition, crosstalk can also promote therapy by inhibiting the main oncogenic pathways. Previous study demonstrates that 'Spleen Tyrosine Kinase pathway' (SYK) orchestrates the crosstalk between endocytosis and signaling. Moreover, phosphorylated SYK recruits and activates multiple downstream signaling pathways crosstalk, including the small GTPases Rac1 and Cdc42, the former of which has been shown to play a role in CFTR trafficking and membrane anchoring(Farinha, Swiatecka-Urban, Brautigan, & Jordan, 2016). Therefore, it is important to analyze the crosstalk of dysfunctional pathways and discern the key regulators of interference crosstalk in CF disease.

DNA methylation, a process of adding a methyl group to DNA done by a DNA methyltransferase is a heritable (epigenetic) alteration leading to cancer, atherosclerosis, nervous disorders (Imprinting disorders), and cardiovascular diseases. Many researches have shown that changes in DNA methylation levels are involved in the development of lung diseases(Magalhaes et al., 2017). Methylation of the promoter maintains differential gene expression patterns in a tissue-specific and developmental stage-specific manner(Caution et al., 2019). Some studies have shown that DNA methylation profiles account for these phenotypic variations, and DNA methylation in lung macrophages has been proved to participated in driving dysfunctional innate immune cells in the CF lung(Y. Chen et al., 2018). Researchers have also shown that some methylation events appear to be essential for correct folding and trafficking of wild-type CFTR in the early secretory pathway(Pankow, Bamberger, & Yates, 2019), which is closely related to the occurrence of CF.

In this research, we developed a computational network biology approach for drug screening to improve the accuracy of treatment plan for CF patients. We first integrated CF disease related data resources, including methylation profiling data, PPI network and drug-related data (Figure 1A). Then, we identified differential genes and disease pathways to construct crosstalk network in patients with different severity of CF (Figure 1B). Finally, the correlation of gene interactions and the abnormality of genes were employed to estimate crosstalk strength of CF dysfunction network, which is the basis of therapeutic optimization (Figure 1C). The complete workflow can be found in Figure 1.

(A) First, we integrated data resources, including methylation profiling data, PPI network data, drug and drug target data. (B) CF-related genes and pathways were detected and then used to calculate the crosstalk weight for any two interrelated pathways. The construction crosstalk networks in different se-