Glycomics and Lipidopics

Extended Abstract

Multiple 'omics'-Analysis Reveals the Role of Prostaglandin E2 in Hirschsprung's Disease

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Abstract:

The etiology and pathogenesis of Hirschsprung's disease (HSCR) remain largely unknown. Here we employed a multiple 'omics'-analysis to explore the important pathway related to the development of HSCR. We examined colon tissues from three independent populations with a combined analysis of metabolomics, transcriptomics and proteomics to understand HSCR. Mouse model was used for examining PGE2 induced clinical presentation of HSCR. SH-SY5Y and SK-N-BE(2) cell lines were used for examining PGE2 inhibited cell migration through EP2.The integrated analysis suggests that the level of PGE2, the expression of the genes encoding its receptor (EP2) (PTGER2) and PGE2 synthesis enzyme genes (PTGS1 and PTGES) increased in HSCR colon tissues, together with a decreased synthesis of PGE2-related byproducts. In animal study, the pregnant mice treated with PGE2 gave birth to offspring with the lack of gangliocytes in colon and gut mobility. *In vitro* study, we confirmed that, when EP2 was blocked, the PGE2-inhibited migration of neural cell was recovered. Our study identified a novel pathway linking expression of PTGS1 and PTGES, level of PGE2, expression of PTGER2, and neural cell migration in HSCR, providing a novel avenue for the future diagnosis and prevention of HSCR. We first perform an exploratory analysis of gene expression data of a number of diseases that involve a strong inflammatory component. The comparison of gene expression between disease and healthy samples reveals the importance of members of gene families coding for signalling factors. Next, we focus on interested signalling gene families and a subset of inflammation related diseases with multi–omic features including both gene expression and DNA methylation. We introduce a phylogenetic–based multi–omic method to study the relationships between multi–omic features of inflammation related diseases by integrating gene expression, DNA methylation through sequence based phylogeny of the signalling gene families. The models of adaptations between gene expression and DNA methylation can be inferred from pre–estimated evolutionary relationship of a gene family. Members of the gene family whose expression or methylation levels significantly deviate from the model are considered as the potential disease associated genes. Applying the methodology to four gene families (the chemokine receptor family, the TNF receptor family, the TGF– *β* gene family, the IL–17 gene family) in nine inflammation related diseases, we identify disease associated genes which exhibit significant dysregulation in gene expression or DNA methylation in the inflammation related diseases, which provides clues for functional associations between the diseases. Inflammation is the body's attempt at removing harmful or irritating affects, which is part of the body's immune response. The inflammatory response is essential for the recruitment and activation of lymphocytes in order to respond to an infection and the subsequent promotion of wound healing and repair. Strong intensity and long duration of unconstrained inflammatory response will cause the consequences of unregulated inflammation, which might result in many acute and chronic autoimmune diseases and comorbidities. The inflammatory system is complex because of comorbidities, which involves depression, immune–inflammatory, oxidative stress, gut–brain pathways and so on. For example, inflammation and altered gut microbiota (dysbiosis) could lead to colorectal cancer carcinogenesis. The severity of inflammatory diseases is strongly correlated with high levels of proinflammatory cytokine. Scientific evidence has shown that gut microbiota plays important roles in the genesis of several inflammatory diseases such as arthritis, systemic lupus erythematosus (SLE), pathogen induced colitis, Crohn's disease, inflammatory bowel disease (IBD). Besides, inflammation has also been reported one of the enabling characteristics of cancer development such as colon cancer and breast cancer. The genesis of cancers are considered to be related with the inflammatory responses to microbial or damaged-self stimuli. Both arms of immunity, innate and adaptive, play important roles during tumorgenesis. Growing attentions have been attracted in identifying early biomarkers for inflammatory diseases by exploring the associated molecular mechanisms, because the genesis of inflammatory diseases usually take a long preclinical period and the identification of early disease markers could provide valuable clues for better clinical therapies. It is reported that a set of circulating proteins such as inflammatory cytokines and endocrine factors (e.g., TGF– *β*, TNF, and chemokines), forming a communicome, are involved in inter-cellular and

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organs communication, which are responsible for spreading inflammation in the body. Recent advances in high–throughput genomics biotechnology such as microarrays and next generation sequencing have produced various omic data such as genome, epigenome, transcriptome, proteome and so on. The rapid growth of the amount of multi–omic data provides great opportunities to understand the mechanisms of complex biological systems such as human diseases from multiple molecular levels. For example, Zhang et al. predicted the driver genes associated with different clinical outcome subtypes of ovarian cancer by integrating genome–wide gene expression, DNA methylation, microRNA expression and copy number alteration profiles. Cabezas-Wallscheid et al. performed a comprehensive analysis of proteome, transcriptome and DNA methylome data to identify coordinated changes at the protein, RNA, and DNA levels during early differentiation steps of hematopoietic stem cells (HSCs). Cantini et al. proposed a multilayer network community detection method to identify cancer related gene modules, which reveals cancer driver genes, through the integration of gene expression, protein interactome and transcription factor regulation network. Chaudhary et al. introduced a neural network model to predict survival in liver cancer by integrating multi–omic data including gene expression, DNA copy number and miRNA expression data. In order to explore the associations between signalling factors and inflammatory diseases as well as cancers, we propose a new methodology based on phylogenetic inference on multi–omic data to identify gene markers of diseases. Taking full advantage of the pre–estimated evolutionary relationship of a gene family with multi–omic information including gene expression and DNA methylation, it is capable of identification of genes exhibiting significant alterations in expression or methylation levels in diseases. A multi–omic approach is necessary as it integrates information from all sources. Phylogenetic information is important as some genetic behaviours may be due to evolutionary inertia. The phylogenetic correlations between gene expression and methylation help in identifying disease relationship due to perturbations of the same or closely related gene family members. Applying the proposed method, we perform a comparative study of the signatures of signalling molecules in several inflammation related diseases, which consists of a two-step analysis: Firstly, we present a systematic study of genomewide molecular signatures, based on gene expression, for several inflammatory diseases as well as cancers. Most of the significant molecular signatures are related to members of a few important gene families. Then, we propose a phylogenetic–based multi–omic approach and apply it to four signalling related gene families selected from the first step to study the correlated or independent roles of the genes as disease markers by integrating the sequences, gene expression and DNA methylation data of the gene families in specific inflammatory diseases. We have performed a comparative study to explore the influence of signalling gene families in several inflammation related diseases. Firstly, we analyse gene expression in a collection of inflammatory diseases, which highlights the importance of gene families involved in extracellular signalling. In particular we have identified four families significantly associated with the inflammatory diseases, which includes the chemokine receptors family, the TNF receptor family, the TGF–*β* family and the IL–17 family. Then, in order to understand the roles these gene families in some specific inflammation related diseases, we propose a phylogenetic–based multi–omic method to study the correlations between gene expression and DNA methylation of the members of each gene family taking into account of their evolutionary relationships. Applying the proposed method to four signalling gene families in nine inflammation related diseases, we identify a number of significant disease associated genes whose expression or methylation levels in the patients significantly deviate from the evolutionary models estimated from the control samples.

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