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Differential gene expression in brain and peripheral tissues in depression across the life span: A review of replicated findings

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ABSTRACT

There is a growing body of research investigating the gene expression signature of depression at the genome-wide level, with potential for the discovery of novel pathophysiological mechanisms of depression. However, heterogeneity of depression, dynamic nature of gene expression patterns and various sources of noise have resulted in inconsistent findings. We systematically review the current state of transcriptome profiling of depression in the brain and peripheral tissues with a particular focus on replicated findings at the single gene level. By examining 16 brain regions and 5 cell types from the periphery, we identified 57 replicated differentially expressed genes in the brain and 21 in peripheral tissues. Functional overlap between brain and periphery strongly implicates shared pathways in a comorbid phenotype of depression and cardiovascular disease. The findings highlight dermal fibroblasts as a promising experimental model for depression biomarker research, provide partial support for all major theories of depression and suggest a novel candidate gene, *PXMP2*, which plays a critical role in lipid and reactive oxygen species metabolism.

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1. Introduction

1.1. Genome-wide gene expression in depression

The application of high-throughput gene expression analyses has gained momentum in the study of molecular signatures of diseases. Microarray and next generation sequencing (NGS) technologies, which permit profiling the expression of many thousands of genes simultaneously, have been applied with success in many areas, including cancer research. Genomic and transcriptome alterations have enabled molecular classifications of cancer and revealed novel biomarkers for diagnosis, prognosis, and predicting response to therapies (Roychowdhury and Chinnaiyan, 2016) and inspired many other fields of medical research to utilize newly developed techniques. In recent decades, the field of psychiatry has adopted these techniques, aiming to elucidate molecular mechanisms, identify biomarkers and provide better treatment for depression, the leading cause of disability affecting more than 350 million people Worldwide (World Health Organization, 2015).

1.2. The problem of non-replication of gene expression findings

A growing amount of genome-wide gene expression data has been analysed using differential expression analysis, the most widely applied statistical method. However, numerous limitations of biological and technical nature, including large biological variations, small sample sizes, data collection details, clinical heterogeneity, comorbidities, differences in microarray platforms, data quality assessment, statistical algorithms used and covariates accounted for, and many others, have resulted in inconsistent results, questioning their validity. Biological findings need to be confirmed by several studies using the same method in order to be accepted. While the lack of replication is a major concern for transcriptome studies in depression, the systematic collection of replicated findings have never been performed. We address this gap by exploring the gene expression signatures of depression derived from both brain and peripheral tissues using replication as the yardstick of reliability.

1.3. The choice of tissue for depression in gene expression research

Depression includes dysfunction at multiple biological levels, from genes (Ripke et al., 2013) to brain regions (Gong and He, 2015) and blood circulating throughout the body (Lopresti et al., 2014). The choice of tissue, therefore, is of particular importance in gene expression research. Studies performed on post-mortem brains have substantially advanced our understanding of the pathophysiological mechanisms of depression. Gene expression signatures derived from various brain regions collectively point towards various molecular processes involving inflammatory, cell survival, apoptotic, oxidative stress and other pathways (Mehta et al., 2010). However, these findings cannot be used for diagnostic purposes. Extensive research on peripheral biomarkers of depression has revealed that peripheral immune response and growth factors, endocrine factors and metabolic markers also contribute to the pathophysiology of depression (Lin and Tsai, 2016). This is consistent with the close interaction between the brain and peripheral tissues. However, whether gene expression pattern in a peripheral tissue, such as blood, is a reflection of brain activity or a separate peripheral tissue process independent of the brain, remains to be understood. It is therefore necessary not only to examine peripheral gene expression but also to compare the brain and periphery gene expression findings to address some of these questions in depression research.

The main challenge is to compile the numerous transcriptome profiles derived from different brain areas or/and peripheral cell types into one coherent analysis in an attempt to explain the mechanisms of depression. In this review, we compare transcriptomes obtained from multiple cell types in order to identify replicated findings. It can be argued that if any particular gene, in the face of various biological and technical limitations, was differentially expressed in depression compared to healthy controls across several cell/tissue types or brain areas, this gene has an increased likelihood of being truly involved in the pathophysiology of depression. We explore the gene expression signature of depression using replicability at the single gene level as a method of maximising true associations.

2. Method

2.1. Articles selection process

Using PubMed and EMBASE databases, we screened for all gene expression studies in depression in humans published in peer-reviewed journals using various permutations of the following search terms: “transcriptome”, “gene expression”, “depression”, “MDD”, “Major Depressive Disorder”. This preliminary literature search resulted in over 72,700 articles. In the second step, based on