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A COHORT TRANSCRIPTOME ANALYSIS OF MONOCYTES AND T CELLS TO INVESTIGATE THE EFFECT OF INTERFERON B IN DELAYING RELAPSE RATE OF MULTIPLE SCLEROSIS

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ABSTRACT

MS is an autoimmune disease in which immune cells such as monocytes and T lymphocytes cause lesions in the Central Nervous System (CNS). Although Interferon (IFN), an immunomodulatory drug, is used as a first-line treatment for MS, the mechanism by which it reduces relapse rates is still partially understood. The goal of this study is to see if interferon (IFN) plays a role in MS relapse prevention. Healthy Controls, MS Untreated (MS_UN), and MS Treated with IFN (MS_INT) were monocyte and T cell sample groups selected from NCBI GEO datasets and analysed using the GEO2R microarray tool to uncover Differentially Expressed Genes (DEGs). PANTHER refines functional annotations and pathways, whereas STRING generates a Protein-Protein Interaction (PPI) network to uncover DEG product connections. Increased IFI16 and HLA-DRB1 gene expression was responsible for immune cell activation and infiltration in MS pathology. Evidence from MS INT patients suggests that elevated FAS promotes T cell apoptosis by interacting with CASP8, FADD, and FASLG. CXCL10, GBP5, MX1, and IFI35 were found to interact with one another, indicating their role in innate immune response. The findings imply that IFN-activated genes have a role in inducing innate immune responses and apoptosis, decreasing the recurrence rate in MS.

KEYWORDS: Multiple Sclerosis, Interferon β (IFNβ), Autoimmune Disease, Differentially Expressed Genes (DEGs), Protein-Protein Interaction network

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune neurological illness that destroys the myelin and axons of the central nervous system (CNS). The lesions in the CNS are mainly due to the infiltration of T cells, monocytes, rarely B cells and plasma cells. Three discrete lesion types have been observed in acute MS. The prevalence of T cells and macrophages are dominant in type 1 lesions whereas type 2 lesions are characterized by activated complement components and immunoglobulins deposition. Oligodenroglial apoptosis is remarkable in type 3 lesions. Though there is no cure for MS, few FDA approved medications known to have immunomodulatory effects such as Interferon-β (IFNβ), Glatiramer acetate (Copaxone), Natalizumab etc., are currently being used to decrease the disease progression and to improve quality of life in patients.

Despite of the wide use of IFNβ as the first line therapeutic option in treating MS, the underlying mechanism of the effect of IFNβ on reducing MS disease progression is not well understood. IFNβ has an inhibitory effect on the proliferation of T cells thus reducing the relapse rate and progression of disease. Interferons belonging to the cytokine family of proteins play a major role in innate

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immune system. Current understanding on the mechanism of IFNβ reveal that on binding to its receptor, JAK/STAT signalling cascade is activated which regulates the transcription of a myriad of both inducible and inhibitory genes[1]. The role of IFNβ in correcting gene dysregulation in MS, its effect on regulating immune response and protection of neurons has been studied recently[2].

Various groups have attempted to study the effect of IFNβ treatment on MS patients by analysing RNA obtained from peripheral blood mononuclear cells as well as whole blood samples using DNA microarray analysis. Gene expression studies were also reported using Illumina Sequencing platform. The present study utilizes an *in silico* approach to perform transcriptomic analysis to understand the underlying mechanism of IFNβ in reducing the disease progression in MS subjects. Computational analysis was done using the bioinformatic tools GEO2R, PANTHER and STRING databases. The research aims to determine the effects of therapeutic drug IFNβ on gene expression as well as protein-protein interactions in MS subjects in comparison to untreated and healthy controls.

MATERIALS & METHODS

Computational Databases like National Centre for Biotechnology Information (NCBI), Gene Expression Omnibus (GEO) Datasets, GEO2R, PANTHER (**P**rotein **AN**alysis THrough **E**volutionary **R**elationships) Database and STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) Databases were utilized for the present study.

2.1 Retrieval of Sample Data from NCBI using GEO Datasets

GEO (Gene Expression Omnibus) datasets were selected from NCBI website and Multiple sclerosis was entered as the search strategy term. Entrez GEO Datasets were searched using the "Datasets" query box on the GEO home page or at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gds and the obtained datasets were used for further analysis[3]. The DEG profile was obtained from GEO database.

2.2 GEO Data Analysis using GEO2R

Gene Expression Omnibus online statistical tool, GEO2R (https://www.ncbi.nlm.nih.gov/geo/geo2r/) was used to identify DEGs among MS_INT, MS_UN Subjects and Healthy Controls. Benjamini and Hochberg false discovery rate method was used along with GEO2R in order to analyse the DEGs. The following criteria were used to confirm the DEGs obtained: adj.P value < 0.05, | logFC | < -1, and, | logFC | > +1.

The sample groups (n=72) were defined and listed as:

a. T-cells:
MS_Untreated (MS_UN) (n=7) vs Healthy Control (n=20), and MS_UN vs MS treated with interferon (MS_INT) (n=3).
b. Monocytes:
MS_UN (n=6) vs Healthy Control (n=17) and MS_UN vs MS_INT (n=3).

The above data were subjected to Microarray analysis and the query was generated.

2.3 Gene List Enrichment Analysis

The datasets obtained from Microarray were subjected to Gene List Enrichment Analysis using PANTHER Database to classify and identify the function of gene products.

2.4 STRING Database

Protein-protein interaction (PPI) network was constructed using an online tool named STRING Database. The network of PPI was then used to analyse the possible relationships among the obtained DEGs to evaluate its role in MS pathogenesis as well as in treated subjects in comparison to healthy controls.

RESULTS

3.1 GEO Datasets and Microarray Analysis

The datasets were obtained for the Series accession number GSE81279 using the GEO software tool. The microarray results (Fig.1) gave

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the information on the up-regulated and down-regulated genes of defined sample groups. The derived datasets were defined and the hits were obtained for the following sample groups.

i) Monocytes:
A) MS_UN vs Healthy Controls
In the microarray analysis (Fig.1A) ICAM4 gene was found to be downregulated and IFI16 and HLA-DRB1 were upregulated.

B) MS_INT vs Healthy Controls
POS_A gene was found to be downregulated whereas upregulation was observed in FAS, IFI35, IFI16, GBP5, SERPING1, MX1 and CXCL10 genes (Fig.1B).

ii) T-Cells:
A) MS_UN vs Healthy Controls
NFKBIA and TNFAIP3 genes were found to be downregulated and CISH were up-regulated in MS_UN T cells (Fig.1C).

B) MS_INT vs Healthy Controls
No hits were observed in the treated sample group for T cells henceforth, not considered for further analysis.

3.2 PANTHER Analysis

i) Monocytes

A) MS_UN vs Healthy Controls

Each DEGs obtained were subjected to PANTHER analysis which revealed its functional annotations (Fig.2A). ICAM4 gene was found to be involved in integrin binding and also acts as an integral component of plasma membrane. IFI16 is the Gamma Interferon-Inducible Protein 16 which is involved in interacting selectively and covalently to the double-stranded DNA. It is also involved in activation of cytokines, cellular response to cytokine stimulus, positive regulation of cytokine production and innate immune response.

B) MS_INT vs Healthy Controls

FAS belong to Tumor Necrosis Factor Receptor Superfamily Member 6 which is involved in transmembrane signalling receptor activity, tumor necrosis factor binding, proteolysis, homeostatic process among many other processes. They form the cellular component of plasma membranes. Additionally, they are involved in the p53 pathway, apoptotic signalling and FAS signalling pathway. Interferon-Induced GTP-Binding Proteins Guanylate-Binding Proteins 5 (GBP5) and MX1 are involved in GTPase activity. C-X-C Motif Chemokine 10 (CXCL10) belonging to the class of chemokine proteins is involved in cytokine activity, chemokine receptor binding, cytokine-mediated signalling pathway, neutrophil migration and inflammatory response. (Fig.2B) (Fig.2C)

3.3 STRING Analysis

Microarray analysis results were subjected to STRING Database to study the interactions of DEGs. All the analyses were done at a high confidence level (>0.7).

MS_UN vs Healthy Controls

In this sample group STRING analysis were done for the query of ICAM4, IFI16 and HLA-DRB1 gene sequences wherein PPI were observed in IFI16 and HLA-DRB1 (Fig.3A). There were no interactions observed in ICAM4 at high confidence level. However, IFI16 showed interaction with TMEM173 which is a stimulator of interferon genes. The interaction of HLA-DRB1 with HLA-DMA, CD74, HLA-DRA and PTPN22 were also observed.

MS_INT vs Healthy Controls

(Fig.3B) depicts the PPI network for the query of SERPING1, IFI35, IFI16, GBP5, FAS, MX1 CXCL10 and POS_A at high confidence level (>0.7). CXCL10 was found to show interaction with CXCR3, GBP5 and MX1. We also noted an interaction between MX1 and IFI35. However, there were no interactions observed in IFI16 and SERPING1 at high confidence level. FAS in the query sequence showed interactions with 3 other proteins namely CASP8, FADD and FASLG. Furthermore, interactions were observed within these genes.

DISCUSSION

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Multiple Sclerosis, an autoimmune disease is a global issue with high prevalence. The characteristic features observed in MS patients are down regulation of apoptotic genes and upregulation of inflammatory genes[4]. Current therapeutic options aim towards modulating the behaviour of immune cells thus preventing the relapse and reducing progression towards the disease.

The present study focused on comprehending the underlying mechanism of IFNβ in reducing the relapse rate of disease in MS subjects. Microarray analysis data shed light on the DEGs in MS lesions[5] . In the untreated subjects genes which are responsible for disease progression were upregulated compared to healthy controls. IFI16, a DNA-binding protein that belongs to the ALR (AIM2-like receptor) family of inflammasomes[6] is a proinflammatory inducer in endothelial cells (EC) that helps in the early stages of inflammatory processes during the onset of autoimmune disorders[7,8]. IFI16 showed interaction with TMEM173 which is a vital component of TLR independent pathway that activates the immune response[9]. It has also been reported to be responsible for autoinflammatory diseases[10]. Though there is an interaction between IFI16 and TMEM173, the underlying mechanism is not well understood. HLA-DRB1 locus is a primary MS susceptible allele that intensifies the risk of disease[11]. It also plays an important role in presenting antigenic peptides to myelin-reactive T-cells[12]. T cell formation and negative inhibition of T cell activation are both important functions of the PTPN22 (Protein Tyrosine Phosphatase) gene[13]. Previous research suggests that though PTPN22 gene is involved in inflammatory responses, direct experimental evidence is not clear[14,15]. In another genome wide association study, HLA-DRA has already been reported as the most significant node of HLA-DRB1[16]. The method of class II-restricted antigen presentation relies heavily on HLA-DMA products [17]. CD74, whose expression has been reported in CNS lesions of MS patients, is a transmembrane protein as well as a receptor of Macrophage Migration Inhibitory Factor (MIF)[18]. The role of MIF in enhanced secretion of pro-inflammatory cytokines is well known[19]. The overall data suggests the activation and infiltration of immune cells in pathogenesis of MS in untreated subjects when compared to healthy controls.

IFNβ treatment has been associated with reduced mortality risk in relapsing course of MS[20]. The genes upregulated in treated subjects include FAS, GBP5, SERPING1, MX1, and CXCL10. PANTHER database revealed their functions as well as the protein class it belonged to and STRING database showed the protein level interactions. CXCL10 is an inflammatory chemokine that binds to CXCR3 thereby initiating the activation of immune response through recruitment of leukocytes[21]. CXC chemokine receptor type 3 is the receptor for CXCL10 which is chemotactic for monocytes and T-lymphocytes. The interaction promotes cell chemotaxis response[22]. Previous studies in mouse have shown the role of CXCL10/CXCR3 in activation of microglia of the CNS thereby recruiting them to the lesion sites. This interaction is an essential factor for neuronal reorganization[23]. GBP5 and MX1 genes upregulated in MS_INT, are well known interferon stimulated GTPases. GBP5 stimulates NF Kappa B-mediated pro-inflammatory cytokine production, which is increased in inflammatory demyelinating MS lesions. By aiding in the formation of protein complexes, it contributes to cell-autonomous immunity[24]. Guanylate-binding protein 5 (GBP5) is an activator of NLRP3 inflammasome assembly that plays a role in innate immunity and inflammation[25]. Recent studies have suggested the endogenous regulatory role of GBP5 in inflammation as well as destruction of tissues[26]. The use of MX1, the gold standard gene has already been demonstrated to be a sensitive measure of IFN bioactivity in MS subjects[27, 28]. IFI35 is an interferon inducible protein that is involved in apoptotic pathway[29.] Earlier studies have reported the role of IFI35 as a biomarker of innate immune response and thereby reflecting its role in neuroinflammation which in turn was responsible for the enhanced expression of IFI35 in interferon-treated sample groups[30]. The data obtained from monocytes in treated subjects signifies that Interferon triggers innate immune response as well as apoptotic pathways which are the key players in lowering the relapse rate.

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Caspase 8 (CASP8) mechanism of apoptosis is defective in MS patients[31]. Our data clearly shows the upregulation of FAS gene in Interferon treated MS subjects which have direct interaction with Caspase 8. FAS belong to tumor necrosis factor receptor superfamily and binding to its ligand (FasL) leads to activation of FADD adaptor molecules which in turn activates Caspase8 initiating apoptosis[32.] Earlier reports have suggested that an increase in FASLG has a role in activation of T cell apoptosis through mitochondrial pathway[33].

From our analysis on T cells of MS subjects treated with IFNβ we could not derive any significant data which is in accordance with previous studies suggesting the limitation of interferons in T cell response due to the production of Anti-Drug Antibodies[34]. However the genes involved in MS pathogenesis were upregulated in untreated subjects compared to healthy controls.

Our experimental analysis using bioinformatic tools gives a supporting evidence for IFNβ treatment in reducing the relapse of disease by destroying the damaged cells via apoptotic pathway and regulating the immune response in a controlled manner.

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FIGURE LEGENDS

Figure 1: Identification of DEGs using GEO2R Analysis Tool: (A) Monocytes: MS_UN vs Healthy Controls (B) Monocytes: MS_INT vs Healthy Controls (C) T cells: MS_UN vs Healthy Controls

Figure 2: PANTHER Gene List Enrichment Analysis for the Functional Annotations of DEGs for Monocytes: (A) Biological Process-IFI16, HLA-DRB1. (B) Pathway-IFI16, GBP5, MX1, CXCL10, IFI35, FAS, SERPING1 (C) Biological Process- IFI16, GBP5, MX1, CXCL10, IFI35, FAS, SERPING1

Figure 3: Network construction by STRING Database based on the PPI information of the DEGs obtained for Monocytes: (A) MS_UN vs Healthy Controls: Interactions of ICAM4, IFI16, HLA-DRB1 (B)

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MS_INT vs Healthy Controls: Interactions of POS_A, IFI16, GBP5, MX1, CXCL10, IFI35, FAS, SERPING1

Figure 1

A

MS_UNTREATED MONOCYTES VS HEALTHY

DOWN REGULATED GENES			
ID	adj.P.Val	P.Value	logFC
ICAM4	0.0197	0.0001943	-0.99041

UPREGULATED GENES			
ID	adj.P.Val	P.Value	logFC
IFI16	0.0361	0.0010796	1.04821
HLA-DRB1	0.026	0.0002998	1.7773

B

DOWN REGULATED GENES			
ID	adj.P.Val	P.Value	logFC
POS_A	0.0235	0.0003418	-1.120554

UP REGULATED GENES			
ID	adj.P.Val	P.Value	logFC
FAS	0.0235	0.0002972	1.16052
IFI35	0.0235	0.0000813	1.2612181
IFI16	0.0235	0.0002117	1.7204963
GBP5	0.0235	0.000207	1.7360706
SERPING1	0.0235	0.000208	2.1151173
MX1	0.0295	0.0005333	2.2599682
CXCL10	0.0235	0.0003183	2.7403724

C

MS_UNTREATED T-CELLS VS HEALTHY T-CELLS

DOWN REGULATED GENES			
ID	adj.P.Val	P.Value	logFC
NFKBIA	0.00768	1.26E-05	-1.19003
TNFAIP3	0.01882	0.000111	-1.06222

UPREGULATED GENES			
ID	adj.P.Val	P.Value	logFC
CISH	0.01882	0.000106	1.71403

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Figure 2

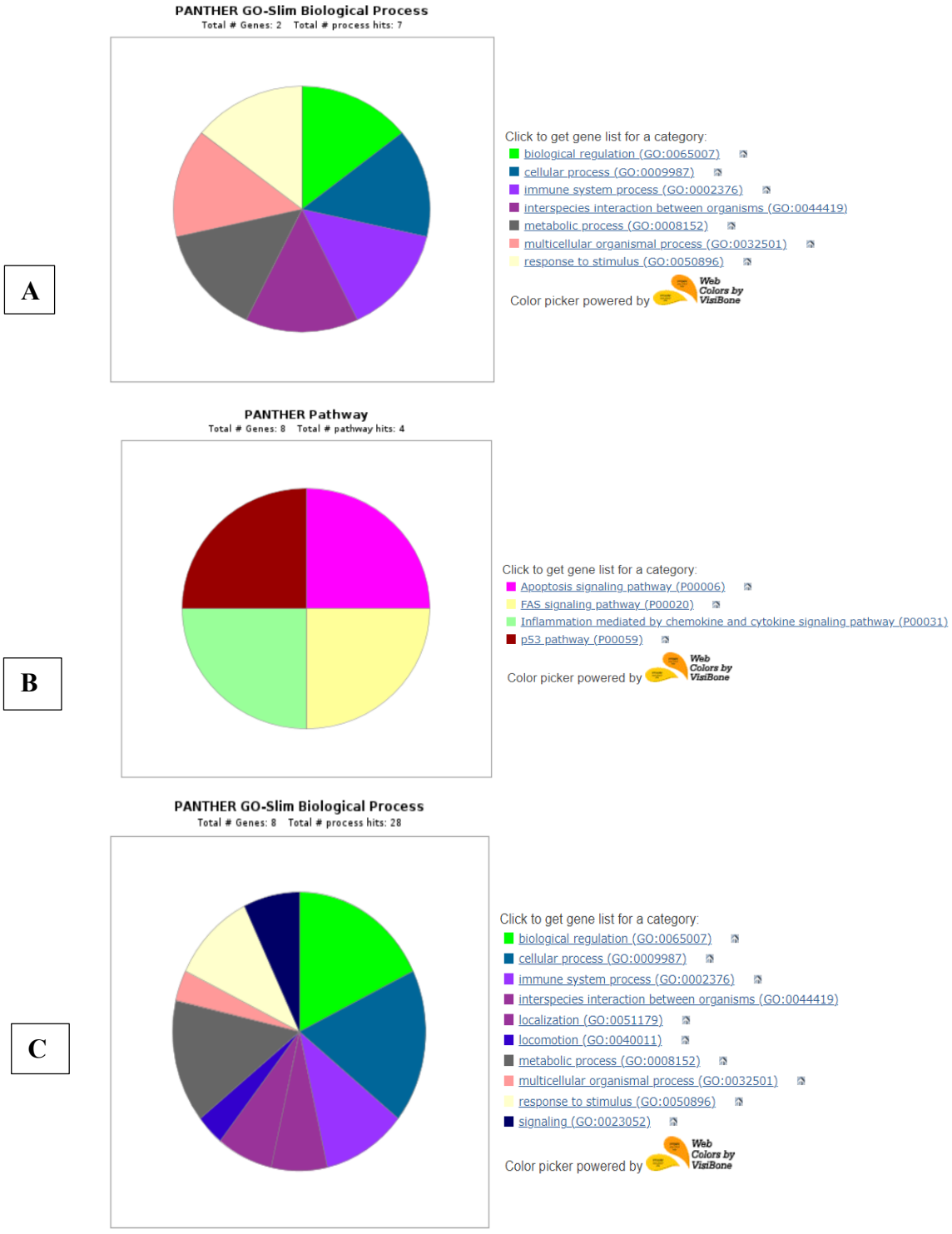

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Figure 3