Anexo

Justificación de los méritos alegados en el Curriculum Vitae

NOMBRE	Nombre y apellidos
DNI	DNI
CONVOCATORIA	Plaza

LISTADO DE DOCUMENTOS

Publicaciones

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Differential Micro RNA Expression in PBMC from Multiple Sclerosis Patients

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Abstract

Differences in gene expression patterns have been documented not only in Multiple Sclerosis patients versus healthy controls but also in the relapse of the disease. Recently a new gene expression modulator has been identified: the microRNA or miRNA. The aim of this work is to analyze the possible role of miRNAs in multiple sclerosis, focusing on the relapse stage. We have analyzed the expression patterns of 364 miRNAs in PBMC obtained from multiple sclerosis patients in relapse status, in remission status and healthy controls. The expression patterns of the miRNAs with significantly different expression were validated in an independent set of samples. In order to determine the effect of the miRNAs, the expression of some predicted target genes of these were studied by qPCR. Gene interaction networks were constructed in order to obtain a co-expression and multivariate view of the experimental data. The data analysis and later validation reveal that two miRNAs (hsa-miR-18b and hsa-miR-599) may be relevant at the time of relapse and that another miRNA (hsa-miR-96) may be involved in remission. The genes targeted by hsa-miR-96 are involved in immunological pathways as Interleukin signaling and in other pathways as wnt signaling. This work highlights the importance of miRNA expression in the molecular mechanisms implicated in the disease. Moreover, the proposed involvement of these small molecules in multiple sclerosis opens up a new therapeutic approach to explore and highlight some candidate biomarker targets in MS.

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Introduction

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS). It begins most commonly during late adolescence, young adulthood, or mid-life, and it is one of the most incapacitating diseases in this age range.

MS causes attacks of neurological dysfunction (loss of vision, difficulty in walking or moving a limb, vertigo, loss of sensation) or progressive dysfunction in these same areas. These "attacks", also known as relapses, typically last for a few days, and resolve spontaneously. However, patients may not always completely recover from an attack and are sometimes left with a disability. Although most patients experience attacks with little or no progressive disability, called recurrent remittent (RR) forms, approximately 10–15% have progressive symptoms from onset, called primary progressive forms. Furthermore, more than 80% of patients that debut with RR will ultimately develop progressive symptoms after a prolonged period of exacerbations, usually after 10–20 years.

Etiologically, MS is a complex disease in which both genetic and environmental factors play a role. The genetics of MS are also complex without a clear inheritance pattern. The most relevant candidate genomic region is the HLA system [1–3], although several other genes are currently being described as important risk factors involved in MS, as for example IL2RA [4] or IL7R genes [5].

Gene expression profiling has been a useful tool to provide information about the molecular pathways involved in MS pathogenesis [6–8]. Several new studies have identified different expression patterns between relapses and remission [9,10] suggesting that this clinical distinction of two states of the disease also has a molecular correlation.

Small non-coding RNA molecules (microRNA or miRNA) are a gene expression and protein synthesis modulating mechanism that has been recently identified in several species ranking from worms to humans. These miRNA are single-stranded RNA molecules of about 20–25 nucleotides (nt) encoded by nuclear genes (70–150 nt) and highly conserved among species. These genes are not translated into proteins but are processed from primary transcripts (called pri-miRNA) to short stem-loop structures called pre-miRNA and finally to functional miRNA. The expression pattern of miRNA varies over time and between tissues. These mature

Table S6 Target genes studied with their gene ID, the miRNA that binds to the gene, the group in which these genes are expected to be down-regulated and the Geneglobe Assay code.
Found at: doi:10.1371/journal.pone.0006309.s006 (0.03 MB DOC)

Table S7 Data from the pathway analysis conducted by panther with the predicted gene target lists from each miRNA. Two different groups of miRNA were studied; coming from the experiment and coming from the chance group
Found at: doi:10.1371/journal.pone.0006309.s007 (0.05 MB DOC)

Text S1 Resume of the panther software methods
Found at: doi:10.1371/journal.pone.0006309.s008 (0.03 MB DOC)

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Author Contributions

Conceived and designed the experiments: DO SEB TCT JO ALdM. Performed the experiments: DO MMC ABA. Analyzed the data: DO SEB RA BC PK II JAL. Contributed reagents/materials/analysis tools: RA TCT ABA JO ALdM. Wrote the paper: DO SEB RA II JAL ALdM.

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Patentes

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