Investigations of Microtubule-associated Protein 2 Gene Expression in Spinal Muscular Atrophy

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ABSTRACT

Aim: Spinal muscular atrophy (SMA) is a devastating genetic disease in childhood and it is caused by the absence of functional survival motor neuron (SMN) protein, which leads to impairments of the cytoskeleton, especially in neurons. Dysregulation of actin dynamics have been linked to SMA pathomechanisms, however involvement of altered microtubule dynamics is largely unknown. In this study, we investigated differentially expressed microtubule-related genes using in vitro and in vivo SMA model systems.

Materials and Methods: By focusing on microtubule-related genes, we re-analyzed publically available gene expression arrays, which were previously performed with induced pluripotent stem cell-derived motor neurons of SMA patients and the spinal cords of SMA mice. We found altered expressions of microtubule-associated protein 2 (MAP2), which was validated by real time reverse-transcription polymerase chain reaction using the SMN knock-down NSC34 cell line and the severe SMA mouse model.

Results: We showed that the expression of MAP2 gene was significantly upregulated in both expression arrays. Upregulation was also detected in the brain and spinal cord tissues of severe SMA mice at different developmental stages.

Conclusion: Our findings suggest that microtubule regulatory proteins may be altered in SMN depleted cells and further research is needed to elucidate the contribution of dysregulated microtubule dynamics towards SMA.

Keywords: Spinal muscular atrophy, exon-array, microtubule-associated protein 2

Introduction

Spinal muscular atrophy (SMA) is an inherited neurodegenerative/neuromuscular disease and the leading genetic cause of infant mortality. The incidence of SMA is reported as 1 in 11,000 live births, however, due to a high rate of consanguinity, it is estimated to be higher in Turkey (1). SMA is characterized by the loss of alpha motor neurons in the spinal cord and progressive muscle atrophy. Since patients have different clinical phenotypes, SMA is grouped into V Types (0-IV) according to the age of disease onset and achieved motor functions (2,3). Type 0 refers to the most severe and the Type IV refers to the mildest form of SMA. Mutations or conversions of the Survival of motor neuron 1 (SMN1) gene are responsible for SMA and regardless of disease severity, homozygous deletion of exon 7 and 8 or exon 7 only is the most frequent mutation in patients (4-6). It has been shown that the absence of ubiquitously expressed, functional SMN protein leads to defects in both axon and dendrite growth, axonal transport and neuromuscular junction formation.
maturation in model systems and also patient samples (7-11). Dysregulation of F-actin dynamics have been linked to these defects due to alterations in either actin-regulatory proteins such as profilin, plastin 3, coronin 1C or Rho-kinase (ROCK) signaling pathways in SMN depleted cells (6,7,12,13). Although significant alterations in some microtubule-related proteins (stathmin and tau) have been shown, the contribution of altered microtubule dynamics to SMA patho mechanisms is largely unknown (14,15).

Re-analysis of publicly available gene expression data is a powerful and cost-efficient technique to better understand disease mechanisms. This technique has been used to explore the molecular mechanisms of various diseases, such as different cancers (16,17), osteoarthritis (18) and degenerative diseases (19). Furthermore, meta-analysis and the comparison of gene expression profiles of different species enables researchers to discover conserved molecular mechanisms (20).

Therefore, in this study, we re-analyzed human and mouse microarray gene expression data and specifically focused on genes regulating microtubule structure and function. We found that the expression of MAP2 was significantly altered in both induced pluripotent stem cell (iPSC) derived motor neurons of SMA patient and the spinal cords of SMA mice when compared to controls. MAP2 is primarily expressed in neurons and localizes to cell bodies and dendrites in mature neurons. The MAP2 protein binds to microtubules and regulates their stability. It also binds to F-actin and bundle filaments in vitro (21). Therefore, we focused on the MAP2 gene and analyzed its expression in both the SMN knock-down motor neuron like NSC34 cell line and the Taiwanese SMA mouse model (22).

Materials and Methods

Human and Mouse Dataset Retrieval

The Gene Expression Omnibus (http://www.ncbi.nlm.nih.gov/geo/), (23,24) database was searched for Human exon arrays of motor neurons samples obtained from an SMA patient and a control. A record GSE27205 (25), which was on the Affymetrix Human Exon 1.0 ST platform (HuEx-1.0-st), was identified and CEL files of spinal cords of homozygous knock-out SMA mice (n=4, SMN2+/+; SMN Δ7+/+; mSmn−/−; FVB.Cg-Tg (SMN2*delta7) 4299Ahmb Tg (SMN2) 89Ahmb Smn1tm1Msd) and heterozygous SMN knock-out mice (n=4, SMN2+/−; SmnΔ7+/−; mSmn+/−; FVB.Cg-Tg (SMN2*delta7) 4299Ahmb Tg (SMN2) 89Ahmb Smn1tm1Msd) (26). CEL files for SMA mouse spinal cord (GSM491297, GSM491298, GSM491299 and GSM491300) and heterozygous SMN knock-out mice spinal cord (GSM491293, GSM491294, GSM491295 and GSM491296) were obtained from the GEO database.

Human and Mouse Gene Expression Analysis

Affymetrix Human Exon 1.0 ST array CEL files of an SMA patient and heterozygous father, and Affymetrix Mouse Genome 430A 2.0 Array CEL files of an SMA and heterozygous SMN knock-out mouse were analyzed via the Transcriptome Analysis Console 4.0.1.36 (TAC, https://www.thermofisher.com). For the human exon array analysis, Gene Level-Core, robust multichip average (RMA)-sketch workflow was applied to create probe level summarization files. For Mouse430A 2 arrays, the RMA algorithm (27,28) was used to normalize CEL files. The annotation files HuEx-1.0-st-v2.na36.transcript.csv for HuEx-1.0-st array and Mouse430A 2.na36.annot.csv for Mouse430A 2 array were used to annotate human and mouse arrays, respectively. Probe sets with ANOVA (eBayes) p-value <0.05 and fold change <-1.5 or fold change >1.5 were considered as differentially expressed for both human and mouse datasets.

Venn Diagram Analysis

The significantly altered genes, which are involved in microtubule structure and regulation of its dynamics, of human and mouse datasets were compared using Venny 2.1 (http://bioinfogp.cnb.csic.es/tools/venny/) (29).

Cell Culture and siRNA Transfections

Motor neuron-like murine NSC34 cells were grown in Dulbecco’s modified Eagle medium (DMEM, 4.5 g/D-glucose), containing 5% fetal calf serum and 1% penicillin/streptomycin at 37 °C, 5% CO2. The cells were transfected with siRNA against murine SMN (5’-CAGAAGUAAAGACACACACGACAA-3’) or scrambled control siRNA (5’-GCGCAAAAAACCCGGAACAC-3’) by using OptiMeM (Thermo Scientific) and Lipofectamine 2000 (Invitrogen) in differentiation medium, containing 1% FSC for 72 hours. The SMN knock down efficiency of NSC34 cells was about 80%, which was routinely tested by Western blot.

RNA Isolation and Real Time RT-PCR

Total RNA was isolated from NSC34 cells by the RNeasy mini kit (Qiagen) using the manufacturer’s protocol. Spinal
cord (p1, p5 and p8) and brain (p8) RNA samples of severe
the SMA Taiwanese mouse model (FVB.Cg-Tg (SMN2) 2Hun
SNM1tm1Hung/j) (22) (Jackson Laboratory) and heterozygous
control littermates, which were previously isolated and
stored at -80 °C, according to German animal welfare
regulations (breeding approved by the Lower Saxony State
Office for Consumer Protection and Food Safety (LAVES,
reference number 15/1774 LAVES). The numbers of mice
used from different developmental stages are provided
in the figure legends. cDNA synthesis was performed as
previously reported (30). Briefly, 2.5 μg of RNA was incubated
with random hexamer primers (3 μg/μl, Invitrogen) at 70 °C
for 2 min, then M-MLV-transcriptase (200U/μl, Invitrogen),
RNase-Inhibitor (40U/μl), DTT (0.1M, Invitrogen) and
dNTP (10mM) was added. The reaction mix was incubated
at 42 °C for 90 min and then 70 °C for 15 min for transcriptase deactivation. Real-time reverse-transcription
polymerase chain reaction (RT-PCR) was performed using
5μl diluted cDNAs (1:200), 7μl SYBR green (Applied
Biosystems, PowerSYBR green mix), 2μl MAP2 primers
(1.75μM, forward: 5'TCTAAGAAATCCCGTCAAGGC3',
reverse: 5'CGTGACCATGTAATTGAGC 3') or PPIA
primers (1.75μM, forward: 5'TGACCTCTCGCGACTGATG
3', reverse: 5'CATTGCAATCTCACAATGTC3') as the
housekeeping gene. The reaction was performed in
triplicate and StepOnePlus Real-time PCR System (Applied
Biosystems) was used with the following conditions; 95
°C for 10 min (initial denaturation), 40 cycles at 95 °C for
15 sec and 60 °C for 1 min. A comparative threshold cycle
method (2-ΔΔCt) was used for the quantitation of the
results.

**Statistical Analysis**

Statistical analyses were performed using Graphpad
prism version 8 (La Jolla California USA). Mann-Whitney
U test was used and a result of p<0.05 was considered as
statistically significant.

**Results**

After the re-analysis of human and mouse array
CEL files, we identified differentially expressed genes of
SMA samples when compared to their related control
samples in both human and mouse datasets (ANOVA
eBayes) p-value <0.05 and fold change <-1.5 or fold
change >1.5). In order to find expressional alterations of
microtubule-related genes in SMA patients and SMA
mice, we analyzed the expression of several transcripts,
which are involved in both microtubule structure and the
regulation of its dynamics. Differentially expressed gene
lists of human and mouse datasets are given in Table I
and II, respectively.

Among the microtubule-related genes that we
analyzed in this study, 5 genes were differentially
expressed in both the SMA patient and mouse model,
while MAP2, MAP7 and TUBB4A showed similar gene
expression alteration patterns (Figure 1A). The MAP2
gene was the only upregulated target, which drew our
attention since the altered protein level of MAP2 was
reported in a mouse model of amyotrophic lateral
sclerosis (ALS), which is another motor neuron disease
(31). Additionally, it has also been reported that either
the protein level or the post-translational modifications
of TAU, which is another microtubule-associated protein
from the same protein family, was altered in ALS and
SMA models, respectively (14,21,31). Therefore, we
subsequently focused on the MAP2 gene. To validate exon
array results, we first used motor neuron-like NSC34 cells,
which are murine neuroblastoma and spinal cord hybrid
cell line as an in vitro model (32). We knocked down SMN
by siRNA in the NSC34 cells and detected an upregulation
in MAP2 gene expression by real time RT-PCR in SMN-
depleted cells compared to scrambled controls (Figure
1B). Since the increase in gene expression was close to
the significance level, we decided to analyze MAP2 gene
expression in the severe SMA Taiwanese mouse model
(22). First, we analyzed MAP2 gene expression in the
total brain and spinal cord of late symptomatic p8 mice.
We found a significant upregulation in both tissues of
SMA mice compared to control littermates (Figure 1C).
Considering that spinal cord motor neurons are primarily
affected by SMN loss, we further analyzed MAP2 gene
expression in the spinal cords of both pre-symptomatic
(p1) and early symptomatic (p5) mice. A significant
increase was detected in p5 but not p1 SMA mice (Figure
1C).

**Discussion**

SMA is a devastating genetic disease of childhood.
Despite the recent therapeutic achievements with
antisense oligonucleotide and successful clinical trials
with gene therapy and small molecules, elucidating the
functions of SMN protein and understanding the patho-
mechanisms of SMA is still needed. Re-analysis of public
gene expression data is a promising tool to understand
disease mechanisms. In this study, we re-analyzed raw
data of previously published human exon-array and mouse
microarray data that we obtained from the GEO database
(23,24) and specifically focused on genes regulating
microtubule structure and/or function, since there is
little knowledge about microtubule dynamics in SMA.
Previously, an altered organization of microtubules in the
presynaptic terminals of the axons innervating transverse
abdominis of SMA mice have been reported in this
commonly affected muscle (33). Additionally, stathmin,
a microtubule depolymerizing protein, is upregulated in
both SMN-depolymerizing NSC34 cells and SMA mice and has
Table I. Expressional alterations of microtubule-related genes in iPSC-derived motor neurons of SMA patient

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Figure 1. Expression analysis of genes regulating microtubule structure and its dynamics, A) Venn diagram of significantly altered genes in induced pluripotent stem cell-derived motor neurons of SMA patient and delta7 SMA mice using HuEx-1_0-st and Mouse430A_2 datasets, respectively. Fold changes of MAP2 transcript level in B) SMN knock down NSC34 cell line, n=4 biological replicates, C) spinal cord and brain tissues of p1, p5 and p8 severe SMA Taiwanese mouse model and heterozygous control littermates, for p1; n=5 (control) and n=4 (SMA) mice, for p5; n=6 (control) and n=5 (SMA) mice, for p8; n=5 (control) and n=5 (SMA) mice. PPIA gene was used for normalization. Mann-Whitney U, *p<0.05, Data are presented as means with standard error of mean.

MAP: Microtubule-associated protein, SMN: Survival of motor neuron, SMA: Spinal muscular atrophy
been linked to defective microtubule polymerization (15). Hyperphosphorylation of TAU protein has been reported in the spinal cord of both SMA mice and patient samples (15). We observed an opposite gene expression profile of microtubule associated protein TAU (MAPT) between human and mouse gene expression results. According to our analysis, this target showed downregulation in human iPSC-derived motoneurons but it was upregulated in the spinal cords of SMA mice, which might be related to the presence of glial cells in the spinal cord (Table I and Table II). We focused on genes which have similar expression pattern in both arrays such as MAP2, MAP7 and TUBB4A. Among them, the MAP2 gene was the only upregulated one in both SMA patient and SMA delta 7 mice. It has been known that MAP2 plays a role on neuronal growth and degeneration (34). Considering its function in regulating microtubule stability in neurons and previous reports on gene expression alterations in ALS, we analyzed MAP2 gene expression for both in vitro and in vivo SMA model systems. Our experimental results were consistent with mouse microarray results, which showed a significant upregulation of MAP2 in the spinal cords of

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We analyzed MAP2 gene expression in the brain and spinal cord tissues of the SMA Taiwanese mouse model and detected a significant increase in MAP2 gene expression in both tissues in the late symptomatic stage, which suggests a global differential expression of the MAP2 gene in the central nervous system. Results obtained from earlier developmental stages of SMA mice showed that MAP2 upregulation in the spinal cord occurs during the onset of disease symptoms. MAP2 induction may be a compensatory mechanism in an impaired cytoskeletal environment to maintain both microtubule stability and actin-microtubule crosslink during disease progression. Detailed studies on MAP2 expression in both neuronal and surrounding non-neuronal cells will help to reveal any functional consequences of this alteration.

**Conclusion**

Our findings may indicate an altered expression of the MAP2 gene during disease progression. Although our work is limited due to a lack of protein studies, our preliminary results indicate that microtubule regulatory proteins may be altered in SMN depleted cells. Further studies will be valuable in understanding the involvement of both MAP2 and other microtubule-related proteins to SMA patho mechanisms.

**Acknowledgement**

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**Ethics**

**Ethics Committee Approval:** The study was approved by the Ethics Committee of Marmara University Medical Faculty (approval number: 09.2016.231).

**Informed Consent:** Informed consent was obtained from the parents of the infants.

**Peer-review:** External and internal peer-reviewed.

**Authorship Contributions**


**Conflict of Interest:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** This study was supported by the Hacettepe University Scientific Research Projects Coordination Unit (International Collaboration Project Number: 13 G 602 003).

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* is used where the probe group is annotated to different gene symbols.
References


