A study on Carbon Nanotube-Gene Interaction in Induction of Glial Cells to Neuron Cell

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Introduction: Reprogramming different cell to neuron have yet remained attractive field in regenerative medicine, so discovery new methods or improve existing methods could be helpful. The aim of this study was to evaluate the Carbon Nanotube-Gene Interaction in Induction of Glial Cells to Neuron Cell. **Materials and Methods:** Accordingly, we analyzed the transcriptome data of glial and neuron cells to determine the different gene expression in both groups. Then, based on this transcriptome data, the gene chemical interaction was determined to find the most important chemical structure which induces glial cell to neurons. Data extract from transcriptome database related rat cerebral cortex cells generated by RNA sequencing transcriptomic (RNAseq) technique. By comparison neuron against glial cells (astrocyte, oligodenderocyte and microglia) determined different gene expression. In Comparative Toxicogenomics Database (CTD) determined the most important chemical to interact with this gene set. Then by using genetrail2 database determined mechanism of gene set associated to chemicals and miRNA enriched. **Results:** Result determined different chemical with the risk factor and protective factor properties related to 500 genes that enriched in a neuron in comparison with glial cells. The carbon nanotube is the first important chemicals that interact with 75 genes of 500. Gene ontology analysis determined the carbon nanotube effect on genes that induce neurogenesis, neurodevelopment, and differentiation. Genetrail2 release the 29 significant miRNAs enriched in gene interacts with carbon nanotube in which miR-34a and miR-449a are the most significant molecules. Network analysis of these genes represents KIT (tyrosine-protein kinase, CD117), Gria1, Syt1, Rab3c, and Tubb3 have central roles in neurogenesis by the carbon nanotube. **Conclusion:** In sum up, the carbon nanotube is an electrical stimulator that has biocompatibility to induce glial cell to the neuron which applies as devise lonely or combination with a cell in damage part of the neural tissue.

Keywords: Carbon Nanotube; Glial Cell; Neuron Cell; Regenerative Medicine; Tissue Engineering

Introduction

Neural tissue engineering is attractive filed of research to eliminate the neuroinflammation, fibrosis and repair damage in central and peripheral nervous system by different strategies such as implantation or directed or undirected delivery of stem cells in the injury site. This strategy encounters with the rejection, tumorigenesis, inflammation and cell migration (1). Another strategy is the delivering induction of neural molecules such as small molecules, morphogens, and miRNAs (2-6). Here, the greatest challenges are delivery, passing blood-brain barrier (BBB), and take by injured site up (7). The third method in neural tissue engineering is implanting the artificial neural tissue convenient to the injury site. In this method, stem cells are used that grow on the biodegradable and biocompatible scaffold. The scaffold has an important role to support cells for differentiation and treating neural tissue injury. There are several types of scaffold in neural tissue engineering which contains liquid hydrogel, aligning scaffold, supportive scaffold, integrative scaffold or combination of all (8, 9). They are so attractive due to the easy formation, low infection risk, and low inflammation respond, synthetic materials.

Neural precursor cells are the origin of the major cell types in the central nervous system (CNS) which consist of neurons and

glial cells. There is a limitation in using neural precursor cells in cell therapy. Therefore, tissue engineering overcome this limitation by reprogramming of resident glial cells and even non-residential cells *in vitro* and *in vivo* to generate functional synapse-forming neurons, spinal motor neurons, functional glutamatergic and dopaminergic neurons (1, 10, 11).

Induction mechanism is related to the present of functional molecules such as cocktails of transcription factors (TF), neuron-specific microRNAs (miRNA), and appropriate scaffolds which influence gene expression and epigenetic conditions to ultimately induce specific signal transduction or cross-talk between distinct signaling pathways (12, 13).

Here, we used the RNA sequencing -transcriptomic study (RNAseq) results of all cells in the rat brain to determine the different genes expression in the neuron against glial cells (astrocyte, oligodenderocyte and microglia) to find the influence of environmental factors on gene expressed during neuron differentiation and finally determine the transcriptional factors and miRNAs related to this chemical-gene interaction.

Materials and Methods

Data

Zhang *et al.* generated a transcriptome database (http://web.stanford.edu/group/barres_lab/brain_rnaseq.html) which comprise all rat brain cells from glial cells (astrocyte, oligodendrocyte, and microglia) to the neuron cells that are characterized by RNAseq technique (13). This database able to enrich gene invariant conditions. In this study, we enriched the genome neuron in contrast to the genome of astrocyte, oligodendrocyte, and microglia.

Chemical-gene interaction analysis

We used Comparative Toxicogenomics Database (CTD) (http://ctdbase.org/) to find the environmental exposures effects on neural differentiation (14). All genes obtained in a comparison of neuron and glial cells were submitted to CTD database to determine all chemicals and agents which interact with the genes. Then, the protective factors were selected that induced the glial cells to the neurons.

Statistical analysis of molecular signatures

GenTrail2 Database (http://genetrail2.bioinf.uni-sb.de/) was used to identify the mechanism of protective chemical and switch molecules (transcription factors and miRNAs) related to chemical-gene interaction in the neuron compared to glial cells (15). Significant TF related gene enrichment, TF complexes, and TF families were determined in GenTrail2 algorism by applying TRANSFAC database. TRANSFAC database in GenTrail2 algorism was used to find the miRNA enrichment-related genome expressed in the neuron compare to glial cell. GenTrail2 algorism also determined the important proteins or genes related to all these miRNA.

Network analysis

We used network analysis to find out the most important proteins in the structural and functional analysis. So we applied open source network visualization software, Cytoscape (16), to construct network and analysis the network to find the hub and bottleneck proteins. Protein-protein network construct base on several databases include InnattDB-IMEx, Intact, MatrixDB, InnateDB, BIND, Reactom Fls, Mentha, MINT, Bhf-ucl, BioGrid, MBinfo, BAR, InnateDB, Uniprot, and APID. For functional analysis, we used Bingo App (17) that run on Cytoscape software. Other structural analysis were performed by Molecular Complex Detection (MCODE) in Cytoscape software to identify the motifs. BiNGO is an open source plugin of cytoscape and applies to determine over-representation of Gene Ontology (GO) categories (biological process, molecular function, and cellular component) from a gene set. This app uses hypergeometric or binomial test to assess significances and Bonferroni (FWER) or Benjamini & Hochberg (FDR) correction and apply for multiple testing corrections (17). MCODE as a cytoscape plugin applies to find clusters based on topological features in a network. Highly connected regions in protein-protein interaction network may imply the complexes or important sub-graph with crucial function. Resulting cluster contains numerous node-scoring and cluster-finding parameters (18).

Results

Gene enrichment of neuron cell against glial cells in tanscriptome database determined the most first genes according to the highest expression which represented in Table 1. Supplementary Table S1 represents all 500 proteins and their fold changes in neuron cells against glial cells.

Chemical-gene interaction analysis determined the number of chemicals and agents in which carbon nanotube with the most interaction enriched as a protective chemical. Carbon nanotube have a large propensity to interact with about 72 genes of 500 genes expressed in the neuron. All genes that interact with the carbon nanotube were represented in Table 2.

Analysis of interactions the genes with carbon nanotube by GenTrail2 based on Gene Ontology were represented in Table 3.

Table 1. Top 10 genes expressed in neurons when compare to glial cells (Expression level estimation was reported as fragments per kilobase of transcript sequence per million mapped fragments (FPKM) value together with confidence intervals for each sample)

GENE	Neuron gene expressions (Mean FPKM)	Glial cells gene expression (Mean FPKM)	Fold change (neuron cell/glial cell)
Reln (a gene required for brain development)	849.03	0.4012	2116.1
Nhlh2 (Nescient Helix-Loop-Helix 2 (a gene for protein Coding)	66.303	0.1003	660.58
Slc17a6 (a gene for protein Coding)	61.818	0.1076	574.23
Trp73 (a gene for protein Coding)	73.153	0.129	566.87
Nxph4 (a gene for protein Coding)	71.761	0.1518	472.49
A930038C07Rik (receptor inhibitor activity)	143.79	0.3364	427.35
Npy (Neuropeptide Y, a gene for protein Coding)	646.48	1.9175	337.13
Lhx5 (LIM Homeobox 5, a gene for protein Coding)	31.156	0.1	311.56

Table 2. List of the Genes that interact with carbon nanotube

Gene Name	Gene Name	Gene Name	Gene Name
Reln	Fam196a	Col6a2	Zmat4
Trp73	Wscd2	Ablim3	Eomes
Npy	Erc2	Necab1	Unc5a
Snhg11	Nsg2	Fibin	Lhx9
Grem2	Smoc2	Penk	Uchl1
P2rx5	Mal2	Bcl11b	Amy1
Mrap2	Mirg	Nxph3	Htr7
Ripk4	Zdhhc22	Ajap1	Fam183b
Kcnj5	Mme	Srrm4	Dact1
Stmn2	Tmem200a	Kit	Gda
Syt1	Disp2	Meg3	Slc38a4
Bmp5	Rnf152	Crmp1	Gria1
Bcl11a	Kcnip4	Dach1	Ndrg4
Ccbe1	Gpr88	C1qtnf1	Sema3c
Cxcl12	Rims3	Kcnmb2	Cpne5
Gap43	Doc2b	Celsr3	Nr2f2
Tubb3	Nrn1	Atp1a3	Igsf9
Robo2	Palmd	Rbms3	Rab3c

Table3. Biological process related the carbon nanotube –gene interaction

Name	Number of hits	Expected number of hits	q-value
neuron projection morphogenesis (6)	15	0.555	9.21E-13
axon development(6)	13	0.424	1.57E-11
regulation of neuron differentiation (7)	14	0.62	4.44E-11
cell morphogenesis involved in neuron differentiation (6)	13	0.517	9.25E-11
Axonogenesis (7)	12	0.399	1.13E-10
regulation of cell projection organization (5)	13	0.572	2.16E-10
positive regulation of neurogenesis (5)	12	0.439	2.43E-10
positive regulation of cell projection organization(5)	11	0.329	3.11E-10

Table 4. KEGG pathway related to gene related gene interaction to carbon nanotube

Type	Name	Number of hits	Expected number of hits	q-value
Enriched	**Axon guidance**	5	0.131	4.83E-04

Table 5. Significantly miRNAs enriched based on TRANSFAC

Type	Name	Number of hits	Expected number of hits	q-value
Enriched	**mmu-miR-34a-5p**	9	0.512	1.53E-06
Enriched	**mmu-miR-449a-5p**	9	0.511	1.53E-06
Enriched	**mmu-miR-15a-5p**	7	0.638	7.24E-04
Enriched	**mmu-miR-15b-5p**	7	0.638	7.24E-04
Enriched	**mmu-miR-16-5p**	7	0.641	7.24E-04
Enriched	**mmu-miR-195a-5p**	7	0.639	7.24E-04
Enriched	**mmu-miR-34b-5p**	5	0.267	9.83E-04
Enriched	**mmu-miR-34c-5p**	5	0.273	9.83E-04
Enriched	**mmu-miR-449b**	5	0.266	9.83E-04
Enriched	**mmu-miR-449c-5p**	5	0.266	9.83E-04

Table 6. The most important proteins derived from network analysis of protein targets of miRNAs

Symbol name	Uniprot name	Degree	Beetweeness centrality
Kit	P05532	13408	0.322146
Ywhae	P62259	76	0.587119
Gria1	P23818	42	0.239724
PIK3R1	P27986	36	0
Syt1	P46096	32	0.267966
Rab3c	P62823	29	0.238238
Tubb3	Q9ERD7	28	0.592183
P29351	P29351	20	0
Q925F2	Q925F2	18	0
P29350	P29350	18	0
AMY1	P00687	17	1
ERC2;Erc2	Q6PH08	15	0.149436
Dlg4	Q62108	14	0.10481
Gda	Q9R111	14	0.034894
Atp1a3	Q8VCE0	13	0.007606
SNCA	P37840	13	0
STMN2	P55821	12	0.041954
P42230	P42230	12	0
Q00993	Q00993	12	0
Dach1	Q9QYB2	11	0.096494
Mme	Q61391	11	0.035675
P41242	P41242	11	0
GAP43	P06837	10	0.10425
Q60707	Q60707	10	0

Table 7. The pathway related the proteins extracted from network

Type	Rank	Name	Number of hits	Expected number of hits	q-value
Enriched	**1**	**Signaling by SCF-KIT**	15	0.243	1.87E-19
Enriched	**2**	**Regulation of KIT signaling**	8	0.074	6.48E-12
Enriched	**3**	**Glutamate Neurotransmitter Release Cycle**	10	0.19	8.91E-12
Enriched	**4**	**Acetylcholine Neurotransmitter Release Cycle**	9	0.153	4.19E-11
Enriched	**4**	**Norepinephrine Neurotransmitter Release Cycle**	9	0.153	4.19E-11
Enriched	**6**	**GPVI-mediated activation cascade**	9	0.269	9.58E-09
Enriched	**7**	**DAP12 signaling**	8	0.211	3.68E-08

Analysis based on KEGG database determined just one significant category related to neuron induction that has been shown in Table 4.

Table 5 shows the 20 first important miRNAs enriched based on TRANSFAC database. This database recognized 29 significant miRNAs of all 183 miRNAs that link to the genes expressed in neurons. All significant miRNAs enriched have been represened in supplementary Table S2. Targeted proteins that were regulated by these miRNAs have been shown in supplementary Table S3.

Network analysis on these target proteins determined the most important structural and functional proteins. Table 6 represented the highest degree and betweenness centrality protein in network. Supplementary Table S4 also represents the whole information of network.

The genetrail2 analysis to get pathways undergo the proteins extracted from network enrich the pathway related to Signaling by SCF (stem cell factor)-KIT that represents in detail in Table 7 and supplementary Table 5.

Discussion

Neural tissue engineering can be a promising way to repair neural damage even in psychological disorders. Today, there are a number of strategies for reprogramming of cell with different origin to neurons. This study focused on finding chemical agents which are able to induce the glial cells to neurons. Based on transcriptome analyzing by comparing neuron and glial cells (astrocyte, oligodendrocyte and microglia) (Table 1), 500 genes with the most difference were determined; their interaction with chemical agents release different agent categories in which carbon nanotube is the scaffold with the role in induction of glial cell to neuron. Chao et al. reported 2D thin film scaffolds composed of carbon nanotubes can selectively differentiate human embryonic stem cells into neuron cells with the excellent cell viability (19).

Carbon nanotube, biomedical substrate, affect proliferation and differentiation by mimicking extracellular matrix which their size comparable to collagen and laminin, suitable flexibility and mechanical strength, constant conductivity that is able them to apply for electrical stimulation in vivo, convenient carbon nanotube to growth and differentiate neurons (20-24). According to Table 2, the most significant protein expressed in the neuron is reelin (Reln), extracellular matrix serine protease that regulates microtubule function in neurons (25). It is down-regulated in several mental disorder and neurodegenerative diseases (26-30). The significant biological process related to gene interaction of carbon nanotube (as has been shown in Table 3) determined the process link to neuron morphogenesis, development, and differentiation. This data exactly mention the role of carbon nanotube in neuron growth and differentiation. More analysis of these genes represented the effect of miRNA on neural growth and differentiation which associated with 29 significant miRNAs. The network analysis on these genes also determined the hubs nodes refer to Kit, Gria1, Syt1, Rab3c, and Tubb3. Kit is a tyrosine-protein kinase receptor for the cytokine KITLG/SCF and can activate several signaling pathways. It plays an essential role in the regulation of long-term neuronal synaptic plasticity, and stem cell differentiation in a number of tissues (31, 32). This protein also contributes to several cancers (33). Our result determined that kit protein was regulated by the most miRNA enriched by genetrail2, miR-34a, and miR-449a. Agostini et al. (2011) has been shown that miRNA-34a regulates neurite outgrowth, spinal morphology, and function (33).

Gria1, Ionotropic glutamate receptor, acts in neuron structure and function (34). One of the important protein interact with Reln is Tubb3, an important protein in cytoskeleton which has critical roles in axon guidance. Its mutation or expression changes known as TUBB3 syndromes (35). The important genes with the higher betweeness centrality are Kit, AMY1, Tubb3, Ywhae, UBC, Syt1, Gria1, Rab3c, Rpgrip1l, ERC2, Ywhab, Dlg4, GAP43, and YWHAZ. Several of these nodes are also hubs. According to the Table 7, the most important pathway represented that induces neurogenesis is SCF-KIT signaling. By presence, the cell with different origin in carbon nanotube scaffold may be induced and active the SCF-KIT cascade that finally lead to release cycle of neurotransmitters glutamate, acetylcholine and norepinephrine, GPVI-mediated activation cascade, DAP12 signaling and other signaling pathways.Since carbon nanotubes have been revealed as a cell culture substrate which able to alter the fate of stem cells (36). In addition, CN has appropriated properties for the design of nano-bio hybrid systems, because of electrophysiological properties and structure that have been found to enhance growth, differentiation, and survival of neurons (37). It also could be applicable in neurosciences as brain-machine interfaces (38). In this study, it is determined the carbon nanotubes provide a matrix that is similar to natural conditions to differentiate into neurons. Even though, new innovative medicines use the carbon nanotube for neuroregeneration and repair (39), the art of reality application of nanomaterial in medicine is at the beginning of the way.

Conclusion

In sum up, the use of carbon nanotube for neural cell growth and differentiation represented the genes which lead to differentiation of the glial cell to the neuron. In addition to biocompatibility, the flexibility and electrical stimulation of carbon nanotube makes it suitable for use in tissue engineering alone or in combination with the cell in damage part of the neural tissue.

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Conflict of Interest: 'None declared'.

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