

## Ginsenoside Rg1 및 Rb1을 처리한 신경세포주(SH-SY5Y세포)의 유전자 발현양상

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### Gene Expression Profiling of SH-SY5Y Human Neuroblastoma Cells Treated with Ginsenoside Rg1 and Rb1

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#### ABSTRACT

**O**bjectives : The ginsenoside Rg1 and Rb1, the major components of ginseng saponin, have neurotrophic and neuroprotective effects including promotion of neuronal survival and proliferation, facilitation of learning and memory, and protection from ischemic injury and apoptosis. In this study, to investigate the molecular basis of the effects of ginsenoside on neuron, we analyzed gene expression profiling of SH - SY5Y human neuroblastoma cells treated with ginsenoside Rg1 or Rb1.

**Methods** : SH - SY5Y cells were cultured and treated in triplicate with ginsenoside Rg1 or Rb1(80 μM, 40 μM, 20 μM). The proliferation rates of SH - SY5Y cells were determined by MTT assay and microscopic examination. We used a high density cDNA microarray chip that contained 8K human genes to analyze the gene expression profiles in SH - SY5Y cells. We analyzed using the Significance Analysis of Microarray(SAM) method for identifying genes on a microarray with statistically significant changes in expression.

**Results** : Treatment of SH - SY5Y cells with 80 μM ginsenoside Rg1 or Rb1 for 36h showed maximal proliferation

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compared with other concentrations or control. The results of the microarray experiment yielded 96 genes were upregulated( 3 fold) in Rg1 treated cells and 40 genes were up - regulated( 2 fold) in Rb1 treated cells. Treatment with ginsenoside Rg1 for 36h induced the expression of some genes associated with protein biosynthesis, regulation of transcription or translation, cell proliferation and growth, neurogenesis and differentiation, regulation of cell cycle, energy transport and others. Genes associated with neurogenesis and neuronal differentiation such as SCG10 and MLP increased in ginsenoside Rg1 treated cells, but such changes did not occur in Rb1 - group.

**Conclusion :** Our data provide novel insights into the gene mechanisms involved in possible role for ginsenoside Rg1 or Rb1 in mediating neuronal proliferation or cell viability, which can elicit distinct patterns of gene expression in neuronal cell line. Ginsenoside Rg1 have more broad and strong effects than ginsenoside Rb1 in gene expression and related cellular physiology. In addition, we suggest that SCG10 gene, which is known to be expressed in neuronal differentiation during development and neuronal regeneration during adulthood, may have a role in enhancement of activity dependent synaptic plasticity or cytoskeletal regulation following treatment of ginsenoside Rg1. Further, ginsenoside Rg1 may have a possible role in regeneration of injured neuron, promotion of memory, and prevention from aging or neuronal degeneration.

**KEY WORDS :** Ginsenoside Rg1 · Ginsenoside Rb1 · Microarray · Gene expression · SCG10.

**서 론**

Ginsenoside Rg1, Rg2, Rg3, Rg4, Rg5, Rg6, Rg7, Rg8, Rg9, Rg10, Rg11, Rg12, Rg13, Rg14, Rg15, Rg16, Rg17, Rg18, Rg19, Rg20, Rg21, Rg22, Rg23, Rg24, Rg25, Rg26, Rg27, Rg28, Rg29, Rg30, Rg31, Rg32, Rg33, Rg34, Rg35, Rg36, Rg37, Rg38, Rg39, Rg40, Rg41, Rg42, Rg43, Rg44, Rg45, Rg46, Rg47, Rg48, Rg49, Rg50, Rg51, Rg52, Rg53, Rg54, Rg55, Rg56, Rg57, Rg58, Rg59, Rg60, Rg61, Rg62, Rg63, Rg64, Rg65, Rg66, Rg67, Rg68, Rg69, Rg70, Rg71, Rg72, Rg73, Rg74, Rg75, Rg76, Rg77, Rg78, Rg79, Rg80, Rg81, Rg82, Rg83, Rg84, Rg85, Rg86, Rg87, Rg88, Rg89, Rg90, Rg91, Rg92, Rg93, Rg94, Rg95, Rg96, Rg97, Rg98, Rg99, Rg100, Rg101, Rg102, Rg103, Rg104, Rg105, Rg106, Rg107, Rg108, Rg109, Rg110, Rg111, Rg112, Rg113, Rg114, Rg115, Rg116, Rg117, Rg118, Rg119, Rg120, Rg121, Rg122, Rg123, Rg124, Rg125, Rg126, Rg127, Rg128, Rg129, Rg130, Rg131, Rg132, Rg133, Rg134, Rg135, Rg136, Rg137, Rg138, Rg139, Rg140, Rg141, Rg142, Rg143, Rg144, Rg145, Rg146, Rg147, Rg148, Rg149, Rg150, Rg151, Rg152, Rg153, Rg154, Rg155, Rg156, 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Rg1513, Rg1514, Rg1515, Rg1516, Rg1517, Rg1518, Rg1519, Rg1520, Rg1521, Rg1522, Rg1523, Rg1524, Rg1525, Rg1526, Rg1527, Rg1528, Rg1529, Rg1530, Rg1531, Rg1532, Rg1533, Rg1534, Rg1535, Rg1536, Rg1537, Rg1538, Rg1539, Rg1540, Rg1541, Rg1542, Rg1543, Rg1544, Rg1545, Rg1546, Rg1547, Rg1548, Rg1549, Rg1550, Rg1551, Rg1552, Rg1553, Rg1554, Rg1555, Rg1556, Rg1557, Rg1558, Rg1559, Rg1560, Rg1561, Rg1562, Rg1563, Rg1564, Rg1565, Rg1566, Rg1567, Rg1568, Rg1569, Rg1570, Rg1571, Rg1572, Rg1573, Rg1574, Rg1575, Rg1576, Rg1577, Rg1578, Rg1579, Rg1580, Rg1581, Rg1582, Rg1583, Rg1584, Rg1585, Rg1586, Rg1587, Rg1588, Rg1589, Rg1590, Rg1591, Rg1592, Rg1593, Rg1594, Rg1595, Rg1596, Rg1597, Rg1598, Rg1599, Rg1600, Rg1601, Rg1602, Rg1603, Rg1604, Rg1605, Rg1606, Rg1607, Rg1608, Rg1609, Rg1610, Rg1611, Rg1612, Rg1613, Rg1614, Rg1615, Rg1616, Rg1617, Rg1618, Rg1619, Rg1620, Rg1621, Rg1622, Rg1623, Rg1624, Rg1625, Rg1626, Rg1627, Rg1628, Rg1629, Rg1630, Rg1631, Rg1632, Rg1633, Rg1634, Rg1635, Rg1636, Rg1637, Rg1638, Rg1639, Rg1640, Rg1641, Rg1642, Rg1643, Rg1644, Rg1645, Rg1646, Rg1647, Rg1648, Rg1649, Rg1650, Rg1651, Rg1652, Rg1653, Rg1654, Rg1655, Rg1656, Rg1657, Rg1658, Rg1659, Rg1660, Rg1661, Rg1662, Rg1663, Rg1664, Rg1665, Rg1666, Rg1667, Rg1668, Rg1669, Rg1670, Rg1671, Rg1672, Rg1673, Rg1674, Rg1675, Rg1676, Rg1677, Rg1678, Rg1679, Rg1680, Rg1681, Rg1682, Rg1683, Rg1684, Rg1685, Rg1686, Rg1687, Rg1688, Rg1689, Rg1690, Rg1691, Rg1692, Rg1693, Rg1694, Rg1695, Rg1696, Rg1697, Rg1698, Rg1699, Rg1700, Rg1701, Rg1702, Rg1703, Rg1704, Rg1705, Rg1706, Rg1707, Rg1708, Rg1709, Rg1710, Rg1711, Rg1712, Rg1713, Rg1714, Rg1715, Rg1716, Rg1717, Rg1718, Rg1719, Rg1720, Rg1721, Rg1722, Rg1723, Rg1724, Rg1725, Rg1726, Rg1727, Rg1728, Rg1729, Rg1730, Rg1731, Rg1732, Rg1733, Rg1734, Rg1735, Rg1736, Rg1737, Rg1738, Rg1739, Rg1740, Rg1741, Rg1742, Rg1743, Rg1744, Rg1745, Rg1746, Rg1747, Rg1748, Rg1749, Rg1750, Rg1751, Rg1752, Rg1753, Rg1754, Rg1755, Rg1756, Rg1757, Rg1758, Rg1759, Rg1760, Rg1761, Rg1762, Rg1763, Rg1764, Rg1765, Rg1766, Rg1767, Rg1768, Rg1769, Rg1770, Rg1771, Rg1772, Rg1773, Rg1774, Rg1775, Rg1776, Rg1777, Rg1778, Rg1779, Rg1780, Rg1781, Rg1782, Rg1783, Rg1784, Rg1785, Rg1786, Rg1787, Rg1788, Rg1789, Rg1790, Rg1791, Rg1792, Rg1793, Rg1794, Rg1795, Rg1796, Rg1797, Rg1798, Rg1799, Rg1800, Rg1801, Rg1802, Rg1803, Rg1804, Rg1805, Rg1806, Rg1807, Rg1808, Rg1809, Rg1810, Rg1811, Rg1812, Rg1813, Rg1814, Rg1815, Rg1816, Rg1817, Rg1818, Rg1819, Rg1820, Rg1821, Rg1822, Rg1823, Rg1824, Rg1825, Rg1826, Rg1827, Rg1828, Rg1829, Rg1830, Rg1831, Rg1832, Rg1833, Rg1834, Rg1835, Rg1836, Rg1837, Rg1838, Rg1839, Rg1840, Rg1841, Rg1842, Rg1843, Rg1844, Rg1845, Rg1846, Rg1847, Rg1848, Rg1849, Rg1850, Rg1851, Rg1852, Rg1853, R

Rb1 glutamate kainic acid  
 excitotoxicity H<sub>2</sub>O<sub>2</sub>  
 가 oxidative stress  
<sup>21)</sup>  
<sup>22)</sup> Rb1  
<sup>23)</sup> (Nerve Growth Factor,  
 NGF) <sup>24)</sup>  
 가  
 , Ginsenoside Rg1 가 가  
 Rb1 (consolidation),  
<sup>25)</sup> Rb1 rat , Liu<sup>35)</sup> Rg1  
<sup>26)</sup> 가 (activity  
 dependent synaptic plasticity) , glutamate excitotoxicity  
 , Rg1 Rb1 weaning mice , rat  
 , Liu Zhang<sup>36)</sup> Rg1 cAMP  
 CA3 가 가 Rg1 가 Rg1  
<sup>27)28)</sup> Mook - Jung <sup>29)</sup> Rg1 Rb1 가  
 mice synaptophysin 가 , Rg1 Rb1 가  
 (synaptic density) 가 , Li Zhang<sup>37)</sup> Rg1  
 Rb1 (A ) Ach , Lee <sup>30)</sup> 가 , LDH ,  
 , DNA  
 Rg1  
 , Lim <sup>31)</sup> Rb1 가 , Rg1 Rb1 Glucocorticoid re-  
 CA1 neuron ceptor(GR) GR ligand가  
 , Rb1 , Lee <sup>38)</sup> Rg1 GR 1~10 μM  
 (free radical) 가 3[H]dexamethasone(Dexa)  
 . Chen <sup>32)</sup> (DA) luciferase reporter gene gluco-  
 Rg1 BCL - 2(B - cell CLL/lymp- corticoid responsive element  
 homa 2) BAX(BCL2 - associated X protein) Rg1 Dexa  
 CASP3(caspase - 3) 2 - 3 가 Rg1 Dexa  
 . Chen <sup>33)</sup> Rg1 DA ROS(reactive , Chung <sup>39)</sup>  
 oxygen species) CASP3 Rg1 GR Rg1 GR  
 Rg1 가 iNOS(inducible NO synthase) NO Rg1 가 GR GR  
 oxidative stress Rg1 Rg1 GR  
 가 DA Rg1 Rb1  
 , Liao <sup>34)</sup> Rg1 methamphetamine  
 Rb1 (supersensitivity)  
 , Rg1 (conditioned place preference, CPP)

,<sup>40)</sup> Rg1 Rb1 CPP metham- phetamine side ginseno-  
 , Kim<sup>41)</sup> Rg1 Rb1  
 Rg1 Rb1 cocaine  
 , Cao<sup>42)</sup> rat brain microsomal Na<sup>+</sup> - K<sup>+</sup> - ATPase Rb1  
 , Rg1 Rb1  
 Jiang<sup>43)</sup> Whole cell patch clamp technique Rb1 rat synaptosome Ca<sup>2+</sup> K<sup>+</sup> Na<sup>+</sup> - ATPase Ca<sup>2+</sup> - Mg<sup>2+</sup> - ATPase 가 Rb1 Ca<sup>2+</sup> ATPase activity 가 . Liu Zhang<sup>44)</sup> Rg1 Rb1 glutamate Ca<sup>2+</sup> neuronal cell Ca<sup>2+</sup>  
 Rg1 Rb1  
 ginsenoside 가 가  
 가  
 microarray ginsenoside  
 가  
 가  
 (proteomics) , mRNA (transcriptomics) transcrip- cDNA mic- roarray assay  
 neuroblastoma<sup>45-47)</sup> Rb1 Rg1 SH - SY5Y human 8 Human cDNA가 microarray

## 실험재료 및 방법

### 1. 세포배양

SH - SY5Y human neuroblastoma 2mM L - glutamate Earle 's balanced salt가 minimal essential medium(MEM) 10% fetal bovine serum 100IU/I penicillin, 10 µg/ml streptomycin 가 37 , 95% air/5% CO<sup>2</sup> 5 × 10<sup>6</sup>cells/10 - mm plate

가 polystyrene tissue culture dish

24

80 µL Rg1 Rb1 (80 µM)

80 µL 0.9% saline

, 12

### 2. MTT assay

가

ginsenoside MTT [3 - (4, 5 - dimethylthiazol - 2 - yl)2, 5 - diphenyl tetrazolium bromide] assay . MTT assay

Mossman<sup>49)</sup>

mitochondrial dehydrogenases MTT (reduction) tetrazolium salt 가

formazan crystal

detergent

가

spectrophotometer

(linear relationship)가

(cell viability)

(cell proliferation)

MTT assay

SH - SY5Y human neuroblastoma 96 -

1 × 10<sup>4</sup> 37 , 5% CO<sub>2</sub>

12

(32 µg/

10mL, 16 µg/10mL, 8 µg/10mL), Rg1 (80 µM, 40 µM,

20 μM), Rb1(80 μM, 40 μM, 20 μM)  
 (12, 24, 36, 48 ) 25  
 μL MTT[3-(4, 5-dimethylthiazol-2-yl)-2, 5-  
 diphenyl tetrazolium bromide](5 mg/mL in PBS)  
 가 37 , 5 % CO<sub>2</sub> 4  
 DMSO 100  
 μL 가 30  
 ELISA reader<sup>48)</sup>

### 3. Total RNA 분리

Chomczynski Sacchi<sup>50)</sup> single-step  
 RNA isolation method TRIZOL(Invitrogen,  
 Carlsbad, CA) Total RNA  
 Rb1 Rg1 36  
 가 phosphate buffered saline  
 (PBS, pH 7.2) 2 1mL TRI-  
 ZOL  
 200 μL (Sigma, USA)  
 가 15  
 12,000g 15 , 4  
 isopropyl alcohol  
 (Sigma, USA) 1  
 12,000g 15 , 4  
 , 75% ethanol(DEPC )  
 가 12,000g 15 , 4  
 15 , DEPC(Amresco, Inc.  
 USA) 3 30 μL 가  
 (spectrophotometer VU 1601, Shimazu, Ja-  
 pan) 260nm 280nm  
 A260/A280 1.7

### 4. cDNA microarray

8170  
 TwinChip™ Human - 8K(Digital Genomics Inc,  
 Korea) cDNA microarray  
 PCR total RNA total RNA  
 annealing (total RNA 100 μg, control  
 mRNA 1ng, oligo dT 2pmol) 70  
 5  
 [5X AMV RT

buffer, low dT dNTP, 1mM Cy3( ), Cy5(  
 ) - dUTP, Rnase inhibitor(40U/μL) AMV reverse  
 transcriptase(100units) , annealing  
 가 42 1  
 . 0.5M EDTA 5 μL 가  
 1N NaOH 10 μL 가 37 10  
 1M Tris HCl(pH 7.5) 25 μL  
 가 . chromaspin column  
 column  
 1,300g, 5  
 100% ethanol 300 μL 3M sodium acetate 10 μ  
 L 가 , -70 30 12,000g  
 15 , 4 ethanol , 70%  
 ethanol 1mL 가 ethanol  
 . Ethanol 15  
 μL hybridization (25% formamide, 5 × SSC,  
 0.1% SDS) . 95 5  
 , pre-hybridization cDNA microarray  
 , hybridization chamber  
 58 16 . 12  
 42 가 I(2 × SSC, 0.1% SDS)  
 , microarray  
 I 42 5  
 II(0.1 × SSC, 0.1% SDS) microarray  
 1 , 4  
 60g, 5 , . Microar-  
 ray scanning Packard Scanarrayseries Quant-  
 Array confocal laser scanning  
 GenePix(Axon, USA)  
 intensity  
 , normalization  
 Rg1 Rb1 Cy5  
 dye signal , Cy3 dye  
 signal image  
 DNA chip  
 intensity/loc-  
 tion - dependent normalization<sup>51)</sup> .  
 LOWESS(f=0.2) nor-  
 malization M value MA plot  
 (signal intensity) Cy5/Cy3  
 (scatter plot) 가 A, M

$M = \log_2(\text{Cy5}/\text{Cy3})$ ,  
 $A = \{\log_2(\text{Cy5} \times \text{Cy3})\} / 2$

Significance analysis of microarrays (SAM)

Tusher <sup>52)</sup> SAM  
 가 가

mRNA 가 , 1 Cy5 signal  
 (2 - fold), -1 Cy3 signal  
 (0.5 - fold)

SAM  
 t -  
 (fudge factor)

2 - fold  
 3 - fold

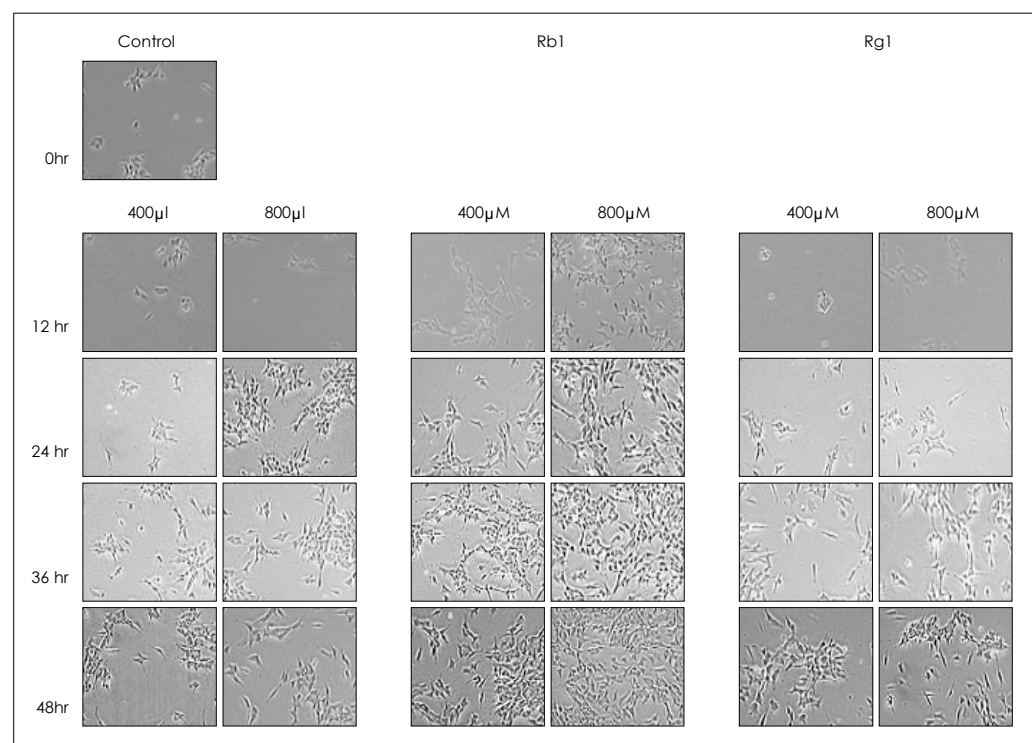
M 1(2 - fold) 1.59  
 Rg1 3 - fold(M=1.59) , Rb1  
 2 - fold(M=1)

**실험 결과**

1. MTT assay 결과

1) 세포증식결과확인(현미경)

Human neroblastoma SH - SY5Y ginsenoside



**Fig 1.** The microscopic pictures (x200) of SH-SY5Y cells treated with ginsenoside Rb1 or Rg1 for 12, 24, 36 and 48 hours. Treatment of SH-SY5Y cells with 80 µM Rb1 for 36hours showed maximal proliferation compared with other concentrations or control.

Rg1 Rb1 40  $\mu$ M 80  $\mu$ M ,  
 0.9% saline 12  
 , 80  $\mu$ M Rb1  
 가 가 가 ( 1).

2) MTT assay

가 total ginsenoside(32  $\mu$ g/10mL, 16  $\mu$ g/10mL, 8  $\mu$ g/10mL),

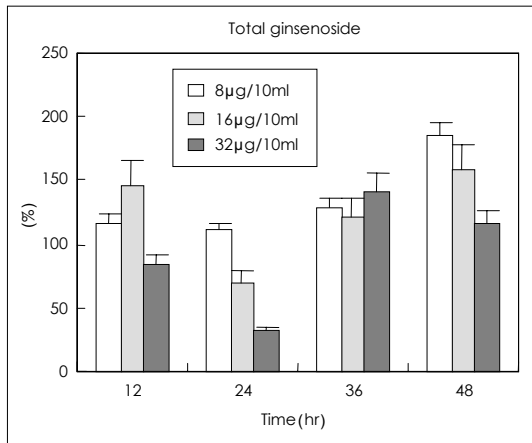


Fig 2. MTT assay of SH-SY5Y cells treated with total ginsenosides. Cells were treated in triplicate with each 8, 16, 32  $\mu$ g of total ginsenosides for 12, 24, 36 and 48 hours and MTT assays were performed. Y axis shows the percentages of each treatment group relative to the untreated matching control.

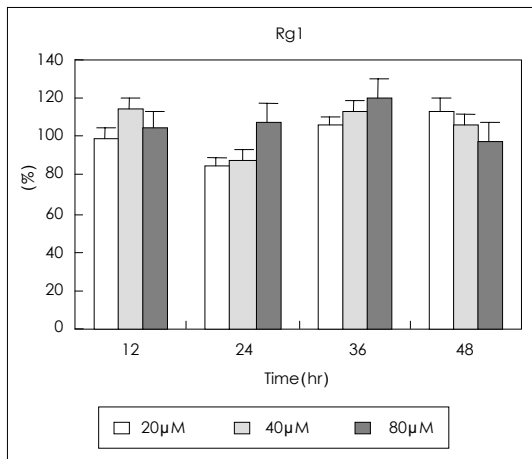


Fig 3. MTT assay of SH-SY5Y cells treated with Rg1. Cells were treated in triplicate with each 20, 40, 80  $\mu$ M Rg1 for 12, 24, 36 and 48 hours and MTT assays were performed. Y axis shows the percentages of each treatment group relative to the untreated matching control.

Rg1(80  $\mu$ M, 40  $\mu$ M, 20  $\mu$ M) Rb1(80  $\mu$ M, 40  $\mu$ M, 20  $\mu$ M)  
 , (12h, 24h, 36h, 48h)  
 MTT assay . MTT assay  
 total ginsenoside, Rg1, Rb1  
 가 , 36  
 가 가 ( 2 - 4).

2. cDNA Microarray 결과

MTT assay Rg1 Rb1 80  $\mu$ M  
 36 total RNA ,  
 Rg1 Rb1 cDNA mic-

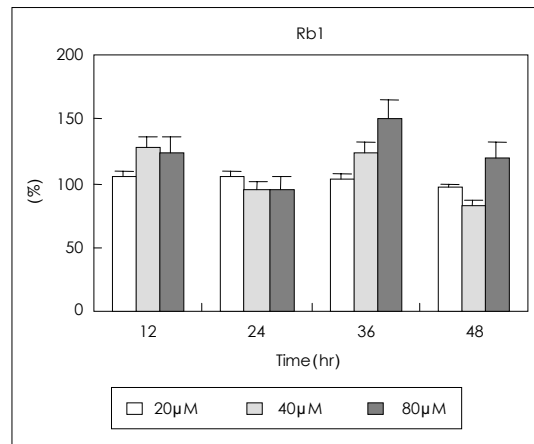


Fig 4. MTT assay of SH-SY5Y cells treated with Rb1. Cells were treated in triplicate with each 20, 40, 80  $\mu$ M Rb1 for 12, 24, 36 and 48 hours and MTT assays were performed. Y axis shows the percentages of each treatment group relative to the untreated matching control.

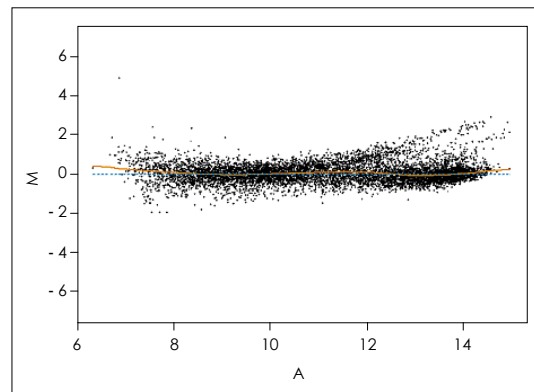


Fig 5. The MA plot of cDNA microarray of SH-SY5Y cells following treated with Rg1 for 36 hours. 96 genes were up-regulated(Cy5/Cy3 > 3) and seven genes were down-regulated(Cy5/Cy3 < 0.33).  
 $M(\text{relative expression ratio}) = \log_2(\text{CY5}/\text{CY3})$ .  
 $A(\text{Signal intensity}) = [\log_2(\text{Cy5} \times \text{Cy3})]/2$ .

**Table 1-1.** Up-regulated genes and average expressed ratio of SH-SY5Y cells treated with ginsenoside Rg1 for 36 hours

Function	Gene symbol	Gene name	*Exp ratio	Gene bank access number
<b>Protein biosynthesis</b>	RPS21	ribosomal protein S21	1.6	AI026740
	RPS15A	ribosomal protein S15a	1.6	AA292861
	RPS15	ribosomal protein S15	1.6	J02984
	UCHL1	ubiquitin carboxyl-terminal esterase L1	1.7	AI928978
	RPL41	ribosomal protein L41	1.8	AI125571
	RPL18A	ribosomal protein L18a	1.8	F28484
	UBA52	ubiquitin A-52 residue ribosomal protein fusion product 1	1.8	AA522790
		ribosomal protein S12		
	RPS12	ribosomal protein S28	1.8	AA314429
	RPS28	ribosomal protein S27a	1.8	AI929726
	RPS27A	ribosomal protein S3A	1.8	AA583926
	RPS3A	ribosomal protein L23	1.9	M77234
	RPL23	ribosomal protein L35	1.9	AI147195
	RPL35	ribosomal protein S10	2.0	AA305945
	RPS10	ribosomal protein L9	2.0	AI066801
	RPL9	ribosomal protein L14	2.0	AI625598
	RPL14	ribosomal protein L31	2.1	D87735
	RPL31	mitochondrial ribosomal protein L3	2.1	AA039258
	MRPL3	ribosomal protein L38	2.1	X06323
	RPL38	ribosomal protein L3	2.1	AI554584
	RPL3	ribosomal protein L23a	2.1	NM_000967
	RPL23A	ribosomal protein S29	2.2	AA857067
	RPS29	ribosomal protein L10a	2.2	AA715449
	RPL10A	ribosomal protein S14	2.2	NM_007104
	RPS14	ribosomal protein L13	2.2	AI928982
	RPL13	ribosomal protein L35	2.3	AI382216
	RPL35	ribosomal protein S3	2.3	AI815757
	RPS3	ribosomal protein S23	2.3	AA593872
	RPS23	ribosomal protein L12	2.4	D14530
	RPL12	ribosomal protein S20	2.4	L06505
	RPS20	ribosomal protein L6	2.5	AL037652
	RPL6	ribosomal protein L17	2.5	AI888138
	RPL17	ribosomal protein L11	2.6	X53777
RPL11	ribosomal protein L7a	2.6	L05092	
RPL7A	ribosomal protein L37	2.6	AI625430	
RPL37	ribosomal protein S4, X-linked	2.6	AI879226	
RPS4X	ribosomal protein S7	2.7	M58458	
RPS7		2.7	AA315981	
<b>Regulation of translation</b>	EIF3S5	eukaryotic translation initiation factor 3, subunit 5 epsilon, 47kDa	1.6	U94855
	EEF2	eukaryotic translation elongation factor 2	1.8	Z11692
	EEF1B2	eukaryotic translation elongation factor 1 beta 2	2.2	X60489
	RPLP0	ribosomal protein, large, P0	2.3	AI92
<b>Regulation of transcription</b>	HMGB1	high-mobility group box 1	1.6	X12597
	HMGB2	high-mobility group box 2	1.6	X62534
	MLL2	myeloid/lymphoid or mixed-lineage leukemia 2	1.9	AF010403
	ZNF45	zinc finger protein 45	2.0	L758479696
<b>Signal transduction</b>	RAN	RAN, member RAS oncogene family	1.6	NM_006325
	YWHAE	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon polypeptide	1.6	U54778
	YWHAQ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, theta polypeptide	1.8	AF070556
	RGS5	regulator of G-protein signalling 5	2.1	AI082260
	PLA2G1B	phospholipase A2, group IB	2.1	M21054
CALM2	calmodulin 2	2.1	D45887	

\* : Expression ratio ; M=log<sub>2</sub>(Cy3/Cy5)



roarray hybridization

Rg1 3 - fold(M=1.59) , Rb1 2 - 1) Rg1  
 fold(M=1) Rg1 Rb1 Rg1 96 3 가  
 가 가 가 , 7 3 (33% )  
 . 2 가 125 , 2

**Table 1-2.** Up-regulated genes and average expressed ratio of SH-SY5Y cells following treatment of ginsenoside Rg1 for 36 hours

Function	Gene symbol	Gene name	*Exp ratio	Genebank access number
<b>Cell proliferation and cell growth</b>	AF1Q	ALL1-fused gene from chromosome 1q	1.6	AL038143
	SUI1	putative translation initiation factor	1.7	AI832315
	DDX5	DEAD/H(Asp-Glu-Ala-Asp/His) box polypep 5	1.9	X15729
	FTH1	ferritin, heavy polypeptide 1	2.2	AA102267
<b>Neurogenesis and differentiation</b>	GPI	glucose phosphate isomerase	1.6	K03515
	SCG10	Superior Cervical ganglion 10(Stathmin-like 2)	1.7	D45352
	MLP	MARCKS-like protein	1.9	AI341990
<b>Regulation of cell cycle</b>	CDK2AP1	CDK2-associated protein 1	1.6	AB006077
	CCND1	cyclin D1	1.8	X59798
<b>Energy transport</b>	ATP5L	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit g	1.6	W94335
	ATP5J	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit F6	1.6	AA452026
	UQCRH	ubiquinol-cytochrom c reductase hinge protein	2.1	NM_006004
<b>Miscellaneous</b>	OK/SW-cl.56	beta 5-tubulin	1.6	AF070561
	SNRPD2	small nuclear ribonucleoprotein D2 polypeptide 16.5kDa	1.6	AI126579
	ACTG1	actin, gamma 1	1.6	X04098
	KATNB1	katanin p80(WD repeat containing) subunit B1	1.6	AF052432
	QP-C	low molecular mass ubiquinone-binding protein(9.5kD)	1.6	AL036415
	AAMP	angio-associated, migratory cell protein	1.7	M95627
	XPO7	exportin 7	1.7	AB018288
	FLJ10468	hypothetical protein FLJ10468	1.7	AA134589
	NPM1	nucleophosmin	1.7	AA173870
	HSPA8	heat shock 70kDa protein 8	1.7	AL044172
	HSPCB	heat shock 90kDa protein 1, beta	1.7	M16660
	H3F3B	H3 histone, family 3B(H3.3B)	1.8	NM_005324
	XAB2	XPA-binding protein 2	1.8	AI613115
	ABCF2	ATP-binding cassette, sub-family F(GCN20), member 2	1.9	AL050291
	GNB2L1	guanine nucleotide binding protein(G protein), beta polypeptide 2-like 1	2.0	AL047767
	PPIA	peptidylprolyl isomerase A	2.1	AA304657
	ART3	ADP-ribosyltransferase 3	2.1	AI201027
	H3F3A	H3 histone, family 3A	2.1	AA313375
	C20orf4	chromosome 20 open reading frame 4	2.2	AI300103
	GNAS	GNAS complex locus	2.4	X04409
	TPT1	tumor protein, translationally-controlled 1	2.5	AI979107
	MDS006	x 006 protein	2.7	AI016298
DKFZp45-1G182	hypothetical protein DKFZp451G182	2.7	AA931319	

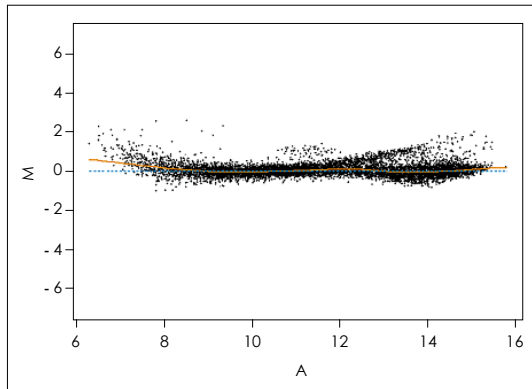
\* : Expression ratio ;  $M = \log_2(Cy3/Cy5)$

Rg1 (50%) 가 33 . HAQ, YWHAE CALM2  
 가 . AF1Q, DDX5  
 ribosomal proteins(RPs) , 가 ( 5)  
 Rb1 ( 1-2).  
 EIF3S5, EEF1b2, RPLP0, HMGB1, Rg1 GPI, MLP, SCG10  
 HMGB2, MLL2, ZNF45 가 (neurogenesis and neuronal differentiation)  
 , (signal transduction) YW- tiation) 3 가 .

**Table 2.** Up-regulated genes and average expressed ratio of SH-SY5Y cells following treatment of ginsenoside Rb1 for 36 hours

Function	Gene symbol	Gene name	*Exp ratio	Genebank access number
<b>Protein</b>	RPL23A	ribosomal protein L23a	1.1	AA857067
<b>Biosynthesis</b>	RPL3	ribosomal protein L3	1.1	NM_000967
	RPS27A	ribosomal protein S27a	1.1	AA583926
	RPS29	ribosomal protein S29	1.1	AA715449
	RPS3A	ribosomal protein S3A	1.1	M77234
	MRPL3	ribosom mitochondrial ribosomal protein L3	1.2	X06323
	RPL10A	ribosomal protein L10a	1.2	NM_007104
	RPL13	ribosomal protein L13	1.2	A1382216
	RPL35	ribosomal protein L35	1.2	A1815757
	RPL38	ribosomal protein L38	1.2	A1554584
	RPS3	ribosomal protein S3	1.2	AA593872
	RPL9	ribosomal protein L9	1.2	A1625598
	RPS10	ribosomal protein S10	1.2	A1066801
	RPL31	ribosomal protein L31	1.3	AA039258
	RPL37	ribosomal protein L37	1.3	A1879226
	RPL7A	ribosomal protein L7a	1.3	A1625430
	RPL17	ribosomal protein L17	1.3	X53777
	RPS20	ribosomal protein S20	1.4	AL037652
	RPS23	ribosomal protein S23	1.4	D14530
	RPL12	ribosomal protein L12	1.4	L06505
	RPL11	ribosomal protein L11	1.5	L05092
	RPL6	ribosomal protein L6	1.5	A1888138
	RPS4X	ribosomal protein S4, X-linked	1.5	M58458
	RPS7	ribosomal protein S7	1.7	AA315981
<b>Regulation of translation</b>	EEF1B2	eukaryotic translation elongation factor 1 beta 2	1.1	X60489
	RPLP0	ribosomal protein, large, P0	1.4	A1929696
<b>Regulation of transcription</b>	XAB2	XPA-binding protein 2	1.1	A1613115
	ZNF45	zinc finger protein 45	1.1	L75847
<b>Cell proliferation</b>	TSPAN-1	tetraspan 1	1.1	AF065388
<b>Miscellaneous</b>	ART3	ADP-ribosyltransferase 3	1.2	A1201027
	C20orf4	chromosome 20 open reading frame 4	1.3	A1300103
	H3F3A	H3 histone, family 3A	1.3	AA313375
	PPIA	peptidylprolyl isomerase A(cyclophilin A)	1.4	AA304657
	TPT1	tumor protein, translationally-controlled 1	1.4	A1979107
	GNAS	GNAS complex locus	1.5	X04409
	DKFZp451	hypothetical protein DKFZp451G182	1.7	AA931319
	MDS006	x 006 protein	1.7	A1016298

\* : Expression ratio ;  $M = \log_2(Cy3/Cy5)$



**Fig 6.** The MA plot of cDNA microarray of SH-SY5Y cells with Rb1 for 36 hours. 40 genes were up-regulated (Cy5/Cy3 > 2) and no single gene was down-regulated (Cy5/Cy3 < 0.5).  
 $M(\text{relative expression ratio}) = \log_2(\text{CY5/CY3})$ .  
 $A(\text{Signal intensity}) = [\log_2(\text{CY5XCy3})]/2$ .

Rb1 가

2) Rb1  
 Rb1 40 2 가  
 , 2 (50% )  
 가

(protein biosynthesis) ribosomal protein  
 (RPs) (transcription) (translation)  
 EEf1B2 RPLP0 XAB2  
 ZNF45가 가 , TS-  
 PAN - 1 가 ( 6)( 2).

**고 찰**

ginsenoside  
 side 가 ginseno- 12 84%  
 microarray 가 가 24 31% , 36 140%,  
 가 가 48 115% . ginsenoside  
 가 . microarray 8 μg  
 48 가 가  
 가 (32 μg)  
 가 가  
 SH - SY5Y  
 Rb1 Rg1 human 8K cDNA mi- 8~16 μg ,

croarray

SH - SY5Y  
 norepinephrine(NE)<sup>53)</sup> dopamine(DA)<sup>54)</sup>  
 55)56)  
 (transporter) 가  
 DA  
 57)  
 SH - SY5Y  
 가 (extension),  
 58)  
 가  
 45 - 47)  
 ginsenoside Rb1 Rg1 SH -  
 SY5Y human neuroblastoma  
 가  
 Rb1 Rg1 가  
 , 12  
 MTT assay

**1. MTT Assay 결과에 대한 고찰**

ginsenoside 8 μg 24  
 가 (12 117%, 24  
 110%), 36 130%  
 (cell viability) 가 48 185%  
 가 . 16 μg 12 146%  
 가 가 24 70%  
 36 120%, 48 158%  
 가 . ginsenoside 32 μg  
 12 84%  
 가 24 31% , 36 140%,  
 48 115% . ginsenoside  
 8 μg  
 48 가  
 가 (32 μg)  
 가 가  
 8~16 μg ,

Rg1

80 μM Rb1

20 μM Rb1 가 Rb1 가

가 12 127%, 122% 가 Rb1 가

가 24 40 μM 80 μM 가 Rb1 가

36 (95%, 94%) 80 μM Rg1

가 48 (123%, 150%) (81%, 120%)

Rg1 Rb1 Schwann 가

36 ,<sup>23)</sup> 5 10, 20, 200 μg/ml,

1mg/ml( 11, 22, 220, 1100 μM ) Rb1

10ug/ml Rb1 DMEM cell culture MTT assay

1mg/ml Rb1

가 200 μg/ml DMEM

20~80 μM

가 36 Rb1

, Rb1 24 Rb1

가 80 μM Rb1 36 Schiwan

가 가 48

가 Hu<sup>59)</sup> 10 μg/ml Rb1

가 Schwann NGF(50 μg/ml)

가 ginsenoside mg/ml Rb1(1

가 Rb1

Rg1 가 0,0003~

0,0005mg/mL(0.3~0.5 μg/mL) Rg1

가 DNA 가

가 ,<sup>21)</sup> 100 가

가 가

12 가 가 (resting

Rb1 cell) Rg1 (mitogenic)

21)

Rg1

36

Rg1

Rb1

## 2. cDNA Microarray 결과에 대한 고찰

(expression pattern)

tern)

가  
 . Microarray  
 ( , nitrocellulose membrane )  
 target DNA(cDNA oligo-  
 nucleotide) array) DNA (micro-  
 DNA DNA  
 probe DNA (hybridization)  
 DNA  
 (sequence) DNA  
 hybridization mRNA cDNA  
 가 cDNA  
 가 DNA microarray data

가 Rg1 Rb1  
 가 Rg1 Rb1 80 μM  
 가 Rg1 Rb1  
 가 Rg1 Rb1  
 가 ginsenoside 36  
 , 36 Rb1  
 , 36 microarray  
 가 36  
 24 , Rg1 Rb1  
 가

μM MTT assay Rb1 Rg1 80  
 36 total RNA  
 , Rb1 Rg1  
 cDNA microarray hybridization  
 , Rb1 40 가  
 2 가 Rg1  
 125 가 2 가 , 3  
 가 96  
 가 2 (50% )  
 34 , 7 가 3  
 (33% ) . Rg1 Rb1  
 가 가 가  
 Rb1 가 Rg1  
 가

1) 전사, 번역 및 단백질 생합성의 조절(Regulation of transcription, translation and protein biosynthesis)  
 Rb1  
 (protein biosynthesis) ribo-  
 somal proteins(RPs) (transcription)  
 eEF1B2 RPLP0가 가 (tran-

slation) XAB2 ZNF45가 가 . XAB2  
 , pre - mRNA splicing  
 ,  
 (global genomic repair)  
 가 (transcription - cou-  
 pled repair)<sup>60)</sup> RNA  
 .<sup>61)</sup> ZNF45

<sup>62)</sup>  
 Rg1 Rb1  
 RPs가 가 ,  
 (transcription) eIF3S5, eEF1b2, RPLP0  
 (translation) HMGB1, HMGB2, MLL2,  
 ZNF45 가 . HMGB1  
 HMGB2 , DNA , , ,  
<sup>63 - 65)</sup> Rg1  
 가 .  
 (translational control)

<sup>66)</sup>  
 (neural circuit)  
 가  
 (long - term synaptic plasticity)  
 , 가  
 Rb1 Rg1  
 (synaptic  
 marker protein) synaptophysin  
 ,<sup>28)</sup> CA3 가가  
 ,<sup>29)</sup>  
 , Rb1 Rg1  
 가

, mRNA 3가  
 .<sup>68)</sup> Initiation phase mRNA methio-  
 ninyl - tRNA가 ribosomal protein(RPs)  
 elongation phase , aminoacyl - tRNA가  
 A P  
 mRNA template polypeptide chain  
 chain

polypeptide가 mRNA (release) .  
 , eukaryote initiation  
 factors(eIF), eukaryote elongation factors(eEF),  
 eukaryote release factors(eRF)  
 .<sup>69)70)</sup> Rb1 Rg1  
 eEF1B2, eIF3S5, eEF1b2  
 가 Rb1 Rg1

(translation)  
 mRNAs, ,  
 (translation factors) . Rb1 Rg1, Rg1  
 RPs 가 , DNA mic-  
 roarray RPs mRNA  
 .<sup>71)</sup> transcriptome  
 RPs  
 .<sup>72)</sup> Rb1 Rg1 RPs  
 가  
 가

## 2) 신호변환조절(Regulation of signal transduction)

Rg1 (signal transduction)  
 RAN, YWHAE, RGS5, PLA2G1B, CALM2  
 3 가 , Rb1  
 RAN RNA (nuclear pore  
 complex) (translocation)  
 GTP ,<sup>73)</sup> DNA  
 . RAS  
 guanine nucleotide . YWHAE  
 (mi-

togenic factors)  
 (mitogenic signal transduction)  
 , (organiza-  
 tion role) 가 .<sup>74)</sup> RGS GTPase -  
 activator heterotrimeric G - protein  
 . Heterotrimeric G protein

. RGS가 G protein - subunit G protein modulin 3가 (no-nallelic genes) , Calmodulin

.<sup>77)</sup> (motility)

.<sup>78)79)</sup>

### 3) 세포증식, 성장 및 세포주기조절(Regulation of cell cycle, proliferation, and growth)

Rb1 , Tetraspanin(TSPAN) 2 가 . TSPAN

anti - TM4SF

(adhesion) (Wright Tomlinson 1994; Hemler 1996)

Rg1 CDK2-AP1 CCND1(cyclin D1) 3 가 AF1Q, SU11, DDX5 가 . CDK2AP1 (ke-ratinocytes) , 가

.<sup>82)</sup> DOC - 1/CDK2AP1 115 12.4kDa peptide p12<sup>DOC - 1/CDK2AP1</sup> (encoding) . cyclin - dependent kinase 2(CDK2)<sup>83)</sup> DNA polymerase /primase (pol - primase)<sup>84)</sup> S phase

. G1 phase cyclins . D - cyclins cyclin E . D - cyclins cyclins D1, D2 D3 가 , Rg1 cyclin D1 가 . D - cyclins

(mitogen challenge)

.<sup>85)</sup> 가 D - cyclin oncogenes . D - cyclins human cancer .<sup>86)87)</sup> D - cyclins cyclin - dependent kinase CDK4 CDK6

D - cyclins kinase - independent manner .<sup>85)</sup> p27<sup>Kip1</sup>

SH - SY5Y

D - cyclin 가

### 4) 신경발생과 분화조절(Regulation of Neurogenesis and Differentiation)

Microarray Rg1 GPI(Glucose - 6 - phosphate isomerase), MLP(Marcks - like protein) SCG10 (superior cervical ganglion 10) 3

가 , Rb1 가 .

GPI neuroleukin(NLK)

.<sup>88)89)</sup>

(neurotrophic factor)

, , , .<sup>90)</sup>

MLP(Marcks - like protein)

(neural tube formation, neurulation)

(neural tube defect)

가 . Wu<sup>91)</sup> MLP가 CNS (neural tube)

(neurulation) (morphogenesis) ,

.<sup>92)</sup>

(cytoskeleton)

. MLP

actin cytoskeletal events

SCG10

(neuronal Gro-

wth - Associate Proteins, nGAPs)  
 , (sprouting)  
 . SCG10, stathmin, GAP43 nGAP , , , 가  
 mRNA 가  
 93) . Rg1 가  
 . 94) SCG10 nGAPs , LTP ,  
 ,  
 . nGAPs 가 가  
 (remodeling) . Rg1  
 . NGAPs SCG10 MLP, SCG10 가  
 (microtubule) (dynamics) 가  
 , 가 (neuronal struc- 가, , 가  
 tural plasticity) 가 .  
 SCG10 (microtubule - des- . 가  
 tabilizing factor) 가 36  
 .  
 가 . 95)  
 ,  
 . 96) nGAP SCG10 **결 론**  
 (microtubule disruption)<sup>97)98)</sup> Rg1 Rb1  
 가 . actin - tubulin (vesicular trafficking) , gins-  
 SCG10 (reorganization) enoside ,  
 . 99-101) SCG10 mRNA .  
 가 가 Rb1 Rg1  
 가 가 Rg1 , ,  
 가 SCG10 가  
 가 ginsenoside 가  
 Okazaki 102) SCG10 . Rg1  
 (senile plaque) SCG10 가  
 (neurofibrillary tangle, NFT) Rg1 (sprouting),  
 , , , 가  
 , 가  
 Rg1 SCG10 가 ,  
 가 . 가  
 가 , Rg1



중심 단어 : Rg1 · Rb1 · SCG10.

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