CP Poly(A) RNA Binding Immunity via Outside-in Glycosyltransfer with MT of BTRC-Activating L12535 and PIN1 Subnetworks for Cognition in PFC|CD14

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Abstract

Background: Ras suppressor protein 1 (L12535) and peptidylprolyl cis/trans isomerase NIMA-interacting 1 (PIN1) common molecular and knowledge subnetworks containing microtubule associated protein 1B-MAP1B_1 (upstream) related to cognition by references were identified in human left hemisphere, based on our established significant high expression beta-transducin repeat containing E3 ubiquitin protein ligase (BTRC)-activating downstream Gene (protein) reconstruction network inference (GRNInfer) and Database for Annotation, Visualization and Integrated Discovery (DAVID).

Results: Our results show the common molecules exostosin-like glycosyltransferase 2 (EXTL2) interaction with MAP1B_1 both activating TERF1_1 with HSP90AB1 from BTRC-activating downstream GRNInfer database; The common biological process and molecular function of MAP1B_1, TERF1_1 as microtubule (MT) binding; HSP90AB1 as poly(A) RNA binding; BTRC, HSP90AB1, PIN1 as innate immune response from BTRC-activating downstream DAVID database; The common cellular component of EXTL2 at integral component of membrane; MAP1B_1, HSP90AB1, TERF1_1 at cytoplasm (CP); The common tissue distributions of L12535 and PIN1 in Prefrontal Cortex (PFC), PB cluster of differentiation (CD)14+Monocytes.

Conclusions: We propose and mutual positively verify CP poly(A) RNA binding immunity via outside-in glycosyltransfer with MT of BTRC-activating L12535 and PIN1 subnetworks for cognition in PFC|CD14.

Background

Microtubule associated protein 1B (MAP1B_1) is not only the more active molecule of our established high beta-transducin repeat containing E3 ubiquitin protein ligase (BTRC)-activating downstream network, but also the common molecule of Ras suppressor protein 1 (L12535) and peptidylprolyl cis/trans isomerase NIMA-interacting 1 (PIN1) subnetworks in human left hemisphere from our established high BTRC-activating downstream network.

MAP1B_1, L12535 and PIN1 or the related family molecules have been previously published associations with cognition in the references. Such as, adenosine A2A receptor inactivation alleviates early-onset cognitive dysfunction after traumatic brain injury involving an inhibition of tau hyperphosphorylation [1]. Cotinine improves visual recognition memory and decreases cortical Tau phosphorylation in the Tg6799 mice [2]. RAS modulation prevents progressive cognitive impairment after experimental stroke as a randomized, blinded preclinical trial [3]. RAS inhibition attenuates cognitive impairment via reducing blood- brain barrier permeability in hypertensive subjects [4]. Activity-dependent isomerization of Kv4.2 by Pin1 regulates cognitive flexibility [5]. PIN-1 promoter polymorphisms in mild cognitive impairment and susceptibility to Alzheimer’s disease as a preliminary report [6]. However, L12535 and PIN1 subnetworks containing MAP1B_1 (upstream) has not been explored for the novel molecular and cellular mechanisms of cognition from high BTRC-activating downstream network.
In the paper, L12535 and PIN1 feedback/up/downstream molecular subnetworks from our established significant high expression BTRC-activating downstream Gene (protein) reconstruction network inference (GRNInfer) [7] database will be constructed in human left hemisphere successively by significance analysis of microarrays (SAM) (fold change $\geq 2$), Pearson positive correlation coefficient (CC $\geq 0.25$) database with BTRC, other mutual positive Pearson correlation (CC $\geq 0.25$), respectively. L12535 and PIN1 common molecular subnetworks containing MAP1B_1 (upstream) will be computed from high BTRC-activating downstream GRNInfer database. L12535 and PIN1 common biological process, molecular function, cellular component subnetworks containing MAP1B_1 (upstream) will be computed from high BTRC-activating downstream Database for Annotation, Visualization and Integrated Discovery (DAVID) GOTERM_BP_DIRECT, GOTERM_MF_DIRECT, GOTERM_CC_DIRECT [8, 9]. L12535 and PIN1 common and different tissue distributions will be calculated from high BTRC-activating downstream DAVID GNF_U133A_QUARTILE and UNIGENE_EST_QUARTILE database.

**Methods**

441 significant high expression molecules in 14 human left hemisphere were identified based on 12,558 genes compared with the corresponding low expression of 15 chimpanzee left hemispheres in GDS2678 [16] (public free from NCBI) by SAM [17] (http://www-stat.stanford.edu/~tibs/SAM/), including the brain cerebrum, anterior cingulate cortex, anterior inferior parietal cortex, anterior inferior temporal cortex, middle frontal gyrus, the frontal pole, etc. Data were processed using a log base of two and two unpaired classes with minimum fold change ($\geq 2$). A false-discovery rate of 0% was chosen.

Low and high expression Pearson positive correlation coefficient (CC $\geq 0.25$) molecules with BTRC were calculated in chimpanzee and human left hemisphere from our established Pearson correlation coefficient database of total 441 significant expression molecules by SPSS. Low and high BTRC-activating downstream molecular lists in chimpanzee and human left hemisphere were calculated from our established significant low and high expression BTRC activation GRNInfer database. GRNInfer is a tool used to construct the activation and inhibition feedback/up/downstream molecular network based on linear programming and decomposition procedure defined by the following equation:

$$\mathcal{J} = (\dot{X} - B) U E^{-1} V^T + Y V^T = \hat{J} + Y V^T$$

The other mutual positive Pearson correlation (CC $\geq 0.25$) molecules except BTRC were computed in chimpanzee left hemisphere based on low BTRC-activating downstream molecular list. Low BTRC-activating downstream molecular network based on the corresponding mutual positive Pearson correlation database was constructed in chimpanzee left hemisphere from our established significant low expression BTRC activation GRNInfer database.

Low BTRC-activating downstream knowledge network was identified in chimpanzee left hemisphere from our established significant low expression BTRC activation DAVID database (https://david.ncifcrf.gov/). Low BTRC-activating downstream common biological process, molecular function, cellular component
network was set up in chimpanzee left hemisphere from low BTRC activation DAVID GOTERM_BP_DIRECT, GOTERM_MF_DIRECT, GOTERM_CC_DIRECT database. Low BTRC-activating downstream common tissue distribution network were set up in chimpanzee left hemisphere from low BTRC activation DAVID GNF_U133A_QUARTILE and UNIGENE_EST_QUARTILE database.

The other mutual positive Pearson correlation (CC $\geq 0.25$) molecules except BTRC were computed in human left hemisphere based on high BTRC-activating downstream molecular list. High BTRC-activating downstream molecular network based on the corresponding mutual positive Pearson correlation database was set up in human left hemisphere from our established significant high expression BTRC activation GRNInfer database. L12535 and PIN1 feedback/up/downstream direct and indirect molecular subnetwork containing MAP1B_1 (upstream) in human left hemisphere was constructed from our established significant high expression BTRC-activating downstream GRNInfer database, respectively. L12535 and PIN1 common molecular subnetworks containing MAP1B_1 (upstream) in human left hemisphere were computed from our established L12535 and PIN1 feedback/up/downstream direct and indirect molecular database.

High BTRC-activating downstream knowledge network in human left hemisphere was identified from our established significant high expression BTRC activation DAVID database. L12535 and PIN1 common biological process, molecular function, cellular component subnetwork containing MAP1B_1 (upstream) were set up in human left hemisphere from our established significant high expression BTRC-activating downstream DAVID GOTERM_BP_DIRECT, GOTERM_MF_DIRECT, GOTERM_CC_DIRECT database, respectively. L12535 and PIN1 common and different tissue distributions were set up in human left hemisphere from high BTRC-activating downstream DAVID GNF_U133A_QUARTILE and UNIGENE_EST_QUARTILE database.

**Results**

L12535 and PIN1 common molecular subnetworks containing MAP1B_1 (upstream) from our established significant high expression BTRC-activating downstream GRNInfer database were identified as EXTL2 (upstream), MAP1B_1 (upstream), NDUFA5 (feedback), HSP90AB1 (downstream), KIAA0423 (downstream), TERF1_1 (downstream) in human left hemisphere successively by SAM and Pearson using GDS2678. MAP1B_1 activates to EXTL2, MAP1B_1 to HSP90AB1, MAP1B_1 to MAP1B_1, MAP1B_1 to TERF1_1, HSP90AB1 to HSP90AB1, HSP90AB1 to NDUFA5, HSP90AB1 to TERF1_1, TERF1_1 to HSP90AB1, TERF1_1 to TERF1_1, NDUFA5 to HSP90AB1, EXTL2 to EXTL2, EXTL2 to MAP1B_1, EXTL2 to TERF1_1, KIAA0423 to EXTL2, KIAA0423 to HSP90AB1, KIAA0423 to TERF1_1, as shown in Fig. 1–2.

L12535 and PIN1 common biological process and molecular function subnetworks containing MAP1B_1 (upstream) were identified MAP1B_1, TERF1_1 as microtubule (MT) binding; HSP90AB1 as poly(A) RNA binding; BTRC, HSP90AB1, PIN1 as innate immune response from high BTRC-activating downstream DAVID GOTERM_BP_DIRECT and GOTERM_MF_DIRECT database. L12535 and PIN1 common cellular
component subnetworks containing MAP1B_1 (upstream) was selected EXTL2 at integral component of membrane; MAP1B_1, HSP90AB1, TERF1_1 at cytoplasm (CP) in human left hemisphere from high BTRC-activating downstream DAVID GOTERM_CC_DIRECT database, as shown in Table 1.
Table 1

L12535 and PIN1 common biological process, molecular function, cellular component subnetworks containing MAP1B_1 (upstream) in human left hemisphere from our established significant high expression BTRC-activating downstream DAVID GOTERM_BP_DIRECT, GOTERM_MF_DIRECT, GOTERM_CC_DIRECT database.

| L12535 subnetwork | PIN1 subnetwork | Terms              |
|-------------------|-----------------|--------------------|
| BTRC (first-core), L12535 (second-core), MAP1B_1 (upstream), HSP90AB1 (downstream), PIN1 (downstream) | BTRC (first-core), PIN1 (second-core), L12535 (upstream), MAP1B_1 (upstream), SMG1 (upstream), PRKCL1 (feedback), GTF2L1 (downstream), HSP90AB1 (downstream) | cytosol |
| BTRC (first-core), HSP90AB1 (downstream), PIN1 (downstream), TERF1_1 (downstream) | BTRC (first-core), PIN1 (second-core), NR1D2_1 (upstream), GTF2L1 (downstream), HSP90AB1 (downstream), TERF1_1 (downstream) | nucleoplasm |
| L12535 (second-core), EXTL2 (upstream), SUB1 (upstream), HSP90AB1 (downstream) | EXTL2 (upstream), L12535 (upstream), PRKCL1 (feedback), HSP90AB1 (downstream), SUB1 (downstream) | extracellular exosome |
| MAP1B_1 (upstream), HSP90AB1 (downstream), TERF1_1 (downstream) | MAP1B_1 (upstream), PDE4DIP (upstream), SMG1 (upstream), PRKCL1 (feedback), C1D (downstream), HSP90AB1 (downstream), TERF1_1 (downstream) | cytoplasm |
| SUB1 (upstream), PIN1 (downstream), TERF1_1 (downstream) | PIN1 (second-core), NR1D2_1 (upstream), PDE4DIP (upstream), SMG1 (upstream), PRKCL1 (feedback), C1D (downstream), GTF2L1 (downstream), SUB1 (downstream), TERF1_1 (downstream) | nucleus |
| EXTL2 (upstream), AB016247 (downstream) | EXTL2 (upstream), AB016247 (feedback), OSBPL8 (feedback) | endoplasmic reticulum membrane |
| EXTL2 (upstream), AB016247 (downstream) | EXTL2 (upstream), AB016247 (feedback), OSBPL8 (feedback), NPAL3 (downstream) | integral component of membrane |
| SUB1 (upstream), TERF1_1 (downstream) | C1D (downstream), SUB1 (downstream), TERF1_1 (downstream) | nucleolus |
| HSP90AB1 (downstream), PIN1 (downstream) | PIN1 (second-core), HSP90AB1 (downstream) | mitochondrion |
| BTRC (first-core), MAP1B_1 (upstream), SUB1 (upstream), HSP90AB1 (downstream), PIN1 (downstream), TERF1_1 (downstream) | BTRC (first-core), PIN1 (second-core), MAP1B_1 (upstream), NR1D2_1 (upstream), PDE4DIP (upstream), SMG1 (upstream), PRKCL1 (feedback), C1D (downstream), GTF2L1 (downstream), HSP90AB1 (downstream), NPAL3 (downstream), SUB1 (downstream), TERF1_1 (downstream) | protein binding |
|---|---|---|
| BTRC (first-core), HSP90AB1 (downstream), PIN1 (downstream) | BTRC (first-core), PIN1 (second-core), HSP90AB1 (downstream) | innate immune response |
| BTRC (first-core), TERF1_1 (downstream) | BTRC (first-core), TERF1_1 (downstream) | G2/M transition of mitotic cell cycle |
| BTRC (first-core), HSP90AB1 (downstream) | BTRC (first-core), HSP90AB1 (downstream) | cellular response to organic cyclic compound |
| MAP1B_1 (upstream), TERF1_1 (downstream) | MAP1B_1 (upstream), TERF1_1 (downstream) | microtubule binding |
| SUB1 (upstream), HSP90AB1 (downstream) | SMG1 (upstream), HSP90AB1 (downstream), SUB1 (downstream) | poly(A) RNA binding |
| NDUFA5 (feedback), AB016247 (downstream) | AB016247 (feedback), NDUFA5 (feedback) | small molecule metabolic process |
| HSP90AB1 (downstream), PIN1 (downstream) | PIN1 (second-core), PRKCL1 (feedback), HSP90AB1 (downstream) | negative regulation of neuron apoptotic process |
| EXTL2 (upstream) | EXTL2 (upstream) | exostosin-like glycosyltransferase 2 (EXTL2) |
| MAP1B_1 (upstream) | MAP1B_1 (upstream) | microtubule associated protein 1B (MAP1B) |
| NDUFA5 (feedback) | NDUFA5 (feedback) | NADH:ubiquinone oxidoreductase subunit A5 (NDUFA5) |
Prefrontal Cortex (PFC), PB cluster of differentiation (CD)14 + Monocytes were identified in L12535 and PIN1 common tissue distributions. ADIPOCYTE, Pituitary, eye_normal, Testis, adrenal tumor_disease, leukemia_chronic myelogenous(k562), retinoblastoma_disease, small intestine_normal as the other common tissue distributions are similar with L12535 and PIN1 differences from high BTRC-activating downstream DAVID GNF_U133A and UNIGENE_EST database, including BM CD71 + EarlyErythroid, BM CD33 + Myeloid, PLACENTA, BM CD34+, Cardiac Myocytes, CD8 + T cells, Cerebellum, PB CD19 + Bcells, PB CD56 + NKCells, SuperiorCervical Ganglion, Prostate, Appendix, Kidney, adrenal gland, Olfactory Bulb, parathyroid_normal, Occipital Lobe, Thymus, etc. as shown in Table 2.
Table 2
L12535 and PIN1 common and different tissue distributions in human left hemisphere from our established significant high expression BTRC-activating downstream DAVID GNF_U133A_QUARTILE and UNIGENE_EST_QUARTILE database.

| Common L12535 and PIN1 | Different L12535 | Different PIN1 |
|------------------------|------------------|----------------|
| ADIPOCYTE_3rd          | BM CD71 + EarlyErythroid_3rd | Prostate_3rd   |
| PB CD14 + Monocytes_3rd| BM CD33 + Myeloid_3rd     | Appendix_3rd   |
| Testis_3rd             | PLACENTA_3rd      | Kidney_3rd     |
| Pituitary_3rd          | BM CD34+_3rd      | adrenal gland_3rd |
| adrenal tumor_disease_3rd | Cardiac Myocytes_3rd | Olfactory Bulb_3rd |
| leukemiachronicmyelogenous(k562)_3rd | CD8 + T cells_3rd | parathyroid_normal_3rd |
| eye_normal_3rd         | Cerebellum_3rd    | Occipital Lobe_3rd |
| retinoblastoma_disease_3rd | PB CD19 + Bcells_3rd | Thymus_3rd     |
| small intestine_normal_3rd | PB CD56 + NKCells_3rd | brain_normal_3rd |
| Prefrontal Cortex_3rd  | SuperiorCervical Ganglion_3rd | dorsal root ganglia_3rd |
|                       | urinary bladder tumor_disease_3rd | embryoo_development_3rd |
|                        | bladder_normal_3rd | Colorectal Adenocarcinoma_3rd |
|                       | bone marrow_normal_3rd | embryonic tissue_normal_3rd |
|                       | Uterus Corpus_3rd | pituitary gland_normal_3rd |
| Whole Brain_3rd        | Hypothalamus_3rd  | heart_normal_3rd  |
| Cingulate Cortex_3rd   | caudatenucleus_3rd | mixed (normal and tumor)_disease_3rd |
|                       | ear_normal_3rd    | salivary gland_normal_3rd |
| testis_normal_3rd      | glioma_disease_3rd |                  |
| Ciliary Ganglion_3rd   | non glioma_disease_3rd |               |
| Smooth Muscle_3rd      | cervical tumor_disease_3rd |             |
| CD4 + T cells_3rd      | chondrosarcoma_disease_3rd |            |
L12535 and PIN1 common and different tissue distributions in human left hemisphere

| Tissue                        | Tissue                  |
|-------------------------------|-------------------------|
| TONGUE_3rd                    | lung_normal_3rd         |
| Adrenal Cortex_3rd            | Thyroid_3rd             |
| bone_normal_3rd               | pancreas_normal_3rd     |
| vascular_normal_3rd           | Medulla Oblongata_3rd   |
| normal_disease_3rd            | Testis Germ Cell_3rd    |
| WHOLE BLOOD_3rd               | tonsil_normal_3rd       |
| BM CD105 + Endothelial_3rd    |                         |
| Uterus_3rd                    |                         |
| juvenile (< 17 years old)_development_3rd |             |
| leukemia_disease_3rd          |                         |
| lymph node_normal_3rd         |                         |
| trachea_normal_3rd            |                         |
| spinalcord_3rd                |                         |
| skin_normal_3rd               |                         |
| uterus_normal_3rd             |                         |
| TemporalLobe_3rd              |                         |
| globus pallidus_3rd           |                         |
| placenta_normal_3rd           |                         |
| Amygdala_3rd                  |                         |
| Pancreas_3rd                  |                         |
| Trachea_3rd                   |                         |
| bone marrow_3rd               |                         |

Discussion

L12535 and PIN1 common molecular subnetworks and the related family members have been reported relationship with cognition including EXTL2 (upstream), MAP1B_1 (upstream), NDUFA5 (feedback), HSP90AB1 (downstream), KIAA0423 (downstream), TERF1_1 (downstream) in the references. For instance, investigation of a functional quinine oxidoreductase (NQO2) polymorphism and cognitive
decline [10]. Microstructural changes in the brain mediate the association of HSPB2 with cognitive decline [11]. TERF1 and TERF2 downregulate telomere length in cognitive deficit at the late period after low-dose exposure [12]. Low BTRC-activating downstream molecular network and the related family members have been reported relationship with cognition including ENPP2_2, MED6, NPC1, RCBTB2, WDR57 in the references. Such as, cognitive deficits associated with a high-fat diet and insulin resistance are enhanced by overexpression of ecto-nucleotide pyrophosphatase phosphodiesterase-1 [13].

Psychiatric and cognitive symptoms associated with niemann-pick type C Disease [14]. Role of Wdr45b in maintaining cognitive function [15].

Our results show the common molecules exostosin-like glycosyltransferase 2 (EXTL2) interaction with MAP1B_1 both activating TERF1_1 with HSP90AB1; The common biological process and molecular function of MAP1B_1, TERF1_1 as microtubule (MT) binding; HSP90AB1 as poly(A) RNA binding; BTRC, HSP90AB1, PIN1 as innate immune response in human left hemisphere from our established high BTRC-activating downstream GRNInfer, DAVID GOTERM_BP_DIRECT and GOTERM_MF_DIRECT database (Fig. 1–2, Table 1, Supp 4–6). Therefore, we put forward and mutual positively verify poly(A) RNA binding immunity via glycosyltransfer with MT of BTRC-activating L12535 and PIN1 subnetworks for cognition.

Low BTRC-activating downstream molecular network from our established significant low expression BTRC activation GRNInfer database was identified as ectonucleotide pyrophosphatase/phosphodiesterase 2 (ENPP2_2), mediator complex subunit 6 (MED6), Niemann-Pick disease type C1 (NPC1), RCC1 and BTB domain containing protein 2 (RCBTB2) in chimpanzee left hemisphere (Supp 1–2). RCBTB2 activates ENPP2_2 to MED6 interaction with NPC1. Low BTRC-activating downstream common biological process and molecular function network shows BTRC, NPC1 as signal transduction; ENPP2_2, MED6 as transcription factor binding from our established low BTRC activation DAVID GOTERM_BP_DIRECT and GOTERM_MF_DIRECT database (Supp 3). We put forward signal transduction via RCC1 and BTB domain containing protein to transcription factor binding of low BTRC-activating downstream network for cognition.

Our results show the common cellular component of EXTL2 at integral component of membrane; MAP1B_1, HSP90AB1, TERF1_1 at cytoplasm (CP) in human left hemisphere; The common tissue distributions of L12535 and PIN1 in Prefrontal Cortex (PFC), PB cluster of differentiation (CD)14 + Monocytes from our established high BTRC-activating downstream DAVID GOTERM_CC_DIRECT, GNF_U133A and UNIGENE_EST database. The other common tissue distributions are similar with the different of L12535 and PIN1 (Fig. 1–2, Table 1–2, Supp 4–6). Therefore, we propose and mutual positively verify CP poly(A) RNA binding immunity via outside-in glycosyltransfer with MT of BTRC-activating L12535 and PIN1 subnetworks for cognition in PFC|CD14.

Low BTRC-activating downstream common cellular component network demonstrates ENPP2_2, NPC1 at integral component of plasma membrane; MED6, NPC1 at membrane from our established low BTRC activation DAVID GOTERM_CC_DIRECT database. Low BTRC-activating downstream most common tissue distribution network appear ADIPOCYTE, BM CD34+, Cardiac Myocytes, PB CD19 + Bcells from our
established low BTRC activation DAVID GNF_U133A and UNIGENE_EST database (Supp 3). We put forward membrane signal transduction via inside-out RCC1 and BTB domain containing protein to transcription factor binding of low BTRC-activating downstream network for cognition in adipocyte|cardiac myocytes|CD34|19+ Bcells, and negatively verify our hypothesis.

**Conclusion**

We put forward and mutual positively verify CP poly(A) RNA binding immunity via outside-in glycosyltransfer with MT of BTRC-activating L12535 and PIN1 subnetworks for cognition in PFC|CD14, and also negatively verify our hypothesis in low BTRC-activating downstream network of chimpanzee left hemisphere. Other BTRC-activating downstream molecular and knowledge subnetworks containing MAP1B_1 (upstream) will be computed and the hypotheses proposed for the whole molecular and cellular mechanisms of cognition in the future.

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

All authors have approved the manuscript for submission.

**Availability of data and materials**

We declare the study data GDS2678 public free from NCBI.

**Competing interests**

The authors report no conflicts of financial and non-financial interests.

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**Authors' contributions**
LW designed the whole experiment and wrote the paper. LW & MJ & QC analyzed the data and look up in references. JH & MJ & ZJ computed CC and GRNInfer. JH & QC & HF prepared figures and tables.

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**Figures**
L12535 direct and indirect molecular subnetwork construction containing MAP1B_1 (upstream) in human left hemisphere from our established significant high expression BTRC-activating downstream GRNInfer database. Solid line with black arrow represents direct activation relationships with L12535 and BTRC, respectively. Dashed line with black arrow represents indirect activation relationships with BTRC.
PIN1 direct and indirect molecular subnetwork construction containing MAP1B_1 (upstream) in human left hemisphere from our established significant high expression BTRC-activating downstream GRNInfer database. Solid line with black arrow represents direct activation relationships with PIN1 and BTRC, respectively. Dashed line with black arrow represents indirect activation relationships with BTRC.
Supplementary Files

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