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Proposed story around Alzheimer's microarray datasets for the AETIONOMY storyboard

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Scenario:

Compare disease mechanisms between the following two cohorts and identify drugs or candidate compounds that target both mechanisms simultaneously in two different brain regions:

Study 1: E-GEOD-16759, samples from parietal lobe of 8 AD subjects and 8 healthy controls

Study 2: E-GEOD-12685, samples from frontal cortex of 6 AD subjects and 8 healthy controls

Materials & Methods:

- *Analysis of gene expression datasets for top markers of AD in tranSMART:* At the time of this analysis (19.08.2015), there were 6 AD-specific gene expression studies with high-dimensional data available for analysis in tranSMART. In tranSMART, comparative analyses between phenotypes (i.e. AD cases versus healthy controls) were conducted and top 50 differentially expressed genes were selected by default. This list was filtered for probe duplicates and unmapped probes.
- *AD-specific BEL model of drug-target interactions:* Previously built Alzheimer's-specific BEL model was enriched with the information about drug-target interactions by extracting the interaction information from their respective publications as cited in the following databases: Comparative Toxigenomics Database (CTD), Therapeutic Target Database (TTD), STITCH Database, and DrugBank. This model contains 9645 nodes and 26660 edges (as of 18.08.2015).
- *Mapping differentially expressed genes onto the AD-specific BEL model:* The list of differentially expressed genes from each study was mapped onto the BEL model and overlap was calculated. The highest overlap out of the 50 top genes of each study to the BEL model was obtained for GSE16759 (AD in parietal lobe) and GSE12685 (AD in prefrontal cortex) with 21 and 19 overlapping genes, respectively. These two lists were initially mapped onto the BEL model separately but later the pooled list was used to investigate mechanistic synergies

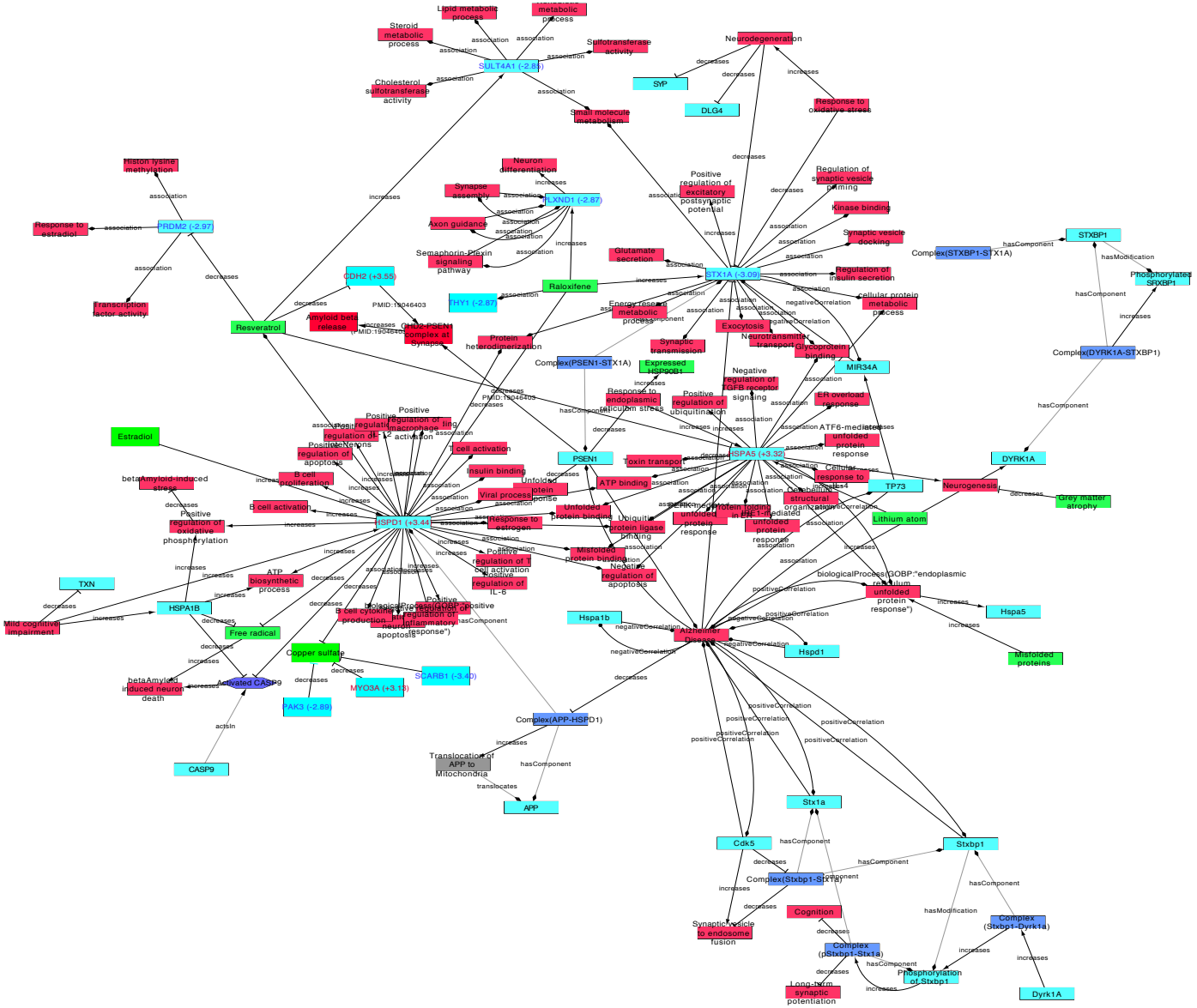
of drug actions between these two brain regions in one model. Gene expression values (fold changes) were imported as attributes and used for mechanistic interpretation in the Cytoscape environment.

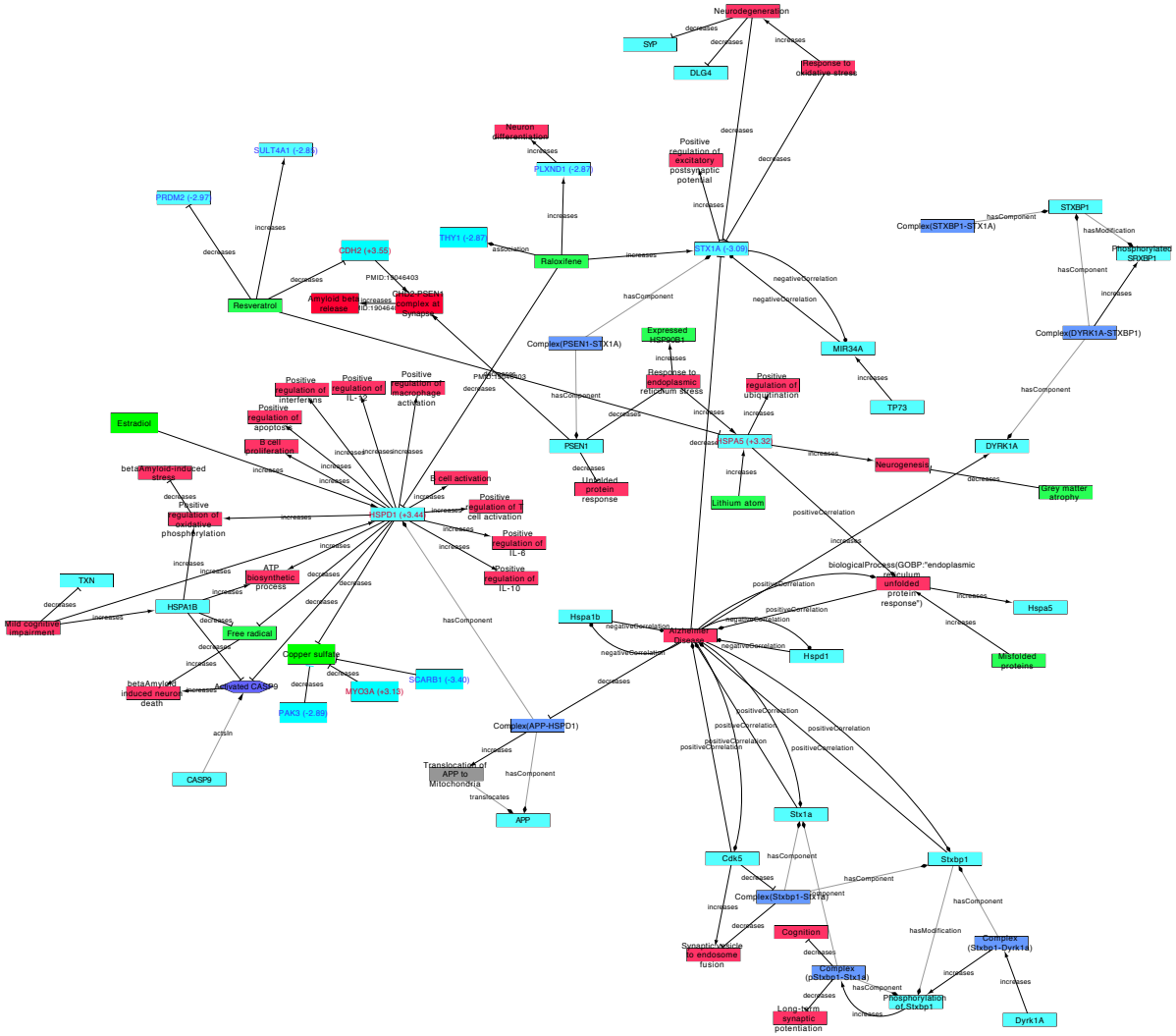
Results:

Mapping pooled differentially expressed genes onto the AD-specific BEL model resulted in identification of a subnetwork with 64 nodes and 103 edges. This subnetwork, although did not contain any downstream effect (i.e. terminal biological process), provided an initial landscape of drugs and compounds targeting top biomarkers. Among these, the following two compounds were selected for further mechanistic analysis: Resveratrol, a phenolic compound in natural products like grapes and red wine, which has been investigated for its protective effects against Alzheimer's disease (PMID: 25309423), and, Raloxifene, an anti-cancer approved drug, which has been implicated in reduced risk of cognitive impairment in postmenopausal women (PMID: 15800139).

The above subnetwork was enriched with more BEL statements around genes that are targeted by Resveratrol and Raloxifene for their downstream biological processes. This increased the number of nodes and edges to 141 and 186, respectively (after cleaning process, i.e. omitting duplicates or unrelated processes). Figure 1 illustrates network visualization of this subnetwork. Upregulated or downregulated biomarker genes have been indicated by red or blue labels, respectively.

The above subnetwork was further subjected to a filter for demonstrating only causal relationships, which is illustrated in Figure 2.


Lipid metabolic process
metabolic process
Steroid metabolic process
Sulfotransferase activity
SULT4A1 (-2.85)
Cholesterol sulfotransferase activity
Small molecule metabolism
Neurodegeneration
SYP
DLG4
Response to oxidative stress
Histon lysine methylation
Neuron differentiation
Synapse assembly
TLXND1 (-2.67)
Positive regulation of excitatory postsynaptic potential
Regulation of synaptic vesicle priming
Kinase binding
Response to estradiol
PRDM2 (-2.97)
Axon guidance
Synaptic vesicle docking
Semaphorin-Plexin signaling pathway
Glutamate secretion
STX1A (-3.09)
Complex(STXBP1-STX1A)
STXBP1
Regulation of insulin secretion
Phosphorylated STXBP1
CDH2 (+3.55)
Raloxifene
Transcription factor activity
THY1 (-2.87)
Energy release metabolic process
Cellular protein metabolic process
Resveratrol
Amyloid beta release
PMID:15046403
GNG3-PSEN1 complex at Synapse
Exocytosis
Neurotransmitter transport
Synaptic transmission
Protein heterodimerization
Glycoprotein binding
Complex(DYRK1A-STXBP1)
Complex(PSEN1-STX1A)
Expressed HSP90B1
MIR34A
Negative regulation of TGFB receptor signaling
Response to endoplasmic reticulum stress
Positive regulation of ubiquitination
ER overload response
Estradiol
Positive regulation of macrophage activation
Positive regulation of IL-12 production
T cell activation
PSEN1
Toxin transport
HSPA5 (+3.32)
ATF6-mediated unfolded protein response
DYRK1A
Positive regulation of apoptosis
B cell proliferation
Insulin binding
Unfolded protein response
ATP binding
Cellular response to beta4
TP73
Neurogenesis
beta-amyloid-induced stress
B cell activation
Viral process
Unfolded protein binding
Ubiquitin protein ligase binding
PERK-mediated unfolded protein response
Grey matter atrophy
Positive regulation of oxidative phosphorylation
HSPD1 (+3.44)
Response to estrogen
Lithium atom
Misfolded protein binding
Positive regulation of T cell activation
Negative regulation of apoptosis
ATP biosynthetic process
Positive regulation of IL-6
biologicalProcess("endoplasmic reticulum unfolded protein response")
TXN
HSPA1B
Hspa5
Mild cognitive impairment
Free radical
Hspa1b
Alzheimer Disease
Hspd1
Misfolded proteins
Copper sulfate
SCARB1 (-3.40)
MYO3A (+3.13)
betaAmyloid induced neuron death
Activated CASP9
PAK3 (-2.89)
Complex(APP-HSPD1)
actsIn
CASP9
Translocation of APP to Mitochondria
APP
Stx1a
Cdk5
Stxbp1
Complex(Stxbp1-STX1A)
Cognition
Synaptic vesicle to endosome fusion
Complex (Stxbp1-Dyrk1a)
Complex (pStxbp1-Stx1a)
Phosphorylation of Stxbp1
Long-term synaptic potentiation
Dyrk1A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ATP biosynthetic process
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Stx1a
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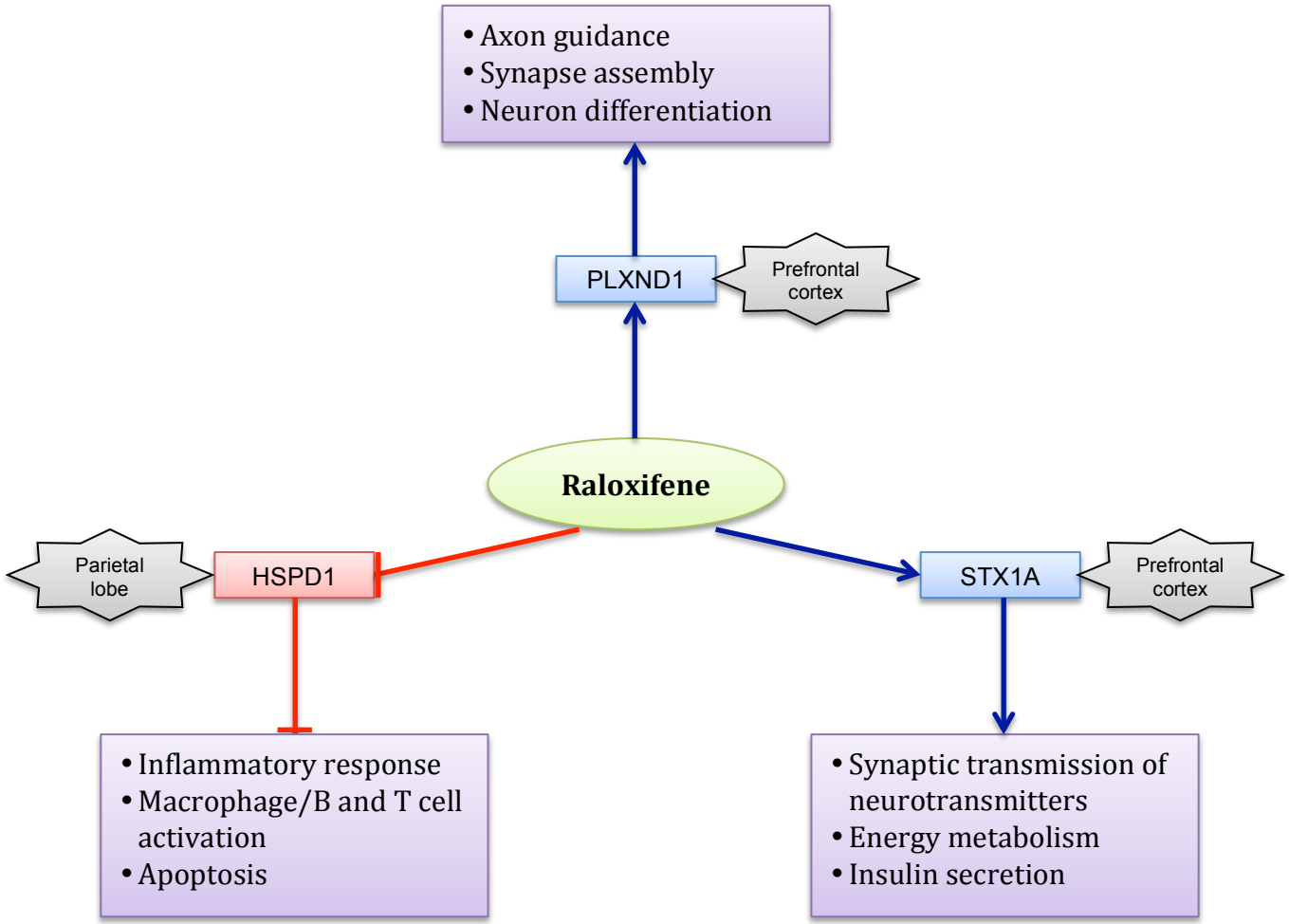
Stxbp1
Complex(Stxbp1-Stx1a)
Cognition
Synaptic vesicle to endosome fusion
Complex (Stxbp1-Dyrk1a)
Complex (pStxbp1-Stx1a)
Phosphorylation of Stxbp1
Long-term synaptic potentiation
Dyrk1A
increases
decreases
hasComponent
positiveCorrelation
negativeCorrelation
translocates
hasModification
PMID:19046403

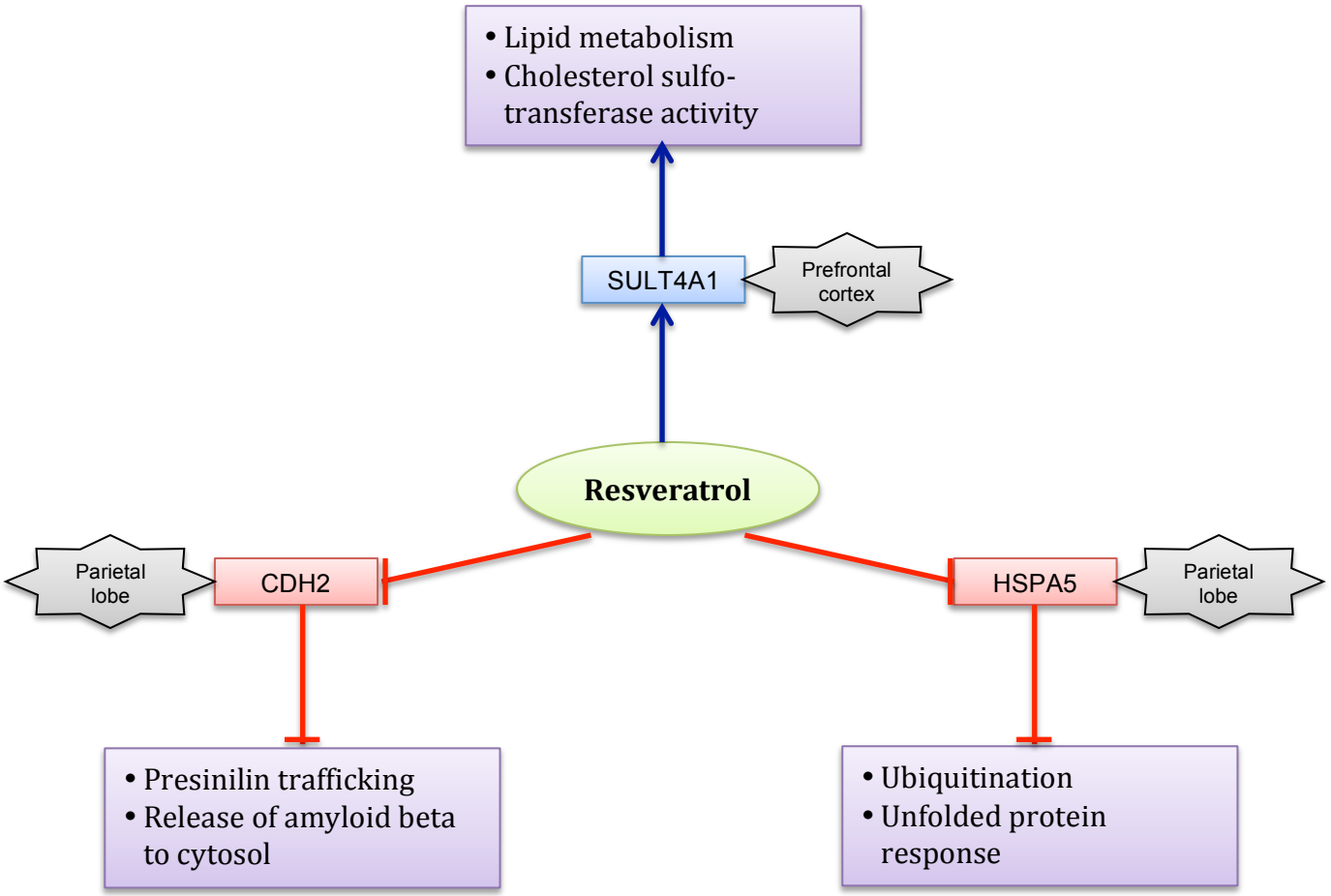
Interpretation:

- *Resveratrol antagonizes expression of biomarker genes in both parietal lobe and prefrontal cortex.* According to the AD model, SULT4A1 is involved in regulation of lipid metabolism and sulfotransferase activity and its downregulation in prefrontal cortex under AD conditions implies suppression of growth factor signaling, axon guidance, and synaptic transmission (PMID: 23065638). Resveratrol reverses this impairment by inducing the expression levels of SULT4A1. In parallel, Resveratrol counteracts massive upregulation of two other genes, namely CDH2 and HSPA5 in parietal lobe of AD brains. Evidently, suppression of CDH2 expression by Resveratrol reduces the formation of CDH2 complex with presenilin (PSEN1) and subsequently decreases the Abeta release. Resveratrol also inhibits HSPA5 activity, which induces the unfolded protein response in response to accumulation of misfolded proteins in the lumen of ER, a process that leads to apoptosis ultimately.
- *Raloxifene balances inflammatory signals and synaptic transmission in parietal lobe and prefrontal cortex, respectively.* According to the AD model, HSPD1 regulates a diversity of immune responses under the AD condition; thus, inhibitory effect of Raloxifene on HSPD1 activity in parietal lobe of brain confers neuroprotective effects via blocking inflammatory signals through this protein. In parallel, Raloxifene antagonizes downregulation effects of STX1A in prefrontal cortex by promoting synaptic transmission and insulin secretion. Raloxifene also compensates for downregulation of PLXND1 in prefrontal cortex and promotes axon guidance and synapse assembly.

Conclusion

According to the literature, the role of Resveratrol in AD is still unclear (PMID: 16766037) and it may modulate multiple mechanisms of AD pathology (PMID: 25525597). Our mechanistic modeling approach suggests that Resveratrol and Raloxifene exert neuroprotective effects through synergistic, multiple, shared mechanisms in both parietal lobe and prefrontal cortices of AD brains. A significant portion of this shared mechanism is dominated by chaperonins that reflects issues with protein aggregation. Enrichment of the mechanistic BEL model with compounds like resveratrol and raloxifene functionally validates the mechanistic involvement of deregulated biomarkers that were derived from data-driven approach in tranSMART.


• Axon guidance
• Synapse assembly
• Neuron differentiation
PLXND1
Prefrontal cortex
Raloxifene
Parietal lobe
HSPD1
STX1A
Prefrontal cortex
• Inflammatory response
• Macrophage/B and T cell activation
• Apoptosis
• Synaptic transmission of neurotransmitters
• Energy metabolism
• Insulin secretion


• Lipid metabolism
• Cholesterol sulfo-transferase activity
SULT4A1
Prefrontal cortex
Resveratrol
Parietal lobe
CDH2
HSPA5
Parietal lobe
• Presinilin trafficking
• Release of amyloid beta to cytosol
• Ubiquitination
• Unfolded protein response