Conclusions: Our results demonstrate that mimicking age-related impairment of mitochondrial function may provide a novel model for age-related dementia.

P4-236  ALZHEIMER’S DISEASE AND THE MICROBIOME
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Background: The realization that the human microbiome (HM) is a significant contributor to nutrition, health and disease is a relatively recent one, however, mechanistic studies linking alterations in microbiota to the etiopathology of disease are relatively few. The HM appears to modulate the regulation of multiple neurochemical pathways through a complex series of highly interactive and symbiotic host-microbiome signaling-systems that mechanistically link the gastrointestinal (GI) tract to the central nervous system (CNS), the enteric nervous system and the neuroendocrine and immune systems. Varying combinations of GI tract bacterial species amongst human populations (i.e., different enterotypes) contribute to the idea of human-biochemical-individuality and differential susceptibility to disease. In these preliminary studies we evaluated the effects of the anti-amyloid, anti-oxidant, anti-inflammatory flavonoid quercetin on growth inhibition of the HM-representative Bacteroides galacturonicus (ATCC 43244). Increases in B. galacturonicus in the GI tract have been associated with high fat-cholesterol (HF-C) diets, insulin resistance, diabetes and systemic inflammation. These studies are the first directly linking a major component of the HM to pathological mechanisms associated with Alzheimer’s disease (AD), a progressive inflammatory neurodegeneration of the human CNS.

Methods: Aβ-peptide assay; B.galacturonicus culture; cell-viability assay; minimal inhibitory-concentration (MIC) assay; human neuronal-glial (HNG) primary co-culture; reactive-oxygen-species (ROS) assay; 5-6-carboxy-2',7'-dichloro-fluorescein diacetate (dicarboxy-DCFDA); quercetin assay; RT-PCR; Western immunoassay. Results: Species of the gram negative, obligate anaerobic Bacteroides constitute up to 35% of all HM bacteria, indicating that this genus is a significant component of the HM system. Quercetin was found to strongly inhibit B. galacturonicus proliferation (MIC<10 µg/ml); using dicarboxy-DCFDA assay quercetin was found to decrease free radical (ROS) production and elicit neuroprotection in stressed HNG cultures. Besides quercetin’s anti-oxidant activities this flavonoid may exert beneficial microbiome effects through its inhibition of B. galacturonicus and the homeostatic stabilization the HM. Conclusions: Neuroprotective functions of quercetin and related-flavonoid polyphenols may be to augment or modify the biochemistry or proliferation of HM-resident bacteria such as B. galacturonicus. Bacteroides infections are associated with the release of nucleic acids, lipo polysaccharide (LPS), metalloprotease and other bacterial endotoxins that contribute to amyloidogenesis and inflammatory degeneration. Several additional potential mechanisms by which Bacteroides-mediated alterations in the HM may contribute to AD include molecular-mimicry of host proteins, generation of toxic-metabolites and endotoxins, modification of absorption across the GI tract, and contribution to systemic and/or chronic CNS inflammation in the host, or by complex combinations of these pathogenic processes. In addition to quercetin’s anti-amyloid and anti-inflammatory activities this phytochemical may also exert health benefits through inhibition of B. galacturonicus-mediated proliferation of pathological signaling in both the GI tract and the CNS.

P4-237  WHOLE GENE-BASED ASSOCIATION OF BASELINE PLASMA HOMOCYSTEINE IN THE ADNI-I COHORT
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Background: Homocysteine (Hcy) is one of the key metabolites in one-carbon metabolism pathway and plasma HCY was shown to be elevated in AD and associated with brain atrophy 1,2. Identification of genetic influence on HCY level can inform which genes will subsequently affect the levels of other metabolites in the one-carbon pathway and can reveal new genetic risk factors for AD through the one-carbon pathway. Methods: Quality-controlled baseline plasma HCY and GWAS data were from 742 non-Hispanic Caucasian participants (Table 1) in the Alzheimer’s Disease Neuroimaging Initiative. Genotype analysis was conducted using an additive genetic model with and without APOE ε 4 status in addition to sex and age as covariates to investigate the overall effect of all genetic variants within each gene using HYS 3. Genes with p<2.13 x 10 -6 (0.05/23,505 genes) were considered to be genome-wide significant. Results: One gene, KLF15, p = 4.02 x 10 -7 w as genome-wide significant, even after adjusting for APOE genotype. TB is a gene h a s n 0 t been previously studied in AD nor has it been associated with plasma HCY level, to date. KLF15 and SP1 are known to synergistically activate acetyl-Coa synthetase 2 (AceCS2) which produces acetyl-Coa for oxidation. 4Acytrol-Coa is a co-enzyme in the synthesis of acetylcholine, an important neurotransmitter involved in learning and memory. SP1 was recently identified in a transcriptional regulation network involving many genes associated with memory impairment using the ADNI cohort 5. Two more genes (VAV3, COX10) show suggestive associations (p<0.98 x 10 -6). VAV3 is known to interact with phospholipase C, gamma 1 (PLCG1), which through diacylglycerol DAG is involved in the degradation of phosphocholine, a phosphonoester elevated in hippocampus in early stages of AD. COX activity was shown to be significantly decreased in the hippocampus of AD patients 6. Conclusions: Our results demonstrate the promise of integrating genetics with quantitative metabolic endophenotypes to better understand

Table 1

| Characteristics | ALL | NC | MCI | AD | p-value* |
|-----------------|-----|----|-----|----|--------|
| Number of samples | 742 | 203 | 360 | 179 | 1.16E-01 |
| Baseline Age (years; mean±SD) | 75.4±6.86 | 76.1±5.0 | 74.9±7.39 | 75.6±7.50 | 2.07E-02 |
| Gender (male/female) | 444/298 | 112/91 | 234/126 | 98/81 | 9.74E-15 |
| Education (years; mean±SD) | 15.6±3.0 | 16.2±2.72 | 15.7±2.98 | 14.8±3.10 | 7.15E-05 |
| APOE (ε4+ε4+) | 374/368 | 149/54 | 163/197 | 62/117 | 9.74E-15 |
| Log10 Plasma HCY (umol/L; mean±SD) | 1.00±0.12 | 0.99±0.12 | 1.01±0.11 | 1.01±0.12 | 1.65E-02 |

*p-values were calculated using Analysis of variance (ANOVA) for continuous characteristics and chi-square for categorical characteristics.