GLUTATHIONE, MITOCHONDRIAL DEFECTS, AND A UNIQUE METABOLIC CYCLE IN OLDER HUMANS: IMPLICATIONS FOR SARCOPENIA

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Sarcopenia in aging leads to decreased muscle mass and physical-function (muscle strength and exercise capacity), but underlying mechanisms are not well understood and effective interventions are limited. We hypothesized that deficiency of the intracellular antioxidant protein Glutathione initiates a unique self-perpetuating metabolic cycle linking impaired fasted mitochondrial fuel-oxidation (fMFO) to protein catabolism and contributes to sarcopenia. We also hypothesized that supplementing the Glutathione precursor amino-acids glycine and N-acetylcysteine (GlyNAC) to correct Glutathione deficiency in older humans could reverse these defects. We tested our hypothesis in a 24-week open-label clinical-trial in 8 older-humans (74y) studied before and 24-weeks after GlyNAC supplementation, compared to 8 gender-matched unsupplemented young-controls (25y), and measured intracellular Glutathione concentrations, fMFO, physical-function, muscle-protein breakdown-rate (MPBR), gluconeogenesis, and urine nitrogen-excretion (UNE). GlyNAC supplementation in older humans corrected Glutathione deficiency and restored impaired fMFO (to levels in young controls), lowered MPBR and UNE, and increased physical-function, but did not affect gluconeogenesis or increase lean-mass, and suggest that muscle amino-acids are utilized for energy needs rather than glucose production. The absence of an increase in lean-mass suggests that GlyNAC should be combined with anabolic agents for potential benefits in combating sarcopenia. Overall, these results indicate the presence of a unique reversible metabolic cycle in older humans initiated by Glutathione deficiency which results in impaired mitochondrial fatty-acid and glucose oxidation, muscle-protein breakdown, UNE, and leads to deficiency of glycine and cysteine which re-initiate the cycle. These data have implications for improving physical-function and muscle mass in age-associated sarcopenia, and warrants further investigation.

MTOR PROMOTES BBB BREAKDOWN IN A MODEL OF ALZHEIMER'S DISEASE

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Cerebral amyloid angiopathy (CAA) is characterized by fibrillar amyloid β (Aβ) association with cerebrovasculature, which leads to impaired brain vascular function, and is present in 87% of people with Alzheimer's disease (AD). We previously showed that inhibition of mTOR by rapamycin prevented BBB breakdown and reduced vascular fibrillar Aβ in 18-19 month old Tg2576 mice that model AD-associated CAA. This finding suggests that mTOR attenuation restores integrity of the blood brain barrier (BBB) and concomitantly reduces vascular Aβ accumulation in this mouse model. Objective: To determine the mechanisms by which mTOR drives BBB breakdown we measured the abundance of tight junction proteins zonula occludens 1 (ZO-1), occludin, and claudin-5. Methods: We used immunofluorescent confocal microscopy on frozen brain tissue sections of the same Tg2576 mice used in the previous study. Results: We confirm BBB breakdown in Tg2576 mouse brains and showed that some, but not all tight junction proteins measured were decreased in cerebrovasculature of Tg2576 mice. Attenuation of mTOR by rapamycin preserved BBB integrity, decreased vascular Aβ accumulation, and increased levels of tight junction protein abundance in Tg2576 mice, which also showed a reduced numbers of cerebral microhemorrhages. Conclusions: Taken together, these data suggest that mTOR promotes brain vascular Aβ deposition, BBB breakdown and vascular damage in the Tg2576 mouse model. Thus, mTOR inhibitors such as rapamycin – an FDA approved drug - may have promise in the treatment of AD and other dementias with related cerebrovascular dysfunction.

NOVEL STAIN SEPARATION METHOD FOR AUTOMATIC STEREOLOGY OF IMMUNOSTAINED TISSUE SECTIONS

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Many studies of brain aging and neurodegenerative disorders such as Alzheimer's and Parkinson's diseases require rapid counts of high signal: noise (S:N) stained brain cells such as neurons and neuroglial (microglia cells) on tissue sections. To increase throughput efficiency of this work, we have combined deep learned (DL) neural networks and computerized stereology (DL-stereology) for automatic cell counts with low error (<10%) compared to time-intensive manual counts. To date, however, this approach has been limited to sections with a single high S:N immunostain for neurons (NeuN) or microglial cells (Iba-1). The present study expands this approach to protocols that combine immunostains with counterstains, e.g., cresyl violet (CV). In our method, a stain separation technique called Sparse Non-negative Matrix Factorization (SNMF) converts a dual-stained color image to a single gray image showing only the principal immunostain. Validation testing was done using semi- and automatic stereology-based counts of sections immunostained for neurons or microglia with CV counterstaining from the neocortex of a transgenic mouse model of tauopathy (Tg4510 mouse) and controls. Cell count results with principal stain gray images show an average error rate of 16.78% and 28.47% for the semi-automatic approach and 8.51% and 9.36% for the fully-automatic DL-stereology approach for neurons and microglia, respectively, as compared to manual cell counts (ground truth). This work indicates that stain separation by SNMF can support high throughput, fully automatic DL-stereology based counts of neurons and microglia on counterstained tissue sections.

SOLUBLE INTERCELLULAR ADHESION MOLECULE (SICAM-1) AS A BIOMARKER OF VASCULAR COGNITIVE IMPAIRMENT IN OLDER ADULTS

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